Epidemiology and Management of Symptomatic Benign Prostatic Hyperplasia

K.M.C. Verhamme

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Epidemiology and Management of Symptomatic Benign Prostatic Hyperplasia

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symptomatische benigne prostaathyperplasie

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Aan de IPCI patiënten en de IPCI artsen

Contents

Manuscripts based on the studies presented in this thesis

Chapter 2
Verhamme KMC, Dieleman JP, Bleumink GS, van der Lei J, Sturkenboom MCJM. Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in Primary Care – The Triumph Project. Eur Urol 2002; 42: 323-328.

Chapter 3
Verhamme KMC, Dieleman JP, Bleumink GS, van Wijk MAM, van der Lei J, Bosch JLHR, Stricker BHCh, Sturkenboom MCJM. Prostate specific antigen testing as part of the diagnostic work-up by general practitioners in patients with incident lower urinary tract symptoms suggestive of benign prostatic hyperplasia – The Triumph Project. (Submitted).

Chapter 4
Verhamme KMC, Dieleman JP, Bleumink GS, Bosch JLHR, Stricker BHCh, Sturkenboom MCJM. Treatment strategies, patterns of drug use and treatment discontinuation in men with LUTS suggestive of benign prostatic hyperplasia : The Triumph Project. Eur Urology 2003; 44: 539-545.

Chapter 5
Verhamme KMC, Dieleman JP, van Wijk MAM, Bosch JLHR, Stricker BHCh, Sturkenboom MCJM. Low Incidence of acute urinary retention in the general male population – The Triumph Project. N Engl J Med 2004; 350: 1359-1361.

Chapter 6
Verhamme KMC, Dieleman JP, Van Wijk MAM, van der Lei J, Bosch JLHR, Stricker BHCh, Sturkenboom MCJM. Non-steroidal anti-inflammatory drugs are associated with an increased risk of acute urinary retention. (Submitted).

Chapter 7
Verhamme KMC, Dieleman JP, Van Wijk MAM, van der Lei J, Bosch JLHR, Stricker BHCh, Sturkenboom MCJM. Anti-psychotic drugs and the risk of acute urinary retention. (Submitted).

Chapter 1 General Introduction

Introduction

1.1 Anatomy

The prostate is a walnut-sized gland located just below the urinary bladder around the urethra. (figure 1) Its primary function is the secretion of the seminal fluid, which functions to nourish and to protect the sperm against the acid pH of the vagina. [1]

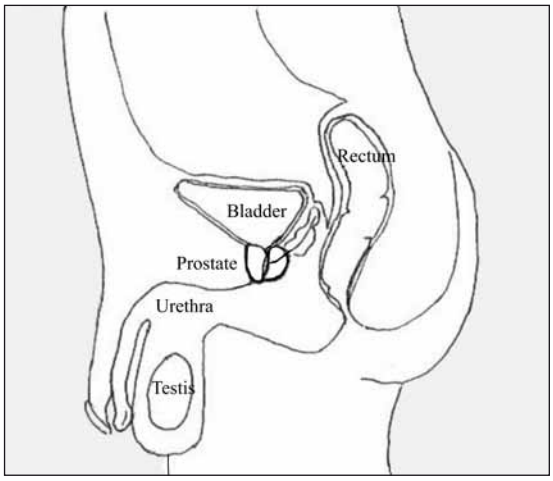

Figure 1: Anatomy of the urogenital system of men

1.2 Pathology

Benign prostatic hyperplasia (BPH) is the most common non-cancerous form of cell growth in men and usually begins with the formation of microscopic nodules in younger men. As BPH progresses, overgrowth occurs in the central area of the prostate, called the transition zone, which wraps around the urethra. The stromal component of the prostate is comprised by smooth muscle and connective tissue, while the epithelial component is primarily glandular. The relationship between the stromal and the epithelial component is approximately 2:1 in the normal prostate. In patients with BPH, the stromal to epithelial ratio increases to 5:1.[2]

1.3 Physiology of micturition

The act of micturition is a very complex mechanism. The lower urinary tract consists of the bladder and the urethra. Most of the time, the bladder serves as a reservoir for urine and expands as the bladder fills. There are two sphincters (internal and external urethral sphincter) in the urethral wall that prevent urine loss as the bladder fills. During storage, the distension of the smooth muscle fibers and the urothelium, evoke afferent activity. Myelinated Aδ sensory fibers respond to passive distension. Unmyelinated C sensory fibers have a higher mechanical threshold and respond to a variety of neurotransmitters. These neurotransmitters include

adenosine triphosphate (ATP), tachykinins, nitric oxide (NO) and prostanoids. (figure 2) These neurotransmitters bind to specific receptors and stimulate or inhibit micturition.[3, 4]

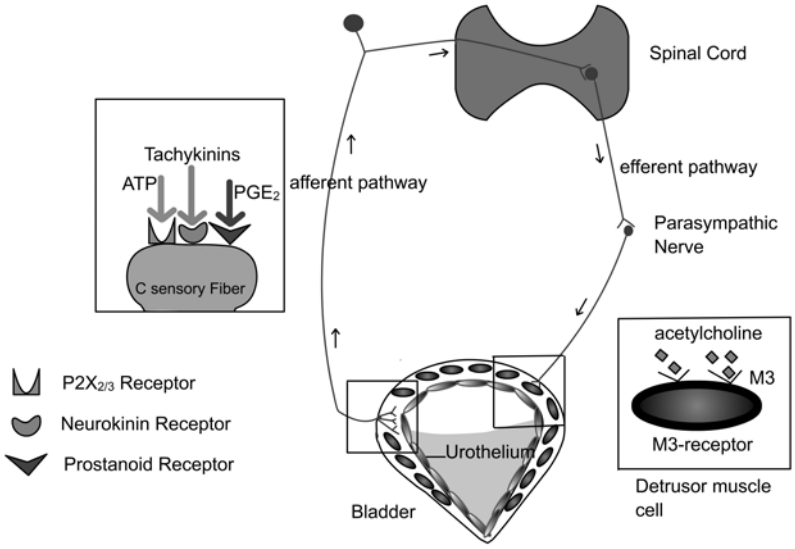

Figure 2: Role of transmitters in the afferent and efferent pathway

With the initiation of normal urination, urethral resistance decreases via relaxation of the internal and the external urethral sphincter, and a phasic contraction of the detrusor muscle empties the bladder. A variety of afferent and efferent neural pathways, reflexes and central and peripheral neurotransmitters are involved in urine storage and bladder emptying.

There are 3 nerves that provide primary control of the bladder, namely the hypogastric (sympathetic nervous system), the pelvic (parasympathetic nervous system) and the pudendal nerves (somatic nervous system). These nerves serve as lower motor neurons and are under control of upper motor neurons in the brain stem and the cerebellum.

Bladder contraction in humans is mainly mediated through stimulation of muscarine receptors in the detrusor muscle (parasympathetic pathway). The storage phase of micturition is mainly mediated through stimulation of ß3 adrenergic receptors (sympathetic pathway), the α-receptors of the urethral internal sphincter (sympathetic pathway) and the urethral external sphincter (somatic nervous system). [3, 5, 6]

1.4 Epidemiology

Many studies have attempted to assess the prevalence of BPH and none has estimated incidence. Assessing the occurrence of BPH is difficult due to the lack of a standardized case definition. Based on autopsy studies, the prevalence of histologically diagnosed BPH increases from 8% in men aged 31 to 40 years, to up to 40-50% in men aged 51 to 60 years, and to more than 80% in men older than 80 years. Based on clinical criteria, approximately 4-25% of men, aged 40 years and older, suffer from BPH. Although the observed prevalence of clinical BPH varies depending on the definition of BPH, all studies confirm that the prevalence of BPH strongly increases with age. [7-13]

Age, normal androgenic function and family history are known risk factors for BPH. Other potential risk factors include race, ethnicity, geographic location and obesity.[2, 7]

1.5 Symptomatology

Patients with BPH often express urinary symptoms such as urge incontinence, dribbling, slow stream and difficult voiding. These symptoms are not specific for BPH alone. Other causes of bladder outflow obstruction (e.g. urethral stricture) and primary disorders of the bladder can produce identical symptoms. These symptoms are called lower urinary tract symptoms (LUTS). The correlation between the severity of LUTS, prostate size and the degree of obstruction is weak. Men with large prostates may be symptom-free while those with small or normal sized prostates may sometimes have symptoms that are more severe than in men with larger prostates. [2, 7, 14]

Symptomatic BPH is usually defined by the concept proposed by Hald in which the LUTS/BPH and bladder outflow obstruction are considered together as presented in fig 3. [15]

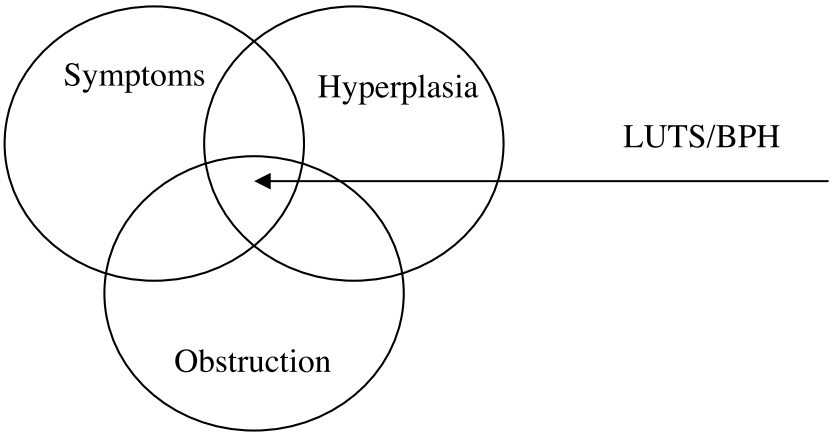

Figure 3: Hald diagram showing the interaction between lower urinary tract symptoms, benign prostate enlargement and bladder outlet obstruction.

Lower urinary tract symptoms are generally classified into voiding symptoms (hesitancy, poor urinary flow and need to strain, incomplete bladder emptying, terminal or postmicturition dribbling) and storage symptoms (frequency, urgency, nocturia and urge incontinence). To quantify the severity and the extent of the LUTS, men are generally asked to complete symptom questionnaires. The International Prostate Symptoms Score (I-PSS) has been adopted by the World Health Organization and is most frequently used. [2, 7, 8] As well as obtaining objective evidence of the severity of LUTS, quantification in terms of effect on quality of life and degree of discomfort is equally important.

1.6 Management of patients with LUTS/BPH

The diagnosis of LUTS/BPH is made on the basis of medical history, physical examination including a digital rectal examination, urinalysis and uroflow measurements. To exclude prostate cancer, prostate specific antigen (PSA), which is a tumour marker for prostate cancer, is often tested. [7, 14] As PSA is often mildly elevated in patients with BPH and thus less conclusive [16], guidelines of the Dutch College of General Practitioners on the management of patients with difficult micturition, only recommend PSA testing in patients younger than 70 years and with an inconclusive digital rectal examination. [17]

BPH is a progressive disease and may lead to important medical conditions such as acute urinary retention (AUR), chronic urinary retention, recurrent urinary tract infections, bladder calculi and bleeding. [7-9]

The primary goals of treatment for BPH are to reduce the symptoms, to improve the urinary flow and eventually to prevent progression. Not every patient with LUTS/BPH is treated and some patients are followed with the watchful waiting strategy. Watchful waiting involves lifestyle changes such as avoiding alcohol, coffee and avoiding the use of certain drugs (e.g. diuretics, decongestants). [2, 7, 14]

The choice between watchful waiting and treatment depends on a number of factors such as the severity of the symptoms, the prostate size and the urinary flow rates. Generally, watchful waiting is recommended in patients with mild symptoms (I-PSS≤7). Patients with moderate (I-PSS between 8-19) or severe symptoms (I-PSS ≥20) are pharmacologically treated or undergo prostate surgery. [18, 19]

The two drug classes primarily used for the treatment of LUTS/BPH are α-blockers and 5α-reductase inhibitors. [20] α-Blockers bind to α1-adrenoreceptors in the bladder neck and in the smooth muscles of the prostate, causing relaxation and thus improving urinary flow. Some of these drugs might also provoke apoptosis of the prostate epithelium. [2, 7, 14] α-Blockers do not only provoke a relaxation of the smooth muscles in the prostate, urethra and the bladder neck but also cause a relaxation of the smooth muscles of the blood vessels. This might interfere with blood pressure regulation, causing all kinds of side effects like (orthostatic) hypotension, syncope, dizziness and asthenia. [21]

5α-Reductase inhibitors suppress the formation of dehydrotestosterone from testosterone. This causes atrophy of the prostatic glandular epithelial cells, resulting in a 20-30% reduction of the prostate volume after approximately 2-6 months. These drugs are mainly prescribed for men with large prostates. [2, 7, 14] Common side effects of 5α-reductase inhibitors are impotence, loss of libido and ejaculatory dysfunction. [7]

Recently, results from large randomized controlled trials (RCTs) have been published, showing that treatment with 5α-reductase inhibitors and especially the combination of 5α-reductase inhibitors with an α-blocker was not only beneficial in the relief of urinary symptoms but was also able to prevent disease progression (in terms of acute urinary retention, prostate surgery, and urinary tract infections). [22, 23]

Plant extracts have been used for many years in Europe. They might improve the urinary flow and relieve nocturia but the exact mechanism of action remains unclear and their efficacy needs to be further tested in well-designed, randomized controlled trials (RCT).[7, 20]

If patients are surgically treated, invasive or non-invasive procedures are available. The most effective procedures, namely the transurethral resection of the prostate (TURP) and the open prostatectomy, are also the most invasive ones. They carry the highest risk of significant complications, including impotence and incontinence. Transurethral incision of the prostate, transurethral needle ablation and thermotherapy procedures are less invasive. [2, 7, 14]

1.7 Aim and outline of this thesis

Data on the incidence, the natural history and the long term treatment of LUTS/BPH are scarce, especially in Europe. Information is only available from some large US cohort studies and some large RCTs. [22-25] However, data from these RCTs are not necessarily representative of real practice as RCTs only study a highly selected group of patients due to stringent in- and exclusion criteria.

The costs related to the treatment of LUTS/BPH are likely to increase over the coming years due to the ageing population and the high prevalence of LUTS/BPH, especially in ageing men. Accurate health care policies for the rational management of LUTS/BPH can only be designed if information on the management of patients with LUTS/BPH in real practice is available. Under the initiative of the European Association of Urology, the Triumph Project (TransEuropean Research Into the Use of Management Policies for LUTS suggestive of BPH in Primary Healthcare) was initiated to study the real life management of patients with LUTS/BPH in various European countries. [26] The Triumph Project consists of 2 parts, namely a prospective and a retrospective part. In the prospective part, a cohort of approximately 10,000 LUTS/BPH patients from 6 European countries is followed over one year to study the various treatment options and to study the time to disease progression. The retrospective part of the Triumph Project uses data from the General Practice Research Database (GPRD) in the UK and the Integrated Primary Care Information (IPCI) project in the Netherlands. [27, 28] The aim of the retrospective part of the

Triumph Project is to look into the epidemiology, the management and the clinical progression of patients with LUTS/BPH.

This thesis represents the results of the retrospective part of the Triumph project using data from the IPCI database plus some studies on risk factors for acute urinary retention in elderly males who do not necessarily have LUTS/BPH. In chapter 2, we describe the incidence and the prevalence of LUTS/BPH. In chapter 3, we describe the diagnostic work-up of patients presenting themselves with LUTS/BPH. Chapter 4 focuses on the treatment of men with LUTS/BPH including compliance aspects such as treatment persistence and treatment adherence. In addition, risk factors for early treatment discontinuation are studied. Chapter 5 describes the incidence of acute urinary retention as a proxy for BPH progression. Chapters 6 and 7 describe the results of a case-control study examining non steroidal anti-inflammatory drugs and antipsychotic drugs as risk factor for AUR.

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Chapter 2 Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care

Abstract

Objective Benign prostatic hyperplasia (BPH) is one of the most common conditions associated with ageing in men. BPH often presents as lower urinary tract symptoms (LUTS) due to difficulties in voiding and irritability of the bladder. We conducted a retrospective cohort study within the Integrated Primary Care Information Database (IPCI), a general practitioners database in the Netherlands, to assess the incidence of LUTS suggestive of BPH (LUTS/BPH) in the general population.

Materials Our study population comprised all males, 45 years or older who were registered for at least 6 months prior to start of follow-up. The study period lasted from 1st January 1995 until December 31st 2000. Cases of LUTS/BPH were defined as persons with a diagnosis of BPH, treatment or surgery for BPH, or urinary symptoms suggestive of BPH that could not be explained by other co-morbidity.

Results The study cohort comprised 80,774 males who contributed 141,035 person-years of follow-up. We identified 2,181 incident and 5,605 prevalent LUTS/BPH cases. The overall incidence rate of LUTS/BPH was 15 per 1000 men-years (95% CI 14.8-16.1). The incidence increased linearly (r^2=0.99) with age from 3 cases per 1000 men-years at the age of 45-49 years (95% CI 2.4-3.6) to a maximum of 38 cases per 1000 men-years at the age of 75-79 years (95% CI 34.1-42.9). After the age of 80 years, the incidence rate remained constant. For a symptom-free man of 46 years, the risk to develop LUTS/BPH over the coming 30 years, if he survives, is 45%. The overall prevalence of LUTS/BPH was 10.3% (95% CI 10.2-10.5). The prevalence rate was lowest among males 45-49 years of age (2.7%) and increased with age until a maximum at the age of 80 years (24%).

Conclusions The incidence rate of LUTS/BPH increases linearly with age and reaches its maximum at the age of 79 years

Introduction

Benign prostatic hyperplasia (BPH) is one of the most common conditions associated with ageing in men, and has been noted at autopsy in approximately 40% of men in their 50s and in up to 70% in their 60s.[1] BPH is a benign enlargement of the prostate that results in increasing pressure on the urethra and subsequent obstruction of the urinary flow. Patients with BPH might be free of symptoms but often present themselves with lower urinary tract symptoms (LUTS) as a result of difficulties in voiding (e.g. hesitancy, straining, weak stream, dribbling) and irritability of the bladder (e.g. urgency, frequency, urge incontinence).[2]

The prevalence of BPH has already been studied in great detail and results vary from a relatively low prevalence of 13% to a high prevalence of 43% depending on the method of BPH assessment, the country and the age range studied.[1, 3-10] Despite the abundance of information on prevalence, incidence rates of BPH are unknown. Only recently, the incidence of symptoms suggestive of BPH has been published.[11,19]

In the Netherlands the General Practitioner (GP) has a central role and he/she acts as a gatekeeper to all further secondary care.[14] Ninety percent of all health problems are dealt with by the GP. Patients who develop LUTS suggestive of BPH (LUTS/BPH) would therefore first consult their GP for medical care. A diagnosis of BPH will be based on an evaluation of the symptoms (e.g. via the International Prostate Symptom Score (I-PSS)), a physical examination including a digital rectal examination and urine analysis.[12] Additional examinations such as rectal ultrasound and serum analysis of prostate specific antigen (PSA) will be done if indicated.[12] As part of the Triumph (TransEuropean Research Into the Use of Management Policies for LUTS/BPH in Primary Healthcare) project[13] we conducted a retrospective cohort study within a database of computerized GP medical records to assess the incidence of LUTS/BPH diagnosed in the Dutch general population.

Methods

Setting

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database, which contains information from computer-based records of GPs in the Netherlands. Within the Netherlands, patients are registered to a single GP and the record for each individual patient can be assumed to contain all medical information on that patient.[14] The IPCI database is maintained by the Department of Medical Informatics of the Erasmus Medical Center Rotterdam.[15] The first practice was enrolled in the IPCI project in 1992 but a large proportion of practices started to contribute from 1998 onwards. Now the number of practices contributing data has increased to 98 and the database contains information on approximately 500,000 patients.

The computer records contain information on patient demographics, symptoms (free text), diagnoses (using the International Classification for Primary Care), referrals, laboratory values, measurements (e.g. blood pressure, cholesterol levels), drug prescriptions plus their ICPC-coded indications, and hospitalizations.[16] Summaries of the hospital discharge letters or information from specialists are entered in a free text format and copies can be provided upon request. Information on drug prescription comprises brand name, quantity, strength, indication, prescribed daily dose and the Anatomical Therapeutical Chemical classification (ATC) code.[17] To maximize completeness of the data, GPs who participate in the IPCI project are not allowed to use paper-based records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research. [18]

Study population

The study population comprised all males of 45 years and older who had at least 6 months of valid history. A valid history meant that the practice had been contributing data to the IPCI database for at least 6 months and that the patient had been registered with the GP for at least 6 months. Follow-up started on January 1st 1995 or the date that 6 months of valid history were obtained, whichever was latest. Follow-up lasted until the first diagnosis of LUTS/BPH, death, transferring out of the GP practice or December 31st 2000, whichever was earliest.

Case identification and validation

Since cases of LUTS/BPH cannot be identified with a specific ICPC code we used a sensitive computerized case identification method that included diagnoses, treatment and non-coded symptoms (text) to minimize the number of undetected cases of LUTS/BPH (false negatives).

The computerized medical records of all potential incident cases were manually reviewed by a medical doctor (KV) and categorized as definite cases of LUTS/BPH if they had LUTS and a first diagnosis of BPH; if they had LUTS and were treated with an alpha-blocker or a 5-alpha-reductase inhibitor for the indication of BPH; if they had two or more LUTS suggestive of BPH in absence of any other co-morbidity that could explain these urinary symptoms; or if they underwent a prostatectomy for BPH during the follow-up period. Possible cases were all persons with a single isolated LUTS and absence of other co-morbidity that could explain the urinary symptom, or persons treated with an alpha-blocker without a clear indication for that use. Patients were classified as non-cases if the identified symptoms were not related to LUTS or if they had LUTS that could be ascribed to other urological conditions (e.g. dysuria related to meatal stenosis or urethral stricture). Patients diagnosed with prostate cancer and/or requiring prostatectomy for other reasons than BPH were excluded from the analysis and thus did not contribute person-years to the denominator. Patients who were first diagnosed with BPH and at a later stage were diagnosed with prostate cancer remained in the study but as for all cases, follow-up ended at the time of the first record of LUTS/BPH. All possible cases were reviewed by

a second medical doctor (GB) and classified as either definite or non-cases after consensus with the first reviewer (KV) was obtained. For the final set of definite cases we determined the index date as the date of first LUTS/BPH.

Persons with a diagnosis of BPH, or LUTS prior to study entry were classified as prevalent LUTS/BPH patients at study entry and did not contribute persontime to the study. We manually validated the medical records of the prevalent LUTS patients who only had one symptom by using the algorithm specified above. Patients with prevalent multiple LUTS/BPH were not further validated.

Statistical analysis

The incidence of LUTS/BPH was calculated by dividing the number of men with a first entry of LUTS/BPH after study entry by the number of men-years accumulated by the study population. Incidence estimates were calculated stratified by age (5-year categories) and calendar year and 95% confidence estimates were calculated around the estimates based on the Poisson distribution.

The cumulative incidence of LUTS/BPH over 10, 20 and 30 years of time was calculated from the age-specific LUTS/BPH incidence rates that were adjusted for the survival probability in each age category. Mortality data (1998) from which we calculated the survival probability were obtained from the Dutch Central Bureau of Statistics. (Infoservice@cbs.nl)

Prevalence of LUTS/BPH between 1995 and 2000 was calculated by dividing the number of patients of a certain age with prevalent LUTS/BPH by the number of men of that age present in the study population. Prevalence estimates were calculated by age with 95% confidence intervals calculated on the basis of the normal distribution.

Results

The total study cohort comprised 80,774 males of whom, after a sensitive computer case identification algorithm search, 8393 potential incident LUTS/BPH patients and 6055 potential prevalent LUTS/BPH patients were identified. After manual validation, 2181 persons were classified as definite incident LUTS/BPH cases and 5605 as prevalent LUTS/BPH cases. The majority of excluded patients were false positives because of the over-inclusive search on symptoms as free text.

The total person time until development of LUTS/BPH, death, transferring out of the practice or December 31st 2000 was 141,035 years. The overall incidence rate of LUTS/BPH was 15 per 1000 men-years (95% CI: 14.8-16.1). The incidence of LUTS/BPH increased with age, from 3 per 1000 men-years at the age of 45-49 to a maximum of 38 per 1000 men years at the age of 75-79 years. After 80 years of age the incidence remained more or less constant (figure 1 and table 1). The increase in incidence was linear between ages 45 to 79 years (r^2 =0.99) with an increase of 6.15/1000 men-years upon each 5-year increase in age.

Figure 2 shows the 10, 20 and 30 year risk to develop LUTS/BPH for men who are still symptom-free at a certain age. For a symptom-free man of 46 years, the risk to develop LUTS/BPH over the coming 10, -20 or 30 years is 5%, 20% or 45 % respectively (figure 2). For a male who arrives at the age of 55 without LUTS symptoms, the risk to develop LUTS/BPH over the next 10, 20 or 30 years if he stays alive is 15, 40 and 70% respectively.

We also investigated potential changes of age-specific incidence rates over time. Overall the incidence of LUTS/BPH was constant over calendar time. The prevalence of diagnosed LUTS/BPH increased with age. The overall prevalence was 10.3% (95%CI: 10.2-10.5). The prevalence of diagnosed LUTS/BPH was lowest at the age of 40-45, namely 2.7% and reached a maximum of 24.0% at the age of 80 (figure 3).

Table 1: Incidence of LUTS/BPH

Age	Number of incident cases	Number of men years	Incidence per 1000 men-years	95%CI
45-49	91	30714.0	2.96	2.40-3.62
50-54	217	31389.7	6.91	6.04-7.88
55-59	278	21354.4	13.02	11.55-14.62
60-64	348	17597.5	19.78	17.78-21.94
65-69	338	14087.1	23.99	21.54-26.66
70-74	378	10969.4	34.46	31.12-38.07
75-79	297	7755.5	38.30	34.12-42.84
80-84	137	4254.4	32.20	27.14-37.94
>84	97	2913.6	33.29	27.15-40.43
Total	2181	141035	15.46	14.83-16.12

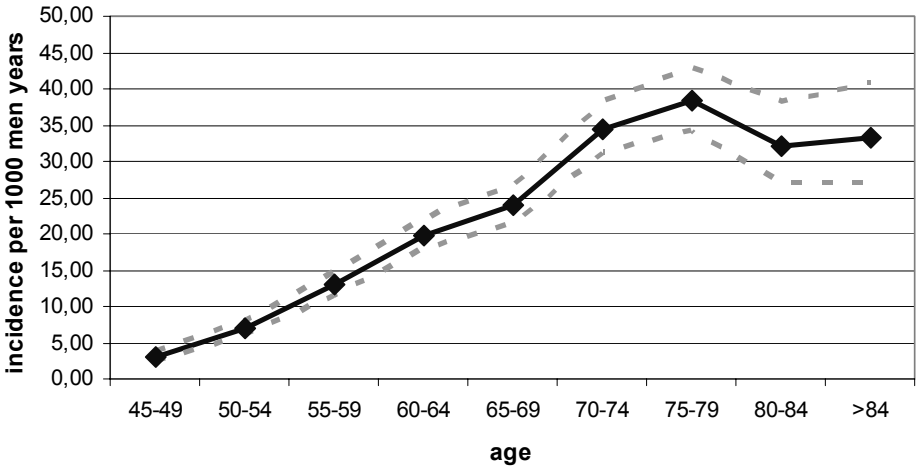

Figure 1: Age-specific incidence of LUTS/BPH (--- 95% confidence intervals)

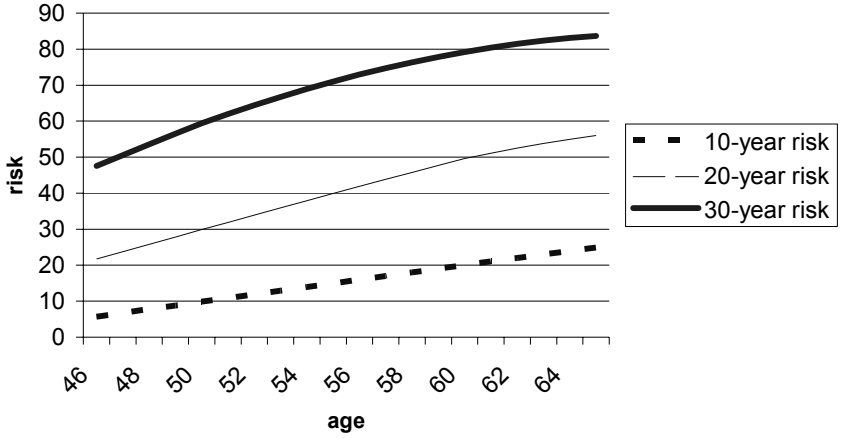

Figure 2: Age-related risk to develop LUTS/BPH over the coming 10, -20 or –30 years

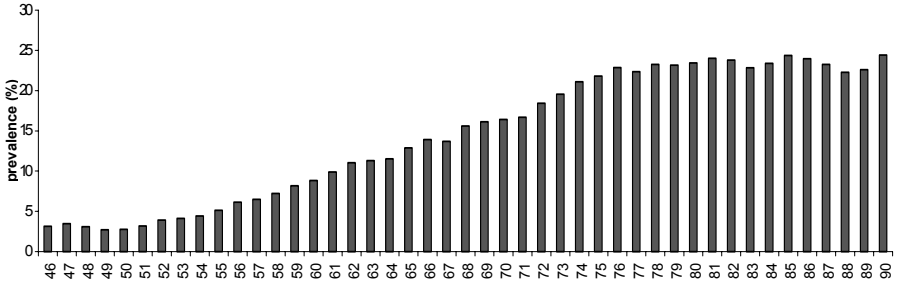

Figure 3: Age-specific prevalence of LUTS/BPH

Discussion

In this study, we observed an overall incidence of LUTS/BPH of 15/1000 men-years among men aged 45 year or older. Our study is one of the first to report on the incidence of LUTS/BPH and we observed a linear association ($r^2 = 0.99$) with age. Within our study population, the incidence was lowest at age 45-49 (3/1000 men-years) and was highest at the age of 75-79 (38/1000 men years). The linear relationship between age and incidence is remarkably consistent with General Practice Research Database results published by Clifford et al. who also reported a linear increase in the incidence of LUTS/BPH from the ages of 45 to 85 ($r^2 = 0.99$). [11,19] Results from that study on the overall incidence rate and the incidence rate by 5-year age categories are not yet published. The observed association between age and BPH occurrence does only describe

a pattern of occurrence and cannot be translated into a conclusion that age would explain 99% of BPH cases; identification of causes of BPH requires another type of study.

In our study, the incidence rate did not further increase after the age of 80 years. This may be explained by both underreporting of LUTS by elderly men, by a so-called 'healthy survivor' effect or by a cohort effect. The healthy survivor effect refers to the natural selection process, such that those who reach elder age will tend to be healthier.

From the data on the cumulative incidence we can expect that 45% of the symptom–free men aged 46 years will develop LUTS/BPH over the coming 30 years. Since the incidence rate increases with age the risk over a fixed period of time increases for men who are older.

Our prevalence falls within the large range of previously reported prevalence estimates. [1,3-10] The large variation in existing prevalence depends on BPH definitions, assessment and geographic region. In 1995, a study was published that aimed to show the differences in prevalence of BPH with different case assessment methods. [6] The prevalence decreased from a high result of 19.3% to a low result of 4% when stricter criteria for case assessment (i.e. combination of prostate volume>30 cm, IPSS>7, max flow rate<10mL/sec and presence of post-voidal volume > 50mL) were used. A multinational study with case assessment based on a standardized symptom questionnaire (I-PSS>7) within a community-based random sampling of subjects with age between 40-79 years, showed prevalences of 14%, 18%, 38% and 56% in France, Scotland, USA and Japan, respectively. [10] In our study, we found an overall prevalence of 10.3%, which is slightly lower than the BPH symptom prevalence of France and Scotland. The differences in prevalence between countries could be explained by true differences in the occurrence of BPH but might also be the result of cross-cultural differences in the perception of the symptoms and the willingness to report them.

Some caution needs to be applied when interpreting our data. First, they should be regarded as an approximation of the true prevalence and incidence of BPH in the general population as we studied the occurrence of reported symptoms suggestive of BPH. It is likely that we have underestimated the actual incidence of BPH due to underreporting and due to asymptomatic BPH. [1] Although we applied a rigorous validation algorithm we may have retained some false positive persons since we did not always have information on objective criteria such as results of rectal ultrasound or uroflowmetry. Also, since there is no international agreement on the definition of BPH, some over-reporting of BPH by the GP's might have occurred.

In conclusion the incidence rate of LUTS/BPH increases linearly with age and reaches its maximum at the age of 79 years. Due to the retrospective character of this study the incidence and prevalence estimates should be seen as conservative, but their size and age-related trend show the important role that BPH will play as one of the major morbidities in men in an ageing population.

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Chapter 3

Prostate specific antigen testing as part of the diagnostic work-up by general practitioners in patients with incident lower urinary tract symptoms suggestive of benign prostatic hyperplasia

Abstract

Objective: Guidelines of the Dutch College of general practitioners (DCGP) on voiding difficulties in older men restrict the use of prostate specific antigen (PSA) in the differential diagnosis of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH).

Methods: We conducted a retrospective cohort study within the Integrated Primary Care Information (IPCI) database to study the use of PSA and digital rectal examination (DRE) as part of LUTS/BPH diagnostic work-up. The source population comprised all males, 45 years or older during the study period (1st January 1995 to 31st December 2000). From this source population, we identified a cohort of men, newly diagnosed with LUTS/BPH and reviewed their medical charts for PSA testing and/or digital rectal examination (DRE) around the time of the diagnosis. In addition we assessed PSA retesting, referrals to an urologist and eventually prostate biopsy within 6 months after initial diagnosis.

Results: A cohort of 1917 men was diagnosed by the GP as having LUTS/BPH and PSA testing was done in 55% of these patients. Of the 277 patients with an abnormal PSA and at least 6 months of follow-up, 131 (47%) were immediately referred to an urologist, 65 (23%) had a PSA retesting and in 81 (29%) no action was taken. Information on DRE was recorded in 1214 of the 1917 patients (63%). Among the referred patients, the prostate cancer detection rate was highest in patients referred for an abnormal DRE in combination with an elevated PSA (HR_{adj} 9.8; 95% CI 4.5-21).

Conclusion: PSA testing occurred in more than 50% of new LUTS/BPH patients but in contrast, information on DRE was only recorded in approximately 60% of all patients. Revision of DCGP guidelines is desirable to clarify the need, interpretation and follow-up of PSA testing in patients with LUTS/BPH.

Introduction

Prostate-specific antigen (PSA) is used as a tumor marker in the detection and follow-up of prostate cancer. PSA testing has become increasingly popular as a screening tool for the early detection of prostate cancer. Unfortunately, PSA testing in patients with benign prostatic hyperplasia (BPH) provides little additional information about the presence of prostate cancer and often leads to false positive results, especially for PSA values between 4-10 ng/ml.[1] While widespread use of PSA testing has resulted in the detection of earlier stage prostate cancers, many of these tumors were unlikely to be a threat to the overall health of the individual.

For this reason, the guidelines of the Dutch College of general practitioners (DCGP) on difficult micturition in elderly men, recommend PSA testing as diagnostic work-up only in patients younger than 70 years with an inconclusive digital rectal examination.[2] Other international guidelines are also in disagreement on the role of PSA testing in the initial evaluation of patients with LUTS/BPH. [3-6]

Currently there is no international consensus about the further evaluation of patients with an elevated PSA. Three scenarios can be anticipated including: immediate referral for prostate biopsy, immediate repeat PSA test or a repeat PSA test after 6-8 weeks. If after repeat testing, PSA remains increased, patients should be referred for biopsy. [7] Guidelines of the DCGP recommend referral to the urologist for patients suspected to have prostate cancer where therapeutic interventions would improve life expectancy or quality of life. This is generally translated into referral of patients, younger than 70 years and without severe co-morbidity, who had a digital rectal examination (DRE) that was suspicious for prostate cancer or who had an elevated PSA test. [2]

Despite the questionable place of PSA testing in improving prostate cancer survival and morbidity, this test appears frequently used. In order to get more insight into the diagnostic work-up in patients with new LUTS/BPH, we quantified the use of DRE and PSA testing. In addition, we assessed the patient management after an abnormal PSA result and estimated the risk of prostate cancer among different types of work-up.

Methods

Setting

This study was conducted in the Integrated Primary Care Information (IPCI) database in the Netherlands. The IPCI database is a general practice research database, containing information from electronic patient records of 150 general practitioners (GPs) covering a total of approximately 500,000 patients. In the Dutch health care system, patients are registered with a single GP who acts as a gatekeeper of medical care and information.[8] The electronic records contain coded and anonymous data on patient demographics, symptoms (using the International Classification for Primary Care (ICPC) and free text), diagnoses (using ICPC and

free text), clinical findings, referrals, laboratory findings (such as PSA), and hospitalisations.[9, 10] Summaries of the hospital discharge letters or information from specialists are entered in a free text format and hard copies can be provided upon request. Information on drug prescription comprises brand name, quantity, strength, indication, prescribed daily dose, the Anatomical Therapeutic Chemical classification (ATC) code and the physician linked indication.[11] To maximize completeness of the data, GPs who participate in the IPCI project are not allowed to use paper-based records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research.[12] The Scientific and Ethical Advisory Group of the IPCI project approved the study.

Source population

The study cohort comprised all males of 45 years or older who were newly diagnosed with LUTS/BPH by the GP, during the study period (1st January 1995 until 31st December 2000). Details on identification and validation of these patients have been published elsewhere. [13] In brief, LUTS/BPH was identified from the medical records by manual chart validation. In addition, we included all men who presented with LUTS/BPH but who were diagnosed with prostate cancer shortly after their first consultation (within 30 days). All cohort members were followed from the date of first diagnosis of LUTS/BPH until the end of the study, leaving the practice, diagnosis of prostate cancer or death, whichever event occurred first.

Diagnostic work-up for LUTS/BPH

Use of diagnostic tools, i.e. DRE and PSA testing around the date of diagnosis of LUTS/BPH was reviewed in the computerized free text medical records for all study subjects. Total PSA values above 4 ng/ml were considered as being abnormal.[14] In addition, we assessed further work-up such as repeat PSA testing, referrals to an urologist, or prostate biopsy within the period of 6 months after a first abnormal PSA result. Only patients with at least 6 months of follow-up after initial PSA sampling were included in this analysis.

According to the DCGP guidelines, the DRE findings as recorded in the patient's files were categorized into 5 categories namely, 1: normal DRE, 2: enlarged DRE, 3: DRE suggestive of prostatitis, 4: DRE suggestive of prostate cancer, 5: DRE difficult to interpret.[2]

Prostate cancer

The occurrence of prostate cancer was assessed during the entire follow-up period after diagnosis of LUTS/BPH. Prostate cancer was identified from the electronic medical records by automated free text search and search on ICPC code (Y77=prostate cancer) followed by validation via manual review. We only included prostate cancers that were either diagnosed or confirmed by the urologist. In case of insufficient information, additional information such as specialist letters was requested from the GP.

Analysis

Descriptive statistics were used to describe the frequency of PSA testing, DRE examination, urologist referral and prostate biopsies in men with LUTS/BPH. Student's t-test was used to study the difference in means of continuous variables. Chi-square statistics were used for the comparison of discrete variables.

Cox proportional hazard analysis was used to study the hazard ratio of prostate cancer in patients referred to the urologist based on an abnormal PSA, abnormal DRE or the combination of both. To calculate the incidence rate of prostate cancer, we divided the number of cases by the total number of person-years, 95% confidence intervals were calculated based on the Poisson distribution. The occurrence of prostate cancer was compared between persons with different initial work-ups after adjustment for age.

Results

We identified 2214 patients with LUTS/BPH and 22 patients with LUTS who were diagnosed with prostate cancer shortly after the LUTS/BPH diagnosis. LUTS/BPH was diagnosed by the GP in 1901 of the 2214 patients (86%). A relationship between LUTS, abnormal DRE and the probability of prostate cancer was assumed by the GP in 16 of the 22 (72.7%) patients who were diagnosed with prostate cancer shortly after their first LUTS-related GP visit. The other 6 patients were referred to the urologist for LUTS.

Digital rectal examination

Information on DRE of the prostate was recorded in 1214 of the 1917 patients (63 %) diagnosed by the GP. The mean age of the patients with a DRE (66 years) was significantly lower than the mean age of the patients without (68 years, $p<0.001$) (table 1). DRE was normal in 366 of the 1214 patients (30%). The prostate was enlarged in 738 patients (61%) and suspicious for prostate cancer in 73 patients (6%). Nine patients (< 1%) had a DRE that was difficult to interpret (table 2).

PSA testing

Of the 1917 patients diagnosed with LUTS by the GP, PSA testing was performed in 1063 patients (55.4%) (figure 1). The mean age of patients with PSA sampling (65 years) was significantly lower than in patients without PSA assessment (68 years, $p<0.001$). PSA testing occurred mainly in patients with a DRE (801/1214 (66%) versus 262/703 (37%)) (table 1). The proportion of PSA testing was the highest for patients with a DRE, suspicious for prostate cancer (63/73 (86%)) and lowest in patients with a DRE, suspicious of prostatitis (10/21 (48%)) (table 2). Even in patients with a normal DRE or a DRE suspicious of BPH, the proportion of PSA testing was substantial (table 2).

PSA turned out to be abnormal in 319 patients (30.0%) with a median PSA level of 7.6 ng/ml. Among these patients, 277 had at least 6 months of follow-up after PSA sampling and were included in the analysis of further work-up. Among these 277 men, no action, defined as no repeat PSA test or no referral to the urologist, was taken in 81 (29%). This group had a median PSA level of 5.4 ng/ml. Sixty-six patients (24%) had a repeat PSA testing done and 152 (52%) of the patients with an abnormal PSA result were referred to an urologist (figure 1).

Table 1: Use of digital rectal examination and PSA testing in the diagnostic work-up of patients with new LUTS/BPH

	DRE n=1214	No DRE n=703	
Mean age	66 ± 10 *	68 ± 11	P<0.001
PSA testing			p<0.001
- PSA	801 (66%)	262 (37%)	
- No PSA	413 (34%)	441 (63%)	

* Mean ± SD

Table 2: Use of PSA testing in the diagnostic work-up of patients with new LUTS/BPH, according to DRE result

	DRE result						
	1 n=366	2 n=738	3 n=21	4 n=73	5 n=9	6 n=7	
No PSA	139 (38%)	249 (34%)	11 (52%)	10 (14%)	3 (33%)	1 (14%)	p< 0,001
PSA	227 (62%)	489 (66%)	10 (48%)	63 (86%)	6 (67%)	6 (86%)	p< 0,001

1=normal DRE, 2=prostate enlarged, 3=suspect for prostatitis, 4=suspect for prostate cancer, 5=DRE difficult to interpret, 6=DRE result lacking

Prostate cancer

Of the 1917 patients diagnosed by the GP as having LUTS/BPH, 1648 patients (86%) had at least 6 months of follow-up. Of these patients, 452 (27%) were referred to an urologist within 6 months after a first diagnosis of LUTS/BPH, 55 (12%) of whom were subsequently diagnosed with prostate cancer (Table 3). The prostate cancer hazard ration was highest for patients who were referred based on a combination of an elevated PSA and a suspicious digital rectal examination (HR_{adj} 9.8; 95% CI 4.5-21) (table 3).

During the entire follow-up (mean of 1.8 years), we identified 102 cases (5%) of prostate cancer amongst the 1917 patients who were diagnosed with LUTS by the GP. This cohort of 1917 patients with LUTS contributed 3,500 person-years of follow-up resulting in an overall incidence rate of prostate cancer of 29.1 per 1000 men-years (95% CI 23.9-35.2). The age adjusted incidence rate of prostate cancer amongst the patients with initial PSA sampling was higher, though not statistically significant, than the incidence rate of prostate cancer amongst the patients without PSA sampling, namely 43.8 per 1000 men-years (95% CI 30.3-57.3) versus 26.2 per 1000 men-years (95% CI 19.0-35.1) respectively.

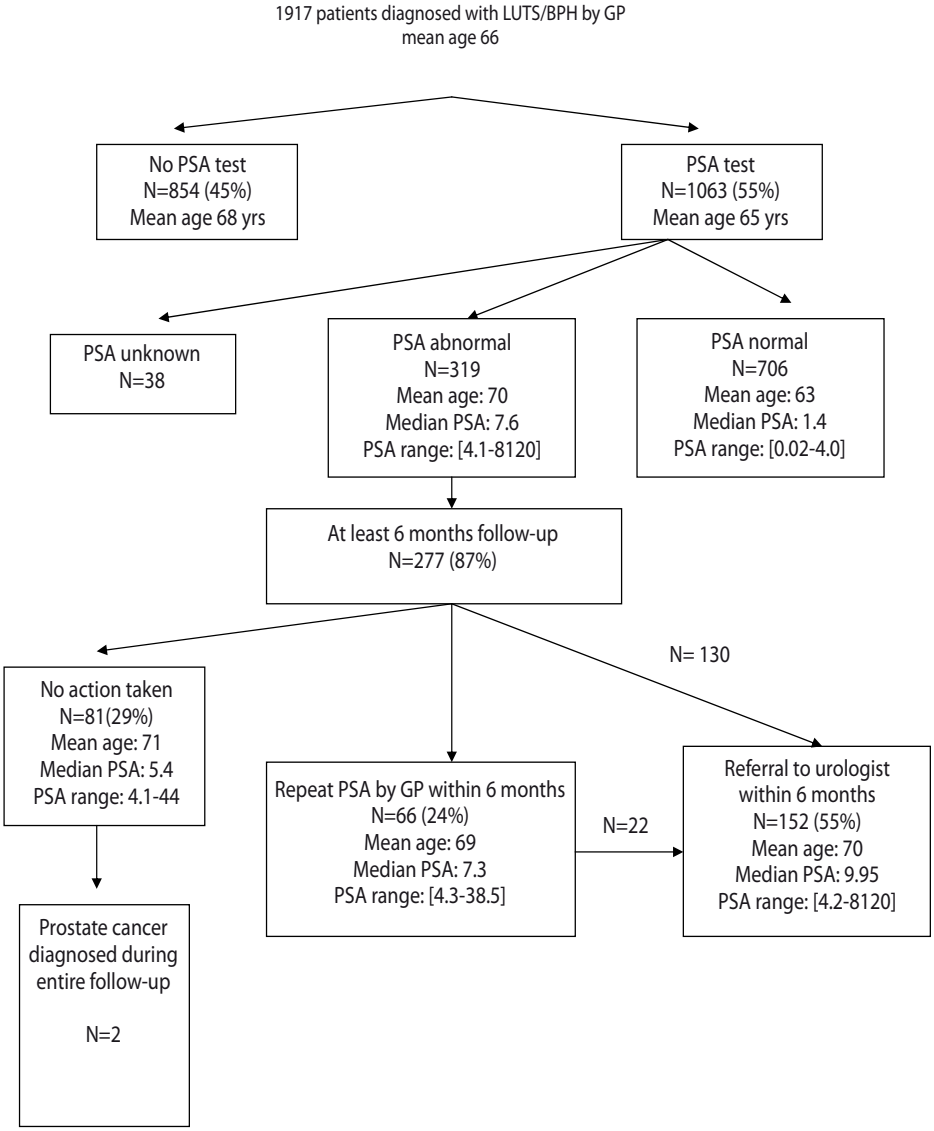

Figure 1: Diagnostic work-up in patients with LUTS/BPH

Table3:Occurrenceofprostatecancerdiagnosedwithin6monthsoffirstLUTS/BPHsymptomsamongthereferredpatients.(n=452)

	Prostate cancer n=55 (%)	No prostate cancer n=397 (%)	HR	95% CI	HRadjΦ	95% CI
Age categories of referred patients						
≥ 45 and < 55	0	44 (11%)	-	-		
≥ 55 and < 65	6 (11%)	111 (28%)	reference	reference		
≥ 65 and < 75	23 (42%)	160 (40%)	2.6	1.0 - 6.5		
≥ 75 and < 85	23 (42%)	68 (17%)	7.2	2.8 - 18.0		
≥ 85	3 (5%)	14 (3%)	3.4	0.8 - 13.8		
Patients getting biopsy	35 (64%)	40 (10%)	-	-	-	-
Reason for referral						
- LUTS only	13 (24%)	270 ((68%)	reference	reference	reference	reference
- abnormal DRE*	3 (5%)	11 (3%)	4.3	1.2-15.2	4.7	1.3-16.7
- abnormal PSA¥	25 (45%)	100 (25%)	3.5	1.7-7.1	3.3	1.6-6.7
- combination of abnormal DRE and abnormal PSA	14 (25%)	16 (4%)	14.3	6.7-30.6	9.8	4.5-21.0

* defined as a DRE suspicious for prostate cancer or a DRE that is difficult to interpret. ¥ defined as PSA>4 ng/ml
DRE= digital rectal examination; PSA= prostate specific antigen Φ adjusted for age

Discussion

In this study we showed that PSA testing as part of diagnostic work-up took place in approximately 50% of all patients diagnosed with LUTS suggestive of BPH. Seventy percent of these PSA tests were normal. The majority of patients with an abnormal PSA were referred to an urologist, but 30% underwent no follow-up action, in terms of referral or repeat PSA-testing at all. DRE was performed in approximately 60% of all patients and mainly in the younger age categories. The prostate cancer detection rate was the highest in patients who were referred for a combination of abnormal PSA and DRE results.

Although Dutch guidelines on the management of patients with BPH discourage the use of PSA sampling, PSA sampling appears to be common practice. [2] Similar results were reported in other studies. Two mail surveys reported that 80-90% of primary care physicians reported that they routinely use PSA testing. [15, 16] Data from the US Health Professional study showed that 30-72% of men with LUTS/BPH, aged 47 to 85 years, had a PSA test done in the previous year.[1] The high rate of PSA testing in our cohort, could partly be explained by the fact that patients with LUTS complaints expect to be tested for the presence of prostate cancer and thus request a PSA sampling.[17] In agreement with the Dutch guidelines, PSA mainly occurred in the younger age categories suggesting that GPs take the patient's life expectancy in consideration when ordering a PSA test.

The proportion of patients with a PSA above 4 ng/ml in those who were tested was 30%, which is higher than the reported 10-20% in prostate screening programs.[7, 18] This result however is not unexpected as we studied a cohort of men with LUTS/BPH and we know that PSA is often elevated in patients with BPH.

Thirty percent of patients with an abnormal PSA result were neither referred to an urologist nor were they tested again. From the patient files, it was unclear if GPs deliberately decided not to take any action e.g. based on the patient's life expectancy or if the patient refused further diagnostic work-up. It could as well be a consequence of a lack on clear guidelines on the management of patients with abnormal PSA results, especially if borderline elevated.

We found information on DRE only in 63% of all men, despite the fact that DRE is mandatory according to the DCGP guidelines. [2] Although recording of the DRE's might have been omitted by the GP, it seems that DRE is not a popular tool in the differential diagnosis for men with micturition difficulties. This might be due to the patient's and physician's reluctance, inadequate skills to interpret the DRE or lack of confidence on the diagnostic value of the DRE. Our results are similar to the findings of a recently published US study showing that DRE was only performed in 47% of patients screened for prostate cancer.[19] In agreement with the DCGP guidelines, mainly patients with DRE recording were tested for PSA. PSA testing however also occurred in 62-66% of men with a normal DRE or a DRE that was suspicious for BPH.

Prostate cancer was detected in 12% of all referred patients. The prostate cancer detection rate was highest above the age of 65, and in presence of both a DRE suspicious for prostate

cancer and an abnormal PSA. This result supports the findings from the Tyrol Screening Project that showed that the combination of PSA levels, DRE findings and age influenced the probability of a positive biopsy. [20]

The incidence rate of prostate cancer in patients with PSA sampling was higher than the incidence rate in patients without PSA testing, though not statistically significant. This suggests that PSA sampling is performed based on the probability of having prostate cancer.

There are limitations to this study and to the interpretation of the findings. First, as this is a retrospective cohort study using clinical practice data, we might have missed non-recorded data on PSA, DRE, patient referral or prostate biopsy. Since GPs who participate in the IPCI project, are not allowed to use paper-based records underreporting will be minimal. Also we requested extra information if data on prostate biopsy were missing. A second possible weakness is that we did not use age specific PSA reference values.[21] This may have made our results more conservative if any. Finally, the incidence rate of prostate cancer should not be extrapolated to the general population of males of 45 years and older. The rates were only used to study the difference between patients with or without PSA testing. Within the source population of 56958 men aged of 45 years and older, 382 cases of prostate cancer were identified resulting in a prostate cancer incidence rate of 2.64/1000 men-years (95% CI 2.39-2.92/1000 men-years). This is slightly lower than reported in the Health Professional Study who found a prostate cancer incidence rate of 3.89/1000 men-years.[22]

Recent guidelines suggest to use PSA not only as a marker of prostate cancer, but also as a tool to identify those patients with BPH who are likely to progress.[23] PSA sampling is very common in this cohort, which underscores the argument that additional PSA sampling to detect BPH progression will not increase healthcare costs as it is already routinely done. We also believe that the importance of digital rectal examination in the differential diagnosis of patients with LUTS/BPH should be re-emphasized, definitely in a GP setting. First of all, DRE is a relative simple test and secondly, studies have shown that the positive predictive value of prostate carcinoma improves with a combination of an abnormal DRE and an abnormal PSA.[24, 25]

As long as the results of the European Randomized Study of Screening for prostate cancer and the US National Cancer Institute-sponsored Prostate, Lung, Colorectal and Ovarian Cancer screening trial on the impact of screening on the prostate cancer mortality are not yet available, we agree with the PSA restrictions as outlined in the DCGP guidelines.[26, 27] However; as daily practice strongly deviates from what is recommended in these guidelines; a revision of the DCGP guidelines is desirable to clarify the need, interpretation and follow-up of PSA testing in patients with LUTS/BPH.

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Chapter 4

Treatment strategies, patterns of drug use and treatment discontinuation in men with LUTS suggestive of benign prostatic hyperplasia

Abstract

Objectives: We aimed to describe treatment strategies for lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH), adherence to and persistence with pharmacological treatment and the association between the type of LUTS/BPH complaints and early treatment discontinuation.

Methods: Within a large GP database (IPCI) in the Netherlands we identified all males ≥ 45 years newly diagnosed with LUTS/BPH during 1995-2000. Details on treatment were assessed from the electronic patient records. Logistic regression analysis was used to estimate the association between the type of main urinary complaints and early treatment discontinuation.

Results: Of the 2214 men with incident LUTS/BPH, 1075 received pharmacological treatment and 238 underwent prostate surgery. The average adherence differed slightly between drugs: 67% for α-blockers, 73% for 5α-reductase inhibitors and 71% for combination therapy. 26% of the treated patients discontinued treatment early. The probability of early discontinuation was higher if patients mainly expressed one type of complaint: voiding- (OR_{adj} 3.38; 95%CI: 1.89-6.04), post micturition- (OR_{adj} 2.37; 95%CI: 1.15-4.87) or storage symptoms (OR_{adj} 1.85; 95%CI: 1.16-2.95) as compared to patients expressing a combination of symptoms. The risk of early discontinuation was higher if patients had a normal PSA measurement. Older age and a higher chronic disease score protected against early treatment discontinuation.

Conclusions: Almost half of newly diagnosed LUTS/BPH patients are pharmacologically treated, and a quarter discontinues very rapidly. Stopping early is more frequent among younger persons, persons with only one type of main urinary complaint, no other co-morbidity and a normal PSA.

Introduction

Benign prostatic hyperplasia (BPH) is a common condition in elderly men. Although patients with BPH can be without symptoms, they often suffer from difficulties in voiding and/or difficulties in storage. The incidence and prevalence of these lower urinary tract symptoms suggestive of BPH (LUTS/BPH) increase with age.[1,2]

Treatments of LUTS/BPH comprise watchful waiting, phytotherapy, pharmacological treatment and surgery. Watchful waiting is recommended in patients with mild complaints without complications, whereas surgery is always considered in those with severe symptoms.[3,4] Drug treatment for symptomatic BPH should be considered in patients with moderately severe symptoms and moderate obstruction.[5] Pharmacological treatment consists of 5α-reductase inhibitors (finasteride) and α-blockers (e.g. alfuzosin, doxazosin, prazosin, terazosin and tamsulosin). α-Blockers inhibit the α_1-adrenergic receptors and have an immediate clinical effect by causing a relaxation of the smooth muscle in the prostate, prostate capsule and bladder neck, thereby improving urinary flow. [6,7] The 5α-reductase inhibitors on the other hand inhibit the formation of dihydrotestosteron, which leads to atrophy of the glandular epithelial tissue and consequently to a volume reduction of the prostate. 5α-Reductase inhibitors are merely used for patients with large prostatic glands and the time to clinical effect takes two to six months.[8]

Little is known about the treatment and adherence to treatment of LUTS/BPH in general practice. We conducted a cohort study in newly diagnosed LUTS/BPH patients to describe the treatment strategies, adherence to pharmacological treatment and the association between the type of main LUTS/BPH complaints and early treatment discontinuation.[9]

Methods

Setting

This study was conducted in a cohort of patients with newly diagnosed LUTS/BPH who were identified from the Integrated Primary Care Information (IPCI) database in the Netherlands. The IPCI database is a longitudinal general practitioners (GPs) database, which contains the electronic patient records of around 500,000 patients. The electronic patient records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses (using the International Classification for Primary Care and free text), clinical findings, referrals, laboratory findings, and hospitalisations.[10-12] Summaries of the hospital discharge letters or information from specialists are entered in a free text format and copies can be provided upon request. Information on drug prescription comprises brand name, quantity, strength, indication, prescribed daily dose and the Anatomical Therapeutic Chemical (ATC) classification code. [13] To maximize completeness of the data, GPs who participate in the IPCI project are not allowed to use paper-based records. The system complies with European Union guidelines on the use of

medical data for medical research and has been proven valid for pharmaco-epidemiological research.[14] The Scientific and Ethical Advisory Group of the IPCI project approved the study.

Study cohort

The study cohort comprised all males of 45 years or older with a first diagnosis of LUTS/BPH during the study period (01-01-1995 until 31-12-2000). Details on identification and validation of these patients have been published elsewhere.[1]

All cohort members were followed from the date of first diagnosis of LUTS/BPH until the end of the study period, leaving the practice, prostate surgery, diagnosis of prostate cancer or death, whichever event occurred first.

Treatment strategies and adherence to therapy

Prostate surgery, pharmacological treatment and phytotherapy were investigated as potential treatment strategies. Prostate surgery (both invasive and minimally invasive procedures) was identified by automated search from the medical files and subsequent manual review of the electronic records. Use of α-blockers (alfuzosin, doxazosin, prazosin, terazosin and tamsulosin), and finasteride was identified from the prescription files. Phytotherapy was identified by manual review of the medical records.

We assessed the first type of LUTS/BPH treatment, the time between diagnosis and first treatment, duration of, and adherence with treatment. In order to estimate duration of and adherence with treatment we created treatment episodes, which accounted for overlap of consecutive prescriptions of the same active ingredient. If a patient switched to another drug or had a gap (t) between prescriptions of the same drug, a new episode of treatment was defined. If two or more different drugs were started on the same day, they were considered to be used concomitantly and classified as combination therapy. Adherence to therapy was calculated by dividing the duration of an episode (X) by the time that lapsed between the start of that treatment episode and the start of a next treatment episode (X+t). (X*100%/(X+t)) Treatment-persistence was calculated by dividing the number of days that the patient received a pharmacological treatment by the follow-up time since start of first treatment.

Patients were considered to have discontinued treatment early if they had only one episode of pharmacological treatment that lasted less than one-fifth of the follow-up time since start of treatment (persistence of less than 20%). The electronic patient records were manually reviewed to identify reasons for early discontinuation.

Risk factors for early treatment discontinuation

Variables investigated as potential risk factors for early treatment discontinuation were LUTS symptoms, chronic co-morbidity, age, dosing regimen of LUTS/BPH treatment (once daily versus multiple dosing), start year of first pharmacological treatment and PSA measurement.

LUTS complaints expressed by the patient at diagnosis and at start of drug treatment were classified according to the Standardization of Terminology of Lower Urinary Tract Function of the International Continence Society.[15] Symptoms were classified as voiding symptoms if the patient expressed one or more of the following as main complaints; slow stream, splitting or spraying, intermittent stream, need to strain, hesitancy or terminal dribble. Patients were classified as primarily having storage symptoms if they had complaints of increased daytime frequency, nocturia, urgency or urinary incontinence. Symptoms were classified as post micturition symptoms if the patient expressed complaints of a feeling of incomplete emptying and/or post micturition dribble. Patients were classified as having a combination of symptoms if they had at least one symptom from the storage, the voiding and/or post micturition category. If the reason for starting pharmacological treatment was only indicated as BPH or prostatism and no specific complaints were listed, the patients were classified as having "prostatism symptoms".

To measure the general extent of chronic co-morbidities, we calculated the chronic disease score (CDS). The CDS is based on the use of drugs as a proxy for long-term diseases, allowing for the construction of an overall index of chronic disease status.[16,17]

PSA measurements were identified up until one week after start of LUTS/BPH treatment. PSA values were categorized into normal or abnormal based on the reference values of the laboratory.

Analysis

The incidence of prostate surgery was calculated by dividing the number of patients with a first surgery for LUTS/BPH by the number of person-years accumulated by the cohort of LUTS patients. Incidence estimates were calculated by age (5-year categories) and calendar year and 95% confidence intervals (CI) were calculated based on the Poisson distribution. Kaplan Meier survival analysis was conducted to assess the time to prostate surgery and to calculate the one-year risk of prostate surgery.

Treatment rates were calculated for the newly diagnosed LUTS/BPH patients. Time to first treatment was analyzed with Kaplan Meier curves. To describe the type of first treatments per calendar year, switching rates, adherence, persistence and early discontinuation the denominator included only the treated persons.

Logistic regression analysis was used to study the association between the type of main LUTS/BPH symptoms at start of treatment and the risk of early discontinuation of pharmacological therapy within the treated population. This analysis was adjusted for all variables that showed an association with treatment-discontinuation in the univariate analysis ($p<0.05$). The patients who continued treatment and had a proportion of treated follow-up time of more than 20% were used as a reference group.

Results

The study cohort comprised 2214 men aged 45 years and older who were newly diagnosed with LUTS/BPH during the period 1995-2000. Patient characteristics are provided in table 1. The average duration of follow-up after diagnosis was approximately 2 years. During follow-up 238 prostate surgeries were identified leading to an overall incidence of 62.0 per 1000 men-years (95%CI: 54.4-70.2). In the first year after the diagnosis of LUTS/BPH, the cumulative risk of prostate surgery was 8.7% (95%CI: 7.5-10%). The incidence of prostate surgery varied highly by age: from 20.7 (95%CI: 4.1-66.3) at the age of 45-49 years to 106.0 per 1000 men-years (95%CI: 81.5-137.0) at the age of 75-79 years (figure 1). The incidence of prostate surgery decreased over time from 141.1/1000 men-years (95%CI: 47.3-336.0) in 1995 to 38.7/1000 men-years (95%CI: 28.7-51.1) in 2000.

In total, 1075 patients (48.5%) received pharmacological treatment for LUTS/BPH during the study period. Only 16 patients received prescriptions for phytotherapy (saw palmetto extract) from their GP. Receiving pharmacological treatment was associated with age ($p<0.001$), the type of urological complaints at diagnosis ($p<0.001$) and was more likely for persons with more co-morbidity ($p<0.001$) (table 1).

Table 1: Patient characteristics at time of LUTS/BPH diagnosis

	Total number of patients (n=2214)	Treated patients (n=1075)	Non-treated patients (n=1139)
Mean age	66.3 ± 10.4*	67.1 ± 10.2*	65.6 ± 10.5*
Type of LUTS/BPH complaints at time of entry in cohort			
Prostatism	750 (33.9%)	373 (34.7%)	377 (33.1%)
Only storage symptoms	496 (22.4%)	243 (22.6%)	253 (22.2%)
Only voiding symptoms	202 (9.1%)	104 (9.7%)	98 (8.6%)
Only post micturition symptoms	157 (7.1%)	57 (5.3%)	100 (8.8%)
Only voiding and post micturition symptoms	147 (6.6%)	55 (5.1%)	92 (8.1%)
Combination of storage and (voiding and/or post micturition) symptoms	462 (20.9%)	243 (22.6%)	219 (19.2%)
Chronic Morbidity Score (CDS-score)			
CDS 0	1153 (52.1%)	491 (45.7%)	662 (58.1%)
CDS 1-4	668 (30.2%)	372 (34.6%)	296 (26.0%)
CDS >5	393 (17.8%)	212 (19.7%)	181 (15.9%)

* mean ±SD

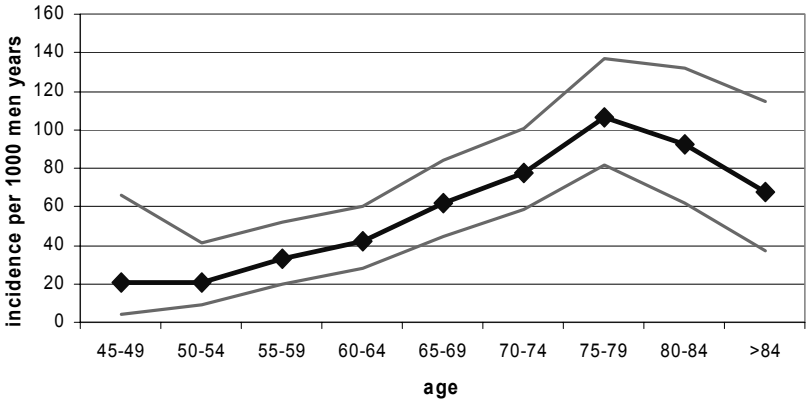

Figure 1 : Incidence of prostate surgery by age
------- : 95% Confidence Interval

During the first year after diagnosis of LUTS/BPH, 45% of the patients received pharmacological treatment, 68% of them received their first prescription within one month after diagnosis.

α-Blockers were the most frequent first line treatment especially in the most recent years (figure 2). The median total duration of use of pharmacological treatment was approximately 3 months (93 days). 645 patients had a follow-up time of more than one year since start of first treatment. The mean treatment-persistence (percentage of follow-up time during which drugs were used) for these patients was 37% (95%CI; 35-40%). The average adherence to α-blockers was 67% (95%CI: 66-68%) which was slightly lower than the adherence rate to 5α-reductase inhibitors (73% (95%CI: 69-77%) and the combination therapy (71% (95%CI: 49-93%). The adherence rates did not vary substantially within drug classes.

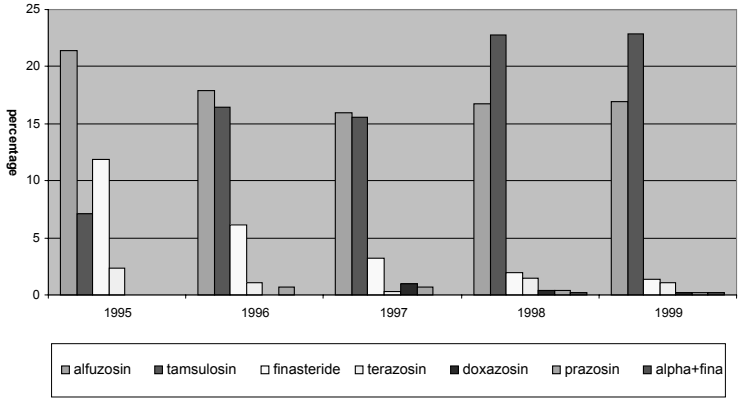

Figure 2: Proportion of patients treated within one year after diagnosis of LUTS/BPH according to calendar year
Legend 2: Bars indicate different types of LUTS/BPH treatment used as first treatment.
Calendar year indicates the year of diagnosis of LUTS/BPH. Only including patients with at least one year follow-up after diagnosis.(n=1591 (72% of total of 2214 patients)).

Of the 1075 treated patients, 133 patients (12.4%) switched their first type of drug to another compound. The proportion of switchers was statistically higher ($p<0.02$) for patients first treated with alfuzosin (56 out of the 405 patients) than for patients first treated with tamsulosin (48 out of the 530 patients). Patients primarily switched because of adverse events, persistence of complaints despite treatment or based on the recommendations from the urologist. Of the 2214 men with LUTS/BPH, 479 (22%) were referred to the urologist. There was no difference in referrals between the treated - or the non-treated group. In the former, patients were mainly referred after start of the first pharmacological treatment.

Two hundred and eighty patients out of 1075 (26.0%) discontinued treatment early after start. A reason for discontinuation could be identified for almost half (n=130) of these patients. The most important reasons were adverse events (n=35), persistence of complaints despite treatment (n=31), resolved complaints (n=25) or other reasons (i.e. urologist referral, start phytotherapy, n=39).

The probability of early discontinuation was higher in patients with complaints of mainly voiding symptoms (OR_{adj} 3.38 (95%CI: 1.89-6.04)), mainly post-micturition symptoms (OR_{adj} 2.37 (95%CI: 1.15-4.87)) or mainly storage symptoms (OR_{adj} 1.85 (95%CI: 1.16-2.95) as compared to patients complaining of a combination of symptoms (table 2). Patients with a normal PSA measurement had a higher risk of early discontinuation (OR_{adj} 1.45; 95%CI: 1.05-2.01) than patients without a PSA measurement. Older age (> 60 years) and a higher chronic disease score were associated with treatment continuation. A simple once daily dosing regimen as opposed to multiple dosing per day was associated with a lower risk of early treatment discontinuation but this was not statistically significant when adjusting for all risk factors (OR_{adj} 0.76 (95%CI:0.55-1.05)).

When repeating the analysis on only these patients who discontinued treatment because of adverse events or persistence of complaints (n=66) we found similar point estimates, but only the increased risk of early discontinuation in patients mainly complaining of voiding symptoms remained statistically significant (OR_{adj} 3.00; 95%CI:1.07-8.43)

Table 2: Risk factors for early discontinuation

	Early discontinuers (n=280)	Continuous users ¥ (n=674)	OR_{adj} * (95% CI)
Type of LUTS/BPH complaints			
Prostatism	97 (34.6%)	266 (39.5%)	1.51 (0.98-2.32)
Only storage symptoms	66 (23.6%)	144 (21.4%)	1.85 (1.16-2.95)
Only voiding symptoms	40 (14.3%)	46 (6.8%)	3.38 (1.89-6.04)
Only post micturition symptoms	17 (6.1%)	32 (4.7%)	2.37 (1.15-4.87)
Only voiding and post micturition symptoms	16 (5.7%)	30 (4.5%)	1.63 (0.79-3.34)
Combination of storage and (voiding and/or post micturition) symptoms	44 (15.7%)	156 (23.1%)	reference
Age			
< 60 years	104 (37.1 %)	157 (23.1%)	reference
60-68 years	70 (25%)	169 (25.1%)	0.66 (0.44-0.97)
69-74 years	62 (22.1%)	158 (23.4%)	0.73 (0.48-1.11)
> 74 years	44 (15.7%)	190 (28.2%)	0.46 (0.30-0.73)
Chronic Morbidity Score (CDS-score)			
CDS 0	141 (50.4%)	275 (40.8%)	reference
CDS 1-4	105 (37.5%)	236 (35.0%)	0.91 (0.65-1.27)
CDS >5	34 (12.1%)	163 (24.2%)	0.54 (0.34-0.86)
Dosing regimen			
Once daily	189 (67.5%)	500 (74.2%)	0.76 (0.55-1.05)
More than once daily	91 (32.5%)	174 (25.8%)	reference
PSA			
No PSA screening	125 (44.6%)	348 (51.6%)	reference
PSA normal	126 (45.0%)	238 (35.3%)	1.45 (1.05-2.01)
PSA abnormal	25 (8.9%)	81 (12.0%)	1.04 (0.62-1.75)
PSA conducted but values not known	4 (1.4%)	7 (1.0%)	1.56 (0.40-6.10)

*adjustedforyearoftreatmentstart,migraine,headache,gastriccomplaints,treatmentforgastriccomplaintsandCVA¥patientswho continued treatment and had a proportion of treated follow-up time of more than 20%

Discussion

This descriptive study on treatment of newly diagnosed LUTS/BPH in the general population showed that 8.7% of the population undergoes prostate surgery and that 45% is pharmacologically treated within the first year after diagnosis. The most frequent first line treatment consists of α-blockers. Treatment is not continuous, the average adherence is 70%, a quarter discontinues treatment early and only during a third of the follow-up period, since start of therapy, pharmacological treatment is used. The incidence of prostate surgery and the age and calendar year pattern is very similar to findings from other studies.[18-24] The percentage of treated patients is quite low, which is in accordance with Dutch guidelines that recommend watchful waiting for mild complaints, and reserve pharmacological treatment for men with moderate to severe symptoms when other measures fail and surgery is contra-indicated. [6]

The main outcomes in evaluating treatment benefits in patients with LUTS/BPH are the improvement of subjective symptoms and the impact on the quality of life and on the bother of the LUTS/BPH. Long-term adherence and treatment duration are the key to a successful therapy, but little has been reported about the actual patterns of use of these drugs in general practice. We observed that overall adherence was around 70% with a small variation between α-blockers (67%) and 5α-reductase inhibitors (73%). We can not compare our data with information from other studies or trials since, to our knowledge; information on adherence to α-blockers or 5α-reductase inhibitors for treatment of LUTS/BPH has not been published.

Persistence with therapy was low, 26% of patients discontinued treatment early after start mainly because of adverse events, or insufficient treatment efficacy. This is very similar to data from two prospective studies that showed that 14-38% of the patients withdrew treatment with α-blockers mainly for reasons of adverse effects or lack of efficacy. [25-26] Younger persons, persons with only one type of symptom, and patients with less chronic co-morbidity were more likely to discontinue treatment early, but this may be confounded by symptom severity. It is known that LUTS/BPH worsens with age and that patients with high symptom scores and with significant bother will complain less about some minor adverse events of drug therapy than a patient with minimal symptoms and bother.[27-28] Especially storage symptoms are very bothersome to the patient and have a great impact on the patients' quality of life.[29-30] Although not statistically significant, our results suggest that early discontinuation is lower in patients with storage symptoms than in patients who have voiding symptoms.

Patients with a normal PSA value were more likely to discontinue treatment early than patients who had no PSA measurement. Men complaining of LUTS/BPH who turn out to have a normal serum PSA value might find reassurance in this result and be less motivated to continue treatment. Further studies are needed to test this hypothesis.

Data from this cohort learns us more about current treatment practice in the general population but some caution is needed when interpreting this data. First, since we do not

have access to the pharmacy dispensing records or actual intake of drugs, prescription records were used to calculate the adherence rate and treatment discontinuation. If patients failed to refill their prescription this would mean that we overestimated the average adherence and underestimated the treatment discontinuation. Second, the type of symptoms may be misclassified or missing because their classification was based on what the GP recorded as primary complaints. Details on the type of complaints were lacking for 363 patients as the GP only recorded prostatism or BPH. Finally, we do not have systematic and objective information on symptom severity since GPs in the Netherlands, according to Dutch guidelines, do not routinely ask patients to complete the International Prostate Symptom Severity Score (I-PSS). [5,6]

Conclusion

Almost half of the patients with LUTS/BPH receive pharmacological treatment within one year after diagnosis. When patients get treated, the median total duration is only 3 months. Treatment is often intermittently used with large gaps between consecutive prescriptions. The chance for early discontinuation was highest for patients with mainly voiding symptoms, younger age and less co-morbidity.

As the impact of pharmacological therapy will probably further increase over the coming years, patient information and education will be important to increase treatment adherence and persistence.

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Chapter 5 Low incidence of acute urinary retention in the general male population

Abstract

Objective: To describe the incidence of acute urinary retention (AUR) in the general male population and in a population of men newly diagnosed with lower urinary tract symptoms suggestive of BPH (LUTS/BPH).

Methods: We performed a retrospective cohort study in the Integrated Primary Care Information (IPCI) database, a general practice research database in the Netherlands, during the period 1995-2000. The study population comprised all males, ≥ 45 years, without a history of AUR or radical cystectomy. AUR was defined as the sudden inability to urinate, requiring catheterization. Comparison of the AUR-risk between men with and without LUTS/BPH was made through Cox-proportional hazard modeling.

Results: Amongst 56.958 males with a mean follow-up of 2.8 years, 344 AUR cases occurred (incidence rate 2.2/1000 man-years). Seventy-seven of the 344 cases were precipitated by a surgical procedure and 204 had a history of LUTS prior to AUR. AUR was the first symptom of LUTS/BPH in 73 (49%) of the 149 AUR cases that occurred in men newly diagnosed with LUTS/BPH. The risk of developing AUR was 11-fold higher in patients newly diagnosed with LUTS/BPH (RR 11.5, 95%CI 8.4-15.6) with an overall incidence rate of 18.3/1000 man-years (95% CI: 14.5-22.8).

Conclusions: The incidence of AUR in the general male population is low. The incidence rate increases with age and is 11-fold higher in patients newly diagnosed with LUTS/BPH. Since 49% of AUR cases amongst the LUTS/BPH patients presented with AUR as first symptom, earlier patient identification is needed if we aim to reduce the incidence of AUR by means of pharmacological treatment.

Introduction

Acute urinary retention (AUR) is a condition characterized by a sudden inability to urinate, which is usually extremely painful and requires catheterization.[1]

The causes of AUR can be classified into three categories. The first relates to any event that increases resistance to the urinary flow such as benign prostatic hyperplasia (BPH).[2] AUR is an important complication of BPH and the reason for surgery in 25 to 30% of patients undergoing prostatectomy.[3]

Secondly, AUR may result from an interruption of either the sensory innervation of the bladder wall or weakness of the detrusor muscle.[2] The third category relates to any situation that permits the bladder to over-distend (e.g. post-surgery, drugs).[2]

The reported cumulative incidence estimates of AUR in males vary widely from 0.4% to 25% per year. This variation is related to differences in design, population (e.g. clinical trials versus cohort studies) and age distribution and differences in the case definition of AUR.[4-5]

The incidence of AUR in the general male population has been studied in two large population–based studies in the US but information in Europe is only available from a small cohort study following 456 men over 5 years. [3,6-7] We therefore aimed to assess the incidence rate of AUR in a large Dutch male population and to compare it to the incidence rate in patients newly diagnosed with lower urinary tract symptoms suggestive of BPH (LUTS/BPH).

Methods

Setting

This study was conducted in the Integrated Primary Care Information (IPCI) database in the Netherlands. IPCI is a general practice research database, containing information from electronic patient records of 150 GPs covering a total of 500,000 patients. In the Dutch health care system, all persons are registered with a single GP, who acts as a gatekeeper of medical care and information.[8] The electronic medical records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses (using the International Classification for Primary Care (ICPC) and free text), clinical findings, laboratory findings, referrals and hospitalisations.[9] Summaries of the hospital discharge letters or information from specialists are entered in a free text format and copies of the letters can be provided upon request. Information on drug prescription comprises brand name, quantity, strength, indication, prescribed daily dose and the Anatomical Therapeutic Chemical classification (ATC) code.[10] To maximize completeness of the data, GPs who participate in the IPCI project are not allowed to use paper-based records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research.[11] The Scientific and Ethical Advisory Group of the IPCI project approved the study.

Study population

The study population comprised all males, 45 years or older, with at least 6 months of valid database history. A valid history means that the practice had been contributing data to the IPCI database for at least 6 months and that the patient was registered with the GP for at least 6 months. Follow-up started on January 1st 1995 or on the date that 6 months of valid history was obtained, whichever was the latest. Patients were excluded when having a history of AUR or radical cystectomy, prior to study entry.

To study the incidence of AUR in patients with LUTS/BPH, we identified a sub-cohort of patients newly diagnosed with LUTS/BPH during the study period (1995-2000). Details on identification and validation of these patients have been published elsewhere. [12] In brief, new LUTS/BPH patients were; patients with LUTS and a new diagnosis of BPH, or patients with LUTS who were pharmacologically or surgically treated for the indication of BPH, or patients with two or more LUTS suggestive of BPH in the absence of any other co-morbidity that could explain the urinary symptoms. Patients with a history of BPH or LUTS/BPH prior to the start of follow-up were considered as prevalent LUTS/BPH patients. Follow-up of the new LUTS/BPH cohort started upon diagnosis of LUTS/BPH.

All subjects were followed from study-entry until the first episode of AUR, radical cystectomy, the end of the study period, transferring out of the practice or death, whichever event occurred first.

Covariates

To measure the general extent of chronic co-morbidities, we calculated the chronic disease score (CDS). The CDS is based on the use of drugs as a proxy for long-term diseases and mortality, allowing for the construction of an overall index of chronic disease status. [13] In addition, we assessed the presence of diabetes mellitus and LUTS/BPH.

Case identification and validation

AUR was defined as the sudden inability to pass any urine, requiring catheterization. The occurrence of AUR was identified from the medical records by searching on ICPC codes U05.2 (retention), U53 (urinary catheterization) and on free text ("reten", "cath", "CAD").

All potential cases of AUR were manually reviewed by a physician (KV) and were categorized into 3 groups (definite AUR, doubtful AUR and no AUR). An endpoint committee consisting of 3 physicians (JLHRB, BS and MVW) reviewed all doubtful cases of AUR. Independently, the physicians classified the cases into 3 categories ("AUR", "no AUR" or "AUR unknown"). If at least 2 of the 3 physicians agreed, the respective category was assigned. If none of the physicians agreed, the AUR case remained doubtful and was not censored in the analysis.

For all definite AUR cases the patient records were reviewed to check whether the AUR was preceded by a procedure (surgery, any urological intervention, and anesthesia), the use of

drugs knowing to cause AUR (drugs with anti-cholinergic effect or narcotic analgesics), or by an underlying medical condition such as urinary tract infection (UTI), neurological disorders and constipation. In addition we checked whether the patients had a history of LUTS consistent with the definitions of the International Continence Society[14] in at maximum one year prior to the AUR.

Analysis

Differences in covariates between patients with or without AUR were tested using Chi-Square for categorical data or Student t-test for continuous variables.

The incidence rate of AUR was calculated by dividing the number of AUR cases by the accumulated person-years. Incidence rate estimates were calculated by age (5-year categories) and calendar year. 95% confidence intervals (CI) were calculated based on the Poisson distribution. Incidence rates were standardized according to the age distribution of the Dutch male population using data from the "Central Bureau of Statistics" of the Netherlands. (infoservice@cbs.nl)

Cox regression analysis was used to calculate the risk of developing AUR in patients with LUTS/BPH (both prevalent and incident), while adjusting for age.

Results

The total study cohort comprised 56,958 males with a mean age of 58 years. At study-entry, 4680 patients (8%) had a prior history of LUTS/BPH, the prevalence of diabetes mellitus was 4% and more than 70% of subjects had no chronic co-morbidity (table 1). The mean duration of follow-up was 2.8 years.

Table 1: Baseline characteristics of the study population

	Patients with AUR (%) n=344	Patients without AUR (%) n=56614	P value #
Mean age	71.4 ± 10.3*	58.1 ± 11.6*	P<0.001
Age categories			P<0.001
≥45 - <50 years	9 (2.6)	17274 (30.5)	
≥50 - <55 years	12 (3.5)	9567 (16.9)	
≥55 - <60 years	26 (7.6)	7289 (12.9)	
≥60 - <65 years	32 (9.3)	6327 (11.2)	
≥65 - <70 years	59 (17.2)	5555 (9.8)	
≥70 - <75 years	75 (21.8)	4396 (7.8)	
≥75 - <80 years	49 (14.2)	3203 (5.7)	
≥80 years	82 (23.8)	3003 (5.3)	
Prevalent LUTS/BPH	84 (24.4)	4596 (8.1)	P<0.001
Diabetes mellitus	20 (5.8)	2266 (4.0)	P=0.088
CDS categories			P<0.001
CDS 0	180 (52.3)	39844 (70.4)	
CDS 1-4	97 (28.2)	11509 (20.3)	
CDS >4	67 (19.5)	5261 (9.3)	

* mean ±SD
# Chi-square/t-test

After validation, 344 patients were classified as having AUR, 244 (59%) had a history of LUTS (storage, voiding or postmicturition symptoms) prior to AUR; 149 of the 344 patients belonged to the incident LUTS/BPH cohort. Although the actual cause may be different, 77 AUR cases (22%) were preceded by a procedure (surgery, urological interventions, anesthesia) and 72 (21%) were preceded by an UTI, presence of neurological disorders, or treatment with a drug that has been associated with AUR.

The overall incidence of AUR in the general male population was 2.2 per 1000 man-years (95% CI: 2.0-2.4). The incidence of AUR increased with age from 0.2 at the age of 45-49 to a maximum of 11.0 per 1000 man-years in patients at the age of 80 or older (table 2 and figure 1). The incidence rate remained stable during the calendar period 1995-1999 and slightly decreased in 2000.

Table 2: Incidence of AUR within the general male population

Age	Number of incident cases	Number of men years	Incidence rate per 1000 man-years	95% CI
45-49	5	31728	0.2	0.1-0.3
50-54	10	32824	0.3	0.2-0.5
55-59	22	23141	0.9	0.6-1.4
60-64	28	19948	1.4	0.9-2.0
65-69	52	16642	3.1	2.4-4.1
70-74	59	13757	4.3	3.3-5.5
75-79	64	10139	6.3	4.9-8.0
≥80	104	9441	11.0	9.0-13.3
Total	344	157620	2.2	2.0-2.4

CI= confidence interval

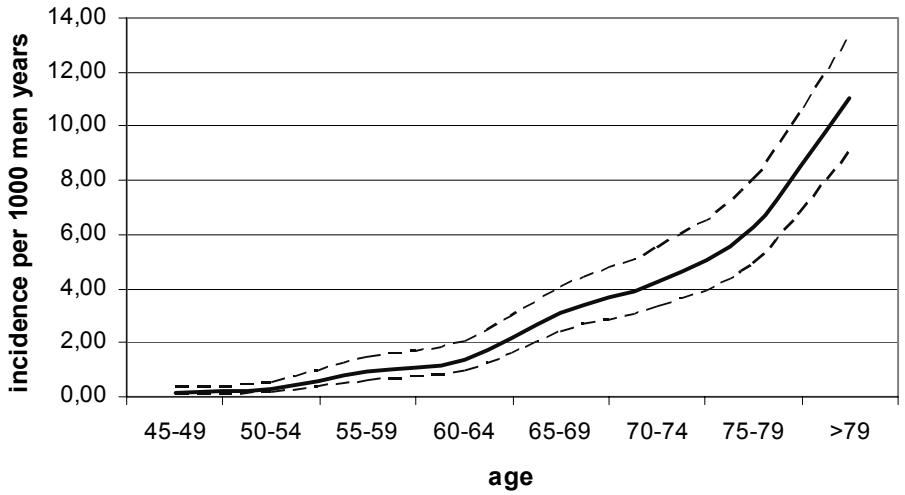

Figure 1: Age specific incidence rate of AUR in the general male population
The full blue line represent the incidence of AUR for the general male population, 45 years or older. The broken lines represent 95 percent confidence intervals.

The overall incidence of AUR within the cohort of 2214 patients newly diagnosed with LUTS/BPH was 35.9 per 1000 man-years (95% CI: 30.5-42.0) and increased with age (figure 2). Seventy-three out of the 149 AUR cases (49%) occurring in the cohort, entered this cohort with AUR as first symptom of BPH. If we excluded these patients, the overall incidence of AUR was 18.3 per 1000 man-years (95% CI: 14.5-22.8) (table 3 and figure 2). A similar pattern between age and incidence of AUR was found as in the general population (table 3 and figure 2). The risk of developing AUR, adjusted for age, was 6-fold higher in patients diagnosed with LUTS/BPH (both prevalent and incident) as compared to patients without symptomatic BPH (RR 6.5, 95% CI: 5.0-8.3). When repeating the analysis, excluding the prevalent BPH patients and the patients with AUR as first symptom of BPH, the RR for AUR was 11.5 (95% CI: 8.4-15.6).

Table3:IncidenceofAURamongpatientsnewlydiagnosedwithLUTS/BPHbutwithoutAURasfirstpresentingsymptom

Age	Number of incident cases	Number of men years	Incidence rate per 1000 man-years	95% CI
45-49	1	98	10.1	0.9-47.3
50-54	0	342	0	0-7.2
55-59	4	502	8.0	2.7-19.0
60-64	7	653	10.7	4.8-21.0
65-69	12	655	18.3	10.0-31.0
70-74	10	780	12.8	6.6-22.8
75-79	18	623	28.9	17.7-44.7
≥ 80	24	498	48.3	31.7-70.6
Total	76	4151	18.3	14.6-22.8

CI: confidence interval

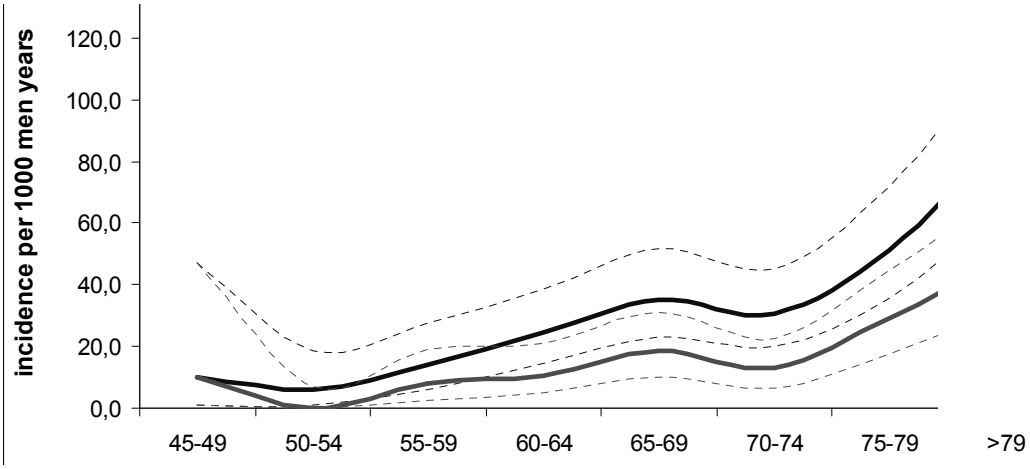

Figure 2: Incidence of AUR in the LUTS/BPH cohort
ThebluelinesrepresenttheincidencewithallcasesofAURincluded.Theredlinerepresentstheincidencewithexclusionofmenwhopresented withAURasthefirstsymptomamongloweurinarytractsymptomssuggestiveofbenignprostatichyperplasia.Thebrokenlinesrepresent95 percent confidence intervals.

Discussion

This population-based cohort study showed that AUR is uncommon in a general male population of 45 years and older. Within the cohort of men newly diagnosed with LUTS/BPH, AUR is the first presenting symptom of BPH in approximately 50% of all AUR cases. The age-adjusted hazard of AUR was about 11-fold higher in men with LUTS/BPH than in the general male population.

Our overall incidence is somewhat lower than the incidence of AUR reported in 2 US cohort studies; the Health Professional Follow-up Study (4.5/1000 man-years; 95% CI 3.1-6.2) and the Olmsted County (6.8/1000 man-years; 95% CI 5.2-8.9) and a smaller Austrian cohort study (3.1/1000 man-years, 7 events per 2270 person years). [3,6-7] This variation in AUR incidence rates cannot be explained by differences in age-distribution since our overall incidence rate slightly decreased when standardizing for the age distribution of the above-mentioned cohorts. Other explanations could be selection bias or differences in AUR diagnosis.

Selection bias could underlie the higher incidence in the US cohort studies, as one of their eligibility criteria was the completion of mailed questionnaires assessing detailed information on BPH and urinary symptoms. This is supported by the fact that the prevalence of LUTS/BPH and/or diagnosis of BPH was much higher in both the Olmsted County (33% of men had an AUA symptom index of more than 8) and the Health Professional Follow-up Study (30% of men had clinical diagnosis of BPH) as compared to our general population cohort (8% of men had LUTS/BPH). In our study, selection bias was excluded as every visit to the physician was prospectively monitored in an automated database.

In all 3 cohorts different ways of AUR identification were used. In the Health Professional Study, patients were asked by mail if they experienced an episode of AUR requiring catheterization. In the Olmsted County, all medical records were reviewed to assess AUR (case definition: urinary bladder catheterization for acute retention). The latter definition is in line with ours since we also required evidence of catheterization in the medical record.

Using data from the IPCI database gave us the advantage of direct access to prospectively gathered and complete access to the medical records of a large population of ageing men. Consequently, there was little chance of information or selection bias. In addition, to our knowledge, this is the largest cohort study so far studying the incidence of AUR. Because the IPCI population is representative of the Dutch population regarding age and gender, we believe that our overall AUR incidence rate is a good reflection of the true AUR incidence rate of the general Dutch population.

The overall incidence of AUR in our LUTS/BPH cohort was within the range that was reported in other studies (3.7 to 130 per 1000 man-years). [4] This wide range is attributable to various factors such as differences in study populations and in case definition. [4-5] Our results are in line with recent data from the Proscar® Long-Term Efficacy and Safety Study (Pless) and the study from Barry et al. [15-17] The Pless study which compared finasteride to placebo in BPH patients reported an AUR-incidence in the placebo treated group of 17/1000 man-years and

an AUR-incidence in the finasteride treated group of 7.2/1000 man-years (overall incidence 12/1000 man-years). Barry et al. followed 371 candidates for elective prostatectomy who were treated non-operatively and found an overall incidence of AUR of 25/1000 man-years. The MTOPS trial reported an AUR incidence rate of 6/1000 man-years for the placebo group and an AUR incidence rate between 1-4/1000 man-years for the active treatment groups (doxazosin, finasteride or combination therapy). However, the MTOPS trial excluded all cases of precipitated AUR (unless a voiding trial without a catheter was unsuccessful). [18] As more than 40% of AUR cases in our cohort were precipitated, this could explain why our AUR incidence rate is higher than the one of the MTOPS study.

Recent studies have demonstrated a beneficial effect of medical treatment on the risk of AUR. [15-19] In our LUTS/BPH population half of the AUR cases never complained of LUTS/BPH prior to AUR which is identical to data from the GPRD. [20] Assuming that medical treatment can prevent long term complications of BPH such as AUR, prostate surgery or renal insufficiency, earlier LUTS/BPH identification seems to be important.

Some caution needs to be applied when interpreting this data. Although we used a rigorous validation algorithm and strictly followed our case definition, there may be some misclassification of the outcome. We might have missed some AUR cases when information on urinary catheterization and the details surrounding the AUR (sudden onset, inability to urinate, painful or not) were not registered in the patient's files. However, because AUR is an acute and severe event and because GPs in the Netherlands hold the complete medical records of their patients, false-negative misclassification is probably modest.

In conclusion, the incidence rate of AUR in the general population is fairly low, especially in the younger age-categories. However, in patients with LUTS/BPH the risk of developing AUR is substantial. A large number of men present with AUR as the first symptom of BPH. Therefore, if we aim to reduce the incidence of AUR by means of pharmacological treatment, early identification of LUTS/BPH patients is essential.

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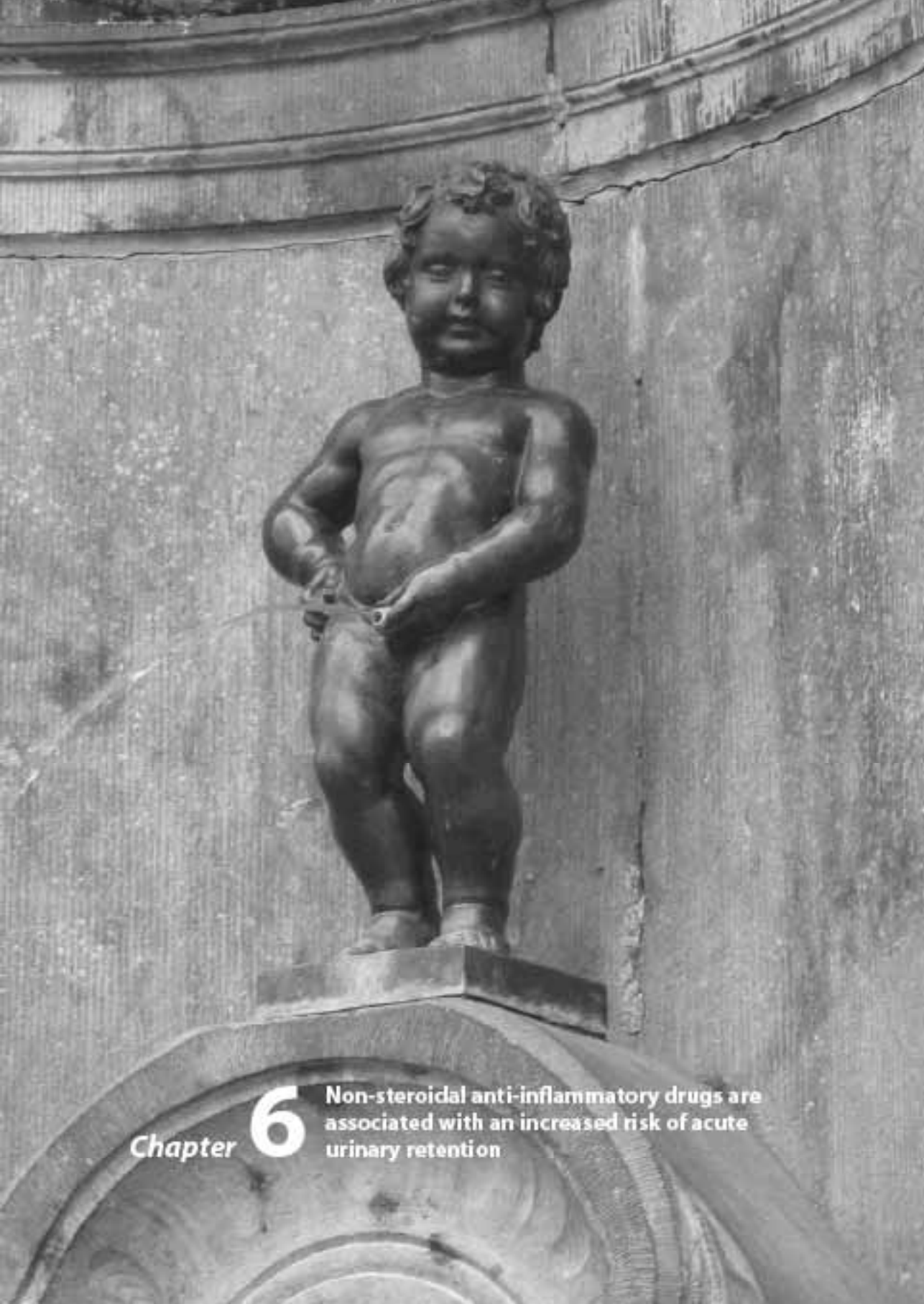

Chapter 6

Non-steroidal anti-inflammatory drugs are associated with an increased risk of acute urinary retention

Abstract

Background: Acute urinary retention (AUR) is characterized by the sudden inability to urinate, which is usually extremely painful and requires catheterization. Prostaglandins play an important role in the genito-urinary function as they provoke contractions of the detrusor muscle. Relaxation of the detrusor muscle, via the inhibition of the prostaglandin synthesis, could result in AUR.

Objective: To investigate whether the use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with an increased risk of AUR.

Design: Population-based case-control study.

Setting: Data from the Integrated Primary Care Information (IPCI) project in the Netherlands.

Participants: The source population comprised all males, 45 years or older, registered in the database between 1995 to 2002 and with at least 6 months of valid history. Cases were all men with a validated diagnosis of AUR. Each case was matched on age and calendar time up to 10 controls.

Main outcome measure: Exposure to NSAIDs in patients with AUR versus exposure to NSAIDs in controls, using conditional logistic regression analysis with odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Within the source population of 72 114 men, we identified 536 cases of AUR and 5348 matched controls. Risk of AUR was 2.26 (95% CI 1.49-3.45) fold higher in current users of NSAIDs relative to no use. This increased risk remained when adjusting for all other AUR risk factors (OR_{adj} 2.02 (95%CI 1.23-3.31)). The highest risk for AUR (OR_{adj} 3.3, 95% CI 1.2-9.2) was observed in patients who recently started using NSAIDs and in those using a high dosage. In studying a dose-effect relationship, the increased risk of AUR was present in patients taking 1 defined daily dose or more, but absent in the ones taking less than 1 defined daily dose.

Conclusion: This study shows that the risk of AUR is about 2-fold higher in men who use NSAIDs.

Introduction

Acute urinary retention (AUR) is a condition characterized by the sudden inability to urinate, which is usually painful and requires catheterization.[1] The causes of AUR can be classified into three categories. The first category relates to any event that increases the resistance to the urinary flow such as benign prostatic hyperplasia (BPH). Secondly, AUR may result from an interruption of either the sensory innervation of the bladder or weakness of the detrusor muscle. The third category relates to any situation that permits the bladder to over-distend (e.g. post surgery).[2]

Drugs that are known to cause AUR, act via different pathways. Some drugs have direct anti-cholinergic effects (such as Parkinson medication, antipsychotic drugs) and thus inhibit the contraction of the detrusor muscle via the inhibition of the parasympathetic chain. Other drugs, such as narcotic analgesics provoke urinary retention via an increased tonus of the external sphincter combined with an impaired contraction of the detrusor muscle. The incidence of AUR is higher in males than in females, especially in the older age categories, as males suffer more often from co-morbidities known to provoke AUR.[3]

In vitro studies have shown that prostaglandins, especially prostaglandin E_2, play an important role in the genito-urinary function. The prostaglandin synthesis in the bladder works via cyclooxygenase-2, and is up-regulated by a number of stimuli such as inflammation, trauma, and over-distention.[4] PGE_2 stimulates micturition by releasing tachykinins which in turn, initiate the micturition reflex by stimulating neurokinin receptors on afferent nerves and detrusor smooth muscle. [5, 6] As non-steroidal anti-inflammatory drugs (NSAID) have a direct effect on the prostaglandin synthesis, they have been tested in clinical trials for the treatment of detrusor instability.[7, 8] Gruenenfelder et al. recently reported 3 cases of AUR that occurred within one week upon starting using cyclooxygenase-2 inhibitors.[9]

The objective of this case-control study in a population of males, 45 years and older, was to investigate whether the use of NSAIDs is associated with an increased risk of AUR.

Methods

Setting

This study was conducted in the Integrated Primary Care Information (IPCI) database in the Netherlands. The IPCI database is a general practice research database, containing information from electronic patient records of 150 general practitioners (GPs) covering a total of approximately 500,000 patients. In the Dutch health care system, patients are registered with a single GP who acts as a gatekeeper of medical care and information.[10] The electronic records contain coded and anonymous data on patient demographics, symptoms (using the International Classification for Primary Care (ICPC) and free text), diagnoses (using ICPC and free text), clinical findings, referrals, laboratory findings, and hospitalisations.[11, 12] Summaries of the

hospital discharge letters or information from specialists are entered in a free text format and hard copies can be provided upon request. Information on drug prescription comprises brand name, quantity, strength, indication, prescribed daily dose, the Anatomical Therapeutic Chemical classification (ATC) code and the physician linked indication.[13] To maximize completeness of the data, GPs who participate in the IPCI project are not allowed to use paper-based records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research.[14] The Scientific and Ethical Advisory Group of the IPCI project approved the study.

Source population

The source population comprised all males, 45 years of age or older with at least 6 months of valid database history. A valid history meant that the practice had been contributing data to the IPCI database for at least 6 months and that the patient had been registered with the GP for at least 6 months. This was required to have background information on all subjects. Follow-up started on January 1st 1995 or the date at which 6 months of valid history was obtained, whichever was latest. Patients having a history of AUR or radical cystectomy prior to study entry were excluded. All subjects were followed from study-entry until either the first episode of AUR, the end of the study period (December 2002), transferring out of the practice or death, whichever event occurred first.

Case identification and validation

AUR was defined as the sudden inability to pass any urine, requiring catheterization. All potential cases of AUR were manually reviewed by a physician (KV) and were categorized into 3 groups (definite AUR, possible AUR and no AUR). An endpoint committee consisting of 3 physicians (JLHRB, BS and MVW) reviewed all cases from the "possible AUR" category. Independently the physicians classified the cases into 3 categories ("AUR", "no AUR" or "AUR unknown"). If at least 2 of the 3 physicians agreed, the respective category was assigned. If none of the physicians agreed, the AUR case remained within the "possible AUR" category. A sample of "possible AUR" cases (5%) was verified with the GP and the diagnosis was confirmed in 93% of all cases.

Review of cases was blinded for exposure to drugs throughout the entire validation process. The index date was defined as the date of the first AUR.

Controls

For each case we sampled up to 10 controls from the source population that was in follow-up at the time the case occurred. The controls were matched on age (year of birth) and calendar time (index date).

Exposure definition

From the prescription records of both cases and controls, all prescriptions for NSAIDs prior to the index date were retrieved. The hazard curves for AUR during the use of NSAIDs are not known. Based on the proposed mechanism we assumed a priori an acute effect with a short carry-over. Hence, exposure to NSAIDs was classified as current (last prescription covers the index date or ends less than 2 days prior to the index date) and past (last prescription ended more than 2 days and less than 6 months prior to the index date). For current users of NSAIDs, the dose effect with daily dose in DDD (< 1 Defined Daily Dose (DDD), 1 DDD, > 1 DDD per day) and the treatment-duration effect were studied. The DDD is the recommended average dosage of a drug for an adult for the main indication, as defined by the World Health Organization.[13] To study the effect of time since first use we categorized current users of NSAIDs into recent starters (patients who received their prescription for an NSAID within one week prior to the index date while not having used NSAIDs in the past 6 months) and long term users (patients currently using NSAIDs for more than one week or patients who had used NSAIDs in the past 6 months and who received their prescription for an NSAID within one week prior to the index date). To investigate the influence of affinity to COX-2, we compared COX-2 selective inhibitors with non-selective COX inhibitors.

In addition, we retrieved all prescriptions for acetylsalicylic acid prior to the index date and we examined the effect of current use of acetylsalicylic acid, using the same definitions as stated above, either as analgesic or as platelet inhibiting agent.

Covariates

Information on the presence of different risk factors for AUR was extracted from the computerized patient records. These concerned current use of concomitant drugs known to cause AUR (drugs with anticholinergic effect, narcotic analgesics and benzodiazepines); a recent (within 30 days prior to the index date) history of urinary tract infection (UTI), nephrolithiasis, constipation, surgery and home bound lifestyle. In addition, we checked for a history of BPH, prostate cancer, incontinence, diabetes mellitus, cardiac diseases, cancer, stroke, dementia and other neurological disorders prior to the index date. Finally, we checked all indications for current use of NSAIDs from the patient's prescription records.

Statistical analysis

The incidence of AUR within this population was calculated by dividing the number of men with AUR by the number of men-years accumulated by the source population. 95% confidence estimates were calculated around the estimates based on the Poisson distribution.

Conditional logistic regression analysis was used to assess the matched unadjusted and adjusted risk estimates for the association between risk factors and AUR and exposure to NSAIDs and the occurrence of AUR. In the adjusted model we first included, one by one, all co-variates that were univariately associated with the outcome ($p<0.05$). Risk factors that changed

the relative risk of AUR following current use of NSAIDs by more than 5% were maintained in the final model.

To estimate the proportion of AUR in the total population that can be attributed to the current use of NSAIDs we calculated the Population Attributable Risk (PAR) using the following formula [15]:

PAR= Attributable risk x proportion exposed

In this formula, the attributable risk is the incidence rate among the exposed minus the incidence rate among the unexposed. The proportion exposed is the proportion of current NSAIDs users among the controls (assuming to be representative of the general population).

All statistical analyses were conducted with the statistical software packages SPSS/PC 11.5.

Results

Within the source population of 72,114 males, 45 years of age or older, we identified 536 definite and 25 possible cases of AUR, the incidence was 2.4 per 1000 men-years (95% CI 2.25-2.65 per 1000 men-years). To avoid false-positive misclassification of the outcome, we only used the definite cases in our case-control analyses. These 536 definite AUR cases were matched to 5348 controls.

The mean age of cases was 73.0 years (SD 10.4). Cases had a higher prevalence of co-morbidity such as BPH, prostate cancer, neurological disorders and cancer and more often had a history of urinary tract infections, constipation, surgery and home bound lifestyle than controls (table 1). Current use of drugs with anticholinergic effects, narcotic analgesics and benzodiazepines was also higher among cases than among controls (table 1).

Table 1: Patient characteristics and the univariate association with AUR

	Cases		Controls		$OR_{matched}$*	95% CI
	(n=536)	%	(n=5348)	%		
Comorbidity						
BPH	228	42.5	966	18.1	3.48	2.88-4.21
Prostate cancer	52	9.7	143	2.7	3.88	2.79-5.40
UTI	45	8.4	14	0.3	39.56	20.44-76.66
Urolithiasis	2	0.4	2	0.0	10.0	1.4-71.0
Urinary incontinence	22	4.1	105	2.0	2.15	1.34-3.46
Surgery	74	13.8	34	0.6	23.89	15.62-36.55
Constipation	22	4.1	23	0.4	9.83	5.44-17.76
Diabetes mellitus#	51	9.5	473	8.8	1.08	0.80-1.46
Cardiac diseases	176	32.8	1491	27.9	1.27	1.05-1.55
Stroke	38	7.1	255	4.8	1.54	1.08-2.20
Dementia	7	1.3	44	0.8	1.6	0.7-3.6
Neurological disorders	12	2.2	61	1.1	1.97	1.05-3.70
Cancer	39	7.3	165	3.1	2.48	1.72-3.56
Home bound lifestyle	159	29.7	476	8.9	5.43	4.30-6.86
Concomitant Medication						
Use of anticholinergic drugs	57	10.6	356	6.7	1.80	1.33-2.43
Use of narcotic analgesics	28	5.2	62	1.2	4.61	2.93-7.26
Use of benzodiazepines	49	9.1	310	5.8	1.68	1.22-2.31

* matched on year of birth and indexdate #risk of AUR was increased in patients with long lasting diabetes mellitus type 1 ($OR_{matched}$ 4.1 (95% CI 1.3-13.5))

The unadjusted OR for AUR was 2.26 (95% CI 1.49-3.45) for current use of NSAIDs compared to no use. This increase in risk remained upon adjustment for other AUR risk factors with an OR of 2.02 (95%CI 1.23-3.31) (table 2). Past use of NSAIDs was not associated with an increased risk of AUR. Among current users, the risk was highest for persons who were new NSAIDs users (OR_{adj} 3.3, 95% CI 1.2-9.2) whereas the risk for long-term users was 1.77 (95% CI 1.01-3.10) (table 2).

The risk of AUR was not linearly related with dose. No association with current use of low doses of NSAIDs (<1 DDD) was observed, and there was a similar increase in risk for patients taking NSAIDs at a dose of 1 DDD or higher (table 2).

Table 2: NSAID use (excluding acetylsalicylic acid) and the risk of AUR

	AUR cases		Controls		$OR_{matched}$* (95% CI)	OR_{adj} # (95% CI)
	(n=536)	%	(n=5348)	%		
NSAID						
No use	448	83.6	4715	88.2	reference	reference
Current use	28	5.2	131	2.4	2.26 (1.49-3.45)	2.02 (1.23-3.31)
Past use	60	11.2	502	9.4	1.26 (0.95-1.67)	0.98 (0.70-1.37)
Duration of NSAID use						
No use	448	83.6	4715	88.2	reference	reference
Current use						
• Started less than 8 days	6	1.1	16	0.3	3.9 (1.5-9.9)	3.3 (1.2-9.2)
• Started more than 8 days	22	4.1	115	2.2	2.02 (1.27-3.24)	1.77 (1.01-3.10)
Past use	60	11.2	502	9.4	1.26 (0.95-1.67)	0.98 (0.70-1.37)
NSAID DDD						
No use	448	83.6	4715	88.2	reference	reference
Current use						
• <1 DDD	2	0.4	41	0.8	0.5 (0.1-2.1)	0.4 (0.1-1.9)
• 1 DDD	11	2.1	37	0.7	3.12 (1.59-6.12)	3.33 (1.56-7.11)
• >1 DDD	15	2.8	53	1.0	3.06 (1.70-5.50)	2.38 (1.18-4.79)
Past use	60	11.2	502	9.4	1.26 (0.94-1.67)	0.99 (0.70-1.38)

*matchedonyearofbirthandindexdate#adjustedforBPH,prostatecancer,UTI,surgery,homeboundlifestyleanduseofnarcoticanalgesics and benzodiazepines.

In a further attempt to explore whether any potential effect would be restricted to NSAIDs with high affinity for COX-2 we estimated the AUR risk for the COX -2 selective inhibiting NSAIDs and the nonselective NSAIDs. Use of COX-2 selective inhibitors was associated with a somewhat higher risk of AUR then use of non-selective NSAIDs (table 3). However, there were few users of COX-2 selective drugs and the risk estimates for COX-2 selective and non-selective NSAIDs were similar after adjustment for the daily dose (rofecoxib is usually prescribed twice the recommended daily dose).

The risk of developing AUR in patients currently using acetylsalicylic acid was not increased (OR 1.25, 95% CI 0.98-1.60), however the majority of persons (95%) used it in low doses (< 100 mg) (table 3).

Table 3: Type of NSAID or acetylsalicylic acid and risk of AUR

	AUR cases		Controls		$OR_{matched}$* (95% CI)	OR_{adj} # (95% CI)	OR_{adj} ¥ (95% CI)
	(n=536)	%	(n=5348)	%			
Type of NSAID							
No use	448	83.6	4715	88.2	Reference	Reference	Reference
Current use of							
- cox-2 selective NSAIDs	3	0.6	8	0.1	4.4 (1.1-17.9)	3.1 (0.5-17.6)	1.8 (0.1-25.4)
- non cox-2 selective NSAIDs	25	4.7	123	2.3	2.15 (1.38-3.34)	1.96 (1.17-3.26)	1.40 (0.38-5.20)
Past use	60	11.2	502	9.4	1.26 (0.95-1.68)	0.96 (0.70-1.37)	0.98 (0.70-1.38)
Acetylsalicylic acid							
Current use	90	16.8	756	14.1	1.25 (0.98-1.60)	0.99 (0.74-1.32)	-
Past use	30	5.6	257	4.8	1.22 (0.83-1.81)	0.86 (0.54-1.38)	-

*matchedonyearofbirthandindexdate#adjustedforBPH,prostatecancer,UTI,surgery,homeboundlifestyleanduseofnarcoticanalgesicsandbenzodiazepines.¥adjustedforBPH,prostatecancer,UTI,surgery,homeboundlifestyleanduseofnarcoticanalgesics,benzodiazepinesandDDD

The indication for NSAIDs was not substantially different between cases and controls and the indication for current use of NSAIDs (both for cases and controls) was locomotoric in more than 70%. Amongst the cases, none of the recent starters of NSAIDs had a urological condition as indication for treatment start.

We explored effect modification by age, presence of urinary tract infection, a history of BPH, prostate cancer, use of concomitant medication such as anticholinergics or narcotics. We did not identify significant effect modification by any of these variables.

Finally, based on an incidence rate of AUR of 4.73 per 1000 men-years amongst the exposed and of 2.34 per 1000 men-years among the unexposed, we calculated a PAR of 57.4/10^6/year. Using demography data from the Dutch Central Bureau of Statistics (infoservice@cbs.nl) and based on an overall AUR incidence rate of 2.4 per 1000 men-years in males 45 years and older, this would mean that for 1998, 6548 new cases of AUR were expected in males 45 years and older of whom 156 (2.4%) could be attributed to the current use of NSAIDs.

Discussion

In this study, we showed that current use of NSAIDs is associated with an increased risk of acute urinary retention (AUR). The risk is highest in patients who recently started using NSAIDs and those who use high daily dosages. To our knowledge, this is the first epidemiological study reporting on the association between the use of NSAIDs and the risk of AUR. The hypothesis as postulated by Gruenenfelder et al. was that the inhibition of cyclooxygenase-2 might result in AUR.[9] After adjusting for all risk factors and for dose, we did not observe a difference in risk between the selective COX-2 inhibitors and the non-selective other NSAIDs. This would seem

plausible, since COX-2 will be inhibited by COX-2 specific inhibitors but also by non-selective NSAIDs.[5] We did not find an association between current use of acetylsalicylic acid and the risk to develop AUR, what is probably due to the fact that acetylsalicylic acid was mainly used at a low cardio-protective dosage without anti-inflammatory activity.

Despite the fact that we did find an association between the use of NSAIDs and risk of AUR in this population-based study, our results need to be interpreted with caution. Our exposure assessment was based on longitudinally collected GP prescriptions rather than dispensing or patient reported intake and did not include over the counter use. Therefore we may have misclassified at least some of the exposure to NSAIDs. However, it is likely that the exposure misclassification will be non-differential and thus the reported risk estimate will be an underestimate of the true risk estimate. To avoid misclassification of the outcome, we manually validated all cases and only included definite cases of AUR in our analysis. Additionally the physicians who reviewed and classified the cases were blinded to the patient's drug exposure. Diagnostic bias will be limited since the first case reports on a possible association between the use of NSAIDs and AUR were only published in September 2002 and moreover a diagnosis of AUR is unlikely to be missed.

Confounding by indication could be a concern in this study, as NSAIDs are used for the treatment of various urological conditions such as urinary tract infections and nephrolithiasis which by themselves could precipitate AUR.[16, 17] To control for confounding by indication, we checked the indication for all current use of NSAIDs in both cases and controls. Only one patient amongst the cases used NSAIDs for a urological condition (chronic prostatitis) and initiated this therapy months prior to the index date suggesting little or no influence of confounding by indication. The highest risk of AUR that was found amongst recent starters of NSAIDs is probably not confounded by indication as none of these cases used NSAIDs for urological conditions.

As potential confounders we considered all known risk factors for AUR, but residual confounding by unknown risk factors for which we did not control may remain. Our study confirmed the association between AUR and the presence of known risk factors such as drugs with anticholinergic effects, use of narcotic analgesics and a history of BPH, prostate cancer, surgery, constipation, UTI, nephrolithiasis, cancer and home bound lifestyle.[18] The risk of AUR was not increased in patients with diabetes mellitus. However, we did find an association between AUR and patients with long lasting diabetes mellitus type 1 ($OR_{matched}$ 4.1 (95% CI 1.3-13.5) when categorizing diabetes mellitus into type 1 or type 2.

In conclusion, we found that the risk of AUR is about 2-fold higher in patients currently using NSAIDs compared to those not taking NSAIDs.

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Chapter 7

Anti-psychotic drugs and the risk of acute urinary retention

Abstract

Context: Acute urinary retention (AUR) is characterized by the sudden inability to urinate, which is usually painful and requires catheterization.

Objective: To investigate whether the use of antipsychotic drugs is associated with an increased risk of AUR.

Design: Population-based case-control study.

Setting: Data from the Integrated Primary Care Information (IPCI) project in the Netherlands.

Participants: The source population comprised all males, 45 years or older, registered in the database between 1995 on through 2002. Cases were all men with a validated diagnosis of AUR. Each case was matched on age and calendar time with up to 10 controls.

Main outcome measure: Exposure to antipsychotic drugs in patients with AUR versus exposure to antipsychotic drugs in controls, using conditional logistic regression analysis with odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Within the source population of 72,114 men, we identified 536 cases of AUR and 5348 matched controls. The risk of AUR was 4.02-fold (95% CI: 2.32-6.97) higher in current users of antipsychotic drugs. This increased risk remained after adjusting for all other known AUR risk factors (OR_{adj} 2.62 [95%CI 1.37-5.02]). The highest risk for AUR (OR_{adj} 8.1 [95% CI 1.7-38.3]) was observed in patients who recently (within one month prior to the index date) started using their antipsychotic drugs and in those using a higher daily dose. Amongst the antipsychotic drugs, there was a strong association between current use of phenothiazines or thioxanthenes and AUR.

Conclusion: The risk of AUR is 2.6 higher in patients using antipsychotic drugs than in non-users.

Introduction

Acute urinary retention (AUR) is a condition characterized by the sudden inability to urinate, which is usually painful and requires catheterization.[1] The causes of AUR can be classified into three categories. The first category relates to any event that increases the resistance of the urinary flow such as benign prostatic hyperplasia (BPH). The second category involves interruption of either the sensory innervation of the bladder or weakness of the detrusor muscle. The third category relates to any situation that permits the bladder to over-distend (e.g. post surgery).[2] The incidence of AUR is higher in males than in females, especially in the older age categories, as males suffer more often from morbidities known to provoke AUR.[3]

AUR has been associated with the use of drugs that possess anticholinergic effects such as antipsychotics.[2] The anticholinergic effect is caused by a blockade of the parasympathetic chain which may result in an inhibition of the contraction of the detrusor muscle and finally in AUR. The anticholinergic activity is not the same for all antipsychotics.[4] Phenothiazines (mainly chlorpromazine and thioridazine) and thioxanthenes (mainly chlorprotixen) have a strong anticholinergic effect. Amongst the atypical antipsychotics, anticholinergic side-effects have been described for clozapine.[5] Antipsychotic drugs are mainly used for the treatment of psychosis, but in the elderly, they are also prescribed to relieve symptoms of agitation and anxiety, especially in patients with Alzheimer's disease.[6]

The association between the use of antipsychotics and the risk of AUR is generally accepted, but to our knowledge, epidemiological studies to quantify this association have not yet been performed. Therefore we conducted a case-control study in a population of males, 45 years and older, to study the association between AUR and the use of antipsychotic drugs.

Methods

Setting

This study was conducted in the Integrated Primary Care Information (IPCI) database in the Netherlands. The IPCI database is a general practice research database, containing information from electronic patient records of 150 general practitioners (GPs) covering more than 500,000 patients. In the Dutch health care system, patients are registered with a single GP who acts as a gatekeeper of medical care and information.[7] The electronic records contain coded and anonymous data on patient demographics, symptoms (using the International Classification for Primary Care (ICPC) and free text), diagnoses (using ICPC and free text), clinical findings, referrals, laboratory findings, and hospitalisations.[8, 9] Summaries of the hospital discharge letters or information from specialists are entered in a free text format and hard copies can be provided upon request. Information on drug prescription comprises brand name, quantity, strength, indication, prescribed daily dose, the Anatomical Therapeutic Chemical classification (ATC) code and the physician linked indication.[10] To maximize completeness of the data, GPs who participate in the IPCI project are not allowed to use paper-based records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research.[11] The Scientific and Ethical Advisory Group of the IPCI project approved the study.

Source population

The source population comprised all males, 45 years of age or older with at least 6 months of valid database history. A valid history meant that the practice had been contributing data to the IPCI database for at least 6 months and that the patient had been registered with the GP for at least 6 months. This was required to have sufficient background information on all subjects. Follow-up started on January 1st 1995, the date at which 6 months of valid history was obtained or the date of the 45th birthday, whichever was latest. Patients having a history of AUR or radical cystectomy prior to study entry were excluded. All subjects were followed from study entry until the first episode of AUR, the end of the study period (December 2002), transferring out of the practice or death, whichever occurred first.

Case identification and validation

AUR was defined as the sudden inability to pass any urine, requiring catheterization. All potential cases of AUR were manually reviewed by a physician (KMCV) and were categorized into 3 groups (definite AUR, possible AUR and no AUR). An endpoint committee consisting of 3 physicians (JLHRB, BS and MVW) reviewed all cases from the "possible AUR" category. Independently, the physicians classified the cases into 3 categories ("definite AUR", "no AUR" or "AUR unknown"). If at least 2 of the 3 physicians agreed on a category, this category was assigned. If none of the physicians agreed, the AUR case remained within the "possible AUR" category. A sample of the

possible AUR cases (5%), assigned after the first validation, was in addition verified by the GP and the diagnosis was confirmed in 93% of all cases.

Review of cases was blinded to drug exposure throughout the entire validation process. The index date was defined as the date of the first AUR.

Controls

For each case we sampled up to 10 controls from the source population that was in follow-up at the time the case occurred. The controls were matched on age (year of birth) and calendar time (index date).

Exposure definition

From the prescription records of cases and controls, all prescriptions for antipsychotic drugs prior to the index date were retrieved. Some of the antipsychotic drugs have a long serum half life and may be used as a depot product.[5] Hence, exposure to antipsychotic drugs was classified as current if the last prescription covered the index date or ended within 1 month prior to the index date and as past if the end of the last prescription fell within 1 to 6 months prior to the index date. Subjects without a prescription within this period were classified as non-users. For current users of antipsychotic drugs, the effects of daily dose and the treatment-duration were studied. In order to aggregate dose of different drugs, daily dosages were expressed as Defined Daily Dose (DDD) equivalents. The DDD is the recommended average dosage of a drug for an adult for the main indication, as defined by the World Health Organization.[10] The respective daily dosages of antipsychotic drug use were categorized into 4 categories based on the distribution of the DDDs in the controls. To study the effect of time since first antipsychotic drug use we categorized current users of antipsychotic drugs into recent starters if started within one month prior to the index date and long term users if started more than one month ago. To look at the effect of different types of antipsychotics, we distinguished 3 groups namely phenothiazines and thioxanthenes (which have the same pharmacodynamic and pharmacotherapeutic profile), butyrophenons and other (diphenylbutamines, tiapride and atypical antipsychotics).

Covariates

Information on the presence of different risk factors for AUR was extracted from the computerized patient records. These concerned current use of concomitant drugs knowing to cause AUR (drugs with anticholinergic effect, antidepressants, anti-Parkinson medication, narcotic analgesics, anxiolytics and non-steroidal anti inflammatory drugs); a recent (within 30 days prior to the index date) history of urinary tract infection (UTI), nephrolithiasis, constipation, surgery and home bound lifestyle. In addition, we checked for a history of BPH, prostate cancer, urine incontinence, diabetes mellitus, cardiac diseases, cancer (exclusive of prostate cancer), stroke, dementia and other neurological disorders prior to the index date. Finally, we identified the indication for antipsychotic drug use from the patient's prescription records of current users.

Statistical analysis

The incidence rate of AUR within this population was calculated by dividing the number of men with AUR by the number of men-years accumulated in the source population. 95% Confidence estimates were calculated around the estimates based on the Poisson distribution.

Conditional logistic regression analysis was used to assess the matched unadjusted and adjusted risk estimates for the association between risk factors and AUR and exposure to antipsychotic drugs and the occurrence of AUR. In the adjusted model we first included, one by one, all co-variates that were univariately associated with the outcome ($p<0.05$). Risk factors that changed the relative risk of AUR during current use of antipsychotic drugs by more than 5% were maintained in the final model. To estimate the proportion of AUR in the total population that can be attributed to current use of antipsychotic drugs, we calculated the Population Attributable Risk (PAR) using the following formula [12]:

PAR= Attributable risk x proportion of exposed in the population

In this formula, the attributable risk is the incidence rate among the exposed minus the incidence rate among the unexposed and the proportion exposed is the proportion of current antipsychotic users among the controls. Data from the Dutch CBS (statline.cbs.nl) were used to extrapolate our results to the entire Dutch male population of 45 years or older.

All statistical analyses were conducted with the statistical software packages SPSS/PC 11.5.

Results

Within the source population of 72,114 males of 45 years and older, we identified 536 definite and 25 possible cases of AUR. The incidence rate was 2.4 per 1000 men-years (95% CI 2.25-2.65 per 1000 men-years). To avoid false-positive misclassification of the outcome, we only included definite cases in our case-control analyses. These 536 definite AUR cases were matched to 5348 controls. The mean age of AUR cases was 73.0 years (SD 10.4). Cases had a higher prevalence of co-morbidity such as BPH, prostate cancer, neurological disorders and cancer and more often had a history of urinary tract infections, constipation, surgery and home bound lifestyle than controls (table 1). Current use of drugs with anticholinergic effects (excluding antipsychotics), narcotic analgesics, NSAIDs, anti-Parkinson medication and anxiolytics was also higher among the cases than among the controls (table 1).

Table 1: Patient characteristics and the univariate association with AUR

	Cases		Controls		$OR_{matched}$*	95% CI
	(n=536)	%	(n=5348)	%		
Comorbidity						
BPH	228	42.5	966	18.1	3.48	2.88-4.21
Prostate cancer	52	9.7	143	2.7	3.88	2.79-5.40
UTI	45	8.4	14	0.3	39.56	20.44-76.66
Urolithiasis	2	0.4	2	0.0	10.0	1.4-71.0
Urinary incontinence	22	4.1	105	2.0	2.15	1.34-3.46
Surgery	74	13.8	34	0.6	23.89	15.62-36.55
Constipation	22	4.1	23	0.4	9.83	5.44-17.76
Diabetes mellitus#	51	9.5	473	8.8	1.08	0.80-1.46
Cardiac diseases	176	32.8	1491	27.9	1.27	1.05-1.55
Stroke	38	7.1	255	4.8	1.54	1.08-2.20
Dementia	7	1.3	44	0.8	1.6	0.7-3.6
Neurological disorders	12	2.2	61	1.1	1.97	1.05-3.70
Cancer	39	7.3	165	3.1	2.48	1.72-3.56
Home bound lifestyle	159	29.7	476	8.9	5.43	4.30-6.86
Concomitant Medication						
Use of anticholinergic drugs	34	6.3	235	4.4	1.49	1.03-2.16
Use of anticholinergic Parkinson medication	3	0.6	6	0.1	5.0	1.2-20.0
Use of narcotic analgesics	28	5.2	62	1.2	4.61	2.93-7.26
Use of antidepressants	16	3.0	116	2.2	1.41	0.83-2.39
Use of NSAIDs	28	5.2	131	2.4	2.26	1.49-3.45
Use of anxiolytics	69	12.9	430	8.0	1.76	1.34-2.32

*matchedonyearofbirthandindexdate#riskofAURwasincreasedinpatientswithlonglastingdiabetesmellitustype1($OR_{matched}$4.1(95%CI1.3-13.5))

The unadjusted OR for AUR was 4.02 (95% CI 2.32-6.97) for current use of antipsychotic drugs compared to no use. Upon adjustment for other AUR risk factors the OR_{adj} lowered to 2.62 (95% CI 1.37-5.02) (table 2). Past use of antipsychotic drugs was not associated with an increased risk of AUR. (OR_{adj} 1.03 [95%CI 0.53-1.98])

The risk of AUR increased with increasing daily dose and the highest risk of AUR was observed in patients using antipsychotic drugs at a dose of 0.4 DDD or higher (Table 2). Also, the association with AUR was highest for patients who recently (within one month prior to the index date) started using antipsychotics and who were antipsychotic naïve (OR_{adj} 8.1; 95% CI 1.7-38.3) (table 2). The risk was highest for patients currently using phenothiazines or thioxanthene. This increased risk remained after adjusting for the daily dose (OR_{adj} 9.0, 95% CI 2.5-33.0) (table 3).

Table 2: antipsychotic drug use and the risk of AUR

	AUR cases		Controls		$OR_{matched}$* (95% CI)	OR_{adj} # (95% CI)
	(n=536)	%	(n=5348)	%		
Antipsychotic drugs						
No use	503	93.8	5188	97.0	reference	reference
Current use	19	3.5	51	1.0	4.02 (2.32-6.97)	2.62 (1.37-5.02)
Past use	14	2.6	109	2.0	1.32 (0.75-2.31)	1.03 (0.53-1.98)
DDD of current use of antipsychotic drugs						
No use	503	93.8	5188	97.0	reference	reference
Current use						
• ≤ 0.125 DDD	7	1.3	26	0.5	2.9 (1.2-7.0)	1.9 (0.8-5.0)
• > 0.125 DDD and ≤ 0.4 DDD	6	1.1	13	0.2	5.0 (1.9-13.1)	3.3 (1.0-10.8)
• > 0.4 DDD	6	1.1	12	0.2	5.1 (1.9-13.6)	3.6 (1.1-12.3)
Past use	14	2.6	109	2.0	1.32 (0.75-2.31)	1.03 (0.53-1.98)
Duration of antipsychotic drugs						
No use	503	93.8	5188	97.0	reference	reference
Current use						
• Started less than 1 month	7	1.3	6	0.1	13.7 (4.3-43.7)	8.1 (1.7-38.3)
• Started more than 1 month	12	2.2	45	0.8	2.9 (1.5-5.5)	2.0 (0.96-4.3)
Past use	14	2.6	109	2.0	1.31 (0.74-2.30)	1.02 (0.53-1.97)

*matched on year of birth and index date #adjusted for BPH, UTI, incontinence, surgery, stroke, homebound lifestyle and use of antiparkinson medication and anxiolytics.

Table 3: Risk of AUR by class of antipsychotic drugs

	AUR cases		Controls		$OR_{matched}$* (95% CI)	OR_{adj} # (95% CI)	OR_{adj} ¥ (95% CI)
	(n=536)	%	(n=5348)	%			
Class antipsychotic drugs							
No use	503	93.8	5188	97.0	Reference	Reference	Reference
Current use of							
- Phenothiazines or thioxanthenes	13	2.4	18	0.3	7.1 (3.5-14.6)	5.6 (2.3-13.9)	9.0 (2.5-33.0)
- Butyrophenons	5	0.9	24	0.4	2.2 (0.8-6.0)	1.5 (0.5-4.3)	1.7 (0.6-5.1)
- Others	1	0.1	8	0.2	1.3 (0.2-10.6)	1.0 (0.1-8.4)	1.3 (0.1-11.2)
Past use	14	2.6	110	2.1	1.31 (0.75-2.31)	1.03 (0.53-1.98)	1.03 (0.53-1.98)

*matched on year of birth and index date #adjusted for BPH, UTI, incontinence, surgery, stroke, homebound lifestyle and use of antiparkinson medication and anxiolytics. ¥additionally adjusted for daily dosage.

To evaluate potential confounding by indication, we verified the indication for use of antipsychotic drugs and found that psychosis, which has been associated with AUR, was the indication for current use of antipsychotics in 2 out of the 19 cases (10.5%) compared to 7 out of the 51 controls (13.7%).

We explored effect modification by age, recent urinary tract infection, a history of BPH, prostate cancer, use of concomitant medication such as anticholinergics or narcotics. We did not identify significant multiplicative effect modification by any of these variables.

Finally, based on an incidence rate of AUR of 6.19 per 1000 men-years amongst the exposed and an incidence rate of 2.36 per 1000 men-years among the unexposed, we calculated a PAR of $38.3/10^6$/year. Using demographic data from the Dutch Central Bureau of Statistics (statline.cbs.nl) and an overall AUR incidence rate of 2.36 per 1000 men-years in males 45 years and older, our data imply that for 1998, 1.6% of the AUR cases in men, 45 years and older could be attributed to current use of antipsychotics.

Discussion

In this study, we showed that current use of antipsychotics is associated with an increased risk of acute urinary retention (AUR). The risk is highest in patients who recently started using antipsychotics, those who use higher daily dosages and those who are treated with phenothiazines or thioxanthenes. These data are consistent with the expected anticholinergic effects of antipsychotics. To our knowledge, this is the first epidemiological study that quantifies this association.

The association between AUR and antipsychotic drugs was the strongest for patients currently using phenothiazines or thioxanthenes, however, we could not distinguish between the individual products in these classes because of small numbers. Amongst the atypical antipsychotic drugs, anticholinergic effects have been described for clozapine and risperidone [4, 5]. We could not confirm an association between AUR and the use of clozapine and risperidone as none of the AUR cases were current users of any of these drugs.

We did find that the association between the current use of antipsychotic drugs and AUR was highest for patients who were antipsychotic naïve until one month prior to the index date. This seems plausible as it is assumed that the risk of AUR is highest during initiation of antipsychotic treatment and declines following weeks of continuous treatment at an unchanged dose. [13]

Despite the fact that we found an association between the use of antipsychotics and risk of AUR in this population-based study, our results should be interpreted with caution. Our exposure assessment was based on longitudinally collected GP prescriptions rather than dispensing or patient reported intake. Therefore we may have misclassified at least some of the exposure to antipsychotics. However, it is likely that the exposure misclassification will be non-differential which implies that the reported risk estimate is an underestimate of the true risk. To avoid misclassification of the outcome, we manually validated all cases and only included definite cases of AUR in our analysis. Additionally the physicians who reviewed and classified the cases were blinded to the patient's drug exposure.

Confounding by indication could be a concern in this study as a possible association between psychosis (in schizophrenic patients) and urinary retention has been described in a case report.[13, 14] In our study, there was a similar frequency of the indication "psychosis' in cases and controls. Therefore, confounding by indication is unlikely. Antipsychotic drugs were mainly prescribed for the relief of symptoms such as anxiety, agitation, and insomnia in this population of ageing men. This also explains the low daily dosage.

Protopathic bias might be a concern if treatment with antipsychotic drugs was started to relief the first symptoms of AUR (e.g. restlessness in ageing, dementing patients). To control for protopathic bias, we checked the treatment start date for both cases and controls and found that the antipsychotics were initiated at least one week prior to the index date. As AUR is an acute event, it is thus unlikely that the association was distorted by protopathic bias. Confounding by drugs, prescribed to reduce the adverse-effects of antipsychotics, could as well

be an issue in this study as extra-pyramidal symptoms (a common adverse-effect of the first generation of antipsychotic drugs) are commonly treated with anticholinergic, anti-parkinson drugs.[15] Therefore, we adjusted for anticholinergic, antiparkinsonian drugs.

Our study confirmed the association between AUR and the presence of known risk factors such as other drugs with anticholinergic effects, use of narcotic analgesics and a history of BPH, prostate cancer, surgery, constipation, UTI, urolithiasis, cancer and home bound lifestyle.[16]

Some cases and studies (both in vitro and in vivo) reported on the occurrence of urinary incontinence as opposed to AUR in patients on antipsychotic treatment, especially clozapine.[17-19] Psychosis by itself can be a direct cause of urinary incontinence, but the use of antipsychotic drugs might as well cause urinary incontinence via an inhibition of the dopaminergic (central) and alpha-adrenergic receptors (peripheral).[20] Antipsychotics thus seem to be able to provoke as well as inhibit micturition and further research is warranted to study its mechanisms and its influencing factors.

In conclusion, we found that the risk of AUR is more than 2.6 higher in patients currently using antipsychotic drugs compared to those not taking antipsychotic drugs. Although the population attributable risk was rather modest, physicians should be vigilant when prescribing antipsychotic drugs, especially in high-risk patients.

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Chapter 8 General Discussion

General Discussion

8.1 Background

Benign prostatic hyperplasia (BPH) is the most common benign neoplasm in men and is present in more than 50% of men aged over 60 years. [1] BPH might cause lower urinary tract symptoms (LUTS) usually categorized into storage or voiding symptoms. Not all men with BPH will develop LUTS and LUTS by itself can also be caused by other urological conditions (e.g. urinary tract infections, detrusor instability) or other non-urological conditions such as heart failure and diabetes mellitus. [1] BPH is a progressive disease and may lead to serious medical conditions such as acute or chronic urinary retention, recurrent urinary tract infections and bleeding. [1-3]

The primary goals of treatment for BPH are to relieve the symptoms and to prevent progression. The different treatment regimens for men with LUTS/BPH consist of watchful waiting, pharmacological treatment or prostate surgery. The decision to opt for a specific treatment regimen is based on LUTS symptom severity and the patient characteristics such as age and medical conditions.[4, 5]

The prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) varies between 4-25% depending on the LUTS/BPH definition used and the population studied. [6]

As little is known on the incidence of LUTS/BPH and the management of men with LUTS/BPH in real life, we aimed to study the epidemiology and management of patients with symptomatic BPH using data from the International Primary Care Information (IPCI) project, a general practitioner's database in the Netherlands.

In this chapter, the most important findings are summarized and the study setting and related methodological considerations are clarified. In addition, the clinical implications of this research and potential for future research within the domain of LUTS/BPH are discussed.

8.2 Main findings

8.2.1 Incidence and prevalence of LUTS/BPH

The prevalence of LUTS/BPH has been studied in detail in the past, but information on the incidence of LUTS/BPH is missing.

The overall prevalence in our cohort of men 45 years or older was 10.3% and increased with age to a maximum prevalence of 24% at the age of 80 years. This prevalence falls within the prevalence rates that were reported in other studies. [7] [6, 8-12] In other studies the variation in prevalence is huge (lowest 4% - highest 56%), depending on the type of cohort studied, the geographic region, and the LUTS/BPH case definition. Data from two community-based studies in the Netherlands showed that the prevalence of LUTS/BPH indeed strongly depends on the case definition. In these studies, the prevalence decreased from a high prevalence of 20% to a lower prevalence of 4-9% when stricter criteria for case assessment were used. [12, 13] Ideally,

LUTS/BPH would be defined as a combination of LUTS (assessed via a symptom questionnaire), prostate size and uroflow-measurement. As we conducted a retrospective cohort study, information on urodynamical findings and I-PSS was often missing. Therefore, we had to use an alternative case definition and defined a case of LUTS/BPH if the patient expressed LUTS that could not be attributed to other (urological) conditions, if he was diagnosed by the urologist as having BPH or if he was treated for LUTS/BPH.

The overall incidence of LUTS/BPH in our cohort of men, 45 years or older, was 15 per 1000 man-years. The incidence was the lowest at the age of 45-49 (3 per 1000 man-years) and almost linearly increased with age until the age of 75-79 (38 per 1000 man-years). From the incidence data, we may expect that 45% of symptom-free men, aged 46 years will develop LUTS/BPH over the coming 30 years.

The results on the incidence and prevalence of LUTS/BPH should be regarded as conservative estimates as only patients presenting themselves with symptoms of LUTS/BPH were considered. It is likely that the true incidence and prevalence of LUTS/BPH in the community is higher. A significant proportion of men may experience urinary symptoms but may be reluctant to visit their physician for fear of surgery or embarrassment, or may dismiss the symptoms as a mere consequence of ageing. Garraway et al. found that only half of the men with bothersome nocturia consulted a physician.[14] It is likely however, that such patients present themselves in a later stage of disease, when symptoms increase in severity.

8.2.2 Diagnostic work-up by general practitioners of patients with LUTS/BPH

Physical examination, including digital rectal examination, and urinalysis are mandatory examinations according to the Dutch GP guidelines on the management of voiding difficulties in older men.[15] Additional examinations are only recommended in specific circumstances such as urine culture in case of suspicion of urinary tract infections. As prostate-specific antigen (PSA) (a tumor marker in the detection and follow-up of prostate cancer) is often mildly elevated in patients with BPH, the Dutch guidelines only recommend use of PSA in patients younger than 70 years and with a digital rectal examination that is difficult to interpret.[15, 16] In addition, there is no consensus about the further evaluation of patients with an abnormal PSA. We suspected that the frequency of PSA testing was much higher than recommended by the Dutch guidelines. A retrospective cohort study was conducted to investigate the frequency of PSA-testing, the management of patients with abnormal PSA results and whether PSA testing, as part of diagnostic work-up, had an impact on the incidence of prostate cancer during follow-up.

PSA testing as part of diagnostic work-up took place in more than 50% of all patients with first LUTS/BPH. PSA turned out to be abnormal (PSA>4 ng/ml) in 30%. When only considering the patients with an abnormal PSA and at least 6 months of follow-up, 47% were immediately referred to an urologist and 23% had a repeat PSA-testing done, whereas no action was taken in approximately 30%.

These findings suggest that Dutch GP guidelines on the management of voiding difficulties in older men are not applied in daily practice. The fact that 30% of patients with an abnormal PSA result were neither referred to an urologist nor were tested again might indicate a lack on clear guidelines on follow-up of patients with abnormal PSA results. However, it could as well be a deliberate decision by the GP, based on the patient's life expectancy, taking into account patient's age and co morbidity. Other studies have shown as well that PSA testing was very common amongst patients with LUTS/BPH although local guidelines advised against the systematic use of PSA in the diagnostic work-up.[16, 17] Although none of these studies had information on the indication for PSA testing, the authors suggested that the decision on PSA testing was mainly influenced by a request from the patient, presence of symptoms suggestive of prostate cancer or potential concern about malpractice litigation.[16, 18] It might as well be a consequence of an overestimation of the diagnostic value of PSA in the early diagnosis of prostate cancer.

We found information on digital rectal examination only in approximately 60% of all patients, despite the fact that this examination is mandatory according to the Dutch guidelines. [15] Although recording of digital rectal examination might have been omitted by the GP, it seems that it is not a popular tool in the differential diagnosis for men with micturition difficulties. The importance of DRE in the differential diagnosis of prostate cancer should not be neglected as we found that the prostate cancer detection rate was highest in patients referred for both a DRE suspicious for prostate cancer and an abnormal PSA.

8.2.3 Therapeutic management of patients with LUTS/BPH

Little is known about LUTS/BPH treatment and the related compliance in general practice. We studied the therapeutic management of patients with LUTS/BPH and the adherence to and persistence with pharmacological treatment. In addition, we studied the association between the type of LUTS/BPH complaints (voiding symptoms, storage symptoms, post-micturition symptoms) and the risk of early treatment discontinuation.[19]

Approximately 50% of all LUTS/BPH patients received pharmacological treatment. Most patients received their first prescription for an α-blocker or a 5α-reductase inhibitor within one year after first symptoms. α-Blockers were the most frequently used first line treatment especially in the most recent years. Treatment is often intermittently used with large gaps between the prescriptions (overall adherence around 70%). Approximately 1 out of ten treated patients switched to a drug of another compound for reasons of adverse events, lack of efficacy or based on recommendations from the urologists. Treatment persistence was low and 26% of the patients discontinued treatment early after start mainly for reasons such as insufficient efficacy or adverse events. The risk of early treatment discontinuation was highest for patients with mainly voiding symptoms, younger age and less co-morbidity.

The percentage of pharmacologically treated patients is quite low. This is in accordance with guidelines of the Dutch society of general practitioners on the management of voiding

difficulties in older men.[15] These guidelines advise watchful waiting for mild complaints and reserve pharmacological treatment for men with moderate to severe symptoms when other measures fail and surgery is contra-indicated. Also in accordance with these guidelines, treatment persistence is low, as guidelines suggest re-evaluation 6 weeks after the first prescription. If the drug proves to be effective, the treatment is continued for another 3 months and then discontinued. If symptoms re-appear, therapy is re-initiated.[15] The true adherence to and persistence with pharmacological treatment might even be lower, as the IPCI project only provides us with information on prescriptions. Therefore, we do not have information on drug dispensing nor on actual drug intake.

The overall incidence rate of prostate surgery was 62.0 per 1000 men-years. This incidence rate increased with age until the age of 75-79 years and declined in the higher age categories. The incidence rate of prostate surgery decreased over time with the lowest incidence in 2000. The incidence rate of prostate surgery and the age and calendar year pattern is similar to findings from other studies. [20-26] There seems to be a clear trend in postponing surgery and using pharmacological treatment as first option in patient with LUTS/BPH who do not respond to watchful waiting. Postponing prostate surgery might implicate that surgery occurs in high risk patients (older age categories with more co-morbidity) with larger prostates and more severe symptoms. This could jeopardize a positive outcome.[27]

8.2.4. Incidence of AUR

Information on the incidence rate of AUR in the general male population is available from 2 large cohort studies in the US. The incidence rate of AUR in the Olmsted County was 6.8 per 1000 man-years, whereas the incidence rate of AUR in the Health Professional Follow-up study was 4.5 per 1000 man-years. [28, 29] As information on the incidence rate of AUR in Europe is scarce, we performed a retrospective cohort study in the IPCI database.

Amongst a population of almost 57,000 males, 45 years or older, we identified 344 first cases of AUR resulting in an overall incidence rate of AUR of 2.2 per 1000 man-years, increasing with age. This incidence rate is thus lower than the incidence rate as reported by the US cohort studies. However, this could be attributed to differences in case definition and selection bias in the US studies. In both the Olmsted county and the Health Professional Follow-up study, participants to the AUR study were selected based on the completion of a questionnaire asking for urological complaints or conditions. This is supported by the fact that the prevalence of LUTS/BPH is much higher in the US cohort studies than in ours. In the Health Professional study, patients were asked by mail if they had experienced an episode of AUR requiring urinary catheterization whereas we, similar to what was done in the Olmsted County, reviewed the patient records for the occurrence of AUR requiring catheterization. Our estimates provide population based incidence rates and do not suffer from selection bias.

In addition we studied a sub-cohort of patients newly diagnosed with LUTS/BPH. Within this cohort, we identified 149 new cases of AUR. Strikingly, almost 50% of AUR cases entered the

cohort with AUR as first symptom of BPH. If we excluded these patients, the overall incidence rate of AUR was 18.3 per 1000 man-years and increased with age. The risk of developing AUR was 11-fold higher in men newly diagnosed with LUTS/BPH.

We know from recent randomized controlled trials that pharmacological treatment, and especially the combination of an α-blocker with a 5α-reductase inhibitor, might prevent BPH progression.[30-32] However, in order for prevention to be effective, earlier LUTS/BPH identification, especially in patients at risk for AUR, seems to be important.

8.2.5 Risk factors for AUR

We investigated, by means of a case-control study, if certain classes of medications are associated with an increased risk of AUR. From the literature, we know that almost 50% of AUR cases in men are associated with BPH, however, AUR might also be precipitated by other factors such as urinary tract infections or preceding surgery.[33, 34] For this reason, the study population was not restricted to men with BPH but included all men, 45 years or older.

In our case-control study, we demonstrated that the risk of AUR was about 2-fold higher in current users of NSAIDs and 2.6 higher in current users of antipsychotic drugs. For both NSAIDs and antipsychotic drugs, the risk was the highest in the higher dosage categories, or in patients who recently started using these drugs. Also the current use of other anticholinergic drugs and narcotic analgesics were associated with AUR. In addition, we confirmed known risk factors for AUR such as BPH, surgery, constipation, urinary tract infection and immobility. [33, 34]

The act of micturition is a very complex mechanism [(see chapter 1)] and the above-mentioned risk factors act via different pathways. All kinds of neurotransmitters and mediators interfere with micturition. Acetylcholine, which interacts with muscarinic receptors on the detrusor muscle, is the predominant peripheral neurotransmitter responsible for bladder contraction. Dopamine and serotonine are central neurotransmitters and are involved in the regulation of the micturition reflex. Serotonergic activity facilitates urine storage by enhancing the sympathetic reflex pathway and inhibiting the parasympathetic voiding pathway. Dopaminergic pathways may exert both inhibitory and facilitatory effects on voiding. D1 receptors appear to have a role in suppressing bladder activity, whereas dopamine D2 receptors appear to facilitate voiding.[35-38]

The distention of the bladder evokes afferent activity via myelinated Aδ fibers. In addition, the distention of the bladder causes the urothelium to release all kind of transmitters (ATP, tachykinins, NO and prostaglandin E_2 (PGE_2)) that interfere with micturition via the afferent pathway. ATP, tachykinins and PGE_2 have a stimulating effect on micturition, whereas NO has an inhibitory effect on micturition. [38-40]

PGE_2 in the bladder is synthesized via cyclooxygenase-2 and is up-regulated by a number of stimuli such as inflammation, trauma and over-distention. [40]

Results of our case-control study showed an association between current use of NSAIDs and the risk of AUR. Based on the various mechanisms as described above, this seems plausible as NSAIDs inhibit the formation of PGE_2 resulting in relaxation of the detrusor muscle.

Some of the antipsychotic drugs have a strong anticholinergic effect. [41] This anticholinergic effect results in the inhibition of the parasympathetic chain, hindering the contraction of the detrusor muscle. Incontinence has also been described in patients using antipsychotic drugs via their direct effect on the dopamine receptors and the α-receptors. [42, 43]

8.3 Methodological considerations

8.3.1 Study setting

All reported studies used data from the Integrated Primary Care Information (IPCI) project in the Netherlands. The IPCI database is a longitudinal observational database that contains information from computer-based records of more than 150 GPs in the Netherlands. Information is available from approximately 500,000 patients and consists of detailed data on patient demographics, symptoms, diagnosis, lab results, referrals, drug prescription and hospitalizations. [44, 45]

Using data from the IPCI project was essential to study the incidence rates of LUTS/BPH and AUR in a population of ageing men for the following reasons. Firstly, we had access to a very large population of men that were followed over time. Secondly, the potential for selection bias [see 8.3.3] was negligible as participation in the IPCI project is based on passive consent and thus most patients contribute data. In addition, as the IPCI project contains the complete medical records of all patients, it gave us good insight into the patient characteristics, co-morbidity and treatment of patients with LUTS/BPH. However, as data was collected retrospectively, some crucial information on symptom severity, urinary catheterization, prostate surgery, prostate biopsy and prostate cancer staging was sometimes missing. In these circumstances, the GPs were contacted by letter to request additional information and a copy of the discharge or specialist letter if available. In addition, not all data in the IPCI database was coded which made the patient validation very labor-intensive. Finally, as the IPCI database is not linked to a pharmacy database, we did not have information on drug dispensing. Neither did we have information on "over-the-counter" use or actual drug intake. This might implicate that we have under- or overestimated pharmacological treatment.

8.3.2. Study design

Our research on the epidemiology and management of symptomatic BPH used descriptive and analytical epidemiological techniques. Descriptive epidemiology focuses on the occurrence and risk factors for the disease in a population.[46] Descriptive epidemiological studies were designed to explore the incidence of LUTS/BPH, prostate surgery, and AUR. In addition, we used descriptive epidemiology to study the diagnostic work-up and the therapeutic management of patients newly diagnosed with LUTS/BPH.

If the aim of the research is to investigate the determinants of the disease, analytical epidemiological designs are used. [46, 47] Analytical studies can be divided into observational or intervention studies (clinical trials). In observational studies, the natural course of the events, in relationship to the exposure of interest are studied. There are two basic types of observational studies namely the case-control and the cohort studies. Both designs were used in our research on the epidemiology of symptomatic BPH and will be described briefly.

Cohort study

In cohort studies, subjects are classified on the basis of the presence or absence of exposure to a particular factor and then followed for a specified period of time to determine the development of disease in each exposure group. Cohort studies are best suited to investigate relatively common outcomes. In retrospective cohort studies, all relevant events have occurred when the study is initiated. In prospective studies, the relevant exposures may or may not have occurred at the time the study started, but the outcomes have certainly not yet occurred.

In general, prospective cohort studies are expensive and labor intensive, as they require a large sample size and a long follow-up before results are known. This is of less concern in retrospective cohort studies, as all relevant outcomes have already occurred at the time the study is initiated. However, as retrospective studies rely on data entered in the past, and this data is generally not entered for the purpose of epidemiological research, crucial information on exposure, co-morbidity and potential confounding factors may be missing. [46-48]

We retrospectively defined a disease specific cohort of men, newly diagnosed with LUTS/BPH to study the risk factors for pharmacological treatment, early treatment discontinuation and AUR. In addition, as part of our descriptive epidemiological approach, we used this design to study the diagnostic work-up of patients with LUTS/BPH and the different treatment regimens they received.

Case-control study

In a case-control study, a case group of patients who have the disease of interest and a control group of individuals without the disease, at the time of case occurrence, are selected and the odds of exposure in each group are compared. The case-control design is particularly efficient for investigation of relatively rare diseases, since it selects a group of individuals that have already developed the outcome. Case-control studies offer the advantage to study associations quickly and allow for the study of multiple exposures at the same time. However, as both disease and exposure have already occurred at the time of study start-up, case-control studies might be more vulnerable to bias such as information and/or selection bias. [see 8.3.3) [49] These arguments apply to de novo initiated case-control studies. In a database as IPCI, exposure and disease are registered prospectively and therefore, information bias is non-differential. Also, due to the possibility to choose either a cohort or a case-control design, arguments such as complexity of exposure become important design items.

8.3.3 Internal and external validity

The validity, or the degree to which a result is likely to be true, is very important, not only in epidemiological research. Commonly, two aspects of validity are considered namely the internal and the external validity.

The internal validity of a study refers to the integrity of the experimental design – i.e. the ability to measure what it sets out to be measured. [50]

Bias (selection bias, information bias and confounding) undermines the internal validity of epidemiological research. [46-48, 51]

Selection bias

Selection bias results from an absence of comparability between the groups that are being compared due to differential participation rates. [46-48, 51]

An important form of selection bias is referral bias where patients voluntary refer themselves to take part in epidemiological research. Since the reason for self referral may be associated with the outcome under study, self referral of participants is generally considered as being a threat for the internal validity. As the IPCI data encompasses the total population and the data is gathered prospectively, without knowledge of the later formulated research questions, the magnitude of selection bias is negligible.

Diagnostic bias or detection bias is a type of selection bias and would occur if the diagnosis of the outcome (AUR in our research) would be influenced by knowledge of the exposure. We call it selection bias, although some experts in the field consider it as information bias. Diagnostic bias was not a concern in the case control study, investigating the relationship between the use of NSAIDs and AUR, as the first case reports on AUR in relation to the use of NSAIDs were only published in 2002.[52] Diagnostic bias might have influenced the study on the association between AUR and the current use of antipsychotic drugs as the anticholinergic side effects of antipsychotic drugs are well established. However, as AUR is an acute event, with unmistakable symptoms (the sudden inability to micturate in combination with abdominal pain and relief on catheterization), it is unlikely to be missed or to be incorrectly diagnosed. [33]

Information bias

Information bias, also known as observation, recall or (mis)-classification bias, results from an incorrect determination of exposure or outcome.[51] This information bias might be random (non-differential) or systematic (differential).

Non-differential misclassification bias generally shifts the risk towards 1, whereas differential misclassification may result in over as well as an underestimation of the actual risk. [47, 48]

To avoid misclassification of the AURs, we manually validated all cases, and only included definite cases of AUR in our analysis. In addition, the physicians who reviewed and validated the patients were blinded to the patient's exposure. Despite these measures, some random

misclassification of the outcome might have occurred which tends to underestimate rather than to overestimate the risk.

Crucial in our case-control study on the association between use of concomitant drugs and risk of AUR was the assessment of drug exposure. Since our exposure assessment was based on longitudinally collected GP prescriptions, rather than dispensing records or patient reported intake, we might have misclassified some of the exposure. In addition, our exposure assessment did not include over-the-counter use. Lack on information on over-the-counter use might have had some influence on the case-control study on current use of NSAIDs and risk of AUR, as in the Netherlands, over-the-counter preparations with some low dose NSAIDs are available. However, the risk of AUR in current users of NSAIDs was associated with dose and was not elevated in low dose NSAID users. Therefore missing information on low dose NSAIDs was probably of less concern. Finally, our exposure assessment did not include the drugs prescribed by the specialist. Because of the health care system in the Netherlands, patients are usually referred back to the general practitioner who will be responsible to continue further prescriptions.

Overall, we may have at least misclassified some of the exposure. However, it is likely that the exposure misclassification was non-differential and therefore the reported association estimates are an underestimate of the true risk.

Confounding

Confounding is one of the major concerns in epidemiological research, as it is one of the most difficult biases to detect and to control for. According to Webster's comprehensive dictionary of the English language, confounding means confusing or mingling (elements, things or ideas) indistinguishably. [53]

A confounding variable is a variable that can cause the disease under study and is also associated with the exposure of interest. There are three criteria for a variable to be a confounder: it must be a risk factor for the disease (also in the non-exposed), it must be associated with the exposure (also in the non-diseased) and it must not be an intermediate step in the causal pathway. (figure 1) [46-48, 51]

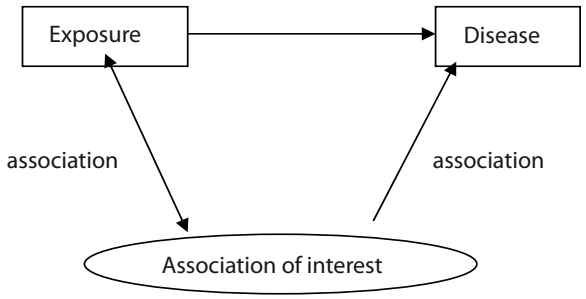

Figure 1: Confounding factor in relationship to exposure and disease

Confounding can lead to an over- or underestimation of the true association between exposure and outcome, depending on the direction of the associations which the confounding factor has with exposure and outcome.

Confounding can be controlled for via restriction, matching, stratification or multivariate techniques (e.g. mathematical modeling via multivariate logistic regression of proportional hazard analysis). [47, 51]

With restriction, the control of confounding is achieved by selecting into the study only individuals with certain homogeneous levels of the potential confounders. Matching involves removing the effect of the confounder by making the case group and the control group equivalent regarding the confounder.[46, 47, 51] Both techniques were applied in the case-control study as we restricted our population to men, 45 years or older, and we matched on age and index date.

In studies of pharmacologic therapies, confounding by indication may arise when the indication for the treatment is a risk factor for the outcome under study. [54, 55] Confounding by indication was definitely a concern in the case-control study on AUR and the use of NSAIDs. NSAIDs are used for the treatment of various urological conditions such as urinary tract infections and urolithiasis which by themselves could precipitate AUR. The same problem was encountered in the case-control study on AUR and the use of antipsychotic drugs because psychosis, which is one of the indications for the use of antipsychotic drugs, can by itself provoke AUR.

To control for confounding by indication, we checked the indication for current use of NSAIDs and antipsychotic drugs in both cases and controls. Only one patient among the cases used NSAIDs for a urological condition (chronic prostatitis) and initiated this therapy months prior to the index date suggesting little or no influence of confounding by indication. The main indication for the use of NSAIDs, both in the cases and the controls, was osteoarthritis. The proportion of patients with psychosis was not higher amongst the cases (10.5%) than among the controls (13.7%), again suggesting negligible confounding by indication. Agitation was the main indication for use of antipsychotic drugs, both in cases and controls.

Protopathic bias occurs when a pharmacological agent is prescribed for an early manifestation of a disease that has not been diagnosed yet.[56] We investigated the potential for protopathic bias in the case-control study on use of NSAIDs and AUR, as NSAIDs might have been prescribed for the relief of abdominal pain which by itself could be the first symptom of AUR. However, as AUR is a very acute event that is unlikely to be missed and NSAIDs use on the index date was excluded, protopathic bias seems unlikely. Also, we checked the indication for current use of NSAIDs and none of the cases used NSAIDs for abdominal pain.

External validity of epidemiological research implies that the observed findings can be generalized to the general population. External validity can be an issue in randomized controlled trials as participating patients tend to be different from patients who wish or can not participate due to stringent in- and exclusion criteria. [51]

As we used data from the IPCI project, a GP research database containing information from more than 500,000 patients, we believe that our findings can be extrapolated to the general population of men, aged 45 years or older.

8.4 Clinical implications

In the study on the diagnostic work-up of patients with LUTS/BPH we showed that PSA testing was done in more than 50%, that no further action was taken in 30% of patients with an abnormal PSA result and that digital rectal examination seems to be unpopular as information on digital rectal examination was only recorded in approximately 60% of all cases. It seems that real life practice differs from what is recommended by the current guidelines of the Dutch Society of General Practitioners on voiding difficulties in older men. Although we agree with the PSA restrictions as outlined in the Dutch guidelines, further clarification on the need, the interpretation and the follow-up of PSA testing in patients with LUTS/BPH might be desirable. In addition, it might be interesting to investigate why daily practice differs from what is outlined in the Dutch guidelines. Currently, the medical society is getting conflicting messages that on the one hand promote PSA testing in all patients with BPH to identify the ones that are likely to progress and on the other hand doubt the value of normal PSA results (≤ 4 ng/ml) to rule out prostate cancer. [57, 58] We also believe that the importance of digital rectal examination in the differential diagnosis of patients with LUTS/BPH should be re-emphasized. First of all, DRE is a relative simple test and secondly, studies, including our own; have shown that the positive predictive value improves for a combination of an abnormal DRE and an abnormal PSA. [59, 60]

In the study on the treatment strategies, the patterns of drug use and the treatment discontinuation in men with LUTS/BPH, we demonstrated that treatment adherence and treatment persistence was quite low. Patients should be informed about the importance of regular drug intake especially when using α-blockers as they have a shorter half-life and require regular intake. [41] Compliance is also important in patients using 5α-reductase inhibitors as prostate volume returns to the volume at start of therapy when treatment is discontinued for a long time.[41]

Results from some recent large randomized controlled trials with long term follow-up have shown that treatment with 5α-reductase inhibitors or the combination of an α-blocker with a 5α-reductase inhibitor might prevent BPH progression and complications such as prostate surgery, AUR, UTI or renal insufficiency.[30-32] In the cohort of newly diagnosed LUTS/BPH patients, half of AUR cases presented with AUR as the first symptom of LUTS/BPH. These patients would not have benefited from preventive pharmacological treatment as they were diagnosed too late. This could have several causes such as absence of prior LUTS/BPH symptoms, underreporting of symptoms by the patient or failure by the GP to recognize LUTS/BPH symptoms. Increasing both physician's and patient's awareness about the symptomatology, natural evolution and treatment of LUTS/BPH might be warranted.

Finally, we observed a positive association between the occurrence of AUR and the concurrent use of NSAIDs or antipsychotic drugs. Although the population attributable risk was rather modest, physicians should be informed about the possibility of provoking AUR in patients using NSAIDs and antipsychotic drugs. Especially in high-risk patients, careful prescribing seems justified.

8.5 Future research

For efficiency reasons, we restricted our research on the incidence and risk factors for AUR to a population of men, 45 years or older. It might be interesting to extend our research to females as, to our knowledge, information on the incidence rate of AUR in females is lacking. Especially younger females are at risk of developing AUR, as childbirth and pregnancy are known risk factors for urinary retention in females. [34, 61]

Our case-control study on the association between AUR and use of NSAIDs or antipsychotic drugs was not able to detect effect modification. It seems plausible that the risk of AUR in patients using NSAIDs or antipsychotic drugs will be highest in AUR-risk groups (e.g. patients with BPH, older age, use of concomitant drugs knowing to provoke AUR). Further research on the presence of effect modification seems warranted.

Recent randomized controlled trials have shown that 5α-reductase inhibitors and especially the combination of an α-blocker with a 5α-reductase inhibitor are effective in the prevention of BPH progression. [30-32] However, these data result from randomized controlled trials that do not necessarily reflect real practice as they use stringent in-and exclusion criteria. So far, few population-based studies have examined the long-term effectiveness of BPH-treatment. [62, 63] A population-based study investigating the long-term effects of BPH treatment would be feasible in the IPCI database. However, one of the main shortcomings when doing retrospective research in the domain of urology is the impossibility to categorize LUTS/BPH as information on symptom severity is often missing. Conducting a pragmatic trial might be the solution, however further experience and research on the feasibility of pragmatic trials is first needed.[64]

Use of α-blockers and 5α-reductase inhibitors has been associated with severe adverse events such as ischemic events in the former and breast cancer in the latter. [65, 66] We aim to explore the safety of these drugs in future research. This research however, will be complex as it will require sufficient follow-up and it will be vulnerable to all kinds of bias and confounding, especially diagnostic bias and confounding by indication. [67, 68] Also in the Netherlands, we might lack the power to study the safety of 5α-reductase inhibitors as the proportion of patients using these drugs decreased over time to only 2% of patients newly diagnosed with LUTS/BPH in 1999. The positive results of the MTOPS trial and the marketing of the newer 5α-reductase inhibitor, dutasteride, might increase the number of patients on 5α-reductase inhibitors which might allow studying rare events. [32, 41]

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Chapter 9

Summary & Samenvatting

Summary

Benign prostatic hyperplasia (BPH) is a common medical condition, especially in ageing men. BPH might become symptomatic resulting in lower urinary tract symptoms generally categorized into voiding or storage symptoms.

The aim of this thesis was to study the epidemiology and the management (in terms of diagnosis and therapeutic options) of symptomatic BPH. In addition we studied the incidence rate and the risk factors for AUR, a common complication in patients with BPH.

Chapter 1 provides a brief overview of BPH and its etiology, diagnosis and treatment. The incidence and prevalence of LUTS/BPH was estimated and is described in chapter 2. Within the IPCI database we defined a retrospective cohort study of all men, 45 years or older during the study period (1995-2000). Cases of LUTS/BPH were defined as persons with a diagnosis of BPH, treatment or surgery for BPH or urinary symptoms that could not be explained by other co-morbidity. In the study cohort, 2181 incident and 5605 prevalent LUTS/BPH cases were identified. This resulted in an overall incidence rate of LUTS/BPH of 15/1000 man-years. The incidence of LUTS/BPH almost linearly increased with age with the lowest incidence (3/1000 man-years) at the age of 45-49 years and the highest at the age of 75-79 years (38/1000 man-years). From the cumulative incidence, we calculated the risk to develop LUTS/BPH for symptom-free men. For a symptom-free man at the age of 46 years, the risk to develop LUTS/BPH over the coming 10, 20 or 30 years was 5, 20 or 45% respectively. The overall prevalence of LUTS/BPH was 10.3% and also increased with age with a maximum at the age of 80 years.

In chapter 3, we describe the diagnostic work-up of patients with LUTS/BPH in terms of use of PSA testing. In a cohort of 1917 men, newly diagnosed by the general practitioner as having LUTS/BPH, PSA testing was performed in 1073 patients (55%). PSA turned out to be abnormal (PSA>4 ng/ml) in 319 patients. We followed the patients with an abnormal PSA who had at least 6 months of follow-up (n=277) and found that follow-up actions (referral to an urologist or repeat PSA testing) were taken in approximately 70% and thus no follow-up action was taken in approximately 30%. Although mandatory according to the Dutch GP guidelines on difficult micturition in men, information on digital rectal examination was only recorded in 63% of all cases. Among the referred patients, the prostate cancer detection rate was highest in patients referred for an abnormal DRE in combination with an elevated PSA (HR_{adj} 9.8; 95% CI 4.5-21).

In chapter 4, the different treatment regimens and compliance issues, such as adherence, persistence and early treatment discontinuation, in patients newly diagnosed with LUTS/BPH were studied. Approximately 50% of all patients were pharmacologically treated, and α-blockers were the most frequent first line treatment, especially in the most recent years. Treatment persistence (37%) and treatment adherence during use (70%) was low and 26% of the treated patients discontinued their treatment early after treatment start. Risk factors for early treatment discontinuation were normal PSA levels, younger age and a lower chronic disease score. Patients with a combination of voiding, post-micturition and storage symptoms had the lowest risk for

treatment discontinuation. During follow-up, 10% of all patients underwent prostate surgery resulting in an overall incidence rate of 62/1000 man-years. The incidence rate of prostate surgery declined over time.

We described the incidence rate of AUR both in the general population of men, 45 years or older, and in the population of men newly diagnosed with LUTS/BPH in chapter 5. The incidence rate of AUR in the general population was quite low namely 2.2/1000 man-years. Of the 344 AUR cases, more than 40% were precipitated by events such as general anesthesia, urinary tract infections and ingestions of drugs knowing to cause AUR. Hundred and forty nine cases of AUR were identified amongst the 2214 patients newly diagnosed with LUTS/BPH. AUR was the first presenting symptom of LUTS/BPH in almost half of these AUR cases. When excluding these cases from the analysis, the incidence rate of AUR in patients with newly diagnosed LUTS/BPH was 18.3/1000 man-years. When all AUR cases were included, the overall incidence rate was much higher (36/1000 man-years). The incidence rate of AUR increased with age, both in the general population and in the population of men, newly diagnosed with LUTS/BPH.

Chapters 6 and 7 describe the results from a case-control study investigating the concomitant use of NSAIDs and antipsychotic drugs, as risk factor for AUR.

Within a population of men, 45 years or older, during the study period from 1st January 1995 until 31st December 2002, 536 definite cases of AUR were identified. To these cases, 5348 random controls were matched on age and calendar time. The risk of AUR was 2 fold higher in current users of NSAIDs relative to no use. The risk was the highest in patients using higher NSAID dosages and in those who recently started using NSAIDs. The association between AUR was even stronger for current use of antipsychotic drugs, which increased the risk 2.6 fold. Here as well, the risk was the highest for patients who recently started using their antipsychotic drugs and in those who used higher dosages.

In the general discussion (chapter 8), the main findings of the studies in this thesis and the methodological aspects are discussed. In addition, the clinical relevance of the findings and the potential for future research are considered.

Samenvatting

Benigne prostaat hyperplasie (BPH) is een aandoening die vaak voorkomt bij de verouderende man. BPH kan zich uiten in mictie klachten, die vaak worden onderverdeeld in klachten van obstructieve of van irritatieve aard.

De bedoeling van het onderzoek in dit proefschrift was om de epidemiologie en het beleid (wat betreft diagnostiek en behandeling) van symptomatische BPH nader te bestuderen. Daarnaast werd ook de incidentie van acute urinaire retentie (AUR), en de mogelijke risicofactoren voor het optreden van AUR nader bestudeerd.

Hoofdstuk 1 geeft een algemeen overzicht van BPH waarbij met name de etiologie, de diagnostiek en de behandeling worden besproken. In hoofdstuk 2 werden de incidentie en de prevalentie van symptomatische BPH bestudeerd. Binnen de IPCI database werd een retrospectief cohort gedefinieerd van alle mannen van 45 jaar of ouder. Binnen dit cohort werd gedurende de studieperiode van 1995-2000, gezocht naar mannen met mictie klachten, suggestief voor BPH. Om aan dit criterium te voldoen dienden mannen gediagnosticeerd en/of behandeld te zijn voor BPH of mictie klachten te hebben, die niet waren toe te schrijven aan andere co-morbiditeit. Binnen het cohort werden 2181 incidente en 5605 prevalente gevallen van symptomatisch BPH geïdentificeerd. Dit resulteerde in een incidentie van symptomatisch BPH van 15/1000 man-jaren. Die incidentie nam bijna lineair toe met de leeftijd. De incidentie was het laagst op de leeftijd van 45-49 jaar (3/1000 man-jaren) en het hoogst op de leeftijd van 75-79 jaar (38/1000 man-jaren). Aan de hand van de cumulatieve incidentie werd het risico op het ontwikkelen van mictie klachten passend bij BPH berekend. Voor een 46-jarige man zonder mictieklachten bedraagt het risico op het ontwikkelen van symptomatisch BPH gedurende de volgende 10, 20 of 30 jaar, respectievelijk 5, 20 en 45%. De prevalentie van symptomatisch BPH bedroeg 10.3% en nam ook toe met de leeftijd tot een maximale prevalentie op de leeftijd van 80 jaar.

In hoofdstuk 3, wordt aandacht besteed aan de diagnostiek van mictieklachten passend bij BPH, met name wat betreft het gebruik van de serumspiegel van prostaat specifiek antigen (PSA). In een cohort van 1917 mannen, door hun huisarts voor de eerste keer gediagnosticeerd met symptomatische BPH, ondergingen 1073 mannen (55%) een PSA analyse in het kader van diagnostiek. PSA was verhoogd (>4 ng/ml) bij 319 mannen. De mannen met een afwijkend PSA en ten minste 6 maanden follow-up (n=277) werden verder gevolgd. Hieruit bleek dat bij 70% maatregelen genomen werden, in de vorm van een verwijzing naar de uroloog of herhaling van de PSA analyse. Bij 30% werden geen verdere maatregelen genomen. Ondanks het feit dat de NHG standaard rond de bemoelijkte mictie bij oudere mannen, stelt dat een rectaal toucher deel uit maakt van het standaard lichamelijk onderzoek, werd informatie rond het rectaal toucher slechts teruggevonden bij 63% van alle mannen. Binnen de verwezen patiënten, was het risico op prostaat kanker het hoogst bij patiënten die verwezen werden omwille van een afwijkend rectaal toucher in combinatie met een verhoogde PSA waarde (Relatieve risico 9.8; 95% betrouwbaarheids interval (BI) 4.5-21).

In hoofdstuk 4 worden de verschillende behandelingen voor symptomatische BPH en aspecten zoals therapietrouw en vroegtijdig stoppen van therapie besproken. Ongeveer 50% van alle patiënten, voor de eerste keer gediagnosticeerd met symptomatische BPH werden gedurende de follow-up farmacotherapeutisch behandeld. Er werden voornamelijk α-blockers voorgeschreven, vooral op het einde van de studieperiode. De continuiteit van de behandeling en de therapietrouw van de gebruikers was laag en 26% van de patiënten stopten vroegtijdig met hun therapie. Risicofactoren voor vroegtijdig stoppen waren normale PSA waarden, een jonge leeftijd en een lage morbiditeitsscore. Het risico op vroegtijdig stoppen was het laagst voor mannen met een combinatie van irritatieve, obstructieve en/of post-mictie klachten. 10% van de mannen ondergingen een prostaat chirurgie gedurende de follow-up resulterend in een incidentie van 62 gevallen van prostaat chirurgie per 1000 man-jaren. De incidentie van prostaatchirurgie nam af over de verschillende kalenderjaren.

De incidentie van AUR, zowel in de totale populatie van mannen, ouder dan 45, als in de populatie van mannen, die voor de eerste keer gediagnosticeerd werden met symptomatische BPH wordt beschreven in hoofdstuk 5. De incidentie van AUR in de totale populatie was laag, namelijk 2.2 gevallen van AUR per 1000 man-jaren. In meer dan 40% van de 344 gevallen van AUR werd de retentie voorafgegaan door mogelijk uitlokkende factoren zoals anesthesie, infecties van de urinewegen en inname van bepaalde geneesmiddelen. Binnen het cohort van 2214 mannen, voor de eerste keer gediagnosticeerd met symptomatisch BPH, traden, gedurende de studie periode, 149 gevallen van AUR op. AUR was de eerste uiting van symptomatische BPH bij ongeveer de helft van de gevallen. Wanneer die patiënten uit de analyse werden gesloten, bedroeg de incidentie van AUR 18 per 1000 man-jaren. Die incidentie was veel hoger, wanneer alle 149 gevallen van AUR in de analyse werden betrokken, namelijk 36 per 1000 man-jaren. In beide cohorten nam de incidentie van AUR toe met de leeftijd.

Hoofdstukken 6 en 7 beschrijven de resultaten van een patiënt-controle onderzoek naar de relatie tussen het gebruik van bepaalde risicoverhogende geneesmiddelen zoals niet steroïdale anti-inflammatoire middelen (NSAIDs) of antipsychotica enerzijds en het optreden van AUR anderzijds. Binnen een populatie van mannen van 45 jaar of ouder, werden 536 gevallen van AUR gediagnosticeerd gedurende de studieperiode 1995-2002. Voor die gevallen van AUR werden, op aselecte wijze, 5348 controles getrokken, gematched op geboortejaar en indexdatum. Het risico op AUR was 2-maal hoger bij gebruikers van niet steroïdale inflammatoire middelen ten opzichte van niet-gebruikers. Het risico was het hoogst bij patiënten die recent met de inname van NSAIDs waren gestart en bij patiënten, die een hogere dosis innamen. De relatie was nog sterker voor gebruikers van antipsychotica, waar het risico op AUR 2.6-maal hoger lag dan bij niet-gebruikers. Ook hier zag men dat het risico het hoogst was bij patiënten die recent met de inname waren gestart of bij patiënten die een hogere dosis van antipsychotica gebruikten.

In de algemene discussie (hoofdstuk 8) worden de belangrijkste resultaten van het onderzoek en de methodologische aspecten besproken. Daarnaast wordt de klinische relevantie bediscussieerd en worden toekomstige potentiële onderzoeksvragen toegelicht.

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List of abbreviations

ASA	Acetyl Salicylic Acid
ATC	Anatomical Therapeutic Chemical classification
ATP	Adenosine Triphosphate
AUR	Acute Urinary Retention
BPH	Benign Prostatic Hyperplasia
CDS	Chronic Disease Score
CI	Confidence Interval
COX	Cyclooxygenase
DCGP	Dutch College of General Practitioners
DDD	Defined Daily Dosage
DRE	Digital Rectal Examination
GP	General Practitioner
GPRD	General Practitioners Research Database
HR	Hazard Ratio
ICPC	International Classification of Primary Care
IPCI	Integrated Primary Care Information
I-PSS-score	International Prostate Symptom Severity score
LUTS	Lower Urinary Tract Symptoms
LUTS/BPH	Lower Urinary Tract Symptoms suggestive of Benign Prostatic Hyperplasia
NO	Nitric Oxide
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	Odds Ratio
PAR	Population Attributable Risk
PG	Prostaglandin
RCT	Randomized Controlled Trial
RR	Relative Risk
SD	Standard Deviation
TURP	Transurethral Resection of the Prostate
UTI	Urinary Tract Infection

Curriculum Vitae

Katia Maria Christina Verhamme was born on September 6th 1965 at Kortrijk (Belgium). She graduated from the "Instituut Maria Middelares" in June 1983. She studied medicine at the University of Ghent, Belgium from 1983-1990.

In 1990 she started her training as general practitioner and graduated in August 1992.

In 1993 she joined Covance, a contract research organization, to work first within the clinical department and from 1997 within de department of drug safety. From October 2001 until September 2003 she worked as researcher at Project Farmaka in Ghent, Belgium.

She started her research project, described in this thesis, at the department of Medical Informatics and the department of Epidemiology & Biostatistics at the Erasmus MC, Rotterdam in October 2000.

In August 2001, she obtained a Master of Science in Clinical Epidemiology at the Netherlands Institute of Health Sciences Rotterdam.

As of September 2003, she works as clinical epidemiologist at the "Onze Lieve Vrouw Ziekenhuis" at Aalst, Belgium.

She is married to Guy Brusselle and they have 3 daughters; Elisabeth (° 1993), Helena (° 1995) and Marie (°1998).