EPIDEMIOLOGIC ASPECTS OF NOCTURIA & NOCTURNAL POLYURIA IN OLDER MEN

A longitudinal analysis in community dwelling older men; the Krimpen study

Boris van Doorn

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EPIDEMIOLOGIC ASPECTS OF NOCTURIA AND NOCTURNAL POLYURIA IN OLDER MEN

A longitudinal analysis in community dwelling older men: the Krimpen study

Epidemiologische aspecten van nycturie en nachtelijke polyuria bij ouder wordende mannen
Een longitudinale analyse van mannen in de algemene populatie: de Krimpenstudie
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 4 september 2014 des middags te 12.45 uur

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Voor mijn familie

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PART I

INTRODUCTION AND STUDY DESIGN

CHAPTER I

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

INTRODUCTION

Nocturia, or waking at night to void, is a common symptom in both men and women (1, 2). It is regarded as one of the most bothersome urinary symptoms which may lead to sleep disturbance (3-6). Although the International Continence Society (ICS) defined nocturia as *waking at night to void one or more times,* only a nocturnal voiding frequency of two or more times seems to generate significant bother and decreased quality of life (7, 8). Furthermore, nocturia is associated with an increase in falls and hip fractures and may even be associated with an increased mortality-rate (9-12).

Traditionally, urologists have considered nocturia as increased urinary frequency at night without paying much attention to urine volume, whereas internists have assumed nocturnal frequency the result of an excessive urine production without focus on other lower urinary tract symptoms (13). Many causes of nocturia have been identified over the years and can be categorized into four main groups: sleep disorders, nocturnal polyuria, 24-h polyuria, and reduced bladder capacity (14). Clearly, nocturia is a symptom, rather than a disease. Regardless of its cause, nocturia appears when the production of urine is greater than the storage capacity of the bladder. Because of the many factors that can contribute to nocturia, the aetiology is not always clear in individual patients.

Nocturnal polyuria (NP) is possibly a frequent cause of nocturia in older people (15). There are several definitions of NP. The one most often used in older men is a definition given by the ICS: a nocturnal urine output (including the first morning void) of >33% of the total 24-hour voided volume in the elderly (8). The definition is based on the arbitrary, and probably incorrect, assumption that "the night/sleeping-time" lasts eight hours in most human subjects. NP might occur as a possible confluence of factors, including disturbance in the endogenous arginine vasopressin (AVP) hormone production, excess production of atrial natriuretic peptide, a daytime third space fluid sequestration with peripheral oedema, and external factors such as medication (e.g.: diuretics) or fluid intake during the night (16).

Since the standardization report by the ICS over a decade ago (8) the interest in nocturia and its causes have been growing (13, 14). This growing interest in nocturia has led to a number of groups that provided consensus statements and concise publications on the current knowledge of nocturia. Mainly, however, these publications emphasized the fact that nocturia is an under-reported, understudied, and underestimated symptom (17, 18).

Previous patient-, population-, and community-based studies on nocturia and NP have provided information on possible causes and consequences of nocturia. However, most of these studies use (validated) questionnaires to determine nocturia instead of frequency-volume charts (19-22). Because it is not possible to measure voided volumes with a questionnaire, nocturnal polyuria could not be estimated. Therefore, the epidemiology of nocturnal polyuria as one of the causes of nocturia has not been studied thoroughly yet. Furthermore, since Hakinnen et al. showed that nocturia symptoms can fluctuate over time, a longitudinal analysis on the causes of nocturia seemed indicated (23).

The Krimpen study was initiated in 1995 to monitor the natural history of lower urinary tract symptoms (LUTS) in the aging male and its burden on the general population of older men. A total of four rounds of data-collection were performed. The three follow-up rounds had a planned follow-up time of 2, 4 and 6 years. Data collection ended in 2004. In addition to the original design, the general practitioner-database was checked again 15 years after baseline (2010) for (possible) date of death. The Krimpen study database contains, alongside extensive data on health status, longitudinal frequency-volume chart (FVC) data. This FVC-data offers insight in the epidemiology and natural history of both FVC-based nocturia and nocturnal polyuria.

OUTLINE OF THE THESIS AND STUDY AIMS

To our knowledge, the Krimpen study is the only longitudinal community-based study that has included FVCs in their data acquirement, giving an unique opportunity to study the changes in FVC parameters and its determinants over time. The aim of this thesis is to describe the natural history of voided volumes, nocturia, and nocturnal polyuria and what factors are associated with changes in these parameters. Furthermore, the relation between nocturia and mortality-risk will be determined.

This thesis exists of six parts:

Part I Introduction and study design
Part II Review of literature and frequency-volume chart dat
Part III Natural history of voided volumes
Part IV Nocturia and nocturnal polyuria, its determinants and mortality risk
Part V General discussion and summary
Part VI Appendices

PART I INTRODUCTION AND STUDY DESIGN

In this part the reasons for the initiation of the study presented in this thesis and the design of the study are explained and discussed **(chapter 2)**.

PART II REVIEW OF LITERATURE AND FREQUENCY-VOLUME CHART DATA

Chapter 3 discusses the literature on nocturia. To emphasize the usefulness of frequency-volume charts in both clinical practice and research settings we explored the properties, indices, and information that can be extracted from them in **chapter 4**.

PART III NATURAL HISTORY OF VOIDED VOLUMES

Because a decreased bladder capacity might be an important cause of nocturia, the natural history of, and the factors associated with, voided volumes were first explored in **chapter 5**.

The following aims are addressed in chapter 5:

1. To determine reference values for voided volumes in older men.
2. To determine how voided volumes develop over time.
3. To explore the determinants of changes in voided volumes over time.

The results of these analyses were used to guide the analyses on nocturia.

PART IV NOCTURIA AND NOCTURNAL POLYURIA, ITS DETERMINANTS AND MORTALITY RISK

Several studies have published data on the prevalence of nocturia. However, only one study has published a longitudinal analysis of nocturia and none have published a longitudinal analysis based on frequency-volume charts. **Chapter 6** describes the prevalence and incidence of nocturia throughout the follow-up rounds.

The following aims are addressed in chapter 6:

4. To determine the prevalence and incidence of nocturia over time.
5. To explore the relationship between questionnaire-, and frequency-volume chart-based nocturia.

Nocturnal polyuria has always been regarded a major contributor to the prevalence of nocturia. Several definitions of nocturnal polyuria have been proposed over the years. In **chapter 7** two definitions of nocturnal polyuria in older men were used to analyse this phenomenon.

The following aims are addressed in chapter 7:

7. To determine the prevalence and incidence of nocturnal polyuria.
8. To explore the relation between nocturnal polyuria and nocturia.

After we determined the natural history of nocturia and the relation with nocturnal polyuria, we wanted to explore the possible (modifiable) risk factors and determinants of nocturia longitudinally. Which are presented in **chapter 8**.

The following aim is addressed in chapter 8:
6. To describe the determinants of nocturia.

After natural history and its determinants were analyzed we wanted to explore the possible negative influence of nocturia on the life expectancy of men. In order to analyze this we determined whether the men were still alive 15 years after baseline. Results are given in **chapter 9.**

The following aim is addressed in chapter 9:
9. To determine the relationship between nocturia and mortality rate

PART V GENERAL DISCUSSION AND SUMMARY

In **chapter 10**, the findings in this thesis are summarized and concluding remarks are made. Finally, in **chapter 11** a summary of this thesis is given in both English and Dutch.

PART VI APPENDICES

List of abbreviations
Publications related to the studies described in this thesis
Acknowledgements (Dutch)
Curriculum vitae

REFERENCES

1. Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol 2010;189(1 Suppl):S86-92.
2. Tikkinen KA, Tammela TL, Huhtala H, Auvinen A. Is nocturia equally common among men and women? A population based study in Finland. J Urol 2006;175(2):596-600.
3. Middelkoop HA, Smilde-van den Doel DA, Neven AK, Kamphuisen HA, Springer CP. Subjective sleep characteristics of 1,485 males and females aged 50-93: effects of sex and age, and factors related to self-evaluated quality of sleep. J Gerontol A Biol Sci Med Sci 1996;51(3):M108-15.
4. Fiske J, Scarpero HM, Xue X, Nitti VW. Degree of bother caused by nocturia in women. Neurourol Urodyn 2004;23(2):130-3.
5. Jolleys JV, Donovan JL, Nanchahal K, Peters TJ, Abrams P. Urinary symptoms in the community: how bothersome are they? Br J Urol 1994;74(5):551-5.
6. Kupelian V, Wei JT, O'Leary MP, Norgaard JP, Rosen RC, McKinlay JB. Nocturia and quality of life: results from the Boston area community health survey. Eur Urol 2012;61(1):78-84.
7. Tikkinen KA, Johnson TM, 2nd, Tammela TL, Sintonen H, Haukka J, Huhtala H, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 2010;57(3):488-96.
8. van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, et al. The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21(2):179-83.
9. Asplund R. Hip fractures, nocturia, and nocturnal polyuria in the elderly. Arch Gerontol Geriatr 2006;43(3):319-26.
10. Bursztyn M, Jacob J, Stessman J. Usefulness of nocturia as a mortality risk factor for coronary heart disease among persons born in 1920 or 1921. Am J Cardiol 2006;98(10):1311-5.
11. Kupelian V, Fitzgerald MP, Kaplan SA, Norgaard JP, Chiu GR, Rosen RC. Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. J Urol 2011;185(2):571-7.
12. Nakagawa H, Niu K, Hozawa A, Ikeda Y, Kaiho Y, Ohmori-Matsuda K, et al. Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. J Urol 2010;184(4):1413-8.
13. Tikkinen KAO. Epidemiology of Nocturia [Academic dissertation]. Tampere: University of Tampere; 2010.
14. Cornu JN, Abrams P, Chapple CR, Dmochowski RR, Lemack GE, Michel MC, et al. A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management--a systematic review and meta-analysis. Eur Urol 2012;62(5):877-90.
15. Weiss JP, van Kerrebroeck PE, Klein BM, Norgaard JP. Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia. J Urol 2011;186(4):1358-63.
16. Gulur DM, Mevcha AM, Drake MJ. Nocturia as a manifestation of systemic disease. BJU Int 2011;107(5):702-13.
17. Van Kerrebroeck P. Nocturia: current status and future perspectives. Curr Opin Obstet Gynecol 2010;23(5):376-85.
18. Weiss JP, Blaivas JG, Bliwise DL, Dmochowski RR, Dubeau CE, Lowe FC, et al. The evaluation and treatment of nocturia: a consensus statement. BJU Int 2011;108(1):6-21.
19. Blanker MH, Bohnen AM, Groeneveld FP, Bernsen RM, Prins A, Ruud Bosch JL. Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol 2000;164(4):1201-5.
20. Fitzgerald MP, Litman HJ, Link CL, McKinlay JB. The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey. J Urol 2007;177(4):1385-9.

21. Markland AD, Vaughan CP, Johnson TM, 2nd, Goode PS, Redden DT, Burgio KL. Prevalence of nocturia in United States men: results from the National Health and Nutrition Examination Survey. J Urol 2011;185(3):998-1002.
22. Tikkinen KA, Auvinen A, Johnson TM, 2nd, Weiss JP, Keranen T, Tiitinen A, et al. A systematic evaluation of factors associated with nocturia--the population-based FINNO study. Am J Epidemiol 2009;170(3):361-8.
23. Hakkinen JT, Hakama M, Shiri R, Auvinen A, Tammela TL, Koskimaki J. Incidence of nocturia in 50 to 80-year-old Finnish men. J Urol 2006;176(6 Pt 1):2541-5; discussion 2545.
24. Bright E, Drake MJ, Abrams P. Urinary diaries: evidence for the development and validation of diary content, format, and duration. Neurourol Urodyn 2011;30(3):348-52.

CHAPTER 2

STUDY DESIGN OF THE KRIMPEN STUDY

INTRODUCTION

In 1995 a longitudinal, community-based study in men aged 50 to 75 years started in *Krimpen aan den IJssel, The Netherlands.* The study was designed to monitor the natural history of lower urinary tract symptoms (LUTS) in the aging male and its burden on the general population of older men.

A total of four rounds of data-collection were performed. The three follow-up rounds had a planned follow-up time of 2, 4 and 6 years. Data collection ended in 2004. Additional to the original design, the general practitioners' (GP)-database was checked again after 15 years (2010) for (possible) date of death.

STUDY POPULATION

Names and addresses of all registered 3.924 men aged 50 to 75 years were obtained (reference date: June 1995) from all primary care physician centers in *Krimpen aan den IJssel*, a commuter town near Rotterdam, The Netherlands with approximately 28,000 inhabitants. All men without radical prostatectomy, prostate- or bladder cancer, neurogenic bladder disease or a negative advice from their GP (in case of a serious disease with a short life-expectancy) and who were able to complete questionnaires and to attend the health centre were found eligible and were invited for participation in the study. In all cases, the GP decided whether the patient/participant could enter the study before invitation. The GP's reasons for excluding any patient/participant were checked by the re-searchers in the electronic medical GP records. Recruitment for the baseline round of the study took place from August 1995 to January 1998.

STUDY DESIGN

All men entering the study provided written informed consent and the Medical Ethics Committee of the Erasmus Medical Centre Rotterdam approved the study (IRB approval number: EUR/AZR-MEC 141.299/1995/12). The baseline study consisted of two phases. In the first phase participants were asked to complete a 113-item questionnaire and to visit the health centre in Krimpen aan den IJssel (where 16 practicing GPs work) for a medical examination. In the second phase of the baseline study, an extensive urological examination was performed at the outpatient urological clinical department of the Erasmus Medical Centre in Rotterdam. Furthermore, during this second phase, before visiting the outpatient clinic, participants were asked to complete a three-day frequency-volume chart. After the baseline round

of the study, three consecutive follow-up rounds were performed after an average follow-up period of 2.1, 4.2, and 6.5 years, respectively. In each of these follow-up rounds all the above-mentioned measurements were repeated, except for the health centre medical examination, which was only performed at baseline. Men who did not respond to the invitation for first or the second follow-up round and did not meet any of the exclusion criteria were also re-invited for participation in the third (and final) follow-up round. A flowchart of the study design and available frequency-volume charts (FVCs) is presented in Figure 4.1.

INFORMATION IN THE 113-ITEM QUESTIONNAIRE

LOWER URINARY TRACT SYMPTOMS

To study the presence of LUTS and related bother, the questionnaire included the International Prostate Symptom Score (I-PSS)(1). And the BPH Impact Index (BII) (2). The I-PSS was used to assess the occurrence and frequency of LUTS, including nocturia. The score range is 0 (no symptoms) to 35 (maximal symptoms). According to the classification of the American Urological Association (AUA), score can be divided into three categories: mild (0-7), moderate (8-19), and severe (20-35). The frequency of nocturia is specified in question number 7: *"During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?"*. Six different answers can be given to this question: 0 (no nocturia), 1 thru 4 (one to four voids per night) and 5 (five or more voids per night)(1). The BII includes questions on the level of bother of LUTS and the impact of LUTS on physical distress, health concerns and interference with daily life activities(2). Sexuality-related questions of the International Continence Society were also included in the questionnaire (ICSsex questionnaire) (3). The ICSsex questionnaire covers four items, each with a bother score ranging from 'no problem' to a 'serious problem' on a four-point scale. In addition the men were asked whether they were sexually active and, if not, how long ago their sexual activities have ceased.

QUALITY OF LIFE AND COPING STYLES

For analyses beyond the scope of this thesis, Quality of life (QOL) and coping styles questionnaires were added. The questionnaire included the mini-Inventory of subjective Health (ISH)(4) and the Sickness Impact Profile (SIP)(5).

At the third follow-up round the generic QOL questionnaire 'EQ-5D'(6) was added to the questionnaire. The EQ-5D has five questions and a visual analogue scale to measure overall QOL. Furthermore, to directly measure the effect of LUTS on the QOL the QOL-question of the I-PSS and the BII were used (1, 2).

For the third follow-up round the questionnaire also included questions on coping styles. To asses coping behavior the Utrecht Coping List (UCL) was used (7, 8). In the UCL, coping behavior is regarded a personal disposition, i.e. a trait. The respondent is asked to imagine his reaction to 'problems in general'. The list consists of seven coping scales, representing different coping styles; a higher score on a certain style represents a higher frequency of use of the style. Two examples of coping styles are: 'active problem solving', and 'avoidance'(7).

AGEING, ERECTILE DYSFUNCTION AND INCONTINENCE

In the third follow-up round the St. Louis University ADAM (androgen deficiency in aging males) questionnaire (9), the International Index of Erectile Function (IIEF) (10), the short form ICS male questions on incontinence (6 items) and a single question on impotence of the Massachusetts Male Aging Study (MMAS) questionnaire were also added to the questionnaire (3). These questionnaires were added as a response to the newly released oral therapeutic options for erectile dysfunction such as sildenafil. The ADAM questionnaire is used as a non-invasive screening tool to detect possible androgen deficiency in aging males and consists of ten items(9). The IIEF is a validated self-administered measure that assesses erectile (dys)function (10).

MEDICAL CONDITIONS AND SOCIO-DEMOGRAPHIC FACTORS

The questionnaire included questions on treatment for chronic diseases (e.g. cardiovascular symptoms, hypertension, diabetes mellitus, and chronic obstructive pulmonary disease), possible history of transurethral surgery of the prostate, family history of prostate cancer, smoking habits, alcohol intake, marital status and level of education.

FREQUENCY-VOLUME CHARTS

In all four rounds, the participants were asked to complete a three-day frequency-volume chart on which each micturition was recorded in one-hour time units. The first day started at midnight, the third day ended at midnight as well. By doing so, two complete nights were incorporated in the three days. During the third and final 24 hours of the FVC, the volume of each void was recorded as well. Bedtime and time of arising were also noted.

Based on the FVC, the following parameters were determined: 24-hour voided volume, average voided volume, maximum voided volume, nocturnal voiding frequency, diurnal voiding frequency, 24-hour voiding frequency, hourly urine production, and the average nocturnal urine production (calculated according to a

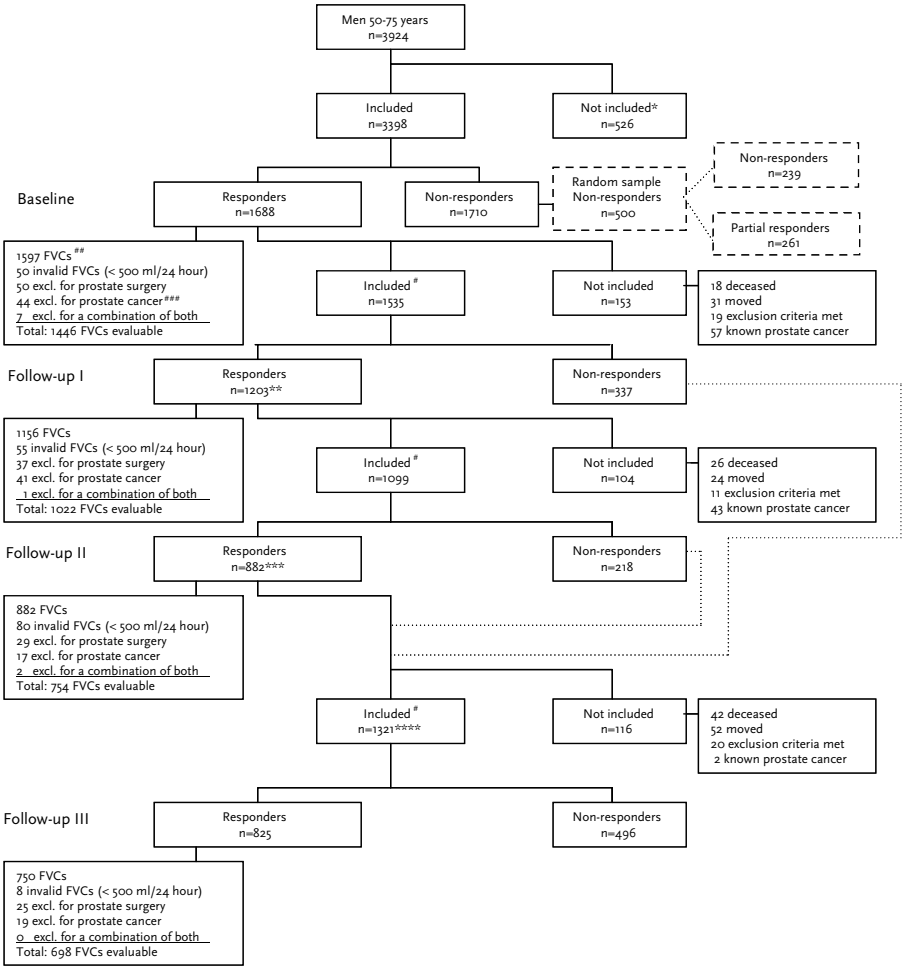

Figure 2.1 Flowchart of the Krimpen study

* Men without radical prostatectomy, prostate or bladder cancer, neurogenic bladder disease or a negative advice from their GP (in case of a serious disease with a short life-expectancy), who were able to complete questionnaires and attend the research center, were invited for the study; # If no prostate cancer was detected, participants had not moved outside the municipality and were alive a re-invitation letter was sent to all responders for follow-up; ** five men did not participate in the baseline study, but entered the study in Follow-up I; *** one man did not respond in Follow-up I, but re-entered the study in Follow-up II; **** Men, who did not respond after baseline, first follow-up or second follow-up and did not meet the exclusion criteria were also re-invited for participation in the third follow-up round (882+ 337+218-116); $ this sample of non-responders was analyzed in a loss to follow-up study (13); ## Frequency Volume chart; ### newly diagnosed prostate carcinomameasurements

method first published by Van Mastrigt and Eijskoot (11). This method is explained in chapter 4. The number of FVCs available in each of the study rounds is shown in Figure 2.1.

HEALTH CENTRE IN KRIMPEN AAN DEN IJSSEL

At the health centre two of our cooperating physicians checked the questionnaires of the participants and completed these with data on currently used medication, using the Anatomical Therapeutical Chemical classification (ATC). Urinalysis was performed using a dipstick, including levels of leucocytes, nitrate, and glucose. Erythrocyte levels were not assessed to avoid unnecessary investigations in men with microscopic hematuria. Finally, systolic and diastolic blood pressure, height and weight were measured.

OUTPATIENT CLINIC OF THE DEPARTMENT OF UROLOGY, ERASMUS MEDICAL CENTRE, ROTTERDAM

Next, appointments were made within four weeks for further urologic measurements at the Erasmus Medical Centre Rotterdam urologic outpatient department. Participants were instructed to complete a FVC and bring it with them at this appointment.

At this visit, the following measurements were done: digital rectal exam (DRE), transrectal ultrasound of the prostate (TRUS), uroflowmetry, post-void residual urine volume, and prostate specific antigen (PSA). Almost all men that visited the health centre also completed this second phase of the study.

On DRE, the volume of the prostate was estimated and the location of possible nodules was noted. The total volume of the prostate and the volume of the transitional zone were measured via TRUS. We used the planimetric procedure to most accurately determine the prostate volume(12). The measurements were performed using the Bruel and Kjaer Medical Falcon Ultrasone Scanner type 2101 equipped with a 7 MHz biplanar endorectal transducer type 8808.

Uroflowmetry was done using a flow meter (Dantec Urodyn 1000, Copenhagen, Denmark). The following parameters were recorded: peak flow rate (Qmax), average flow rate (both noted in ml/s), delay time, total voiding time, total flow time, and the total voided volume. Men were asked to visit the clinic with a full bladder.

The post-void residual volume was measured with a transabdominal ultrasound device (Aloka Model SSD-1700 Dyna View) with a 3.5 MHz electronic convex probe, using the formula $\pi/6$*width*height*depth. The post-void residual was not computed if a man was unable to void in the flow meter.

A blood sample (serum and plasma) was obtained by venapuncture. From this sample the serum PSA level was determined using the Tandem-R method

(Hybritech, San Diego, USA). Three portions of 3 ml each from the blood sample were stored in a freezer.

PROSTATE BIOPSIES

To detect possible prostate carcinoma, a protocol was followed. Prostate biopsies were performed when: (I) PSA levels were above 10 ng/ml at baseline and above 4 ng/ml during follow-up, (II) PSA levels were between 2 and 10 ng/ml at baseline or between 1 and 4 ng/ml at follow-up in case of abnormal findings on DRE or TRUS (i.e. suspect for carcinoma), and (III) when PSA levels were f 1 to 2 ng/ml and DRE was clearly abnormal. No biopsies were taken to confirm the histopathololgic diagnosis of BPH.

ASSEMBLY OF GP DATA

In The Netherlands, virtually all inhabitants are registered at a GP's office (12). When a patient visits an emergency room, a specialist, or another GP outside office hours, his or her GP will always be informed. Data on these visits, contacts and prescription of medication are logged in electronic medical records. In the present study all practicing GPs (n=16) in *Krimpen aan den IJssel* allowed access to the medical records of all participants of the Krimpen study (n=1,688). The files were checked with the "N6" computer program (QSR International Pty. Ltd. Melbourne, Australia). This program can search text files on keyboards and select files base on keywords. Two researchers independently analyzed the files selected by the N6-program and filled in a score form. They both scored whether or not there was a history of LUTS (i.e. before the start of the study) and noted whether the participant had visited his GP for these symptoms and at what date this first took place. The treatment choice was also noted. When a record showed another reason for LUTS-like symptoms (e.g. uncontrolled diabetes mellitus) the visit was not taken into account. When the medical file showed that a person was deregistered from the GP's practice (lost to follow-up) or was deceased, the date of this event was noted. To validate the use of the N6-program the medical files that showed no hits by the N6 (using 82 keywords) were checked manually. This check gave a 100% negative predictive value for the search by the N6-program (no ne of the files reported visits for LUTS). No cases of loss to follow-up occurred during the gathering of GP data during this phase of the study.

Fifteen years after baseline (August 2010), all patient files in the GP database were checked for (possible) date of death. Men who had moved out of the study area were censored and those whose files could not be retrieved were excluded from analysis. If a file could not be found or data were missing, the last known

date from the study database was used as the day of censoring. The exact cause of death for many participants could not be determined because the description from the GP was too general (e.g. cardiac arrest), even though the underlying cause was clearly different. Therefore, cause of death data were not included in any analysis.

REFERENCES

1. Barry MJ, Fowler FJ, Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol 1992;148(5):1549-57; discussion 1564.
2. Barry MJ, Fowler FJ, Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK. Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. Med Care 1995;33(4 Suppl):AS145-55.
3. Frankel SJ, Donovan JL, Peters TI, Abrams P, Dabhoiwala NF, Osawa D, et al. Sexual dysfunction in men with lower urinary tract symptoms. J Clin Epidemiol 1998;51(8):677-85.
4. Joosten J DM. [The reliability and comparability of the three versionsof the ISH] De betrouwbaarheid en vergelijkbaarheid van de drie versies van de VOEG. Gezondheid & Samenleving 1987;51(8):251-265.
5. Jacobs HM, Luttik A, Touw-Otten FW, de Melker RA. [The sickness impact profile; results of an evaluation study of the Dutch version]. Ned Tijdschr Geneeskd 1990;134(40):1950-4.
6. Group T. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.
7. PJG Schreurs GVD Willige JF Brosschot ea. [Utrecht Copinglist: UCL] De Utrechtse copinglijst: UCL. Lisse: Swetz & Zeitlinger; 1993.
8. Schreurs PJG, De Willige GV, Brosschot JF, et, al. [Utrecht Copinglist: UCL] De Utrechtse copinglijst: UCL. Lisse: Swetz & Zeitlinger; 1993.
9. Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, McCready D, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism 2000;49(9):1239-42.
10. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997;49(6):822-30.
11. van Mastrigt R, Eijskoot F. Analysis of voided urine volumes measured using a small electronic pocket balance. Scand J Urol Nephrol 1996;30(4):257-63.
12. Bosch JL, Bohnen AM, Groeneveld FP, Bernsen R. Validity of three calliper-based transrectal ultrasound methods and digital rectal examination in the estimation of prostate volume and its changes with age: the Krimpen study. Prostate 2005;62(4):353-63.

PART II

REVIEW OF LITERATURE AND FREQUENCY-VOLUME CHART DATA

CHAPTER 3

LITERATURE REVIEW OF NOCTURIA AND NOCTURNAL POLYURIA

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INTRODUCTION AND DEFINITIONS

The International Continence Society (ICS) defined nocturia as '*the complaint that the individual has to wake at night one or more times to void'*[1]. Each void must be preceded and followed by sleep. This definition does not include waking for other reasons at night (e.g. noise) followed by voiding for convenience, which is proposed to be termed 'night-time frequency' [2]. Therefore, the current definition of nocturia is very strict and based on the number of voids rather than patient complaints and is, therefore, still subject to debate [2, 3].

The ICS standardization report also defines nocturnal polyuria (NP) and 24-hour (or global) polyuria. Since these two types of polyuria are associated with nocturia in a significant number of cases, it is appropriate to repeat these definitions here as well: 24-hour polyuria is defined as a urine output exceeding 40 ml kg bodyweight per 24 hour; NP is defined as a nocturnal urine output (including the first morning void) of >33% of the total 24-hour voided volume in the elderly [4].

Despite the strict ICS definition of nocturia, only *two or more* nocturnal voids seem to negatively affect quality of life (QoL) [5]. Although this is mainly attributed to sleep fragmentation and a decline in sleep quality [6, 7], another serious problem seems to be an increased risk of falls and (hip) fractures [8, 9], (co-)morbidity and, some even postulate, an increased mortality rate [6, 10-12]. However, the latter association seems mainly to apply to adults aged 65 years and under [12].

PREVALENCE AND INCIDENCE

The prevalence of nocturia in older men is high and increases with age: a review on this subject showed that of men in their 70s and 80s, 68.9% to 93%, respectively, reported at least 1 void per night, and 29% to 59.3% reported at least 2 voids per night [13]. This high prevalence rate is seen in populations of various ethnicity and nationality throughout the world [14-22].

Multiple ways of assessing nocturia have been used to determine the prevalence of nocturia in the general population: questionnaires, such as the international prostate symptom score (IPSS), and the Danish Prostate Symptom Score (DAN-PSS-1), as well as frequency-volume charts (FVCs) [23, 24]. Although no evidence-based consensus is available, a 3-day FVC seems to be preferable to questionnaires in terms of patient compliance and because it tends to avoid recall bias [15, 25]. It has also been shown that a large proportion of patients tend to overestimate or underestimate their nocturia on questionnaires [26, 27]. Furthermore, different definitions of (clinically relevant) nocturia have been used. This may explain the variability in prevalence rates among different studies.

Hakkinen et al. were the first to report on incidence rates of nocturia; however, they also showed that nocturia, just like all lower urinary tract symptoms (LUTS), is a fluctuating symptom [17]. Fluctuating symptoms are those present at a certain point in time but which seem to be resolved at the next point. Therefore, prevalence estimates seem to be more relevant than incidence rates when aiming to gain insight in the epidemiology of nocturia [17, 28].

CLINICAL PRESENTATION, BOTHER AND IMPACT OF NOCTURIA

Bladder storage symptoms (like nocturia) are more bothersome than voiding symptoms such as incomplete emptying [29]. Furthermore, nocturia is associated with a significant decline in health-related QoL (HRQoL) as measured on the 15D HRQol questionnaire. This questionnaire measures the QoL in various aspects (dimensions) of daily life. The decline was seen in almost all of the 15 dimensions measured, including: sleeping, sexual activity, comfort, mental function and vitality, as well as increased depression [5]. Kupelian et al. reported similar results on QoL and presence of depressive symptoms [30]. Nocturia is also reported to decrease the disease-specific QoL in prostate cancer patients [31].The degree of bother seems to be related to sleep quality, as it would interfere with slow-wave (deep) sleep [6, 7, 32]. However, a study by Bal et al. in patients with benign prostatic obstruction, showed that most nocturia episodes occurred during the superficial and rapid eye movement (REM) part of sleep and therefore had no significant impact on sleep quality [33]. Nevertheless, in patients with stable heart failure and with a nocturnal voiding frequency of three or more, a decrease in REM stage sleep and stage 3 and 4 (deep sleep) was found which would indicate a decrease in sleep quality [34].

Despite the significance of these complaints, not many men seek help from a healthcare professional for an isolated complaint of nocturia. In an analysis of the Krimpen study, only 9.5% of the population sought help for LUTS, whereas the prevalence of nocturia was 34.6% [35]. Furthermore, a recent study from Singapore showed that of men with moderate to severe LUTS less than 30% seeks medical attention for these complaints [36]. Thus, there seems to be a discrepancy between the presumed negative impact on QoL and actual healthcare-seeking behaviour in older men with nocturia; possibly an isolated symptom of nocturia is less bothersome than nocturia as a part of a symptom complex.

PHYSIOLOGY OF DIURESIS

Diuresis, or the production of urine, is a vital part of homeostasis in the human body. Many issues in medicine arise because of abnormalities in the systems that control the volume and composition of body fluids. The production of urine plays a pivotal role in this balance [37, 38].

Fluid enters our body in two ways: the first is by drinking and eating, the second is water synthesized by the body as a result of oxidation of carbohydrates. Fluid leaves the body via various ways, but the major contributors to water loss are the kidneys. They are the body's most important means by which it controls the balance between water intake and output. Furthermore, the kidneys control the balance of most electrolytes [37].

A kidney contains approximately one million nephrons. Nephrons are the smallest functional unit in a kidney capable of forming urine. Each nephron contains a small cluster of capillaries called the glomerulus, which is encapsulated by Bowman's capsule. Fluid filtered in the glomerulus flows into Bowman's capsule and then into the proximal part of the tubule. From the proximal tube the fluid flows into the loop of Henle. After this loop, the fluid flows by a 'plaque' on the wall of the tubule, called the macula densa. This is followed by the distal tubule, a connecting collecting tubule, and the cortical collecting tubule, respectively (Figure 3.1). Next, the several cortical collecting tubules conjoin into a larger collecting duct which turns into a medullary collecting duct which merges into progressively larger ducts. Eventually, these ducts empty into the renal pelvis.

The production of urine starts with a large amount of fluid filtered from the blood and transported into Bowman's capsule. Almost all substances available in plasma are freely filtered, thus the concentration of the filtrate is like that of plasma. As this fluid passes through the tubule, its composition is modified by reabsorption and secretion. Each of the processes (glomerular filtration, tubular reabsorption, and tubular secretion) is regulated according to the needs of the body. Compared to urine production, the rates of filtration and reabsorption are extremely large: per minute, about 1100 ml of plasma is filtered by the kidneys, whilst they only produce about 1400 ml of urine per 24 hours under normal circumstances [37].

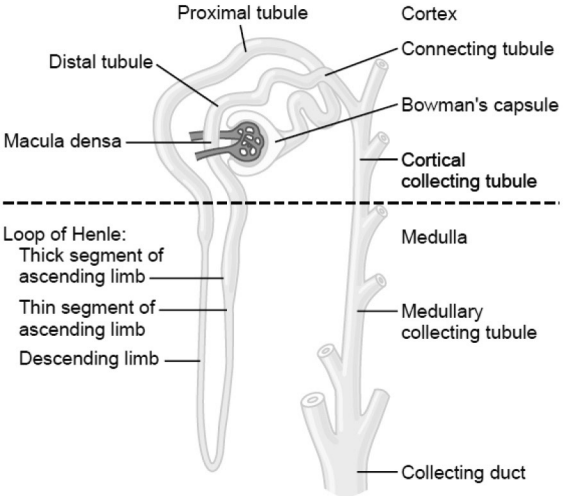

Figure 3.1 A schematic overview of a nephron. Reproduced from [38.]

Many factors affect the filtration, reabsorption and secretion in the nephrons. The glomerular filtration rate (GFR) s influenced by (amongst others) renal blood flow, arterial pressure, serum levels of angiotensin II, sympathetic activity, and vasoconstrictor hormones (e.g. norepinephrine). Reabsorption is the product of both passive mechanisms such as osmosis and diffusion, and active transcellular transport. Water reabsorption by osmosis is mostly passive due to sodium reabsorption. The water reabsorption moves through the tight junctions in between the luminal cells of the tubules. In the more distal parts of the nephron, starting in the loop of Henle, the tight junctions become less permeable to water and solutes. Therefore, water cannot move as easily by osmosis. Antidiuretic hormone (ADH) significantly increases the permeability of the tubules for water (see below). Furthermore, reabsorption is regulated by factors like the GFR, peritubular capillary flow, interstitial hydrostatic and colloid pressures. The regulation of reabsorption is also largely determined by hormones. Aldosterone, angiotensin II, ADH, atrial natriuretic peptide, and parathyroid hormone are some of the most important hormones in these processes.

It is beyond the scope of this thesis to describe all of these hormones in detail, but ADH seems to play a central role in the etiology of nocturia [39, 40]. The paramount action of ADH, which is released by the pituitary gland in the brain, in the kidney is to increase the water permeability of the distal tubules, collecting tubules, and collecting duct epithelia. This effect helps the body to conserve water when the circumstances demand this. ADH binds to specific V_2 receptors, increasing the formation of cyclic AMP and activating protein kinases. This, in turn, stimulates

the movement of an intracellular protein called aquaporin-2 (AQP-2) to the luminal side of the cell membranes. The molecules of AQP-2 cluster and fuse with the cell membrane to form water channels that permit rapid diffusion of water through cells. When the concentration of ADH decreases, the AQP-2 molecules are moving back to the cell cytoplasm, removing the water channels from the membrane and reducing the water permeability to its original level [40]. Furthermore, there seems to be a physiological circadian rhythm of ADH secretion. Specifically, the secretion is higher at night [14, 41]. This circadian rhythm seems to be blunted in men under 65 years of age [14].

PHYSIOLOGY OF MICTURITION

After urine leaves the kidney it flows down the ureters into the urinary bladder. The bladder has two main functions: storage and periodic elimination of urine [37, 38, 42]. Coordinated activities of the peripheral nervous system innervating the bladder and urethra during storage and voiding depend on multiple pathways organized in the brain and spinal cord.

STORAGE PHASE

When the urinary bladder is empty, the intravesical pressure is about nil. The pressure remains relatively constant when bladder volume is below the threshold for inducing voiding [37, 42]. The accommodation of the bladder to increasing volumes of urine is primarily a passive phenomenon dependent on the intrinsic properties of the vesical smooth muscle tissue and quiescence of the parasympathetic efferent pathway. The bladder-to-sympathetic reflex also contributes as a negative feedback or urine storage mechanism that promotes closure of the urethral outlet and inhibits neurally mediated contractions of the bladder during bladder filling.

Reflex activation of the sympathetic outflow to the lower urinary tract can be triggered by afferent activity induced by distention of the bladder. This can be seen on an electromyogram [42]: during bladder filling the activity of the sphincter electromyogram also increases, reflecting an increase in outlet resistance that contributes to the maintenance of urinary continence.

Under physiological circumstances, an electromyogram will show a gradual increase in activity, but no apparent changes in bladder pressure. When a voluntary void starts, an increase of bladder pressure is associated with synergic sphincter relaxation. Loss of the reciprocal relationship between bladder and sphincter (detrusor-sphincter dyssynergia) interferes with bladder emptying.

EMPTYING PHASE

The storage phase can be switched to the voiding phase either involuntarily (reflexly) or voluntarily. The former is readily demonstrated in young infants and in patients with a neurogenic bladder, for example, due to spinal cord trauma. When bladder volumes reach the micturition threshold, afferent activity originating in the bladder mechano (stretch) receptors triggers micturition reflexes. These bladder afferents in the pelvic nerve synapse on neurons in the sacral spinal cord, which then send their axons rostrally to the pontine miction centre (PMC) via the periaquaductal gray (PAG). Activation of the PMC reverses the pattern of efferent outflow of signals to the lower urinary tract, producing firing in the sacral parasympathetic pathways and inhibition of sympathetic and somatic pathways. The activation of the PMC, in turn, is controlled by the diencephalon and cortex that determine whether or not a void is desirable [42].

The expulsion phase consists of an initial relaxation of the urethral sphincter followed (in a few seconds) by a contraction of the bladder, resulting in the flow of urine through the urethra. Thus, voiding depends on a spinobulbospinal pathway, that passes through an integrative center in the brain. Secondary reflexes elicited by flow of urine through the urethra help to continue the facilitation of bladder emptying until the flow of urine stops.

Figure 3.2 presents a schematic overview of the neurological pathways of both the storage and emptying phase.

It is possible that some causes of nocturia are nestled within this long and complicated cascade of neurological events.

PATHOPHYSIOLOGY OF NOCTURIA

Nocturia is a condition of diverse etiology. However, the causes can generally be categorized into: 1) bladder storage problems: decreased (nocturnal) functional bladder capacity either caused by benign prostatic hyperplasia (BPH) with detrusor overactivity, decreased compliance, and/or post-void residual volume or by an isolated overactive bladder (OAB) syndrome, 2) nocturnal polyuria (NP), 3) 24-hour polyuria, and 4) sleep disturbance, or a combination of these factors [39]. Not all problems are equally common: in a population-based study by Tikkinen et al., the most common causes of nocturia were: urinary urgency, BPH, and snoring as a proxy of obstructive sleep apnea syndrome (OSAS). Other causes were obesity and the use of anti-depressants [43]. Obesity is a common co-morbidity throughout all western countries and is related to LUTS. Asplund et al. found that the number of

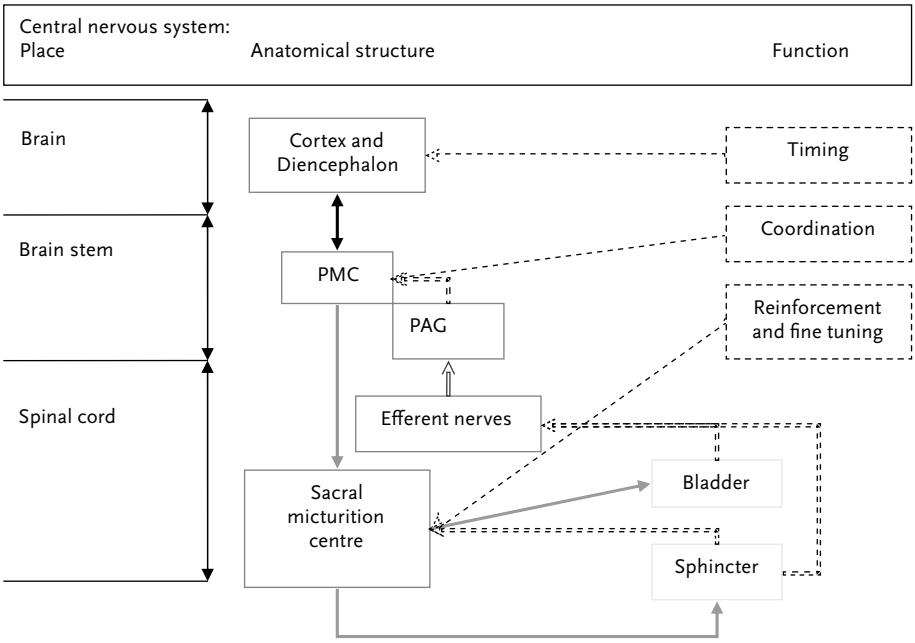

Figure 3.2 A schematic overview of the storage and voiding phase neurologic pathways.
Grey boxes: spinal cord, brain stem and brain
Light grey boxes: lower urinary tract
Dotted boxes: higher cognitive influences on the bladder reflexes
Double dotted arrows: afferent pathways
Grey arrows: efferent pathways
Black arrow: both efferent and afferent pathway
PMC: pontine miction center
PAG: periaquaductal gray

nocturia events increases with a rise in body mass index (BMI) [44]. Diabetes mellitus (also a common condition in the western world) was associated with nocturia, after correction for confounders like age, cardiac disease and BMI [45]. Another study showed that loop diuretics in combination with other antihypertensive medication such as beta-blockers also increase the prevalence of nocturia in men with hypertension [46]. Furthermore, a vitamin D deficiency has been associated to nocturia [47].

OVERACTIVE BLADDER

The ICS defines overactive bladder (OAB) as a symptom defined condition characterized by urinary urgency, with or without urinary incontinence, usually with increased daytime frequency and nocturia [4]. The association between nocturia and OAB is not well understood, but in the population-based FINNO study 17% of

all men aged >60 years reported urgency, and 31% of men with nocturia reported urgency [28]. A recent study from China reported similar results and found that nocturia was the most prevalent symptom in men with OAB [48].

NOCTURNAL POLYURIA

NP is another important cause of nocturia. An Austrian study in nocturia patients showed that 50% of all men had NP [49]. A study by Weiss et al. showed an even slightly higher prevalence rate of 57% [50]. NP was defined as a nocturnal voided volume of >33% of the total 24-hour voided volume. However, Blanker et al. suggested a nocturnal urine production of >90 ml/hour as a more appropriate (albeit only modest) predictor of nocturia in older men [26]. In this respect a clear difference is made between the ICS definition, which includes a night to 24-hour ratio in urine production, and the definition by Blanker et al. (originating from the Krimpen Study), in which only nocturnal urine production is used for defining NP.

Two important causes of NP are identified: incorrect arginine vasopressin levels which might be present in up to 4% of the elderly [51], and the re-absorption of third space lower extremity fluid during sleep [52].

In a study on 72 women with overactive bladder syndrome, who showed no abnormalities on their filling cystometry van Venrooij et al. showed more detrusor overactivity when diuresis was stimulated with a diuretic [53]. Although not formally investigated, this might indicate that an increased diuresis, which is found in nocturnal polyuria, could cause or worsen detrusor overactivity which, in turn, could lead to urgency and therefore nocturia.

24-HOUR POLYURIA

24-hour polyuria is most commonly caused by diabetes mellitus and diabetes insipidus. Polydipsia can exist concurrently with polyuria to prevent circulatory collapse [54]. Another cause is primary (behavioral) polydipsia. An overnight water deprivation test can distinguish between diabetes insipidus and primary polydipsia.

SLEEP DISTURBANCE

In the FINNO study, sleep disruption (defined by snoring, as an indicator for OSAS: Obstructive Sleep Apnea Syndrome) was an important cause of nocturia [43]. However, there are some limitations to this conclusion: there are no validated nocturia instruments that determine why the patient woke up, why he voided (e.g. convenience, habit or urge), and whether the patient went back to sleep [55]. A polysomnographic study suggests that nocturia may indeed not be the major cause of sleep disruption but that OSAS negatively interferes with sleep efficacy, total and rapid eye movement (REM) sleep duration [56]. Another study, however, pointed out that nocturia was the most prevalent symptom in patients with OSAS (38%) and

showed a significant decline in the prevalence of nocturia after six months of treatment [57].

CO-MORBIDITY AND MORTALITY

Nocturia is an independent risk factor for lowered sleep quality which, in turn, might be associated with an increased mortality, hypertension, obesity and glucose intolerance [58, 59]. It has also been associated with an increase in fall-related fractures [8, 11, 60] and incident cardiac disease in men under 65 years of age [61]. Nocturia in itself also seems to be associated with an increased mortality risk in some studies. Five questionnaire-based studies have been reported which showed a significantly higher mortality rate [increased hazard ratio (HR) in subjects with nocturia] [10-12, 61, 62]. All studies corrected for age in their multivariable analysis, except the study of Bursztyn et al. in which only 70-year-olds were included; they described an increased HR for nocturia only in men and women who also suffered from congestive heart disease. The largest study, by Kupelian et al., showed that the relation in older men was attenuated, but still significant [12].

MANAGEMENT OF NOCTURIA

DIAGNOSTIC EVALUATION

Nocturia has been identified as the most bothersome and prevalent LUTS. Therefore, it is surprising that in clinical practice men do not often present with an isolated complaint of nocturia. Therefore, clinicians should be alert for the possibility of the existence of nocturia in their patients with LUTS. Initial assessment should involve a thorough history to clarify the patient's complaints, possible underlying diseases, such as cardiovascular disease, and fluid intake (including alcoholic beverages and drinks containing caffeine).

Questionnaires such as the 15D HRQoL instrument are useful when quantifying the effect of nocturia on daily bother [63]. Urinalysis, urine culture and, when suspicion of urothelial cell carcinoma is present, cytology should also be carried out [55]. Next, and most importantly, a 3-day FVC should be completed on which the patient records the volume and timing of each void during the day and night [15, 25]. The use of a FVC is preferable to the use of questionnaires (like the IPSS) because of discrepancies in recorded nocturnal voiding frequencies between the two [14]. The patterns revealed by the FVC provide valuable information on the etiology and may suggest treatment options.

TREATMENT OPTIONS

A successful treatment of nocturia should result in a clinical (and not just statistically significant) reduction in nocturnal voiding frequency. Furthermore, therapy should have a positive effect on bother, quality of life and, possibly, on the sleep pattern. Unfortunately, there is only limited evidence of the efficacy of available options [55].

Behavioral treatment

The initial response of most patients to nocturia is to apply some lifestyle changes such as pre-emptive voiding (before going to sleep), nocturnal dehydration and the avoidance of caffeinated beverages and alcohol intake [55]. Recently, a research group from Seoul (South Korea) published the first, short-term results of their prospective study concerning behavioral therapy in nocturia patients, which consisted of watching videos about normal physiology of storage and emptying function of the bladder, regulation of fluid intake, explanation by giving specific examples, and discussion with a specialized nurse practitioner. After four months, patients had a significant decrease (from 2.6 to 1.1) in nocturnal voids and a significant increase in quality of life [64]. Another study in patients with OAB also showed a decrease in nocturia with behavioral therapy [65]. Although these are the first studies on this subject, for a physician the recommendations seem intuitively correct for patients with nocturia.

Pharmacotherapy

Alpha-blockers & 5-alpha reductase inhibitors, alone or in combination

Data from the Veterans' Administration Cooperative Study Program trial in men aged 45-80 years with BPH was secondarily analyzed, and showed a significantly greater improvement in nocturia frequency for the terazosin arm compared to the finasteride, combination (finasteride + terazosin) and placebo arm. Men who started on terazosin improved from 2.5 to 1.8 nocturnal voids, while finasteride + terazosin resulted in a reduction from 2.5 to 2.0 nocturnal voids. The placebo arm showed a reduction from 2.4 to 2.1 voids per night. Although the improvement with terazosin was significant compared to placebo, it only improved the nocturnal voiding frequency (NVF) by 0.4 over placebo [66]. Yoshimura et al. showed a clinical improvement of NVF (<2 after treatment) in only 13.9% of patients treated with tamsulosin [67].

In an analysis of the Medical Therapy of Prostatic Symptoms trial (MTOPS) nocturia frequency improved significantly compared to placebo after using the combination of finasteride and doxazosin and doxazosin alone for one year. However,

finasteride + doxazosin and doxazosin resulted in clinically negligible improvements in mean nocturia frequency of 0.58 and 0.54, respectively, in comparison to placebo [68].

An analysis of the COMBAT study, a randomized, double-blind, parallel-group study designed to investigate the benefits of combination therapy in men aged >50 years with LUTS, showed that after 4 years of treatment the mean reductions in the question 7 score of the IPSS (nocturia question) were significantly ($p<0.008$) greater with combined therapy than with dutasteride or tamsulosin alone [69]. Unfortunately, the actual change in nocturia frequency was not reported. However, the total IPSS change after 4 years was 1.4, 1.9 and 2.3 points for the tamsulosin, the dutasteride and the combination group, respectively; this implies that the nocturia frequency change in the combination group was less than 0.4 and 0.9 lower than in the tamsulosin and the dutasteride group, respectively. Clinically this is not very relevant.

In summary, *5-alpha reductase inhibitors*, either alone or in combination with an alpha-blocker, or an alpha-blocker alone seem to have a minimal to negligible effect on the nocturnal voiding frequency (NVF) in men with BPH. Moreover, it must be emphasized that none of the above-mentioned studies was designed with nocturia as a primary outcome measure. Therefore, it is possible that all significant results are type II errors.

Anti-muscarinics, alone or as add-on to alpha-blocker treatment

Zinner et al. found in 389 (74.4%) female and 134 (25.6%) male patients with OAB symptoms, that after 12 weeks of treatment with trospium chloride, the average NVF decreased by 0.47 vs. 0.29 in the placebo group [70].

In a study population of 836 (of which 201 men) fesoterodine resulted in a statistically significant improvement in NVF, by -0.59 for 4 mg daily vs. -0.39 for the placebo group [71]. A head-to-head comparison between fesoterodine and tolterodine showed no significant improvement of NVF for either medication vs. placebo [72].

Several studies in men have reported the effect of an anti-muscarinic drug used as an add-on after an unsatisfactory response to an alpha-blocker alone. Tolterodine-ER 4 mg was added to an (unspecified) alpha-blocker and compared to placebo added to the alpha-blocker: there were no significant differences in change in nocturnal micturitions or nocturnal urgency episodes [73].

The ASSIST study group reported that among three treatment arms (tamsulosin 0.4 mg + placebo vs tamsulosin 0.4 mg + solifenacin 2.5 mg vs tamsulosin 0.4 mg + solifenacin 5 mg) there were no significant differences in change in bladder diary-recorded nocturia episodes per 24 hours, or in the night-time frequency score [74]. A study by Kojima et al. concluded that tamsulosin significantly reduced the nocturnal urine production; however, these results seem clinically irrelevant as

they only show a difference of 20 ml and did not influence the nocturnal voiding frequency [75]. Furthermore, they compare a NP with a non-NP group so that their result is not surprising. In summary, also anti-muscarinics either alone or as an add-on to alpha-blocker treatment seem to have a minimal to negligible effect on NVF in men with BPH.

Timed diuretic therapy

Diuretics are often prescribed for peripheral edema but without considering the time of day at which they would be most effective [55]. In patients with NP due to re-absorption of third-space lower extremity fluid at night, mis-timing could even lead to an exacerbation of NP. Therefore, it has been recommended (anecdotally) to administer diuretics during the mid-to-late afternoon, when diuresis before going to bed is the goal. Unfortunately, no studies have examined the effectiveness of this strategy.

Anti-diuretic therapy

Anti-diuretic therapy may be appropriate in patients whose nocturia is caused by NP, but who do not have a high nightly fluid intake, and in whom other causes of NP have been excluded. In some countries, anti-diuretic therapy with the synthetic analog of arginine vasopressin, desmopressin, is the only pharmacological therapy which is indicated specifically for nocturia [55]. Because of the evidence base of its specific anti-diuretic action, desmopressin has a level of evidence 2, grade A recommendation from the International Consultation on new developments in prostate cancer and prostate diseases for the treatment of nocturia [76]. However, although several randomized placebo-controlled trials showed a significant improvement compared to placebo [72, 73], patients still had a rounded average NVF of 2 or more. Therefore, the clinical significance seems limited.

An important adverse event found in both studies was hyponatremia. The primary predictor for hyponatremia is age and being female; therefore, desmopressin use is currently not indicated in patients aged > 65 years. However, recent studies have shown that a lower dose of desmopressin is more effective in women and might give rise to less adverse events [77, 78]. Serum sodium monitoring at baseline and early in treatment in older patients can greatly reduce the risk of developing hyponatremia.

Anti-inflammatory drugs

Two studies have shown a favorable effect of non-steroidal anti-inflammatory drugs on the nocturnal voiding frequency in patients with nocturia [79, 80]. Falahatkar et al. showed a decrease from 5.2 to 2.5 voids per night in the celecoxib group vs. 5.3 to 5.1 voids in the placebo group. Addla et al. also showed a significant

decrease of 0.3 voids per night for patient receiving diclofenac. Although both studies showed significant results, the clinical relevance remains unclear: both studies were performed in small groups of patients (both n<100). Furthermore, a more recent post-hoc analysis in a cohort study performed by Sutcliffe et al. showed no favorable effects of anti-inflammatory drugs on nocturia [81]. In conclusion: the evidence in support of their use in clinical practice for nocturia management remains weak [39].

Melatonin

One study compared melatonin to placebo for the treatment of nocturia in men with bladder outlet obstruction [82]. The nocturnal voiding frequency in patients using melatonin changed from 3.1 to 2.8 vs. 3.1 to 3.0 (p=0.07) in the placebo group. These results do not support the use of melatonin in the treatment of nocturia.

Alternative pharmacotherapy

A technique patients often initially try is the use of herbal supplements. In the USA, 50% to 90% of men have tried supplements before seeking medical treatment for their LUTS/BPH [83]. The most frequently used supplement for complaints of nocturia is *Serenoa Repens*, a saw palmetto berry extract. However, a placebo-controlled trial showed no improvement in LUTS measured by the AUA-SS [84]. This was confirmed in the recently updated Cochrane systematic review [85]. Therefore, it seems that natural supplements are not helpful in the treatment of nocturia.

Surgical options

Procedures such as transurethral resection of the prostate (TURP) are offered to patients with BPH [55]. However, nocturia is the least responsive symptom to treatment of BPH, both medically and surgically [86]. In a study by Yoshimura et al. a prevalence reduction of only 19.6% in nocturia was found after TURP [67]. However, in a pilot study in men who underwent robot-assisted laparoscopic prostatectomy, those with severe nocturia had a significant improvement in their complaints. On the other hand, men with only minimal bother from nocturia had a worsening of their complaints after this procedure [87]. BPH patients should be counselled on the effects of TURP on nocturia: specifically, a reduction should not be expected when nocturnal polyuria is a part of the problem.

REFERENCES

1. van Kerrebroeck, P., et al., *The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society.* Neurourol Urodyn, 2002. **21**(2): p. 179-83.
2. Homma, Y., *Lower urinary tract symptomatology: Its definition and confusion.* Int J Urol, 2008. **15**(1): p. 35-43.
3. Abrams, P., et al., *Reviewing the ICS 2002 terminology report: the ongoing debate.* Neurourol Urodyn, 2009. **28**(4): p. 287.
4. Abrams, P., et al., *The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society.* Neurourol Urodyn, 2002. **21**(2): p. 167-78.
5. Tikkinen, K.A., et al., *Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland.* Eur Urol, 2010. **57**(3): p. 488-96.
6. Asplund, R., *Nocturia in relation to sleep, health, and medical treatment in the elderly.* BJU Int, 2005. **96 Suppl 1**: p. 15-21.
7. Marschall-Kehrel, D., *Update on nocturia: the best of rest is sleep.* Urology, 2004. **64**(6 Suppl 1): p. 21-4.
8. Asplund, R., *Hip fractures, nocturia, and nocturnal polyuria in the elderly.* Arch Gerontol Geriatr, 2006. **43**(3): p. 319-26.
9. Temml, C., et al., *The natural history of lower urinary tract symptoms over five years.* Eur Urol, 2003. **43**(4): p. 374-80.
10. Bursztyn, M., J. Jacob, and J. Stessman, *Usefulness of nocturia as a mortality risk factor for coronary heart disease among persons born in 1920 or 1921.* Am J Cardiol, 2006. **98**(10): p. 1311-5.
11. Nakagawa, H., et al., *Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study.* J Urol, 2010. **184**(4): p. 1413-8.
12. Kupelian, V., et al., *Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey.* J Urol, 2011. **185**(2): p. 571-7.
13. Bosch, J.L. and J.P. Weiss, *The prevalence and causes of nocturia.* J Urol, 2010. **184**(2): p. 440-6.
14. Blanker, M.H., et al., *Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men.* J Urol, 2000. **164**(4): p. 1201-5.
15. Bright, E., M.J. Drake, and P. Abrams, *Urinary diaries: evidence for the development and validation of diary content, format, and duration.* Neurourol Urodyn, 2011. **30**(3): p. 348-52.
16. Chute, C.G., et al., *The prevalence of prostatism: a population-based survey of urinary symptoms.* J Urol, 1993. **150**(1): p. 85-9.
17. Hakkinen, J.T., et al., *Incidence of nocturia in 50 to 80-year-old Finnish men.* J Urol, 2006. **176**(6 Pt 1): p. 2541-5; discussion 2545.
18. Lee, Y.J., et al., *Prevalence and correlates of nocturia in community-dwelling older men: results from the korean longitudinal study on health and aging.* Korean J Urol, 2012. **53**(4): p. 263-7.
19. Kupelian, V., et al., *Are racial /ethnic disparities in the prevalence of nocturia due to socioeconomic status? Results of the BACH survey.* J Urol, 2009. **181**(4): p. 1756-63.
20. Liew, L.C., et al., *A population study of nocturia in Singapore.* BJU Int, 2006. **97**(1): p. 109-12.
21. van Dijk, L., Kooij, D.G., and Schellevis, F.G., *Nocturia in the Dutch adult population.* BJU Int, 2002. **90**(7): p. 644-8.
22. Lee, Y.S., et al., *Prevalence of overactive bladder, urinary continence, and lower urinary tract symptoms: results of the Korean EPIC study.* World J Urol, 2011. **29**(2): p. 185-90.
23. Barry, M.J., et al., *The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association.* J Urol, 1992. **148**(5): p. 1549-57; discussion 1564.

24. Meyhoff, H.H., et al., *A new patient weighted symptom score system (DAN-PSS-1). Clinical assessment of indications and outcomes of transurethral prostatectomy for uncomplicated benign prostatic hyperplasia.* Scand J Urol Nephrol, 1993. **27**(4): p. 493-9.
25. Yap, T.L., Crommwell, D.C., and Emberton, M., *A systemetic revies of the reliability of frequency-volume charts in urological research and its implications for the optimum chart duration.* BJU Int, 2007. **99**(1): p. 9-16.
26. Blanker, M.H., et al., *Relation between nocturnal voiding frequency and nocturnal urine production in older men :a population-based study.* Urology, 2002. **60**(4): p. 612-6.
27. van Haarst, E.P., J.L. Bosch, and E.A. Heldeweg, *The international prostate symptom score overestimates nocturia assessed by frequency-volume charts.* J Urol, 2012. **188**(1): p. 211-5.
28. Tikkinen, K.A.O., *Epidemiology of Nocturia*, in *Medicine*. 2010, University of Tampere: Tampere. p. 165.
29. Eckhardt, M.D., et al., *Prevalence and bothersomeness of lower urinary tract symptoms in benign prostatic hyperplasia and their impact on well-being.* J Urol, 2001. **166**(2): p. 563-8.
30. Kupelian, V., et al., *Nocturia and quality of life: results from the Boston area community health survey.* Eur Urol, 2012. **61**(1): p. 78-84.
31. Namiki, S., et al., *Impact of nocturia on disease-specific quality of life for men with localized prostate cancer.* Qual Life Res, 2011. **20**(10): p. 1609-15.
32. van Dijk, L., et al., *Nocturia: impact on quality of life in a Dutch adult population.* BJU Int, 2004. **93**(7): p. 1001-4.
33. Bal, K., et al., *Sleep analysis of patients with nocturia and benign prostatic obstruction.* Urology, 2012. **80**(2): p. 383-8.
34. Redeker, N.S., et al., *Nocturia, sleep and daytime function in stable heart failure.* J Card Fail, 2012. **18**(7): p. 569-75.
35. Kok, E.T., et al., *Patient's quality of life and coping style influence general practitioner's management in men with lower urinary tract symptoms: the Krimpen Study.* Qual Life Res, 2006. **15**(8): p. 1335-43.
36. Chong, C., et al., *The prevalence of lower urinary tract symptoms and treatment-seeking behaviour in males over 40 years in Singapore: a community-based study.* Prostate Cancer Prostatic Dis, 2012. **15**(3): p. 273-7.
37. Guyton, A.C.a.H., J.E., ed. *Textbook of Medical Physiology*. 11 ed. 2006, Elsevier inc.: Philadelphia, Pennsylvania, USA.
38. Wein, A.J., ed. *Campbell-Walsh Urology*. 10 ed. 2012, Elsevier: Philadelphia, Pennsylvania, USA. 3831.
39. Cornu, J.N., et al., *A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management--a systematic review and meta-analysis.* Eur Urol, 2012. **62**(5): p. 877-90.
40. Juul, K.V., *The evolutionary origin of the vasopressin/V2-type receptor/aquaporin axis and the urine-concentrating mechanism.* Endocrine, 2012. **42**(1): p. 63-8.
41. Weiss, J.P. and J.G. Blaivas, *Nocturnal polyuria versus overactive bladder in nocturia.* Urology, 2002. **60**(5 Suppl 1): p. 28-32; discussion 32.
42. Corcos, J.a.S., E., *Textbook of the Neurogenic Bladder.* 1st ed. 2004, London: Martin Dunitz, Taylor, and Francis group plc. 779.
43. Tikkinen, K.A., et al., *A systematic evaluation of factors associated with nocturia--the population-based FINNO study.* Am J Epidemiol, 2009. **170**(3): p. 361-8.
44. Asplund, R., *Obesity in elderly people with nocturia: cause or consequence?* Can J Urol, 2007. **14**(1): p. 3424-8.
45. Plantinga, L., M.N. Rao, and D. Schillinger, *Prevalence of self-reported sleep problems among people with diabetes in the United States, 2005-2008.* Prev Chronic Dis, 2012. **9**: p. E76.

46. Hall, S.A., et al., *Commonly used antihypertensives and lower urinary tract symptoms: results from the Boston Area Community Health (BACH) Survey.* BJU Int, 2012. **109**(11): p. 1676-84.
47. Vaughan, C.P., et al., *Vitamin D and lower urinary tract symptoms among US men: results from the 2005-2006 National Health and Nutrition Examination Survey.* Urology, 2012. **78**(6): p. 1292-7.
48. Wang, Y., et al., *Prevalence, risk factors, and impact on health related quality of life of overactive bladder in China.* Neurourol Urodyn, 2011. **30**(8): p. 1448-55.
49. Klingler, H.C., et al., *Nocturia: an Austrian study on the multifactorial etiology of this symptom.* Neurourol Urodyn, 2009. **28**(5): p. 427-31.
50. Weiss, J.P., et al., *Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia.* J Urol, 2011. **186**(4): p. 1358-63.
51. Asplund, R. and H. Aberg, *Diurnal variation in the levels of antidiuretic hormone in the elderly.* J Intern Med, 1991. **229**(2): p. 131-4.
52. Hirayama, A., et al., *Relationship between nocturnal urine volume, leg edema, and urinary antidiuretic hormone in older men.* Urology, 2011. **77**(6): p. 1426-31.
53. van Venrooij, G.E. and T.A. Boon, *Extensive urodynamic investigation: interaction among diuresis, detrusor instability, urethral relaxation, incontinence and complaints in women with a history of urge incontinence.* J Urol, 1994. **152**(5 Pt 1): p. 1535-8.
54. Stember, D.S., et al., *Nocturia in men.* Int J Clin Pract Suppl, 2007(155): p. 17-22.
55. Weiss, J.P., et al., *The evaluation and treatment of nocturia: a consensus statement.* BJU Int, 2011. **108**(1): p. 6-21.
56. Bal K, A.S., Issi Y, Bolukbasi A, Akhan G, *Sleep analysis of nocturic patients with benign prostatic obstruction.* J. Urol (supp.), 2011: p. e-abstract 1735.
57. Cruz, I.A., M. Drummond, and J.C. Winck, *Obstructive sleep apnea symptoms beyond sleepiness and snoring: effects of nasal APAP therapy.* Sleep Breath, 2012. **16**(2): p. 361-6.
58. Bliwise, D.L., et al., *Nocturia and disturbed sleep in the elderly.* Sleep Med, 2009. **10**(5): p. 540-8.
59. Gottlieb, D.J., et al., *Association of sleep time with diabetes mellitus and impaired glucose tolerance.* Arch Intern Med, 2005. **165**(8): p. 863-7.
60. Galizia, G., et al., *Association between nocturia and falls-related long-term mortality risk in the elderly.* J Am Med Dir Assoc, 2012. **13**(7): p. 640-4.
61. Lightner, D.J., et al., *Nocturia is associated with an increased risk of coronary heart disease and death.* BJU Int, 2012. **110**(6): p. 848-53.
62. Asplund, R., *Mortality in the elderly in relation to nocturnal micturition.* BJU Int, 1999. **84**(3): p. 297-301.
63. Sintonen, H., *The 15D instrument of health-related quality of life: properties and applications.* Ann Med, 2001. **33**(5): p. 328-36.
64. Cho, S.Y., et al., *Short-term effects of systematized behavioral modification program for nocturia: a prospective study.* Neurourol Urodyn, 2012. **31**(1): p. 64-8.
65. Burgio, K.L., et al., *Behavioral versus drug treatment for overactive bladder in men: the Male Overactive Bladder Treatment in Veterans (MOTIVE) Trial.* J Am Geriatr Soc, 2012. **59**(12): p. 2209-16.
66. Johnson, T.M., 2nd, et al., *Changes in nocturia from medical treatment of benign prostatic hyperplasia: secondary analysis of the Department of Veterans Affairs Cooperative Study Trial.* J Urol, 2003. **170**(1): p. 145-8.
67. Yoshimura, K., et al., *Nocturia and benign prostatic hyperplasia.* Urology, 2003. **61**(4): p. 786-90.
68. Johnson, T.M., 2nd, et al., *The effect of doxazosin, finasteride and combination therapy on nocturia in men with benign prostatic hyperplasia.* J Urol, 2007. **178**(5): p. 2045-50; discussion 2050-1.
69. Montorsi, F., et al., *The effects of dutasteride or tamsulosin alone and in combination on storage and voiding symptoms in men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH): 4-year data from the Combination of Avodart and Tamsulosin (CombAT) study.* BJU Int, 2011. **107**(9): p. 1426-31.

70. Zinner, N., et al., *Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial.* J Urol, 2004. **171**(6 Pt 1): p. 2311-5, quiz 2435.
71. Nitti, V.W., et al., *Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome.* J Urol, 2007. **178**(6): p. 2488-94.
72. Herschorn, S., et al., *Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial.* BJU Int, 2010. **105**(1): p. 58-66.
73. Chapple, C.R., et al., *Efficacy and safety of tolterodine extended-release in men with overactive bladder symptoms treated with an alpha-blocker: effect of baseline prostate-specific antigen concentration.* BJU Int, 2010. **106**(9): p. 1332-8.
74. Yamaguchi, O., et al., *Solifenacin as add-on therapy for overactive bladder symptoms in men treated for lower urinary tract symptoms--ASSIST, randomized controlled study.* Urology, 2010. **78**(1): p. 126-33.
75. Kojima, Y., et al., *Tamsulosin reduces nighttime urine production in benign prostatic hyperplasia patients with nocturnal polyuria: a prospective open-label long-term study using frequency-volume chart.* Neurourol Urodyn, 2012. **31**(1): p. 80-5.
76. Chapple C, Artibani W, Berges R, et al., *Male lower urinary tract dysfunction; evaluation and management. 6th international consultation on new developments in prostate cancer and prostate diseases.* Edition 21, Paris, France, 2006: p. 143-94.
77. Juul, K.V., B.M. Klein, and J.P. Norgaard, *Long-term durability of the response to desmopressin in female and male nocturia patients.* Neurourol Urodyn, 2012.
78. Juul, K.V., et al., *Gender difference in antidiuretic response to desmopressin.* Am J Physiol Renal Physiol, 2012. **300**(5): p. F1116-22.
79. Addla, S.K., et al., *Diclofenac for treatment of nocturia caused by nocturnal polyuria: a prospective, randomised, double-blind, placebo-controlled crossover study.* Eur Urol, 2006. **49**(4): p. 720-5.
80. Falahatkar, S., et al., *Celecoxib for treatment of nocturia caused by benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled study.* Urology, 2008. **72**(4): p. 813-6.
81. Sutcliffe, S., et al., *Non-steroidal anti-inflammatory drug use and the risk of benign prostatic hyperplasia-related outcomes and nocturia in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.* BJU Int, 2012. **110**(7): p. 1050-9.
82. Drake, M.J., I.W. Mills, and J.G. Noble, *Melatonin pharmacotherapy for nocturia in men with benign prostatic enlargement.* J Urol, 2004. **171**(3): p. 1199-202.
83. Lowe, F.C. and J.C. Ku, *Phytotherapy in treatment of benign prostatic hyperplasia: a critical review.* Urology, 1996. **48**(1): p. 12-20.
84. Bent, S., et al., *Saw palmetto for benign prostatic hyperplasia.* N Engl J Med, 2006. **354**(6): p. 557-66.
85. MacDonald, R., et al., *Serenoa repens monotherapy for benign prostatic hyperplasia (BPH): an updated Cochrane systematic review.* BJU Int, 2012. **109**(12): p. 1756-61.
86. Homma, Y., et al., *Significance of nocturia in the International Prostate Symptom Score for benign prostatic hyperplasia.* J Urol, 2002. **167**(1): p. 172-6.
87. Hutchinson, R.C., et al., *The effect of robot-assisted laparoscopic prostatectomy on nocturia.* J Endourol, 2012. **26**(7): p. 861-5.

CHAPTER 4

VOIDING DIARY BASED ANALYSIS OF NOCTURIA

Extracted from:
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Diary-based population analysis of nocturia in older men: the Krimpen study.

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INTRODUCTION

Both increased diurnal and nocturnal voiding frequency are common and bothersome symptoms in older men and interfere with daily activities. Nocturia is especially bothersome because it may result in sleep disturbance, daytime fatigue, a lower level of general well-being and is a risk factor for nightly falls [1]. In the Finnish National Nocturia and Overactive bladder (FINNO) study, health related quality of life was not impaired when subjects voided once a night, but slightly or moderately, yet significantly, impaired with 2 or 3 or more voids per night, respectively [2]. In addition to the association with urological conditions, such as prostate enlargement, diurnal and nocturnal urinary frequency are reported as symptoms of various diseases [3]. Many physicians consider increased nocturnal voiding frequency a sign of increased nocturnal urine production, which may represent a pathologic condition reflective of congestive heart failure, venous stasis or hormonal changes with ageing. Besides the relation to nocturnal urine production, nocturnal voiding frequency has been described as a result of diuretic use and awakenings for other reasons such as sleep disorders or anxiety [3].

With growing attention to urologic problems and the increasing number of older men, it is expected that physicians will see more men with these problems.

According to the most recent ICS definition, nocturia is the number of voids recorded during a nights' sleep. Each void must be preceded and followed by sleep [4].

When evaluating these patients, physicians are hampered by a paucity of population-based data on normal voiding patterns and related factors. Mostly, normal voiding patterns have been determined with the use of questionnaires. Validated questionnaires are useful for recording symptoms, their frequency, severity and bother, as well as the impact of LUTS on QoL, but are generally influenced by recall bias [5]. Frequency-volume charts are not subject to this type of bias and, therefore, they are a more valid tool for measuring urinary frequency [6]. Reports on the agreement between chart data and questionnaires however, have been contradictory [7, 8].

According to the most recent ICS definition, nocturnal polyuria is present when an increased proportion of the 24-hour output occurs at night [4]. Normally, the night is considered to be a period of about eight hours whilst the patient lies in bed. A weakness of this definition is the fact that the time a person is actually in bed varies, and depends on age. The ICS standardization report on terminology further states that the normal range of nocturnal urine production differs with age, and the normal ranges remain to be defined. Therefore, nocturnal polyuria is present when >20% (young adults) to >33% (over 65 years) is produced at night. Hence the precise definition is dependent on age [4]. Thus, normal values on nocturnal urine

production and its relation to nocturnal frequency in older men were lacking before the analyses of the Krimpen study.

In general, previously suggested definitions of nocturnal polyuria, most of which refer to a day/night ratio in urine production were not based on normal distributions and were not properly validated [9]. Also, the incidence of nocturia and nocturnal polyuria in the community needed to be studied.

FREQUENCY VOLUME CHARTS

The ICS report on standardization of terminology in lower urinary tract function defines a frequency volume chart as follows: a FVC records the volumes voided as well as the time of each micturition, day and night, for at least 24 hours. This is usually commenced after the first void produced after rising in the morning and is completed by including the first void on rising the following morning [4]. We may add to this that for a proper analysis of nocturia and nocturnal polyuria, it is necessary that subjects record the time of going to bed and time of rising.

Why do FCVs give a better insight in the condition "nocturia" than studies based on questionnaire data? Clearly, FCVs [but not questionnaires] are excellent tools to evaluate nocturnal urine production in an epidemiological setting. Furthermore, the relationship between nocturia and [nocturnal] polyuria can only be explored using FCVs. As already stated, data derived from questionnaires like the International Prostate Symptom Score (IPSS) are prone to recall bias [5]. There are some differences between IPSS-based and FVC-based data that need further attention. The IPSS refers to a period of one month preceding the moment of completion of the questionnaire, whereas a FVC covers a period of at least 24 hrs but preferably 3 days. One might ask whether FCVs are therefore more prone to fluctuation than the IPSS, when serially administered? Because of the burden of completing a FVC, the response rate may be lower. And inevitably, some subjects will complete the FVC incorrectly.

PARAMETERS DERIVABLE FROM A FREQUENCY-VOLUME CHART

The following (basic) measurements can be abstracted from frequency-volume charts (table 2.1):

1. voiding frequency
2. total voided volume
3. voided volume per void

These measurements can be abstracted for daytime, nighttime and 24-hour periods. With this data several parameters can be derived, such as maximum voided volume (in previous studies often referred to as functional bladder capacity), average voided volume, and the hourly urine production [10].

Hourly urine production can be calculated via a method first introduced by Van Mastrigt and Eijskoot: when urine production is assumed constant between two voids the hourly urine production can be estimated as the volume of each micturition divided by the number of hours that passed since the previous micturition (Figure 4.1).

Once the hourly urine production is computed, nocturnal urine production can also be determined. In the Krimpen study we estimated it as the mean hourly urine production (ml/hr) from 1 am to 6 am. This period of time was chosen because (approximately) 90% of the men were 'asleep' during these hours [11]. Furthermore, additional calculations can be made for the evaluation of the etiology of nocturia [12]. For an overview, please see table 2.1.

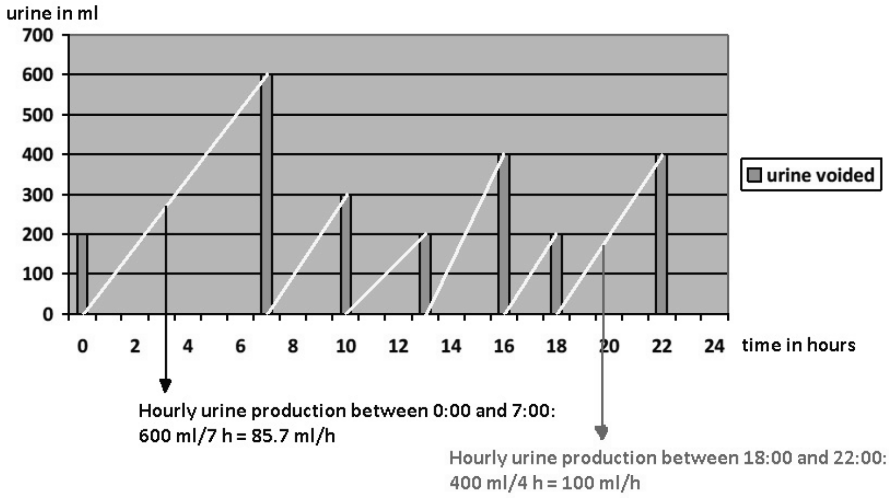

Figure 4.1 Example of the computation of the hourly urine production by the method of Van Mastrigt van Eijskoot: urine production is assumed constant between two voids the hourly urine production can be estimated as the volume of each micturition divided by the number of hours that passed since the previous micturition.

Table 2.1 Parameters derivable from a frequency-volume chart

24HVV (24-hour voided volume)	Total voided volume during one 24-hour period
NVF (nocturnal voiding frequency)	Total number of voids between going to bed and arising in the morning
DVF (diurnal voiding frequency)	Total number of voids between arising in the morning and going to bed at night
MVV (maximum voided volume)	Largest single void during a 24-hour period
NBC (Nocturnal bladder capacity)	Largest single void between going to bed and arising in the morning
Hourly urine production	Urine production per hour*
NUP (nocturnal urine production)	The average urine production between 1 and 6 a.m.
NUV (nocturnal urine volume)	Nightly voided volume plus the first morning voided volume
NPi (Nocturnal Polyuria index)	NUV/24HVV

*As calculated by the method of Van Mastrigt and Eijskoot (10)

REFERENCES

1. Asplund, R. and H. Aberg, *Health of the elderly with regard to sleep and nocturnal micturition.* Scand J Prim Health Care, 1992. **10**(2): p. 98-104.
2. Tikkinen, K.A., et al., *Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland.* Eur Urol, 2010. **57**(3): p. 488-96.
3. Barker, J.C. and L.S. Mitteness, *Nocturia in the elderly.* Gerontologist, 1988. **28**(1): p. 99-104.
4. Abrams, P., et al., *The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society.* Am J Obstet Gynecol, 2002. **187**(1): p. 116-26.
5. Coughlin, S.S., *Recall bias in epidemiologic studies.* J Clin Epidemiol, 1990. **43**(1): p. 87-91.
6. Abrams, P. and B. Klevmark, *Frequency volume charts: an indispensable part of lower urinary tract assessment.* Scand J Urol Nephrol Suppl, 1996. **179**: p. 47-53.
7. McCormack, M., C. Infante-Rivard, and E. Schick, *Agreement between clinical methods of measurement of urinary frequency and functional bladder capacity.* Br J Urol, 1992. **69**(1): p. 17-21.
8. Donovan, J.L., et al., *The ICS-'BPH' Study: the psychometric validity and reliability of the ICSmale questionnaire.* Br J Urol, 1996. **77**(4): p. 554-62.
9. Weiss, J.P. and J.G. Blaivas, *Nocturia.* J Urol, 2000. **163**(1): p. 5-12.
10. van Mastrigt, R. and F. Eijskoot, *Analysis of voided urine volumes measured using a small electronic pocket balance.* Scand J Urol Nephrol, 1996. **30**(4): p. 257-63.
11. Blanker, M.H., et al., *Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men.* J Urol, 2000. **164**(4): p. 1201-5.
12. Weiss, J.P., et al., *Evaluation of the etiology of nocturia in men: the nocturia and nocturnal bladder capacity indices.* Neurourol Urodyn, 1999. **18**(6): p. 559-65.

PART III

NATURAL HISTORY OF VOIDED VOLUMES

CHAPTER 5

THE NATURAL HISTORY AND PREDICTIVE FACTORS OF VOIDED VOLUMES IN OLDER MEN

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ABSTRACT

BACKGROUND: Although the functional capacity of the bladder as expressed in the maximum voided volume (MVV) and other frequency-volume chart (FVC) parameters are important determinants of lower urinary tract symptoms, no population-based data are available on changes in voided volumes.

PURPOSE: To determine changes (and determinants) in voided volumes and voiding frequency measured with FVCs with advancing age and over time.

MATERIALS AND METHODS: A longitudinal, population-based study was conducted among 1,688 men aged 50-78 years with follow-up rounds at 2.1, 4.2 and 6.5 years. Data were obtained using FVCs for MVV, 24-hour voided volume (24HVV), average voided volume (AVV), and 24-hour voiding frequency (24hfreq), physical and urological measurements, and self-administered questionnaires. A linear mixed effect model determined the predictive factors for changes in the volumes.

RESULTS: Median MVV and AVV decreased over time (from 400-380 ml and 245-240 ml, respectively) and were smaller in older age groups, whereas 24HVV showed no change. The 24hfreq increased over time and with advancing age. MVV, 24HVV and AVV were positively related to alcohol intake. MVV and AVV were negatively related to higher age at baseline and passage of time. Hypertension, use of diuretics and post-void residual volume were related to a higher 24HVV.

CONCLUSIONS: In older men, MVV and AVV show a small but statistically significant decrease over time and with advancing age, whereas 24HVV does not. Predictive factors for change in MVV or AVV are alcohol intake and higher age.

INTRODUCTION

In older men, lower urinary tract symptoms (LUTS) increase in prevalence and severity with advancing age and can have a negative impact on the quality of life (1-4). The most common LUTS are those embedded in the International Prostate Symptom Score (IPSS) (4). Generally, benign prostatic enlargement leading to benign prostatic obstruction (BPO) was considered the main cause of LUTS in older men (1). Although often associated with BPO, LUTS frequently occur without it. Conditions such as bladder dysfunction, congestive heart failure and poly-pharmacy are among those associated with LUTS (2).

Because frequency-volume charts (FVCs) are a reliable and easy method to objectify LUTS, they are indispensable when evaluating LUTS (5). FVCs were used to determine reference values for voided volumes in older men in the general population (1), and in patients without voiding symptoms (6). Especially maximum voided volume (MVV) is reported to be strongly related to LUTS (1).

However, no data are available on changes in FVC parameters, or on the determinants of these changes. Therefore this study investigates how the MVV, 24-hour voided volume (24HVV) and average voided volume (AVV) change in men aged ≥50 years, and which determinants are related to these changes in the general population.

MATERIAL AND METHODS

The Krimpen study is a longitudinal study on urogenital tract dysfunction and its impact on general health status. The design of the study has been extensively described elsewhere (7, 8). In brief, all men aged 50 to 78 years (reference date June 1995; n=3,924) in the Dutch municipality *'Krimpen aan den IJssel'*, were investigated. Men without a history of prostatectomy, prostate or bladder cancer, neurogenic bladder disease, or a negative advice from their general practitioner (GP) and who were able to complete questionnaires and visit the health center were invited to participate. First, participants were asked to complete a validated 113-item questionnaire; for the present study including questions on COPD, diabetes, smoking, and alcohol intake. Next, they visited the local primary health center for medical examination. Lastly, urological measurements were performed at the urological outpatient department of the Erasmus MC and the participants completed a 3-day FVC.

FREQUENCY-VOLUME CHARTS

Participants completed the 3-day FVC on which each micturition was recorded in one-hour time units, and on the third day the volume of each void was recorded. Fluid intake was not recorded. The definition of a FVC was not well established when this study was initiated. However, in 2002 an International Continence Society standardization report stated that a FVC "records the volumes voided as well as the time of each micturition, day and night, for at least 24 hours" (9). Our FVCs comply with that definition. From the FVC the following variables were determined: the MVV, single largest voided volume in 24 hours *[previously referred to as the functional bladder capacity in other Krimpen Study publications (1), but this is no longer the preferred nomenclature as MVV is less confusing* (9)], 24HVV, and AVV (calculated by dividing the 24HVV by the number of micturitions that day). Data of men with a 24HVV ≤500 ml were considered incomplete and therefore not used.

UROLOGICAL MEASUREMENTS

When participants visited the urology outpatient department measurements included transrectal ultrasonometry of the prostate (TRUS; planimetric determination of prostate volume), uroflowmetry (i.e. the maximum flow-rate in ml/s: Qmax), and transabdominal ultrasonometry for post-void residual (PVR) volume. Prostate enlargement was defined as a prostate volume >30 cm^3 on TRUS (1). Prostate biopsies were taken according to a previously described protocol (10).

FOLLOW-UP

Three consecutive follow-up rounds were performed with an average follow-up period of 2.1, 4.2 and 6.5 years, respectively (11). Because all participants were registered with one of the local GPs (as is usual in the Netherlands), death of a participant or change of address was registered. No attempts were made to track participants who had moved out of the area. If no exclusion criteria were met, the GPs were asked to send a re-invitation letter to all participants for a first and second follow-up round. For the third follow-up round, additionally, all non-responders who did not meet any of the exclusion criteria were re-invited. Those who refused further participation were not contacted again, and no reminders were sent to those not responding (Figure 1).

STATISTICAL ANALYSIS

At baseline, men were categorized into age strata: 50 to 54, 55 to 59, 60 to 64, 65 to 69, and 70 to 78 years. To provide an overview of changes in MVV, 24HVV and AVV, descriptive data are presented.

Table 5.1 Characteristics of the study population

	Baseline	Follow-up I	Follow-up II	Follow-up III
Age group (years)	Percentage			
50-54	20.7 %	19.4 %	20.7 %	24.7 %
55-59	25.7 %	26.1 %	27.9 %	29.1 %
60-64	23.8 %	25.6 %	25.7 %	24.1 %
65-69	19.4 %	18.8 %	18.0 %	16.1 %
70-78	10.2 %	10.0 %	7.6 %	6.0 %
IPSS	Median (IQR)			
	4 (1-7)	4 (2-8)*	5 (2-8)*	5 (3-10)*
IPSS categories	Percentage			
No to Mild LUTS (0-7)	75.4 %	78.1 %	75.9 %	68.7 %
Moderate LUTS (8-19)	21.8 %	19.4 %	21.0 %	27.8 %
Severe LUTS (20-35)	2.8 %	2.5 %	3.1 %	3.5 %
Prostate volume (cm^3)	Median (IQR)			
	30.5 (25.0-38.3)	31.9 (25.9-41.1)*	33.7 (26.8-43.3)*	34.9 (28.0-45.6)*
24h-voiding frequency	Median(IQR)			
	6.0 (5.0-7.5)	6.5 (5.5-7.5)	6.5 (5.5-7.5)*	6.5 (5.5-8.0)*

*p-value < 0.001 as compared to baseline (Wilcoxon signed rank test)

To determine possible predictive factors for changes in MVV, 24HVV and AVV, a linear mixed effect (LME) model was used (12). This model is able to adjust for correlated measurements within persons and, importantly, also takes into account measurements of men not participating in all four rounds.

Univariable linear regression analyses were performed to test potential predictive factors separately for MVV, 24HVV and AVV. The variables age at baseline (as a categorical variable) and time passing in years (continuous variable) were used. Also, measured dichotomous variables were used; prostate enlargement and PVR >50 ml. Questionnaire-based dichotomous variables were: alcohol consumption (≥2 units [glasses] daily), smoking, COPD, diabetes, cardiac symptoms, hypertension, chronic lower urinary tract infection, and use of diuretic drugs. Variables with a p-value <0.20 were entered in the multivariable LME models. A manual backward selection procedure was used to create a final model including only variables that were significant (p <0.05). The final models are presented together with the univariable results. In these predictive models IPSS and Qmax were not taken into account because they might be the result of a reduced MVV and altered voided volumes.

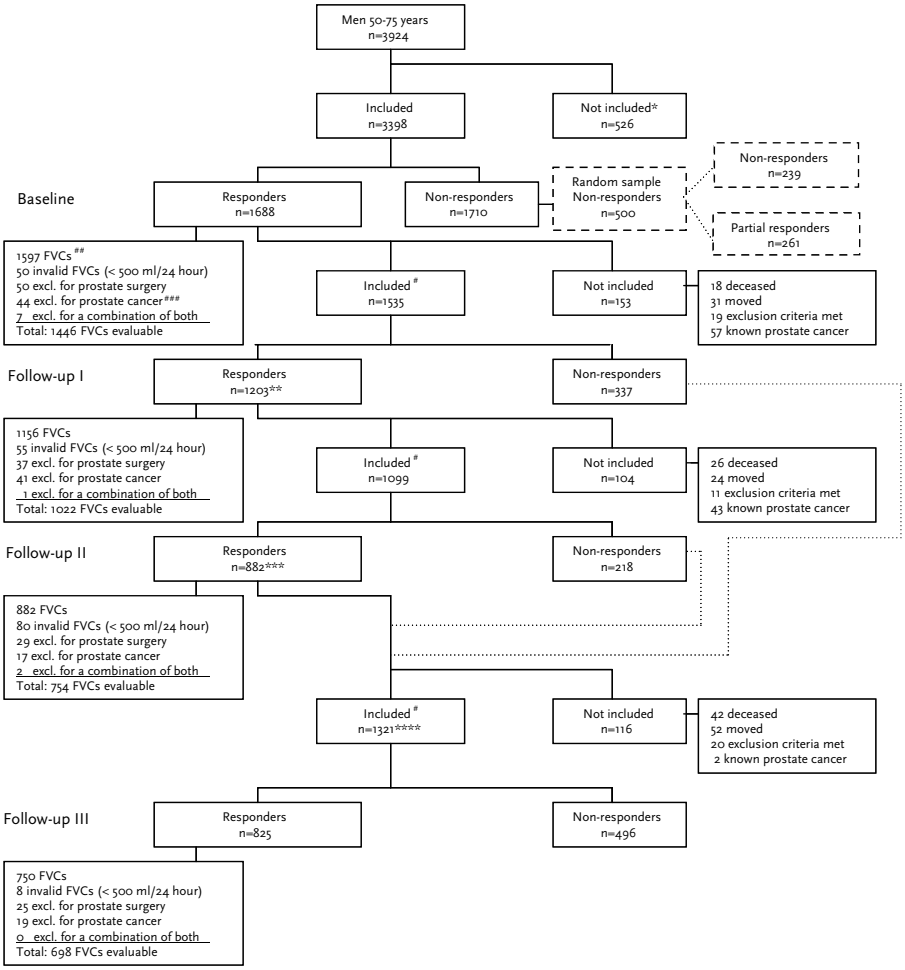

Figure 5.1

* Men without radical prostatectomy, prostate or bladder cancer, neurogenic bladder disease or a negative advice from their GP (in case of a serious disease with a short life-expectancy), who were able to complete questionnaires and attend the research center, were invited for the study; # If no prostate cancer was detected, participants had not moved outside the municipality and were alive a re-invitation letter was sent to all responders for follow-up; ** five men did not participate in the baseline study, but entered the study in Follow-up I; *** one man did not respond in Follow-up I, but re-entered the study in Follow-up II; **** Men, who did not respond after baseline, first follow-up or second follow-up and did not meet the exclusion criteria were also re-invited for participation in the third follow-up round (882+ 337+218-116); $ this sample of non-responders was analyzed in a loss to follow-up study (13); ##Frequency Volume chart; ### newly diagnosed prostate carcinoma

The Wilcoxon signed-rank test was used to determine longitudinal changes in IPSS, 24-hour voiding frequency (24hfreq) and prostate volume. For all analyses the Statistical Package for Social Sciences (SPSS) version 15.0 (Chicago, Ill, USA) was used.

RESULTS

Some characteristics of the population at baseline and the follow-up rounds are listed in table 5.1. At baseline the vast majority of the men had no or only mild LUTS. Although there was a slight increase of IPSS over time ($p < 0.001$), most men remained in the 'mild' group (75.4% at baseline to 68.7% after 6.5 years). Both the 24hfreq and the average prostate volume showed slight but increasing trends ($p<0.001$): median 6.0 to 6.5 times and 30.5 to 34.9 ml, respectively.

Figure 5.1 shows the number of responders, those excluded, and the total number of FVCs available for analyses in each round. Of the 1,688 men who responded at baseline, 1,446 completed valid FVCs and did not meet the exclusion criteria. Thus, the present study comprises the 1,446 FVCs available at baseline plus 1,022, 754, and 698 completed and valid FVCs at each follow-up round, respectively. This yields a total of 3,920 FVCs. A larger depiction of this flowchart can be found in chapter 4, figure 1.

Voided volumes over time

A slight decrease in MVV was found over the years: median: 420 (IQR: 308-520) ml to 400 (IQR: 300-550) ml for the youngest age group and with higher age: and from 420 (308-520) ml to 350 (300-450) ml, in the youngest versus the oldest group at baseline. AVV also showed a slight decrease over time and with higher age: from 266 (208-346) ml to 251 (213-345) ml and from 266 (208-346) ml to 223 (183-271) ml, respectively. The 24HVV showed a slight increase over time and with increasing age: from 1500 (1121-200) ml to 1550 (1200-1900) ml, and from 1550 (1121-2000) ml to 1650 (1200-2100) ml, respectively), see Table 5.2

Maximum voided volume

Table 5.3 presents results of the univariable analyses and the final LME model for MVV. The following variables were significantly related to lower MVV values: higher age at baseline when the difference was 10 years or more, time passing in years, a PVR >50 ml, and an enlarged prostate. Alcohol intake of ≥2 units a day was related to a higher MVV.

Table 5.2 Data on maximum voided volume (MVV), 24-hour voided volume (24HVV), and average voided volume (AVV) by age group at each follow-up round

	Age group *at baseline*					
	50-54 years	**55-59 years**	**60-64 years**	**65-69 years**	**70-78 years**	**Total**
MVV						
Baseline	420 (308-520)	400 (300-545)	400 (300-500)	378 (283-500)	350 (300-450)	400 (300-500)
Follow-up I	400 (300-500)	400 (300-500)	375 (300-500)	400 (300-500)	350 (250-450)	400 (300-500)
Follow-up II	400 (300-550)	400 (300-500)	375 (290-495)	375 (275-480)	345 (295-413)	400 (300-500)
Follow-up III	400 (300-550)	400 (300-500)	350 (250-450)	350 (250-450)	360 (300-443)	380 (300-500)
24HVV						
Baseline	1500 (1121-2000)	1400 (1100-1900)	1550 (1183-1958)	1540 (1213-2021)	1550 (1200-1900)	1506 (1160-1950)
Follow-up I	1560 (1250-1950)	1500 (1200-1950)	1555 (1246-2031)	1600 (1214-2100)	1600 (1218-1998)	1550 (1215-2000)
Follow-up II	1550 (1200-2040)	1540 (1215-1900)	1500 (1224-1836)	1490 (1150-1845)	1680 (1240-2050)	1525 (1214-1920)
Follow-up III	1650 (1200-2100)	1593 (1150-2025)	1578 (1244-2059)	1470 (1125-1875)	1700 (1420-2065)	1580 (1200-2020)
AVV						
Baseline	266 (208-346)	250 (198-331)	249 (193-316)	238 (173-305)	223 (183-271)	245 (192-319)
Follow-up I	269 (213-333)	259 (197-324)	243 (186-307)	244 (180-313)	221 (172-287)	250 (192-320)
Follow-up II	258 (208-333)	258 (203-320)	229 (183-287)	227 (172-288)	229 (178-262)	243 (191-308)
Follow-up III	251 (213–345)	244 (193-311)	232 (181-295)	220 (163-280)	213 (185-288)	240 (188-307)

Changes in parameter values (that occur when moving from left to right through the columns) represent changes occurring with advancing age. Changes occurring when moving down through one column (one age stratum) represent changes occurring with increasing follow-up time. Data are median values in ml (interquartile range).

Table 5.3 Univariable analyses and final linear mixed effect (LME) model for maximum voided volumes (MVV)

Variable	Univariable		Multivariable LME model			
	β*	p-value	β (mean)	95% CI		p-value
Intercept		.	320	264	377	0.000
Age at baseline 50-54**	0	.	0	.	.	.
Age at baseline 55-59	-3	0.762	-9	-27	12	0.434
Age at baseline 60-64	**-29**	**0.002**	**-34**	**-51**	**-11**	**0.002**
Age at baseline 65-69	**-36**	**0.001**	**-39**	**-58**	**-15**	**0.01**
Age at baseline 70-78	**-54**	**0.000**	**-52**	**-79**	**-26**	**0.000**
post-void residue >50 (ml)	-12	0.046	NS	.	.	.
prostate volume >30 (ml)	-11	0.035	NS	.	.	.
Alcohol intake >2 (units/day)	**30**	**0.000**	**23**	**9**	**38**	**0.001**
Smoking	9	0.193	NS	.	.	.
Use of diuretics	-16	0.077	NS	.	.	.
Cardiac symptoms	5	0.572	NI	.	.	.
Diabetes mellitus	13	0.362	NI	.	.	.
Hypertension	-6	0.410	NI	.	.	.
COPD	17	0.166	NS	.	.	.
CUTI	20	0.416	NI	.	.	.
Time passing in years	**-3**	**0.000**	**-3**	**-5**	**-2**	**0.000**

* The β shows the number of millimeters the predicted AVV changes with or without the variable
**reference group
NS = not significant, NI = not included in the final analyses
COPD = chronic obstructive pulmonary disease; CUTI = chronic lower urinary tract infection

Table 5.4 Univariable analyses and final linear mixed effect (LME) model for 24-hour voided volume (24HVV)

Variable	Univariable		Multivariable LME model			
	β*	p-value	β (mean)	95% CI		p-value
Intercept			1874	1764	1984	0.000
Age at baseline 50-54**	0	.	NI	.	.	.
Age at baseline 55-59	-32	0.414	.	.	.	.
Age at baseline 60-64	3	0.944	.	.	.	.
Age at baseline 65-69	11	0.804	.	.	.	.
Age at baseline 70-78	-2	0.971	.	.	.	.
Post-void residue >50ml	**73**	**0.003**	**68**	**19**	**117**	**0.006**
Prostate volume > 30 ml	22	0.316	NI	.	.	.
Alcohol intake >2 (units/day)	**78**	**0.008**	**70**	**11**	**129**	**0.021**
Smoking	-2	0.953	NI	.	.	.
Use of diuretics	**80**	**0.033**	**86**	**5**	**166**	**0.037**
Cardiac symptoms	20	0.631	NI	.	.	.
Diabetes mellitus	109	0.066	NS	.	.	.
Hypertension	**80**	**0.009**	**71**	**11**	**132**	**0.019**
COPD	89	0.073	NS	.	.	.
CUTI	118	0.250	NI	.	.	.
Time passing in years	5	0.116	NS	.	.	.

* The β shows the number of millimeters the predicted 24HVV changes with or without the variable

**reference group

NS = not significant, NI = not included in the final analyses

COPD = chronic obstructive pulmonary disease; CUTI = chronic lower urinary tract infection

Table 5.5 Univariable analyses and final linear mixed effect (LME) model for average voided volume(AVV)

Variable	**Univariable**		**Multivariable LME model**			
	β*	p-value	β (mean)	95% CI		
Intercept			345	301	389	p-value
Age at baseline 50-54**	0	.	0	.	.	.
Age at baseline 55-59	-5	0.317	-13	-30	3	0.103
Age at baseline 60-64	**-22**	**0.000**	**-19**	**-34**	**-3**	**0.019**
Age at baseline 65-69	**-27**	**0.000**	**-32**	**-47**	**-16**	**0.000**
Age at baseline 70-78	**-42**	**0.000**	**-39**	**-55**	**-22**	**0.000**
Post-void residual volume >50 (ml)	-5	0.104	NS	.	.	.
Prostate volume > 30 (ml)	-9	0.002	NS	.	.	.
Alcohol intake >2 (units/day)	**14**	**0.001**	**10**	**2**	**18**	**0.012**
Smoking	4	0.247	NI	.	.	.
Use of diuretics	-13	0.010	NS	.	.	.
Cardiac symptoms	-11	0.030	NS	.	.	.
Diabetes mellitus	2	0.813	NI	.	.	.
Hypertension	-2	0.598	NI	.	.	.
COPD	-2	0.802	NI	.	.	.
CUTI	15	0.248	NI	.	.	.
time passing in years	**-1**	**0.003**	**-1**	**-2**	**-1**	**0.003**

*The β shows the number of millimeters the predicted AVV changes with or without the variable
**reference group
NS = not significant, NI = not included in the final analyses
COPD = chronic obstructive pulmonary disease; CUTI = chronic lower urinary tract infection

The multivariable analyses showed that alcohol intake of ≥2 units a day was related to a higher MVV. A higher age at baseline (≥10 years), and time passing in years was related to a lower MVV.

24-HOUR VOIDED VOLUME

Table 5.4 shows results of the univariable analyses and the LME model for 24HVV. A significant relation was found between a higher 24HVV and PVR >50 ml, alcohol intake, use of diuretics, and hypertension. The final LME model showed the same relationships. No relation was found between 24HVV and age at baseline or the passage of time.

AVERAGE VOIDED VOLUME

Univariablely a significant relation was found between a higher AVV and alcohol intake, and between reduced AVV and a higher age at baseline (≥ 10 years), an enlarged prostate, use of diuretics, and time passing in years (Table 5.5). In the final LME model there was a significant relation between a lower AVV and higher age at baseline (≥ 10 years), and time passing in years. Alcohol intake was related to a higher AVV.

DISCUSSION

This is the first large longitudinal study to investigate FVC parameters in older community-dwelling men. The 24hfreq increased over time (i.e. per age stratum during the 6.5 years follow-up) and with advancing age. The MVV and AVV decrease slightly but statistically significant over time (from 400 to 380 ml, and 245 to 240 ml, respectively) and are smaller in older age groups, whereas 24HVV shows no significant change. MVV, 24HVV and AVV were positively related to alcohol intake. MVV and AVV were negatively related to higher age at baseline and the passage of time. Hypertension, use of diuretics and a PVR volume >50 ml were related to a higher 24HVV.

In the multivariable analyses no relation was found between MVV and prostate enlargement. This confirms that the bladder function is an important determinant of LUTS in men (1, 2). Hypertension and its treatment influence 24HVV. This may be due to the use of diuretics, which often induce thirst and give rise to a higher renal output. This might explain why these changes in predicted 24HVV are similar.

Considering the amount of effort required from the responders and the number of invasive tests, the overall response rate was remarkably high at baseline and at the follow-up rounds (50%, 78%, 80% and 63%, respectively). The lower response rate at follow-up III is probably due to the fact that a re-invitation letter was also

sent to non-responders of follow-up rounds I and II. The high response rates might indicate that participants felt involved with the study, which may explain the good compliance with completion of the FVCs.

Extensive analyses on loss to follow-up (LTFU) were performed for the first three rounds, and showed a relation between LTFU and LUTS, i.e. those with mild and moderate symptoms (IPSS=1-19) showed a tendency towards higher participation rates compared with those with no (IPSS=0) and severe symptoms (IPSS ≥20) (13). However, no dose-effect relation emerged. Therefore, it seems unlikely that the slight overrepresentation of men with LUTS had a significant effect on the relations found with the LME models. Despite the fact that our participants had to complete a 3-day FVC in each round, they only recorded their voided volumes on the last day. During follow-up III they also recorded the volumes on the second day; however, these measurements show no significant differences between the various days (data not presented).

FVCs are a powerful tool; they are reliable, non-invasive, easy-to-use, and inexpensive. They give a GP or urologist good insight into the voiding pattern of patients with LUTS (14). Based on a recent systematic review on their reliability, the use of FVCs ≥3 days seems to be the most defensible policy (15).

Because we know of no other longitudinal studies using FVCs, we can compare our findings only with cross-sectional analyses. Such analyses reported declining AVV and MVV with age (16, 17). In an analysis of the Olmsted County Study, a median annual slope of -2.1% for voided volumes with a steeper slope for men over 60 years was found (18). This is similar to our findings, although the latter authors used uroflowmetry to find the MVV. In our opinion, MVV recorded with a FVC better reflects the actual volumes voided on a daily basis. It does show, however, that similar results are found when comparing our longitudinal analysis with other cross-sectional analyses. Also, the prevalence of LUTS (in our study population expressed in the IPSS and general health status) is similar to that of older men in other studies (e.g. the BACH, EPIC, and FINNO study) as well as a study in Japanese men that reported similar results (19-24). This suggests that our reference values presented in Table 3 may be more generalizable.

CONCLUSIONS

The present study provides age-specific reference values of voided bladder volumes for older men in the general population: it shows how these FVC parameters change over time, and which determinants influence these changes. Clearly abnormal volumes in older men (i.e. values outside the range of the IQRs), may help to focus the primary urologic work-up on the bladder and not just on the outflow tract, in those men who seek treatment for their bothersome LUTS.

REFERENCES

1. Blanker MH, Groeneveld FP, Bohnen AM, Bernsen RM, Prins A, Thomas S, et al. Voided volumes: normal values and relation to lower urinary tract symptoms in elderly men, a community-based study. Urology 2001;57(6):1093-8 discussion 1098-9.
2. Chapple CR, Roehrborn CG. A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: focus on the bladder. Eur Urol 2006;49(4):651-8.
3. Dubeau CE. The aging lower urinary tract. J Urol 2006;175(3 Pt 2):S11-5.
4. Naslund MJ, Gilsenan AW, Midkiff KD, Bown A, Wolford ET, Wang J. Prevalence of lower urinary tract symptoms and prostate enlargement in the primary care setting. Int J Clin Pract 2007;61(9):1437-45.
5. Abrams P, Klevmark B. Frequency volume charts: an indispensable part of lower urinary tract assessment. Scand J Urol Nephrol Suppl 1996;179:47-53.
6. van Haarst EP, Heldeweg EA, Newling DW, Schlatmann TJ. The 24-h frequency-volume chart in adults reporting no voiding complaints: defining reference values and analysing variables. BJU Int 2004;93(9):1257-61.
7. Blanker MH, Bohnen AM, Groeneveld FP, Bernsen RM, Prins A, Ruud Bosch JL. Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol 2000;164(4):1201-5.
8. Blanker MH, Groeneveld FP, Prins A, Bernsen RM, Bohnen AM, Bosch JL. Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. BJU Int 2000;85(6):665-71.
9. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21(2):167-78.
10. Blanker MH, Groeneveld FP, Thomas S, Prins A, Bohnen AM, Bosch JL. Prostate cancer detection in older men with and without lower urinary tract symptoms: a population-based study. J Am Geriatr Soc 2003;51(7):1041-2.
11. Kok ET, Groeneveld FP, Busschbach JJ, Hop WC, Bosch JL, Thomas S, et al. Influence of coping styles on quality of life in men with new and increasing lower urinary tract symptoms. The Krimpen Study in community-dwelling men. Urol Int 2007;79(3):226-30.
12. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982;38(4):963-74.
13. Blanker MH, Prins J, Bosch JL, Schouten BW, Bernsen RM, Groeneveld FP, et al. Loss to follow-up in a longitudinal study on urogenital tract symptoms in Dutch older men. Urol Int 2005;75(1):30-7.
14. Gisolf KW, van Venrooij GE, Eckhardt MD, Boon TA. Analysis and reliability of data from 24-hour frequency-volume charts in men with lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol 2000;38(1):45-52.
15. Yap TL, Cromwell DC, Emberton M. A systematic review of the reliability of frequency-volume charts in urological research and its implications for the optimum chart duration. BJU Int 2007;99(1):9-16.
16. Graugaard-Jensen C, Schmidt F, Thomsen HF, Djurhuus JC. Normal voiding patterns assessed by means of a frequency-volume chart. Scand J Urol Nephrol 2008;42(3):269-73.
17. Huang Foen Chung JW, van Mastrigt R. Age and volume dependent normal frequency volume charts for healthy males. J Urol 2009;182(1):210-4.

18. Rule AD, Jacobson DJ, McGree ME, Girman CJ, Lieber MM, Jacobsen SJ. Longitudinal changes in post-void residual and voided volume among community dwelling men. J Urol 2005;174(4 Pt 1):1317-21; discussion 1321-2; author reply 1322.
19. Tsukamoto T, Kumamoto Y, Masumori N, Miyake H, Rhodes T, Girman CJ, et al. Prevalence of prostatism in Japanese men in a community-based study with comparison to a similar American study. J Urol 1995;154(2 Pt 1):391-5.
20. Chute CG, Panser LA, Girman CJ, Oesterling JE, Guess HA, Jacobsen SJ, et al. The prevalence of prostatism: a population-based survey of urinary symptoms. J Urol 1993;150(1):85-9.
21. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 2006;50(6):1306-14; discussion 1314-5.
22. Koskimaki J, Hakama M, Huhtala H, Tammela TL. Prevalence of lower urinary tract symptoms in Finnish men: a population-based study. Br J Urol 1998;81(3):364-9.
23. Sagnier PP, MacFarlane G, Richard F, Botto H, Teillac P, Boyle P. Results of an epidemiological survey using a modified American Urological Association symptom index for benign prostatic hyperplasia in France. J Urol 1994;151(5):1266-70.
24. Robertson C, Link CL, Onel E, Mazzetta C, Keech M, Hobbs R, et al. The impact of lower urinary tract symptoms and comorbidities on quality of life: the BACH and UREPIK studies. BJU Int 2007;99(2):347-54.

PART IV

NOCTURIA AND NOCTURNAL POLYURIA, ITS DETERMINANTS AND MORTALITY RISK

CHAPTER 6

ONCE NOCTURIA, ALWAYS NOCTURIA? NATURAL HISTORY OF NOCTURIA IN OLDER MEN BASED ON FREQUENCY-VOLUME CHARTS

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ABSTRACT

PURPOSE: Nocturia is a highly prevalent and bothersome symptom that might (spontaneously) resolve. However, no longitudinal data are available on incidence and resolution of nocturia assessed with frequency-volume charts (FVCs). Objectives are to determine prevalence, incidence and resolution-rates of nocturia assessed by FVCs, and to compare nocturnal voiding frequency (NVF) over time as assessed by FVCs and by questionnaires.

MATERIALS AND METHODS: A longitudinal, population-based study was conducted among 1,688 men aged 50-78 years with follow-up rounds at 2.1, 4.2 and 6.5 years. NVF was determined with FVCs and, for comparison purposes, with a question from the International Prostate Symptom Score (IPSS). Nocturia was defined as NVF≥2. Prevalence, incidence and resolution-rates were determined.

RESULTS AND CONCLUSIONS: At 2.1 year follow-up, the incidence-rate was 23.9% and the resolution-rate 36.7%. Incidence was highest in the oldest group (70-78 years) and lowest in the youngest (50-54 years), whereas resolution was highest in the group aged 55-59 years and lowest in the oldest group. Because of the high resolution-rate, no reliable incidence-rates can be calculated. Despite fluctuation, prevalence of nocturia increased with age and over time (from 34.4-44.7% for the total group; $p<0.05$). Men who had a FVC-NVF<IPSS-NVF (6% of the population) more often had this later on.

In this population, FVC-assessed nocturia shows considerable fluctuation. Nevertheless, prevalence increases over time and with increasing age. Men who once had FVC-NVF<IPSS-NVF, are more likely to have this again. Therefore, both FVC and IPSS should be used when evaluating nocturia.

INTRODUCTION

Nocturia is a condition for which terminology was standardized by the International Continence Society (ICS) in 2002 (1, 2). It is reported that *less* than two voids each night seem to generate no bother and that two *or more* voids give rise to impaired quality of life (3-5).

Because of different definitions used in earlier studies and various ways of assessing nocturnal voiding frequency (NVF), e.g. questionnaires or frequency-volume charts (FVCs), a range of prevalence rates have been reported (6, 7). Nevertheless, the prevalence of nocturia in community-dwelling older men increases with age. Furthermore, nocturia is the most bothersome lower urinary tract symptom (LUTS) (8, 9).

Longitudinal data on the course of nocturia in community-dwelling men are limited to the TAMUS study, which showed fluctuation of nocturia in individuals over time (3). The value of this information for daily practice is uncertain for several reasons. First, the TAMUS study is based on the DAN-PSS-1 questionnaire (10), which fails to emphasize the important point of getting out of bed to void at night and therefore does not comply with the ICS definition of nocturia (2). Second, because of the DAN-PSS-1 response categories, the exact NVF could not be determined (11). Third, it is unclear whether fluctuation is an effect of the assessment tool used. FVCs represent a different, possibly more objective, method of assessing nocturia because no recall bias is involved (12). Furthermore, the correlation between questionnaire-data and FVCs is only modest (13) and, untill now, no longitudinal data are available on FVC-assessed nocturia.

Therefore this study determines the prevalence, incidence and resolution rates of nocturia based on FVCs in community-dwelling older men. The longitudinal relation between NVF as assessed with FVCs and with questionnaires is also examined.

MATERIAL AND METHODS

The Krimpen study is a longitudinal study on urogenital tract dysfunction and its impact on general health status. The design of this IRB-approved study has been described elsewhere (13, 14). In short, all men aged 50-78 years (reference date: June 1995, n=3924) in the Dutch municipality *Krimpen aan den IJssel* were investigated. Exclusion criteria for participation were: *transurethral or open prostatectomy,* prostate or bladder cancer, neurogenic bladder disease, or negative advice from their general practitioner (GP) based on poor health (e.g. bedridden).

At baseline participants completed a 113-item questionnaire, including the International Prostate Symptom Score (IPSS), and visited the local GP health centre for medical examination. Next, urological measurements were performed at the urological outpatient department of the Erasmus Medical Centre Rotterdam, and participants completed a 3-day FVC.

FOLLOW-UP

The follow-up rounds were performed after an average interval of 2.1, 4.2 and 6.5 years (15). If the participant had not died or moved away, and no exclusion criteria were met, the GPs were asked to send a re-invitation letter for a first, second and third follow-up round. Men who had undergone lower urinary tract surgery during follow-up were censored. Additionally, for the third follow-up round, all non-responders of the previous rounds were re-invited.

NOCTURIA DETERMINED FROM FREQUENCY-VOLUME CHARTS

On the 3-day FVC, participants recorded each micturition in 1-hour time units (first 2 days) and the volume of each void (third day). The time of arising and bedtime were also noted. Fluid intake was not recorded. *Retrospectively,* this complies with the 2002 ICS definition of a FVC (1).

We determined the 24-hour voiding frequency from the FVC. Since nocturia is defined as getting out of bed to void, NVF was determined from bedtime to time of arising. This method is more accurate than using fixed sleeping times which leads to significant misclassification of NVF (16). A minimum of 4 recorded sleeping hours was required for inclusion as an adequately completed FVC. NVF was estimated as the mean of two nights (when available) or the frequency of one night, to allow analyses of as many participants as possible.

NOCTURIA, INCIDENCE AND RESOLUTION

Nocturia was defined as a NVF ≥2. Resolution was defined as nocturia at baseline but *no* nocturia at follow-up 1 (FU-1). The incidence rate was determined by dividing the number of new cases of nocturia at FU-1 by the total number of participants without nocturia at baseline. The resolution rate was determined by dividing the number of men who did not have nocturia at FU-1 by the number of men who had nocturia at baseline.

NOCTURIA FROM IPSS-QUESTIONNAIRE

We used the IPSS nocturia question to determine IPSS-NVF. IPSS-NVF and FVC-NVF were compared by subtracting IPSS-NVF from FVC-NVF. We defined *scores* ≥1 as FVC-NVF>IPSS-NVF and scores ≤ -1 as FVC-NVF<IPSS-NVF

STATISTICAL ANALYSES

All men were divided into 5-year age strata and their general characteristics were noted. For each stratum the prevalence rate for nocturia was determined and compared throughout the FU-rounds using the McNemar's test. Incidence and resolution rates were also determined. Finally, the results of the FVCs were compared with IPSS data on nocturia to establish whether men had a higher or lower estimated NVF. A p-value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS® version 15.0.

RESULTS

Baseline characteristics of the study population are presented in table 6.1. The median age was 60.9 (IQR: 56.1-66.2) years. Most men (75.6%) had an IPSS≤7.

At baseline 1,597 men (95% of the responders) completed a 3-day FVC. Because of missing data on bedtime and time of rising (n=372) and exclusion criteria (n=103), the NVF could be determined in 1,122 men at baseline (71% of the completed charts); 701 (74%), 360 (76%), and 302 (76%) charts were used for analyses in the follow-up rounds after 2.1 (FU-1), 4.2 (FU-2) and 6.5 years (FU-3), respectively. In the excluded men, scores on the IPSS nocturia question did not differ from those in men who provided exact data on sleeping hours (p=0.251).

Table 6.2 shows prevalence rates of nocturia (by age strata) at baseline and follow-up. In the total group, prevalence of nocturia increased significantly over time from 34.4% at baseline to 44.7% after 6.5 years (p<0.01). After 6.5 years there was a significant increase in prevalence for all baseline age strata, except for the 65-69 year-olds.

Table 6.1 Baseline characteristics of the study population (n=1,122)

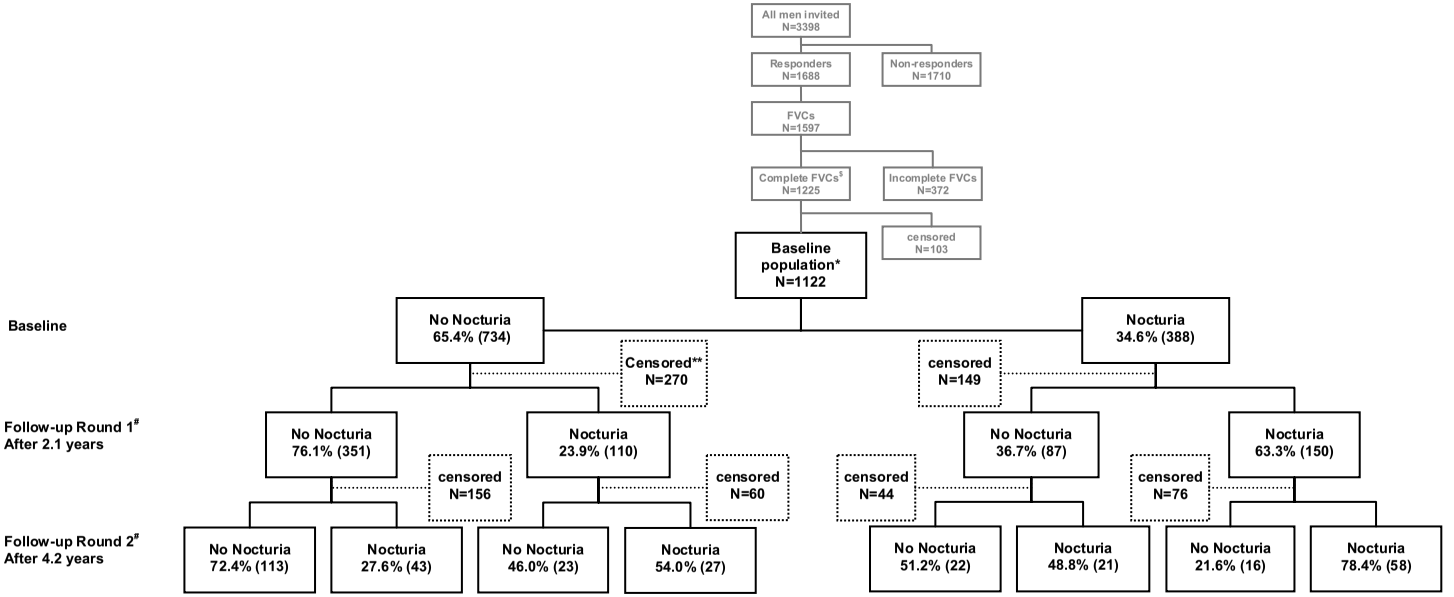
Age (years)	**Median (IQR)**
	60.9 (56.1-66.2)
Age group (years)	**n (%)**
50-54	213 (19.0)
55-59	297 (26.5)
60-64	265 (23.6)
65-69	215 (19.2)
70-78	132 (11.8)
IPSS	**Median (IQR)**
	4 (1-7)
IPSS categories	**n (%)**
None (0)	113 (10.1)
Mild (1-7)	735 (65.5)
Moderate (8-19)	246 (21.9)
Severe (20-35)	28 (2.5)
NVF per age group (years)	**Median (IQR)**
50-54	1.0 (0.5-1.5)
55-59	1.0 (0.5-1.5)
60-64	1.5 (1.0-2.0)
65-69	1.5 (1.0-2.0)
70-78	2.0 (1.0-2.5)
Total	*1.5 (1.0-2.0)*

IQR: inter quartile range, NVF: nocturnal voiding frequency, IPSS : International Prostate Symptom Score

Table 6.2 Prevalence (in %) of nocturia based on frequency-volume charts

Age group (years)	**Baseline n=1122 % (95% CI*)**	**Follow-up 1 2.1 years n=701 % (95% CI)**	**Follow-up 2 4.2 years n=360 % (95% CI)**	**Follow-up 3 6.5 years n=302 % (95% CI)**
50-54	*19.7 (14.3-25.1)*	23.4 (15.8-30.9)	39.0 (26.2-51.8)#	33.8 (22.3-45.4)#
55-59	*24.6 (19.7-29.5)*	28.6 (22.1-35.1)	33.0 (24.1-42.0)	34.8 (24.7-44.9)#
60-64	*36.6 (30.8-42.4)*	40.2 (32.9-47.6)	45.7 (35.5-56.0)	52.6 (41.2-64.1)#
65-69	*46.1 (39.3-52.8)*	44.2 (35.8-52.6)	60.9 (48.7-73.2)	58.7 (43.9-73.5)
70-78	*56.8 (48.3-65.4)*	61.8 (50.7-73.0)	55.9 (38.3-73.5)	60.9 (39.3-82.5)#
Total	*34.4 (31.6-37.2)*	*37.2 (33.7-40.8)*	*44.4 (39.3-49.6)#*	*44.7 (39.1-50.3)#*

*95% Confidence Interval; #McNemar's test compared to baseline, p<0.05;



Flowchart showing fluctuation of nocturia (defined as 2 or more nocturnal voids) in open population of older men as declared on FVCs. Asterisk indicates all men who completed FVC and did not meet exclusion criteria at baseline. Double asterisk indicates censored or lost to follow-up, including men who moved out of area, did not respond to re-invitation, were deceased or met exclusion criteria. Pound sign indicates that number of men and prevalence rates do not concur with numbers in flowchart per round because in prevalence rate, men who did not complete FVC in previous rounds can be included while this is not possible in flowchart. Dollar sign indicates FVCs with reported sleeping hours.

Table 6.3 Incidence and resolution rates after 2.1 years#

Age group (years)	Incidence (n=464) % (95% CI*)	Resolution (n=237) % (95% CI*)
50-54	18.6 (10.7-26.4)	59.3 (39.5-79.1)
55-59	20.4 (13.7-27.1)	46.8 (32.0-61.6)
60-64	25.7 (17.5-33.8)	32.8 (20.7-44.9)
65-69	24.4 (14.6-34.1)	30.0 (18.1-41.9)
70-78	47.1 (29.4-64.7)	26.2 (12.3-40.1)
total	*23.9 (20.0-27.8)*	*36.7 (30.5-52.9)*

#Based on frequency-volume charts
* 95% Confidence Interval

Table 6.3 presents incidence and resolution rates of nocturia after 2.1 years. The overall incidence rate was 23.9% after 2.1 years: incidence was highest in the oldest group (70-78 years) and lowest in the youngest group (50-54 years). The overall resolution rate was 36.7%, being highest in the youngest group and lowest in the oldest group. The incidence rate is lower than the resolution rate; however, since the absolute number of men with incident nocturia is higher, the prevalence rate increases over time.

Figure 6.1 shows the pattern of incidence and resolution of nocturia during follow-up. Of the men with nocturia at baseline, 36.7% did not have nocturia after 2.1 years; of the latter group, 48.8% had nocturia again after 4.2 years. Of the men who had nocturia at baseline and after 2.1 years, 21.6% did not have nocturia after 4.2 years. Thus, most men who did not have nocturia at baseline did not develop nocturia during 4.2 years of follow-up, and of those with nocturia at baseline the majority still had nocturia after 4.2 years.

COMPARISON OF IPSS AND FVC

Table 6.4 presents a comparison of the IPSS and FVC data. Of the men who completed both their FVC and IPSS at baseline (n=1122), 33.3% reported a lower NVF on their FVCs, 60.3% scored an equal frequency, and 6.3% claimed a higher NVF on the IPSS questionnaire than on the FVC. A lower frequency on the IPSS nocturia question than on FVC was least prevalent in the youngest age group. Of the men who had FVC-NVF<IPSS-NVF at baseline, 23.3% had this again after 2.1 years. Men who made a correct estimation or who had FVC-NVF>IPSS-NVF, showed a similar pattern in the subsequent follow-up. However, men who had FVC-NVF<IPSS-NVF more often had FVC-NVF<IPSS-NVF again in the subsequent follow-up. Overall, most men do not estimate their IPSS-NVF to be higher than the recorded NVF on their FVC.

Table 6.4 Consistency of under-, correct, and overestimation of the nocturnal voiding frequency (NVF), based on the IPSS* nocturia question and on FVC** data, with FVC used as reference

Baseline: n=1,122		**Follow-up 1: n= 698**		
		FVC-NVF>IPSS-NVF	*FVC-NVF=IPSS-NVF*	*FVC-NVF<IPSS-NVF*
FVC-NVF>IPSS-NVF #	(%)	(%)	(%)	(%)
<65 years	32.6	*37.9*	*60.1*	*2.0*
≥65 years	34.9	*51.4*	*44.4*	*4.2*
total	33.3	*42.2*	*55.1*	*2.7*
FVC-NVF=IPSS-NVF ##		*FVC-NVF>IPSS-NVF*	*FVC-NVF=IPSS-NVF*	*FVC-NVF<IPSS-NVF*
<65 years	59.9	*27.1*	*67.6*	*5.4*
≥65 years	61.4	*28.2*	*65.6*	*6.1*
total	60.3	*27.4*	*67.0*	*5.6*
FVC-NVF<IPSS-NVF ###		*FVC-NVF>IPSS-NVF*	*FVC-NVF=IPSS-NVF*	*FVC-NVF<IPSS-NVF*
<65 years	7.5	*21.2*	*51.5*	*27.3*
≥65 years	3.7	*50.0*	*40.0*	*10.0*
total	6.3	*27.9*	*48.8*	*23.3*

*International Prostate Symptom Score-questionnaire

**frequency-volume chart

FVC-NVF>IPSS-NVF indicates that NVF was estimated lower on IPSS than on FVC

FVC-NVF=IPSS-NVF indicates that NVF was estimated equally high on IPSS as on FVC

FVC-NVF<IPSS-NVF indicates that NVF was estimated higher on IPSS than on FVC

DISCUSSION

This study shows that the prevalence rate of nocturia increases with age and over time, and that the incidence and resolution rates are relatively high. Because this is the first report on FVC-based longitudinal data on prevalence, incidence and resolution of nocturia, a direct comparison with other studies is not possible.

The TAMUS study provided longitudinal data on nocturia based on questionnaires (DAN-IPSS-1) (3). However, the methodology of that study differs from ours regarding: 1) the inclusion criteria: specific birth years vs. men in a specified age range, 2) the follow-up period: 5 years vs. 2.1 years, 3) the definition of nocturia: categorized as mild (1-2 times), moderate (3-4) or severe (5+) vs. NVF ≥2, 4) definition of resolution: change from any DAN PSS-1 symptom category to a lower category vs. change to NVF<2, and 5) the assessment tool used: questionnaire vs. FVC. This

rules out a straightforward comparison. Moreover, the DAN-PSS-1 nocturia question: "*How many times do you have to urinate during the night?"* does not imply that one has to get up out of bed to void (10). Thus, the DAN-PSS-1 does not concur with the ICS definition of nocturia (2).

In the Krimpen study, the incidence rate of 23.9% expressed in cases per 1000 person years (PY) i.e. 129/1000 PY after 2.1 years, is considerably higher than the TAMUS rate of 75/1000 PY after 5 years. The Krimpen study resolution rate is also considerably higher than in the TAMUS study (214/1000 PY vs. 35/1000 PY). The difference in incidence and resolution might be explained by differences in the follow-up period: in a 5-year period an individual's nocturia might resolve but then become incident again (see Fig. 6.1). Furthermore, epidemiological studies have shown that a longer follow-up period can result in lower incidence rates in diseases with a tendency to resolve (17). The difference in resolution rate might be due to the different response categories used in the DAN-PSS-1. For example, most men have moderate nocturia; therefore men who change from 2 voids to 1 void would be classified as resolved in our study, but not in the TAMUS study where they would remain in the same response category. Nevertheless, it is a fact that nocturia fluctuates over time. This also implies that fluctuation in nocturia is independent of the assessment method used. Moreover, this fluctuation implies that it is almost impossible to calculate reliable incidence rates. Preferably, future studies should try to create a sample size sufficient for a focus on subgroups with more durable prevalence and durable resolution of nocturia.

One limitation of the present study is that we used exact sleeping hours to define "the night", thereby excluding some men from the analysis. However, the scores on the IPSS question in the excluded men did not differ from those in men with exact sleeping-hour data. In addition, because the oldest age groups had fewer men with missing data on sleeping hours, this might have led to slight overestimation of the prevalence of nocturia in the total population.

Resolution of nocturia might be due to medical treatment. Although we did not conduct a pharmaco-epidemiological analysis, we believe that medical treatment does not explain the fluctuation. Our earlier study showed that only 9.5% of all participants sought medical help for LUTS (18); of these, 3.1% received medical treatment, 2.6% watchful waiting, and 3.8% underwent surgical treatment. Furthermore, treatment was not specifically focused on nocturia, and participants who underwent prostate surgery were censored in the current analyses. It has also been shown that nocturnal voiding frequency as a symptom in men with BPH was reduced in only 13.9% of these men, after the start of treatment with an alpha-blocker (19). In a similar study population, equally low medical treatment rates for LUTS were reported (20), reflecting the conservative prescription policy of Dutch

GPs. The low treatment rates also reflect the nature of our study, i.e. a population-based study rather than a (urological) patient study. It is therefore highly unlikely that medical therapy for BPH has a large mitigating effect on nocturia in our study

The second aim was to compare the NVF as estimated on the IPSS and FVCs. About 60% of the men equally estimated their NVF with both assessment methods. Of the men with FVC-NVF<IPSS-NVF, a higher proportion again had a FVC-NVF<IPSS-NVF in the subsequent follow-up; this mainly occurred among men aged <65 years. This might indicate that these men are more focused on nocturia than men aged >65 years. An explanation for this could be that most men >65 years are retired and do not have to get up early for work. However, when treating nocturia, it is important to let patients complete both an IPSS and a FVC for optimal insight into actual NVF, quality of life, and possible cause of nocturia (e.g.: nocturnal polyuria).

CONCLUSION

Because of the high incidence and resolution rates nocturia is often a transient phenomenon. Fluctuation is seen irrespective of the assessment method used. Due to this fluctuation, it is almost impossible to provide reliable incidence rates of nocturia in community-dwelling older men. Because fluctuation of nocturia might, in part, be due to its multi-factorial etiology, it is important to further elucidate the cause(s) of nocturia. To establish the determinants of incident nocturia, it is advisable to focus on incident nocturia that does not resolve in the subsequent follow-up round. Based on the discrepancy between NVF on FVC and IPSS, this study also underlines the importance of using an FVC as a confirmatory way of assessing nocturia before considering therapeutic interventions.

REFERENCES

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21(2):167-78.
2. Van Kerrebroeck P. Standardization of terminology in nocturia: commentary on the ICS report. BJU Int 2002;90 Suppl 3:16-7.
3. Hakkinen JT, Hakama M, Shiri R, et al. Incidence of nocturia in 50 to 80-year-old Finnish men. J Urol 2006;176(6 Pt 1):2541-5; discussion 2545.
4. Hernandez C, Estivill E, Prieto M, et al. Nocturia in Spanish patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). Curr Med Res Opin 2008;24(4):1033-8.
5. Tikkinen KA, Johnson TM, 2nd, Tammela TL, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 2009;57(3):488-96.
6. Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol 2010;184(2):440-6.
7. Markland AD, Vaughan CP, Johnson TM, 2nd, et al. Prevalence of nocturia in United States men: results from the national health and nutrition examination survey. J Urol 2011;185(3):998-1002.
8. Andersson SO, Rashidkhani B, Karlberg L, et al. Prevalence of lower urinary tract symptoms in men aged 45-79 years: a population-based study of 40 000 Swedish men. BJU Int 2004;94(3):327-31.
9. Coyne KS, Zhou Z, Bhattacharyya SK, et al. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int 2003;92(9):948-54.
10. Tibaek S, Dehlendorff C. Validity of the Danish Prostate Symptom Score questionnaire in stroke. Acta Neurol Scand 2009;120(6):411-7.
11. Meyhoff HH, Hald T, Nordling J, et al. A new patient weighted symptom score system (DAN-PSS-1). Clinical assessment of indications and outcomes of transurethral prostatectomy for uncomplicated benign prostatic hyperplasia. Scand J Urol Nephrol 1993;27(4):493-9.
12. Bright E, Drake MJ, Abrams P. Urinary diaries: evidence for the development and validation of diary content, format, and duration. Neurourol Urodyn 2011;30(3):348-52.
13. Blanker MH, Bohnen AM, Groeneveld FP, et al. Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol 2000;164(4):1201-5.
14. Blanker MH, Groeneveld FP, Prins A, et al. Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. BJU Int 2000;85(6):665-71.
15. Kok ET, Groeneveld FP, Busschbach JJ, et al. Influence of coping styles on quality of life in men with new and increasing lower urinary tract symptoms. The Krimpen Study in community-dwelling men. Urol Int 2007;79(3):226-30.
16. Blanker MH, Bernsen RM, Bosch JL, et al. Relation between nocturnal voiding frequency and nocturnal urine production in older men:a population-based study. Urology 2002;60(4):612-6.
17. Schouten BW, Bosch JL, Bernsen RM, et al. Incidence rates of erectile dysfunction in the Dutch general population. Effects of definition, clinical relevance and duration of follow-up in the Krimpen Study. Int J Impot Res 2005;17(1):58-62.
18. Kok ET, Bohnen AM, Bosch JL, et al. Patient's quality of life and coping style influence general practitioner's management in men with lower urinary tract symptoms: the Krimpen Study. Qual Life Res 2006;15(8):1335-43.
19. Yoshimura K, Ohara H, Ichioka K, et al. Nocturia and benign prostatic hyperplasia. Urology 2003;61(4):786-90.
20. Verhamme KM, Dieleman JP, Bleumink GS, et al. Treatment strategies, patterns of drug use and treatment discontinuation in men with LUTS suggestive of benign prostatic hyperplasia: the Triumph project. Eur Urol 2003;44(5):539-45.

CHAPTER 7

PREVALENCE, INCIDENCE AND RESOLUTION OF NOCTURNAL POLYURIA IN A LONGITUDINAL COMMUNITY-BASED STUDY OF OLDER MEN: THE KRIMPEN STUDY

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ABSTRACT

BACKGROUND: Nocturnal polyuria (NP) is common in older men and can lead to nocturia. However, no longitudinal data are available on the natural history of NP.

OBJECTIVE: To determine prevalence, incidence and resolution rates of NP.

DESIGN, SETTING AND PARTICIPANTS: A longitudinal, community-based study was conducted among 1,688 men aged 50-78 years in Krimpen aan den IJssel, The Netherlands, reference date 1995, with planned follow-up rounds at 2,4, and 6 years. NP was determined with frequency-volume charts. Two definitions of NP were used: a nocturnal urine production of >90 ml/h (NUP90), and the nocturnal voided volume plus first morning void being >33% of the 24 h voided volume (NUV33). Nocturia was defined as ≥2 voids per night. We determined the prevalence of NP at each study round. At first follow-up, we determined the incidence in men without baseline NP, and the resolution in men with baseline NP. Prevalence of NP in men with(out) nocturia was also determined.

RESULTS AND LIMITATIONS: At baseline, the prevalence of NUP90 was 15.0% and increased to 21.7% after 6.5 years, whereas the prevalence of NUV33 was 77.8% at baseline and 80.5% after 6.5 years. At 2.1-years of follow-up, for NUP90 and NUV33 the incidence rate was 13.6% and 60.3% and the resolution rate 57.0% and 17.8%, respectively. Because of this fluctuation in NP no reliable long-term incidence rates could be calculated. At baseline NUP90 was prevalent in 27.7% of the nocturics and in 8.0% of the non-nocturics. At baseline, NUV33 was prevalent in 91.9% of the nocturics and in 70.1% of the non-nocturics.

CONCLUSIONS: Due to the fluctuation of NP it is advisable to first determine its chronicity and cause before starting treatment for NP. Because of the high prevalence in non-nocturics, NUV33 should be reconsidered as a discriminative definition of nocturnal polyuria.

INTRODUCTION

Nocturia is a common symptom in older men and is an important cause of sleep disruption. In 2002 the International Continence Society (ICS) defined nocturia as waking one or more times at night to void [1, 2]. Tikkinen *et al*. showed that nocturia becomes clinically relevant if a person has to get out of bed two or more times per night [3].

Basically, nocturia occurs when the urine production at night is greater than the functional capacity of the bladder. An important cause of this phenomenon is nocturnal polyuria (NP). A high nocturnal urine production, or nocturnal polyuria can, amongst others, be caused by conditions such as [subclinical] cardiovascular disease, sleep apnea syndrome, anxiety, excessive fluid intake and the use of medication, such as diuretics [4-7]. Various definitions of NP have been proposed. The most widely accepted and used definition defines NP as a nocturnal urine production of ≥ 33% of the total 24-h urine production [1]. Blanker et al. proposed a urine production of ≥ 90 ml/h as the threshold for NP, as this would be the best predictor for nocturia in older men in a general population [8].

Although NP seems to play an important role in the pathophysiology of nocturia, there are few data on its prevalence and incidence. Furthermore, based on longitudinal analysis, our group demonstrated that nocturia fluctuates over time in individual community-dwelling men [9, 10]; therefore, we hypothesized that NP might also fluctuate over time.

To investigate this we determined the prevalence and fluctuation of NP over time (according to two definitions) community-dwelling men aged 50-78 years in using frequency-volume charts (FVCs). Furthermore, we explored the relationship between NP and clinically relevant nocturia as defined by nocturnal frequency that leads to QOL decrease [2].

MATERIAL AND METHODS

The Krimpen study is a longitudinal study on urogenital tract dysfunction and its impact on general health status. The design of this IRB approved study has been described previously [11, 12]. In short, all men aged 50-78 years [reference date June 1995, n=3,924] in the Dutch municipality *Krimpen aan den IJssel* were investigated. Exclusion criteria for participation were: (previous) transurethral or open prostatectomy, prostate or bladder cancer, neurogenic bladder disease, or negative advice from their primary care physician (PCP) based on poor health (e.g. bedridden). These exclusion criteria were chosen because we aimed to study the natural history

in a community-dwelling population without previous surgical procedures of the lower urinary tract or existing neurogenic bladder disease.

At baseline participants completed a 113-item questionnaire, including, amongst others, the International Prostate Symptom Score (IPSS) and a medication list. Subsequently, participants visited the local PCP health center for medical examination. Next, within 4 weeks, appointments were made for further, urological measurements at the Erasmus Medical Centre Rotterdam urological outpatient department. Participants were instructed to complete a FVC and bring it with them at this appointment. Subsequently, all data were entered in the data base by a data manager.

FOLLOW-UP

The follow-up rounds were planned after an average interval of 2, 4 and 6 years [13]. All baseline measurements, including the FVC, were repeated in the same conditions at the respective follow-up rounds. If the participant had not died or moved away, and no exclusion criteria were met, the PCPs were asked to send a re-invitation letter for a first, second and third follow-up round. Men who had undergone lower urinary tract surgery during follow-up were excluded. Additionally, for the third follow-up round, all non-responders of the previous rounds were re-invited.

Data collection for the baseline round started early 1996; the data base was closed in April 2004 after completion of data collection of FU-3.

NOCTURNAL URINE PRODUCTION AND VOIDED VOLUME DETERMINED FROM FVCS

On the FVC, participants reported each micturition in one-hour time units for three days. Additionally, they recorded the volume of each void on the third day. The recording of each day started at midnight (00:00) and ended at midnight (24:00), thus ensuring that the first morning void was always included [8]. The time of arising and bedtime were also noted. Fluid intake was not recorded. Retrospectively, this complies with the 2002 ICS definition of a FVC which states that a FVC should at least record voided volumes for 24 hours [1].

We computed the hourly urine production according to the method of Van Mastrigt and Eijskoot [14]: urine production was assumed to be constant between voids, and hourly urine production was estimated as the volume of each micturition divided by the number of hours that had passed since the previous micturition. Nocturnal urine production (NUP) was estimated as the mean hourly urine production (in millilitres per hour) from 1 a.m. to 6 a.m., when more than 90% of the men were asleep.

The total nocturnal voided volume was determined by using participant-reported sleeping hours: the voided volumes between the hour of going to bed

and the hour of rising plus the first morning void within one hour of arising were summed for each participant.

DEFINITIONS OF NOCTURNAL POLYURIA

Two definitions of NP were used for the purpose of this analysis: nocturnal urine volume > 33% of 24-h total urine volume (NUV33) [1] and an average NUP > 90 ml/h (NUP90) [8]. For each round the prevalence of NP was determined for the different age strata based on the two definitions. Resolution was defined as NP at baseline but *no* NP at follow-up 1 (FU-1). The incidence rate was determined in the subgroup of men who had no NP at baseline and also were investigated at FU-1, by dividing the number of new cases of NP at FU-1 by the total number of participants without NP at baseline.

The resolution rate was determined in the subgroup of men who had NP at baseline and also were investigated at FU-1, by dividing the number of men who did not have NP at FU-1 by the number of men who did have NP at baseline.

We only determined the incidence at FU-1 because of the fluctuation of nocturia which might imply a possible fluctuation of one of its most important causes i.e. NP [10].

We also determined how many men with and without nocturia had NP according to the two definitions, i.e. 'NP prevalence according to nocturia status'. Nocturia was defined as a nocturnal voiding frequency of ≥2.

STATISTICAL ANALYSES

All men were grouped into 5-year age strata and their general characteristics were noted. For each stratum the prevalence rate for NP was determined and compared throughout the FU-rounds using McNemar's test. A p-value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS® version 15.0.

RESULTS

At baseline, 1,597 men completed the FVC. Of these, due to incomplete data, 1,396 were available for analyses. In the consecutive follow-up rounds, due to drop-outs, 958, 720 and 598 FV-charts were available for analyses on NUP90. Because of missing sleeping hours, analyses on NUV33 were possible using 1,067, 793, 393, 400 FVCs.

Characteristics of the baseline population are given in Table 7.1. Median age was 60.7 (q1-q3: 55.8-66.1) years. Most men (75.4%) had no (9.9%) or mild (65.5%) lower urinary tract symptoms, and 27.1% had nocturia.

NP DEFINED AS A URINE PRODUCTION OF >90 ML/H (NUP90)

The overall prevalence of NUP90 increased from 15.0% to 21.7% after 6.5 years (Table 7.2). Table 7.3 shows the prevalence of NUP90 in men with and without nocturia. NUP90 was prevalent in 27.7% of the nocturics at baseline and increased to 55.9% at FU-3; and was prevalent in 8.0% of the non-nocturics at baseline and in 19.8% at FU-3.

Table 7.4 shows the incidence and resolution rates after 2.1 years. The overall incidence rate for NUP90 was 13.6%, whilst the overall resolution rate was 57.0%. The incidence rate was highest in men aged 60-64 and lowest in the youngest group aged 50-54 years. The resolution was highest in men aged 55-59 and lowest in those aged 65-69 years.

Table 7.1 Baseline characteristics of the study population (n=1,396)

Age (years)	**Median (q1-q3)**
	60.7 (55.8-66.1)
Age group (years)	**n (%)**
50-54	289 (20.7)
55-59	360 (25.8)
60-64	335 (24.0)
65-69	265 (19.0)
70-78	147 (10.5)
IPSS	**Median (q1-q3)**
	4 (1-7)
IPSS categories	**n (%)**
None (0)	138 (9.9)
Mild (1-7)	914 (65.5)
Moderate (8-19)	304 (21.8)
Severe (20-35)	40 (2.9)
Prevalence n (%)	
Nocturia*	27.1 (379)

q1-q3; 1st and 3rd quartile, IPSS ; International Prostate Symptom Score, *defined as ≥2 voids per night

Table 7.2 Prevalence of nocturnal polyuria [using 2 different definitions] at baseline and at successive follow-up rounds

Prevalence (in %) of noctural polyuria >90 ml/h

Age group (years)	Baseline n=1396 % (95% CI*)	Follow-up 1 at 2.1 years n=958 % (95% CI)	Follow-up 2 at 4.2 years n=720 % (95% CI)	Follow-up 3 at 6.5 years n=598 % (95% CI)
50-54	11.8 (8.0-15.5)	14.7 (9.7-19.8)	19.3 (12.9-25.7)	19.3 (12.8-25.8)
55-59	12.2 (8.8-15.6)	12.1 (8.0-16.1)	15.9 (10.8-21.0)	18.3 (12.5-24.2)
60-64	12.5 (9.0-16.1)	21.6 (16.4-26.8)	15.3 (10.2-20.5)	**26.4 (19.2-33.5)**[#]
65-69	20.4 (15.5-25.3)	21.1 (15.0-27.3)	23.2 (15.7-30.7)	22.0 (13.7-30.3)
70-78	23.8 (16.8-30.8)	23.2 (14.8-31.7)	18.2 (7.7-28.7)	27.8 (12.4-43.2)
Total	*15.0 (13.1-16.9)*	*17.8 (15.4-20.3)*	*17.9 (15.1-20.7)*	***21.7 (18.4-25.1)***[#]

Prevalence (in %) of noctural polyuria 33% of total 24-h voided volume

Age group (years)	n=1067 % (95% CI*)	n=793 % (95% CI)	n=393 % (95% CI)	n=400 % (95% CI)
50-54	*70.8 (64.5-77.1)*	65.1 (57.5-72.8)	75.4 (64.6-86.1)	74.5 (65.7-83.3)
55-59	74.2 (67.0-79.4)	73.1 (67.0-79.2)	82.1 (74.9-89.4)	78.2 (70.3-86.0)
60-64	*78.4 (73.3-83.5)*	77.4 (71.7-83.1)	80.8 (73.1-88.5)	83.0 (75.8-90.3)
65-69	85.7 (80.9-90.5)	84.1 (78.1-90.2)	88.3 (81.0-95.7)	89.8 (81.9-97.8)
70-78	*83.3 (76.7-89.9)*	86.3 (78.5-94.0)	94.3 (86.2-100)	81.5 (65.8-97.1)
Total	*77.8 (75.4-80.4)*	*76.0 (73.1-79.0)*	*83.0 (79.2-86.7)*	*80.5 (76.9-84.4)*

*95% Confidence Interval; [#]McNemar's test compared to baseline, p<0.05

NP DEFINED AS A NOCTURNAL URINE PRODUCTION >33% OF THE TOTAL 24-H URINE PRODUCTION (NUV33)

The overall prevalence of NUV33 increased from 77.8% at baseline to 80.5% at FU-3 (Table 7.2). Table 7.3 shows the prevalence of NUV33 in men with and without nocturia. NUV33 was prevalent in 91.9% of the nocturics at baseline and in 93.9% at FU-3; it was also prevalent in 70.1% of the non-nocturics at baseline and 78.0% at FU-3.

Table 7.4 shows the incidence and resolution rates after 2.1 years. The overall incidence rate was 60.3%, and the overall resolution rate was 17.8%. The incidence rate was highest in men aged 65-69 and resolution was highest in those aged 50-54 years.

Table 7.3 Prevalence of nocturnal polyuria [NP] in men with and without nocturia [nocturia defined as night time frequency ≥2]

NP defined as a nocturnal urine production >90 ml/h

Age group (years)	Baseline		Follow-up 1		Follow-up 2		Follow-up 3	
	Nocturia n=379 (%)	Non-nocturia n=697 (%)	nocturia n=132 (%)	Non-nocturia n=675 (%)	Nocturia n=92 (%)	Non-nocturia n=330 (%)	nocturia n=68 (%)	Non-nocturia n=343 (%)
50-54	26.8	8.8	60.0	11.6	50.0	17.4	66.7	21.1
55-59	27.1	8.9	38.9	11.2	52.9	9.9	63.6	15.4
60-64	25.3	3.1	56.8	15.4	25.0	13.6	52.2	24.1
65-69	26.3	12.6	30.8	16.7	34.5	27.5	46.7	18.4
70-78	33.8	7.4	42.9	12.7	31.3	4.8	60.0	22.2
Total	27.7	8.0	43.9	13.4	35.9	14.8	55.9	19.8

NP defined as >33% of the total 24-h voided volume

Age group (years)	*n=370*	*n=689*	*n=128*	*n=656*	*n=86*	*n=306*	*n=66*	*n=372*
50-54	85.0	67.3	90.0	63.8	100	74.2	74.7	75.0
55-59	89.4	69.2	82.4	72.3	100	78.9	100	76.3
60-64	93.5	69.0	94.4	73.5	100	75.3	100	78.0
65-69	94.9	76.9	94.7	80.0	96.4	83.7	86.7	90.9
70-78	91.8	71.7	100.0	78.8	100	89.5	100	70.6
Total	91.9	70.1	93.8	72.6	98.8	78.4	93.9	78.0

Table 7.4 *Incidence and resolution rates of nocturnal* polyuria (NP) after 2.1 years

NP defined as a nocturnal urine production >90 ml/h

Age group (years)	Incidence (n=779) % (95% CI*)	Resolution (n=135) % (95% CI)
50-54	10.7 (5.8-15.6)	60.0 (36.5-83.5)
55-59	11.3 (7.0-15.6)	78.3 (60.0-96.5)
60-64	17.8 (12.5-23.1)	*52.9 (35.3-70.6)*
65-69	12.8 (7.0-18.5)	*43.8 (25.6-61.9)*
70-78	16.7 (7.9-25.5)	*57.7 (37.3-78.0*
Total	*13.6 (11.2-16.0)*	*57.0 (48.6-65.5)*

NP defined as >33% of the total 24-h voided volume

Age group (years)	Incidence (n=131) % (95% CI)	Resolution (n=472) % (95% CI)
50-54	58.6 (39.6-77.7)	25.0 (14.8-35.3)
55-59	70.7 (56.2-85.3)	24.8 (17.1-32.5)
60-64	48.6 (31.2-66.0)	14.9 (8.4-21.3)
65-69	66.7 (39.6-93.7)	12.1 (5.6-18.7)
70-78	54.6 (19.5-89.6)	9.1 (1.25-16.9)
Total	*60.3 (51.8-68.8)*	17.8 (14.3-21.3)

*95% confidence interval

DISCUSSION

This study shows that the prevalence of nocturnal polyuria in community-dwelling older men is largely dependent on the definition used. NP is present in about 15% of older men in the open population when we apply a cut-off value of a nocturnal urine production of >90 ml/h to indicate NP [8]. However, when using the more common definition of NP of >33% of the total 24-h voided volume, NP would be present in about 80% of older men. Resolution rates were high when using the NUP90 definition, whilst the incidence was very high when using the NUV33 definition.

Furthermore, NUP90 was prevalent in 27.7% of the nocturics and in 8.0% of the non nocturics, whilst NUV33 was prevalent in 91.9% of the nocturics but also in 70.1% of the non-nocturics. As NP is not the only cause of nocturia, no definition will give a perfect match between NP and nocturia.

Since, to our knowledge, this is the first report on the prevalence and incidence of NP in an open population of older men, it is not possible to make comparisons with other studies. However, a recent study by Weiss et al. showed that in male noc-

turia patients, 90% had NUV33 [15]. Koseoglu et al. found similar results in a Turkish population of benign prostatic hypertrophy (BPH) patients with nocturia [16]. Unfortunately, neither of those studies included non-nocturics for comparison. Our study shows that NUV33 is highly prevalent in both nocturics and non-nocturics. Asplund et al. found that 36.7% of elderly men (mean age 73.0 years) in Sweden have NP, but this was determined by a question: "I am passing large amounts of urine at night" and therefore highly subjective [17]. In our opinion that method is not sufficiently accurate to determine whether or not one has an increased NUP. In women aged > 50 years in the open population, Swithinbank et al. reported that NUV33 was present in 53% with a prevalence of >60% in women aged ≥ 70 years; they also showed that there was no relation between NUV33 and nocturia [18].The study by Weiss et al. also showed that NUV33 was less prevalent in women [15].

Because NUV33 is highly prevalent in both nocturics and non-nocturics, we question the discriminative value of this definition for NP as a cause of nocturia. In our opinion this is due to the fact that the NUV33 definition was first described for a group of nocturia patients [19], but its specificity has never been tested in the open population. The proposed definition of NUP90, albeit only a modest predictor of nocturia, seems to be a more discriminative definition of NP [8].

The high variability (i.e.: incidence and resolution) of NP might in part be explained by the fact that volumes were only recorded over a period of 24 hours at each measurement. However, in a large epidemiological study such as ours, one has to find a balance between precision of the data and a response rate for the particular measurement that is as high as possible. In our study, 95% of the men who responded to the invitation to participate in this longitudinal study completed the FVC at baseline. Furthermore, the large number of participants may attenuate possible variability.

A limitation of our study is that we only used sleeping hours reported by participants for the determination of NUV33, even though this led to the exclusion of some men from the analysis. However, the characteristics of the men without data on sleeping hours did not differ from those who did report them [20]. Moreover, using fixed sleeping hours could lead to a miscalculation of the prevalence of NP due to the wide range in individual sleeping hours [11].

Another possible limitation of our study is the fact that the lost to follow-up rates might create a risk of bias. However, previous analysis of non-responders showed that there was no difference in characteristics in men who did or did not respond [21]. Furthermore, analysis showed that there is no difference in characteristics between men who did or did not reported their sleeping hours [data not shown].

The resolution of NP might be explained, in part, by medical treatment. However, none of our men received desmopressin and almost none stopped using

diuretics. Furthermore, only a few men (3.1%) used alpha-blockers for BPH treatment, despite that they have no significant effect on NP [16]. Therefore we feel that medical treatment, if any, had a negligible impact on the resolution of NP. Another explanation for fluctuation in the prevalence of NP might lie in the multifactorial etiology [4-6]. For example, excessive fluid intake can easily be resolved without the need of a healthcare professional. Therefore we feel it is important to determine the cause of NP before starting treatment.

Although NP seems to be an important cause of nocturia, this study shows that it is often a transient phenomenon. Therefore, we feel that multiple FVCs should be completed by a nocturia patient over a period of time, and that lifestyle changes (such as restricting fluid intake in the evening) should be implemented before the diagnosis NP can be justified and medical treatment started. The proposed NP definition of NUP90 [8] has a higher discriminative value than NUV33.

However, more studies should apply the NUP90 definition to determine its generalizability. Moreover, since both NP definitions are only modest predictors of nocturia [8] more attention should be paid to other possible predictors of nocturia, such as nocturnal bladder capacity (NBC) or the interaction between NP and NBC.

Future studies should also focus on the etiology of NP, to determine what causes resolving and continuous NP. Furthermore, future randomized controlled trials for possible treatment of NP should also take the fluctuation of NP into consideration when calculating sample size. Now that incidence, prevalence and fluctuation of NP are established, it will be possible to study the possible determinants and prognostic factors.

CONCLUSION

Nocturnal polyuria is highly prevalent in older community-dwelling men, but is often a transient phenomenon. Fluctuation in the prevalence of NP occurs regardless of the definition used, and might be due to the multifactorial etiology of NP. Before starting treatment for NP, as a cause of nocturia, it is advised to first determine the cause and chronicity. Furthermore, because of the high prevalence of NP in men with and without nocturia when using the NUV33 definition, this definition of NP does not discriminate between nocturics and non-nocturics.

REFERENCES

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21[2]:167-78.
2. van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, et al. The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21[2]:179-83.
3. Tikkinen KA, Johnson TM, 2nd, Tammela TL, Sintonen H, Haukka J, Huhtala H, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 2010;57[3]:488-96.
4. Asplund R. Nocturia, nocturnal polyuria, and sleep quality in the elderly. J Psychosom Res 2004;56[5]:517-25.
5. Bosch JL, Weiss JP. The Prevalence and Causes of Nocturia. J Urol 2010;184[2]:440-446.
6. Weiss JP, Blaivas JG. Nocturnal polyuria versus overactive bladder in nocturia. Urology 2002;60[5 Suppl 1]:28-32; discussion 32.
7. Cornu JN, Abrams P, Chapple CR, Dmochowski RR, Lemack GE, Michel MC, et al. A Contemporary Assessment of Nocturia: Definition, Epidemiology, Pathophysiology, and Management-a Systematic Review and Meta-analysis. Eur Urol 2012 Jul. 20 *e-pub ahead of print*.
8. Blanker MH, Bernsen RM, Bosch JL, Thomas S, Groeneveld FP, Prins A, et al. Relation between nocturnal voiding frequency and nocturnal urine production in older men:a population-based study. Urology 2002;60[4]:612-6.
9. Hakkinen JT, Hakama M, Shiri R, Auvinen A, Tammela TL, Koskimaki J. Incidence of nocturia in 50 to 80-year-old Finnish men. J Urol 2006;176[6 Pt 1]:2541-5; discussion 2545.
10. van Doorn B, Blanker MH, Kok ET, Westers P, Bosch JL. Once nocturia, always nocturia? Natural history of nocturia in older men based on frequency-volume charts: the Krimpen study. J Urol 2011;186[5]:1956-61.
11. Blanker MH, Bohnen AM, Groeneveld FP, Bernsen RM, Prins A, Ruud Bosch JL. Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol 2000;164[4]:1201-5.
12. Blanker MH, Groeneveld FP, Prins A, Bernsen RM, Bohnen AM, Bosch JL. Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. BJU Int 2000;85[6]:665-71.
13. Kok ET, Groeneveld FP, Busschbach JJ, Hop WC, Bosch JL, Thomas S, et al. Influence of coping styles on quality of life in men with new and increasing lower urinary tract symptoms. The Krimpen Study in community-dwelling men. Urol Int 2007;79[3]:226-30.
14. van Mastrigt R, Eijskoot F. Analysis of voided urine volumes measured using a small electronic pocket balance. Scand J Urol Nephrol 1996;30[4]:257-63.
15. Weiss JP, van Kerrebroeck PE, Klein BM, Norgaard JP. Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia. J Urol 2011;186[4]:1358-63.
16. Koseoglu H, Aslan G, Ozdemir I, Esen A. Nocturnal polyuria in patients with lower urinary tract symptoms and response to alpha-blocker therapy. Urology 2006;67[6]:1188-92.
17. Asplund R. Hip fractures, nocturia, and nocturnal polyuria in the elderly. Arch Gerontol Geriatr 2006;43[3]:319-26.
18. Swithinbank LV, Vestey S, Abrams P. Nocturnal polyuria in community-dwelling women. BJU Int 2004;93[4]:523-7.
19. Weiss JP, Blaivas JG, Stember DS, Brooks MM. Nocturia in adults: etiology and classification. Neurourol Urodyn 1998;17[5]:467-72.

20. van Doorn B, Kok ET, Blanker MH, Westers P, Bosch JLHR. Mortality in Older Men With Nocturia. A 15-Year Followup of the Krimpen Study. Journal of Urology 2012;187[5]:1727-1731.
21. Blanker MH, Prins J, Bosch JL, Schouten BW, Bernsen RM, Groeneveld FP, et al. Loss to follow-up in a longitudinal study on urogenital tract symptoms in Dutch older men. Urol Int 2005;75[1]:30-7.

CHAPTER 8

DETERMINANTS OF NOCTURIA: A LONGITUDINAL ANALYSIS OF A COMMUNITY-BASED GROUP OF OLDER MEN

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ABSTRACT

PURPOSE: Many conditions and characteristics are cross-sectionally associated with nocturia. However, longitudinal associations of frequency-volume chart-based (FVC) nocturia have not yet been studied. We aim to identify [modifiable] determinants of nocturia in older men, in a longitudinal setting.

MATERIALS AND METHODS: A longitudinal, community-based study was conducted among 1,688 men aged 50-78 years in *Krimpen aan den IJssel*, The Netherlands with planned follow-up rounds at 2, 4 and 6 years. Men without radical prostatectomy, transurethral surgery, or bladder or prostate cancer were included. Data were obtained using FVCs, from which the nocturnal voiding frequency (NVF), maximum voided volume (MVV), and (nocturnal) urine production were determined. Nocturia was defined as NVF ≥2. Polyuria was defined as >2800 ml/24h. For nocturnal polyuria two definitions were used: >33% of the 24-h voided volume (NUV33) and a nocturnal urine production of >90 ml/h (NUP90).

Conditions and characteristics were determined via medical examinations and questionnaires. A generalized linear mixed effect model was used to determine factors longitudinally associated with nocturia.

RESULTS: Age (50-55 vs. >60 years), MVV (>300 ml vs. <300 ml), 24-h polyuria, nocturnal polyuria (both definitions), and LUTS were all longitudinally associated with an increased prevalence of nocturia in older men.

CONCLUSIONS: A smaller MVV, LUTS, 24-h polyuria, and nocturnal polyuria [NP] are significant and potentially modifiable determinants of nocturia. The finding that both definitions for NP are independent significant determinants may point at a two-step etiologic process for NP.

INTRODUCTION

Nocturia is a prevalent symptom that may cause considerable bother in the case of ≥ 2 episodes per night (1-5). Cross-sectional associations have been shown between nocturia and conditions such as nocturnal polyuria (NP), obesity, benign prostatic enlargement (BPE), and depression (5-8). Longitudinally however, analyses on determinants of nocturia are limited to the TAMUS study (1). Although well performed, the value of the information from the TAMUS study remains uncertain. That study is based on the DAN-PSS-1 questionnaire (2); because of its response categories, it does not allow the determination of exact nocturnal voiding frequency (NVF) (3, 4). Furthermore, voided volumes and urine production estimates are not taken into account. Moreover, the follow-up period is relatively short.

Frequency-volume charts (FVCs) may represent a more objective method of assessing nocturia because no recall bias is involved (6). The association between questionnaire data and FVCs is only modest (7) and no longitudinal data are available on FVC-assessed nocturia. Such analyses are needed to identify modifiable determinants of nocturia. The present analysis aims to identify longitudinal determinants of nocturia.

MATERIAL AND METHODS

The Krimpen study is a longitudinal study on urogenital tract dysfunction and its impact on general health status. The design of this study has been described extensively elsewhere (9).

In short, all men aged 50-78 years (reference date: June 1995, n=3,924) in a Dutch municipality were investigated. Exclusion criteria were: prostatectomy, prostate or bladder cancer, neurogenic bladder disease, or negative advice from their general practitioner (GP) based on poor health.

At baseline, participants completed a 113-item questionnaire, including questions on chronic diseases, smoking, alcohol intake, and the I-PSS. Subsequently, participants visited the local GP health centre for a medical examination. Next, appointments were made for urological measurements at the Erasmus Medical Center Rotterdam urological outpatient department. Participants were also instructed to complete a FVC.

FOLLOW-UP

Follow-up (FU) rounds were planned after 2, 4 and 6 years (10). All baseline measurements, were repeated under the same conditions at the respective follow-up rounds. If participants had not died or moved away, and no exclusion criteria were

met, the GPs were asked to send a re-invitation letter for the follow-up rounds. At the third follow-up round, all non-responders of the previous rounds were re-invited.

Nocturnal urine production and voided volumes determined via FVCs

On their FVC, participants reported each micturition in 1-h time units (e.g. "n" micturitions between 12:00–13:00) for three days. Additionally, they recorded the volume of each void on the third day. Recording of each day started at midnight (00:00) and ended at midnight (24:00), ensuring the first morning void was always included (8). Night-times, as defined by the ICS (4), were noted, fluid intake was not recorded. This complies with the ICS definition of a FVC (11).

We computed the hourly urine production according to the method of Van Mastrigt and Eijskoot (12): urine production was assumed constant between voids, hourly urine production was estimated as the volume of each micturition divided by the number of hours that passed since the previous micturition. Nocturnal urine production (NUP) was estimated as the mean hourly urine production from 1 a.m. to 6 a.m., when >90% of the men were asleep(8). Four consecutive hours of night-time was the minimum for inclusion.

Nocturnal voided volume (NUV) was determined by using participant-reported night-times: the voided volumes between bedtime and hour of rising plus the first morning void were summed.

The following variables were also determined via FVC: maximum voided volume (MVV), defined as the largest voided volume during 24h, 24-h voided volume (24HVV), and the nocturnal voiding frequency (NVF), defined as the number of voids between declared hours of night time. NVF does not include voids before going to sleep and at time of rising. Nocturia was defined as NVF≥1 by the ICS. However, because this is very prevalent and because NVF<2 does not seem to cause bother, we defined nocturia as NVF ≥2 in order to study the determinants of nocturia that might be clinically relevant (5, 7).

Polyuria and nocturnal polyuria [NP]

For polyuria, the ICS definition was used: a 24HVV >2800 ml (11). Although usually weight-corrected, we used this fixed definition for practical purposes. We applied two definitions of NP. First, we used the definition proposed by the ICS where NP is defined as NUV being >33% of the 24HVV (NUV33) in people over 65 (4). Although the median age at baseline of our participants was 61.6 years, we used this definition for all our subjects for practicality.

For comparison, NP defined as a nocturnal urine production >90 ml/h (NUP90) was used; this definition was chosen because a previous study determined this to be the strongest predictor of nocturia (8).

LOWER URINARY TRACT SYMPTOMS

The 7-item I-PSS-questionnaire was used to determine the severity of lower urinary tract symptoms (LUTS) in our study. However, in the present analysis we did not use question no. 7 on nocturia to prevent outcome association (13, 14). For clarity, we renamed it 'I-PSS-6'.

STATISTICAL ANALYSES

We analyzed all men who completed their FVC, including reported night-times. Data on these participants were collected during the four rounds. To examine generalizability, we compared baseline characteristics of men included and those excluded because they failed to declare their night-times. For dichotomous variables chi-square tests were used, and for age and LUTS the Mann-Whitney U-test was used.

A generalized linear mixed effect model (GLMM) was used to examine the determinants of nocturia. A GLMM is, essentially, similar to multiple regression analysis, but allows correlation between repeated measurements and is able to adjust for unequal follow-up times, missing data, and fluctuating variables (e.g. hypertension, nocturia), (1, 14, 15). Because of these characteristics a GLMM is cannot give ORs for single end points. Furthermore, in longitudinal studies participant characteristics might change over time, also due to drop out. A GLMM is based on all participants and not just on those who do not drop out. Therefore, the chance of bias due to the changing population characteristics is small in this analysis.

First, we performed univariable linear regression analyses to examine the association of variables with nocturia. Variables with an association of $p<0.25$ were selected for a multivariable GLMM. After manual backward selection a final model was created with only variables with a significant association with nocturia. Significance was defined as p-value <0.05.

The following factors were included: age, I-PSS-6, reduced flow rate (qmax <15 ml/s), post-void residual >50 ml (PVR50), prostate volume >30 ml, 24-h polyuria, NP (NUV33 and NUP90), MVV, diabetes, hypertension, cardiac symptoms, chronic obstructive pulmonary disease (COPD), alcohol intake >2 units/day, and smoking. For clarity, we categorized age (5-year age strata), and MVV (150 ml volume strata). For MVV we took the interquartile range of a previous analysis on the normal values of voided volumes as our reference value (300-450 ml) (16). We checked for interactions between characteristics by adding dummy variables to the model. All analyses were performed with IBM-SPSS® 20.0.

RESULTS

At baseline, 1,597 (95% of the participants) men completed a FVC, of which 109 (1%) met the exclusion criteria. 346 (23%) men failed to indicate night-times and were also excluded. Therefore, FVC-based nocturia could be determined in 1,142 men (77% of the participants with a FVC). Median [IQR] NVF at baseline for all men in the study was 1.5 [1.0-2.0]. During follow-up nocturia could be determined in 687, 351 and 350 men, respectively. Because of missing data on different variables, 920, 556, 289, and 319 measurements in the respective rounds could be taken into account.

At baseline, the prevalence of nocturia was 34.3%. Table 8.1 compares characteristics of men included and excluded at baseline. Age was the only variable with a significant difference (61.6 years vs. 59.9 years).

Table 8.1. Comparison of baseline characteristics of participants included in the analysis and those excluded because of incompletely declared actual sleeping hours.

	Included n=1,142	**Excluded n=346**	**p-value**
Age (in years) (median)[$]	61.6	59.9	<0.001
IPSS* (points) (median)[$$]	5.3	5.3	0.519
NPi[$$$] mean (95%CI)			
– Nocturics	0.38 (0.16-0.63)	N/A****	
– Non-nocturics	0.32 (0.14-0.56)	N/A****	
Prevalence (%)[$$$]			
Nocturia	34.3	N/A****	
Qmax<15 ml/s**	22.7	27.0	0.469
Post-void residue >50 ml	11.0	12.0	0.531
Hypertension	16.0	15.0	0.999
Diabetes	3.0	2.0	0.363
COPD***	5.0	4.0	0.675
Cardiac symptoms	6.0	8.0	0.123
Smoking	24.1	25.4	0.844
Alcohol intake > 2 units/day	19.1	16.4	0.525

[$]: Mann-Whitney U test, [$$]: Chi-square test, [$$$]:Nocturnal polyuria index: total nocturnally produced urine divided by the total 24-hour produced volume, *International Prostate Symptom Score,**maximum flow-rate <15 ml/s,***Chronic Obstructive Pulmonary Disease, ****N/A: in men without a complete FVC, NPi and nocturia could not be determined

Table 8.2. Univariable and multivariable generalized linear mixed effect models for the determinants for nocturia.

	Univariable analysis		GLMM[#] (n=2.403)	
Characteristic	**OR (95% CI*)**	**p-value**	**OR (95% CI)**	**p-value**
Age group (in years):				
50-55	Reference		Reference	
55-60	1.345 (0.982-1.841)	0.064	1.223 (0.876-1.707)	0.238
60-65	2.217 (1.624-3.026)	<0.001	1.773 (1.274-2.469)	0.001
65-70	3.863 (2.799-5.331	<0.001	2.487 (1.765-3.504)	<0.001
70-75	5.783 (3.980-8.401)	<0.001	3.204 (2.148-4.780)	<0.001
75 and over	5.470 (3.348-8.937)	<0.001	2.833 (1.696-4.734)	<0.001
MVV[##] (in ml):				
1-150	1.915 (1.065-3.443)	0.030	3.676 (1.712-7.894)	0.001
150-300	1.558 (1.245-1.950)	<0.001	1.609 (1.271-2.038)	<0.001
300-450	Ref.		Ref.	
450-600	0.690 (0.538-0.885)	0.004	0.534 (0.410-0.695)	<0.001
600 and over	0.661 (0.481-0.908)	0.011	0.346 (0.242-0.495)	<0.001
24-hour polyuria[†]	2.101 (1.403-3.146)	<0.001	3.791 (1.898-7.571)	<0.001
Nocturnal polyuria[††]:				
NUV33	4.584 (3.657-5.746)	<0.001	3.081 (2.421-3.922)	<0.001
NUP90	4.996 (3.929-6.354)	<0.001	5.956 (4.432-8.005)	<0.001
Post-void residual >50 ml	1.894 (1.465-2.450)	<0.001	NS	--
Qmax<15 ml/s	1.982 (1.595-2.464)	<0.001	NS	--
Prostate volume >30 ml	1.198 (0.997-1.440)	0.054	NS	--
IPSS-6[###]	1.123 (1.103-1.143)	<0.001	1.083 (1.063-1.104)	<0.001
Hypertension**	1.658 (1.291-2.130)	<0.001	NS	--
Diabetes	1.179 (0.743-1.871)	0.485	NI	--
COPD***	1.778 (1.172-2.698)	0.007	NS	--
Cardiac symptoms	2.417 (1.662-3.515)	<0.001	NS	--
Smoking	0.561 (0.447-0.706)	<0.001	NS	--
Alcohol intake >2 units/day	0.567 (0.449-0.716)	<0.001	NS	--

*Confidence Interval, **as declared on their questionnaire, ***Chronic Obstructive Pulmonary Disease, [#]Generalized linear mixed effect model, [##]Maximum Voided Volume per 24 hours, [###]International Prostate Symptom Score minus the points for the nocturia question.

[†]24-hour polyuria: defined as a urine production of >2800 ml per 24 hours

[††]Nocturnal polyuria:

NUV33: nocturnal polyuria defined as the nocturnal voided volume being >33% of total 24-hour voided volume. NUP90: nocturnal polyuria defined as a nocturnal urine production of >90 ml/h between 1 a.m. and 6 a.m.

N/A: not applicable, NS: not significant, NI: not included in the final analyses.

Table 8.2 shows the univariable associations with nocturia: age, 24-h polyuria, NP (both definitions), PVR50, qmax<15, IPSS-6, hypertension, COPD, and cardiac symptoms are longitudinally associated with nocturia. MVV >450 ml, smoking, and alcohol intake ≥ 2 units per day are associated with not having nocturia.

In the GLMM (Table 2) higher age, a MVV <300 ml, polyuria, NP (both definitions!), and IPSS-6 are associated with increased prevalence of nocturia, whereas a MVV >450 ml is associated with decreased prevalence. One interaction was found; between polyuria and NUP90 (P<0.001). For this we corrected in the final model.

DISCUSSION

We conclude that an increased prevalence of nocturia is longitudinally associated with age, 24hr-polyuria, NP [both definitions], LUTS, and a smaller MVV. Previous cross-sectional studies indicated four major causes of nocturia: polyuria, NP, decreased bladder capacity, and sleep disturbance (17). These earlier results (expect for sleep disturbance on which we had no data) are confirmed by this longitudinal, FVC-based study.

Although our results seem to confirm previous studies, to the best of our knowledge, we are the first to report on which factors are longitudinally associated with nocturia; therefore, a direct comparison is not readily possible. However, Hakkinen et al. reported on the determinants of incident nocturia and concluded that, after 5 years of follow-up, the determinants of mild nocturia were: being single, diabetes, heart disease, arthritis, and for moderate to severe nocturia (≥3) depressive symptoms or the use of anti-depressants (18). These results do not match ours and are possibly explained by the following differences: the TAMUS study based their nocturia data on questionnaires, whilst our data are derived from FVCs. Previous analyses showed modest agreement between questionnaire-, and FVC-derived nocturia (7, 14). Using FVCs to determine the NVF might be preferable, due to lack of recall bias (6). Additionally, Hakkinen et al. categorized their nocturia into three categories, whereas we defined nocturia as ≥2 voids per night which might be a more relevant definition since Tikkinen et al. showed this cut-off value gives rise to bother (5). Furthermore, the Krimpen study included urological measurements. Cross-sectionally, urological parameters are associated with nocturia and could have influenced the results. Another difference is the follow-up time and number of follow-up rounds. The TAMUS study had one follow-up round. Because of the fluctuating character of nocturia, one follow-up round might not provide sufficient information. Furthermore, only men from certain birth years (1924, 1934,

and 1944) were included whereas studying men in an age range would be a better representation of a population and therefore more generalizable.

Five studies have determined factors cross-sectionally associated with nocturia among various populations. The BACH study included 5,506 individuals (2,301 men) aged 30-79 years (19). The FINNO study included 3,307 participants (1,594 men) (median 40 years) (20). Bing et al. included men (n=1,486) and women (n=1,313) aged 60-80 years (21). The NHANES study published an analysis on nocturia and included 15,988 persons, of whom 7,455 men aged 20-90 years (22). A baseline analysis of the Krimpen study was also performed (7). These studies show similar results: all associated age and BPH [or LUTS s/o BPO] with an increased prevalence and most associated a higher BMI (>25) with nocturia as well as hypertension, diabetes, and cardiac symptoms. In our study, many of the predictive factors cross-sectionally associated were not longitudinally associated with nocturia. Previous studies showed that nocturia fluctuates over time (1, 12, 14). It is possible that a person has, for example, hypertension during the entirety of the study but does not have nocturia continuously and, therefore, the association no longer exists when analyzed longitudinally.

We previously discussed the ICS definition (NUV33) of NP (8, 10). In our cross-sectional analyses, NUP90 appeared to be a stronger predictor for nocturia than NUV33. Interestingly, the current analyses showed that both definitions remained significant in the multivariable analyses. There was no interaction between these two definitions. This seems to acknowledge the differences between the definitions: NUP90 refers to an increased nocturnal urine production whereas NUV33 refers to the ratio between night and daytime volumes. This might indicate that both estimates are of importance. Possibly, a shift in day/night ratio is the first step and a nocturnal overproduction of urine per hour the second step in the etiology of NP.

Treatment of LUTS might have influenced the results. However, of all men included in this analysis, only 20 received medical (n=12) or herbal (n=8) treatment for LUTS at FU-1, so we believe that the influence was minimal (23).

A limitation of this analysis is that we only included men with known night-times, even though >20% of all data on night-times were missing. Our rationale for this is that the use of arbitrary night-times would lead to a considerable miscalculation of the prevalence of nocturia (7). However, our results show that, apart from a clinically irrelevant difference in age, there was no difference in characteristics between men included and excluded.

Another limitation is that we used six questions of the I-PSS. Although the I-PSS officially is a seven question tool, we decided not include the nocturia question as this would interact with FVC-nocturia (13, 14). However, in our opinion, it is important to include some form of measurement of LUTS because earlier studies have shown that an I-PSS >7 is a proxy for clinical BPH which predicts higher GP consultation rates (23, 24).

Future studies should focus on both urological measurements and extended questionnaires to confirm our conclusions and to search for additional modifiable determinants. Specifically, studies should focus on causes of NP, impaired bladder function, and small MVVs as these factors are important determinants of nocturia.

CONCLUSION

Although many conditions and characteristics are associated with nocturia cross-sectionally, only age, a small MVV, LUTS, polyuria, and NP are associated when analyzed longitudinally. Importantly, a smaller MVV, LUTS, 24-h polyuria, and nocturnal polyuria [NP] are potentially modifiable determinants of nocturia. The finding that both definitions for NP are independent significant determinants may point at a two-step etiologic process for NP.

REFERENCES

1. Hakkinen JT, Hakama M, Shiri R, Auvinen A, Tammela TL, Koskimaki J. Incidence of nocturia in 50 to 80-year-old Finnish men. J Urol 2006;176(6 Pt 1):2541-5; discussion 2545.
2. Tibaek S, Dehlendorff C. Validity of the Danish Prostate Symptom Score questionnaire in stroke. Acta Neurol Scand 2009;120(6):411-7.
3. Meyhoff HH, Hald T, Nordling J, Andersen JT, Bilde T, Walter S. A new patient weighted symptom score system (DAN-PSS-1). Clinical assessment of indications and outcomes of transurethral prostatectomy for uncomplicated benign prostatic hyperplasia. Scand J Urol Nephrol 1993;27(4):493-9.
4. van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, et al. The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21(2):179-83.
5. Tikkinen KA, Johnson TM, 2nd, Tammela TL, Sintonen H, Haukka J, Huhtala H, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 2010;57(3):488-96
6. Bright E, Drake MJ, Abrams P. Urinary diaries: evidence for the development and validation of diary content, format, and duration. Neurourol Urodyn 2011;30(3):348-52.
7. Blanker MH, Bohnen AM, Groeneveld FP, Bernsen RM, Prins A, Ruud Bosch JL. Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol 2000;164(4):1201-5.
8. Blanker MH, Bernsen RM, Bosch JL, Thomas S, Groeneveld FP, Prins A, et al. Relation between nocturnal voiding frequency and nocturnal urine production in older men:a population-based study. Urology 2002;60(4):612-6.
9. Blanker MH, Bernsen RM, Ruud Bosch JL, Thomas S, Groeneveld FP, Prins A, et al. Normal values and determinants of circadian urine production in older men: a population based study. J Urol 2002;168(4 Pt 1):1453-7.
10. van Doorn B, Blanker MH, Kok ET, Westers P, Bosch JL. Prevalence, Incidence, and Resolution of Nocturnal Polyuria in a Longitudinal Community-based Study in Older Men: The Krimpen Study. Eur Urol 2013;63(3):542-7.
11. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21(2):167-78.
12. van Mastrigt R, Eijskoot F. Analysis of voided urine volumes measured using a small electronic pocket balance. Scand J Urol Nephrol 1996;30(4):257-63.
13. Barry MJ, Fowler FJ, Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol 1992;148(5):1549-57; discussion 1564.
14. van Doorn B, Blanker MH, Kok ET, Westers P, Bosch JL. Once nocturia, always nocturia? Natural history of nocturia in older men based on frequency-volume charts: the Krimpen study. J Urol 2011;186(5):1956-61.
15. Hox JJ. Multilevel analysis: techniques and applications. 2nd ed. New York: Routledge; 2010.
16. van Doorn B, Kok ET, Blanker MH, Martens EP, Bohnen AM, Bosch JL. The natural history and predictive factors of voided volume in older men: the Krimpen Study. J Urol 2011;185(1):213-8.
17. Cornu JN, Abrams P, Chapple CR, Dmochowski RR, Lemack GE, Michel MC, et al. A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management--a systematic review and meta-analysis. Eur Urol 2012;62(5):877-90.

18. Hakkinen JT, Shiri R, Koskimaki J, Tammela TL, Auvinen A, Hakama M. Depressive symptoms increase the incidence of nocturia: Tampere Aging Male Urologic Study (TAMUS). J Urol 2008;179(5):1897-901.
19. Fitzgerald MP, Litman HJ, Link CL, McKinlay JB. The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey. J Urol 2007;177(4):1385-9.
20. Tikkinen KA, Auvinen A, Johnson TM 2nd, et al. A systematic evaluation of factors associated with nocturia--the population-based FINNO study. Am J Epidemiol. 2009 Aug 1;170(3):361-8.
20. Bing MH, Moller LA, Jennum P, Mortensen S, Lose G. Nocturia and associated morbidity in a Danish population of men and women aged 60-80 years. BJU Int 2008;102(7):808-14; discussion 814-5.
21. Markland AD, Vaughan CP, Johnson TM, 2nd, Goode PS, Redden DT, Burgio KL. Prevalence of nocturia in United States men: results from the National Health and Nutrition Examination Survey. J Urol 2011;185(3):998-1002.
23. Kok ET, Groeneveld FP, Gouweloos J, Jonkheijm R, Bosch JL, Thomas S, et al. Determinants of seeking of primary care for lower urinary tract symptoms: the Krimpen study in community-dwelling men. Eur Urol 2006;50(4):811-7.
24. Kok ET, Bohnen AM, Jonkheijm R, Gouweloos J, Groeneveld FP, Thomas S, et al. Simple case definition of clinical benign prostatic hyperplasia, based on International Prostate Symptom Score, predicts general practitioner consultation rates. Urology 2006;68(4):784-9.

CHAPTER 9

MORTALITY IN OLDER MEN WITH NOCTURIA: A 15-YEAR FOLLOW-UP STUDY

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ABSTRACT

PURPOSE: Although nocturia seems to be related to increased mortality in older men, it is unclear whether this is an independent association. Therefore, we determined the association of nocturia and mortality in community-dwelling older men.

MATERIALS AND METHODS: A longitudinal, population-based study was conducted among 1,688 men aged 50-78 years. Recruitment started in 1995; at baseline all men completed a questionnaire and a 3-day frequency-volume chart (FVC). Nocturnal voiding frequency was derived from the FVC and nocturia was defined as ≥2 voids/night.

In 2010 all general practitioners' patient records were checked for possible date of death. Univariable and multivariable Cox regression analyses were performed. A sub-analysis was performed to determine the role of three longitudinal nocturia patterns (i.e. incident, persistent or transient/resolved) on mortality rate.

RESULTS: 1,114 men were eligible for analysis. Median follow-up time was 13.4 (Q1-Q3: 10.3-14.1) years, for a total of 12,790 person-years of follow-up. Univariably, nocturia was associated with increased mortality rate (HR: 1.63, 95%CI: 1.20-2.21, p=0.002). After correction for possible confounding factors nocturia had no significant influence on mortality (p=0.838), in contrast to age, COPD, smoking, and hypertension (all p<0.05). Persistent nocturia had the highest mortality rate as compared to men without nocturia; however, this association was not significant (p=0.083).

CONCLUSIONS: In an analysis based on FVC data, the association between nocturia and mortality was explained by confounding factors: predominantly, age. Furthermore, the mortality risk was not associated with the three nocturia patterns.

INTRODUCTION

Nocturia is a prevalent condition, generally described as a frequent and bothersome lower urinary tract symptom associated with an impaired quality of life, particularly when two or more episodes occur per night (1-4). Moreover, an increased mortality rate has been reported for men and women with nocturia (5-8). However, most studies on the association between nocturia and mortality were based on a (relatively) short follow-up period or on a selected population. Furthermore, the studies were questionnaire based, which is probably a disadvantage in view of the modest correlation between questionnaire data and the number of nocturnal voids recorded on a frequency-volume chart (FVC) (9).

Based on longitudinal analysis of FVCs we introduced the concept of fluctuation of nocturia over time (1, 10). This fluctuation can be divided into three patterns: incident nocturia, persistent nocturia, and transient/resolved nocturia. These patterns might indicate different causes of nocturia, possibly resulting in different mortality rates.

The aim of this study was to determine associations between mortality and nocturia based on long-term FVC data, and to evaluate differences in long-term mortality rate among men with different nocturia patterns.

MATERIAL AND METHODS

The Krimpen study is a longitudinal study on urogenital-tract dysfunction and its impact on general health status. The design of this IRB-approved study has been described elsewhere (9, 11). In short, all men aged 50-78 years (reference date: June 1995, n=3924) in the Dutch municipality *Krimpen aan den IJssel* were investigated. Exclusion criteria for participation were: a history of transurethral or open prostatectomy, prostate or bladder cancer, neurogenic bladder disease, or negative advice from their general practitioner (GP) based on poor health.

At baseline, participants completed a 113-item questionnaire, including the International Prostate Symptom Score (IPSS), and visited the local health centre for medical examination (i.a.: blood pressure, height, weight); the completeness of the questionnaire was checked by their GP. Next, urological measurements were performed at the urology outpatient department of the Erasmus Medical Centre Rotterdam, and participants completed a 3-day FVC. This was repeated after 2, 4, and 6 years.

Frequency-volume chart, nocturnal voiding frequency, and nocturia

On the FVC, participants recorded each micturition in 1-hour time units (first 2 days) and the volume of each void (third day). Bedtime and time of arising were also noted. Fluid intake was not recorded. Retrospectively, this complies with the International Continence Society-definition of a FVC (12). A minimum of 4 recorded consecutive sleeping hours was regarded as an adequately completed FVC. Since nocturia is defined as getting out of bed to void, the nocturnal voiding frequency (NVF) was defined as all voids between bedtime and time of arising. This method is more accurate than using fixed sleeping times, which would lead to misclassification of the NVF (13). The NVF was estimated as the mean of two nights (when available), or the frequency of one night, to allow analyses of as many participants as possible. Nocturia was defined as an NVF ≥2. Fifteen years after baseline (August 2010) all patient files in the GPs' database were checked for (possible) date of death. Men who had moved out of the study area were censored. Men whose files could not be retrieved were excluded. If a file could not be found or data were missing, the last known date from the study database was used as day of censoring.

Exact cause of death in many participants could not be determined because the GP's description was too general (e.g. "cardiac arrest"), even though the underlying cause was clearly different. Therefore, these data were not included in any analysis.

Analyses

All men with complete FVCs were selected and baseline characteristics were analyzed. Possible differences in characteristics between men with and without complete FVCs, and between men with and without nocturia, were analyzed using the Mann-Whitney-U test and the Chi-square test, respectively.

The association between nocturia and mortality was assessed with Kaplan-Meier (KM) survival curves. A univariable proportional hazard ratio (HR) was calculated to determine the association between nocturia and mortality. To correct for other variables, based on previously suggested risk factors for mortality (7, 8), univariable proportional HR analyses were performed on the following characteristics: age, albuminuria (determined with a dipstick), obesity (body mass index >30), hypertension (defined as a resting systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of 90 mmHg, or men who are taking antihypertensive medication), and questionnaire extracted: diabetes mellitus, chronic obstructive pulmonary disease (COPD), cardiac symptoms, smoking (yes/no), and alcohol consumption (>2 units/day). Variables with a p-value <0.25 were included in the multivariable Cox regression analysis. First, a Cox regression model for nocturia corrected for age was created (model 1). Second, a manual backward selection procedure was performed to create a final model including nocturia and all sig-

nificant variables ($p<0.05$) (model 2). The final HRs of nocturia in the models are presented, as well as the univariable results.

To test the influence of different patterns of nocturia on mortality rate, a sub-analysis was performed: all men who completed an FVC both at baseline (BL) and follow-up 1 (FU-1; i.e. 2 years after baseline) were included and their nocturia status was checked at both rounds. Men with no nocturia at BL and nocturia at FU-1 were considered "incident nocturics", if men had nocturia at both BL and FU-1 their nocturia was considered to be "persistent", and if their nocturia had resolved (i.e. nocturia at BL, but not at FU-1) their nocturia was considered to be "transient/resolved". Men with no nocturia at both rounds were considered "non-nocturics". Possible difference in mortality between these 4 groups were plotted in KM curves and also analysed via univariable and multivariable Cox regression. For all statistical analyses SPSS® version 15.0 was used.

RESULTS

At baseline, 1,597 men (95% of the responders) completed both the questionnaire and a 3-day FVC (133 men met exclusion criteria). Due to missing data on bedtime and time of rising ($n=342$, with no significant differences in BL characteristics with the analyzed group), the NVF could be estimated in 1,122 men. Eight deceased participants were excluded from analysis because their GP records could not be retrieved and no date of death could be determined. This leaves 1,114 men available for analysis.

During follow-up, 185 men were censored. The median follow-up period was 13.4 [1st and 3rd quartile (Q1-Q3): 10.3-14.1] years, for a total of 12,790 person-years. In this period 169 men died, yielding a mortality rate of 165/1,000.

The median age was 60.8 (Q1-Q3: 56.0-66.2) years. Most men (75.6%) had an IPSS ≤7 and 34.4% had nocturia.

Men with FVCs including sleeping hours were slightly older than men with missing sleeping hours (60.8 vs. 59.4 years, respectively; $p<0.001$), but did not differ in other characteristics. Particularly, they did not differ in nocturia frequency recorded in the IPSS.

Hypertension, cardiac symptoms, and albuminuria were more prevalent in men with nocturia. Less nocturics smoked, and they were also older: 64.0 (Q1-Q3: 58.7-68.8) vs. 59.3 (Q1-Q3: 55.3-64.8) years, $p<0.001$.

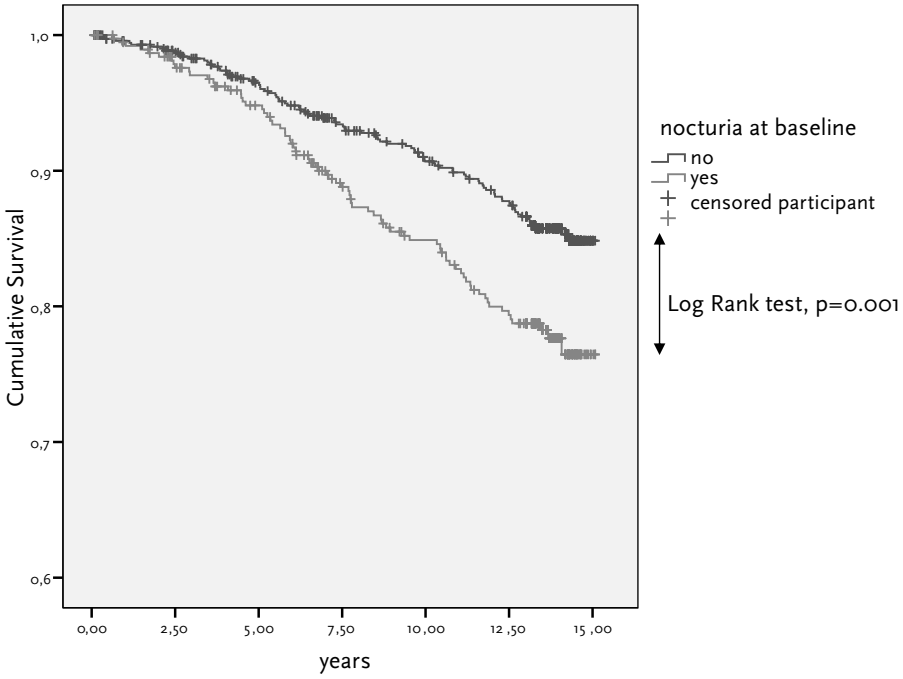

Figure 9.1 Kaplan-Meier curves for men with and without nocturia

Number at risk	Baseline n	5-year follow-up n	10-year follow-up n	15-year FU n
No nocturia	731	636	561	4
Nocturia	383	337	278	3
total	1114	973	839	7

Figure 9.1 presents the KM curves. Estimated 15-year survival rate of men with nocturia was 76.5%, compared to 84.8% for men without nocturia. The univariable HR for mortality in nocturics was 1.63 (95%CI: 1.20-2.21, p=0.002). Age, hypertension, diabetes mellitus, COPD, cardiac symptoms and smoking were related to mortality (Table 9.1, all p<0.05), and were entered in the multivariable Cox regression. After correction for age, the HR of nocturia was 1.05 (95%CI: 0.76-1.42), model 1. The HR of nocturia in the multivariable Cox regression was 1.03 (95%CI: 0.75-1.42). Age, COPD, hypertension, and smoking were independently associated with mortality (model 2).

Table 9.1 Participants' characteristics and their univariable and multivariable relation to all-cause mortality

	Univariable	Multivariable model 1#	Multivariable model 2##
characteristic	**HR (95% CI) p-value**	**HR (95% CI) p-value**	**HR (95% CI) p-value**
Nocturia 2 times or more	1.63 (1.20-2.21) 0.002	1.05 (0.76-1.42) 0.804	1.03 (0.75-1.42) 0.838
Age at baseline	1.14 (1.12-1.17)<0.001	1.14 (1.11-1.17) <0.001	1.14 (1.11-1.16) <0.001
Albuminuria	1.24 (0.66-2.35) 0.507	--	--
Obesity*	0.92 (0.53-1.59) 0.760	--	--
Hypertension**	2.10 (1.55-2.85)<0.001	--	1.51 (1.10-2.06) 0.012
Questionnaire extracted variable (yes/no)			
Diabetes	1.04 (0.46-2.35) 0.928	--	--
COPD***	2.19 (1.26-3.78) 0.005	--	1.90 (1.10-3.29) 0.022
Cardiac symptoms	1.87 (1.12-3.13) 0.017	--	--
Smoking	1.46 (1.05-2.02) 0.023	--	1.68 (1.21-2.33) 0.002
Alcohol intake > 2 units/day	0.67 (0.18-2.99) 0.742	--	--

*Body mass index >30, **Blood pressure >140/90 mmHg or use of antihypertensive medication, ***chronic obstructive pulmonary disease

Model 1: nocturia corrected for age, ##Model 2: final model including nocturia and all variables that were significant in multivariable analysis

Sub-analysis of nocturia patterns was performed in 662 men who completed BL and FU-1. Of these, 50.3% were non-nocturics, 16.0% were incident nocturics, 21.3% had persistent nocturia, and 12.4% had transient/resolved nocturia. 89 men were censored during follow-up. The median follow-up time starting after FU-1 was 11.4 (IQR: 11.0-12.1) years and 87 deaths occurred. The estimated 12.5-year survival rates were: 86.2% for the non-nocturics, 85.8% for the incident nocturics, 80.2% for the persistent nocturics and 87.3% for the transient/resolved nocturics (Fig. 9.2). The univariable HRs for the different nocturia patterns vs. non-nocturia were: 1.10 (95%CI: 0.60-2.02, p=0.758) for incident nocturia, 1.57 (95%CI: 0.94-2.60, p=0.083) for persistent nocturia, and 0.86 (95%CI: 0.42-1.76, p=0.671) for transient/resolved nocturia, respectively.

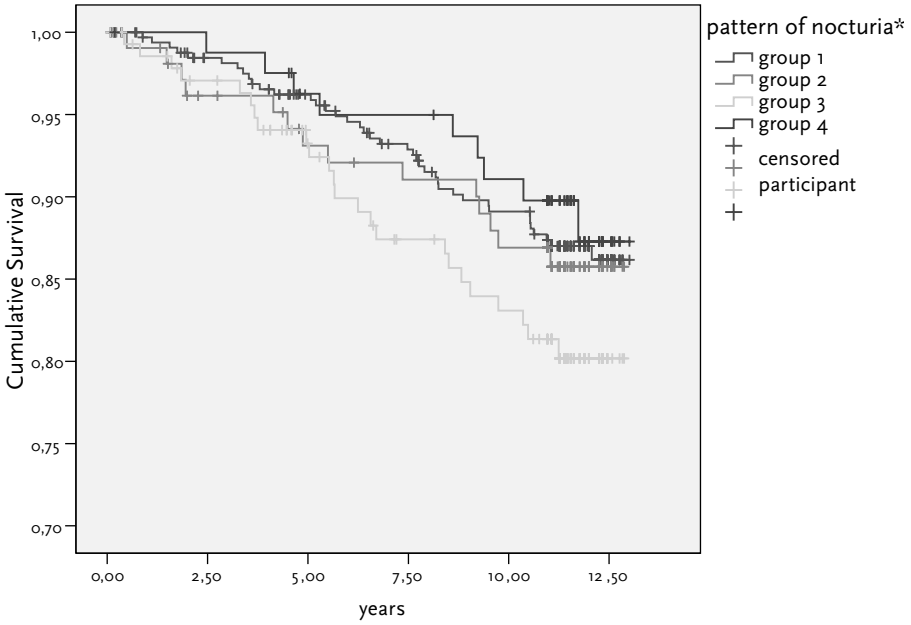

Figure 9.2 Kaplan-Meier curves for the various time-dependent patterns of the prevalence of nocturia

Number at risk	Baseline n	2.5-year follow-up n	7.5-year follow-up n	12.5-year FU n
No nocturia	333	310	275	33
Incident	106	97	88	9
Persistent	141	130	102	4
Transient/resolved	82	81	74	9
total	662	618	539	55

Group 1: no nocturia at baseline and follow-up round 1 (non-nocturia)
Group 2: incident for nocturia at follow-up round 1 (incident nocturia)
Group 3: nocturia at both baseline and follow-up round 1 (persistent nocturia)
Group 4: nocturia at baseline, but not at follow-up round 1 (transient/resolved nocturia)

DISCUSSION

This study shows that the association between nocturia and mortality in community-dwelling older men aged 50-78 years largely depends on a confounding effect of age. It seems that especially men with persistent nocturia might have an increased risk of dying. However, this result is not significant.

Since this is the first FVC-based mortality analysis no direct comparison with other studies is possible. However, four questionnaire-based studies have been reported (5-8). There are some important differences compared with our study: all four studies showed a significantly higher mortality rate (increased HR) in subjects with nocturia after correction for confounders. All studies corrected for age in their multivariable analysis, except the study of Bursztyn et al. in which only 70-year-olds were included; they described an increased HR for nocturia only in men/women who also suffered from coronary heart disease. Although the results of these studies differ from ours, they are not necessarily contradictory: the difference might, in part, be explained by the fact that they all use questionnaires instead of FVCs. It is reported that there is only a moderate correlation between the nocturnal voiding frequency recorded on an FVC and the estimated number on a questionnaire (9). However, when we used the IPSS nocturia question in our mortality analyses or defined nocturia as a NVF≥3, no association was found either (14).

Additional differences between the present study and those of others are as follows: Asplund et al. had a shorter follow-up period (4.5 years), and used a more severe definition of nocturia (NVF≥3) (5). Bursztyn et al. studied a very selected group of older men and women: only 70-year-olds were included (6). Nakagawa et al. had a selected group of subjects (aged ≥70 years) as well as a relatively short follow-up period of 4.5 years (8). Therefore, an age adjustment might have less influence on the significance of nocturia than in our study which had a wider age range. Kupelian et al. reported on the largest population (n=15,988) with a median follow-up of 8.8 years. The age range in their population was 20-90 years, and the corrected HR for nocturia was significant but attenuated in older men (i.e. the age range comparable to our study) (7). The difference in outcome between our study and that of Kupelian et al. may lie in the different study populations. They included more subjects with characteristics related to the prevalence of nocturia: 46.1% of their study population was Caucasian, compared with 98% in our study; it is reported that non-Caucasian males more often have nocturia (15). Furthermore, they included more obese men (19.7% vs. 9.0%), more smokers (32.0% vs. 23.8%) and more diabetics (5.1% vs. 3.6%). The difference in outcome might also be due to the larger number of older men (n=3,424) in their study, causing the effect of nocturia on mortality to be significant.

Treatment for nocturia might influence the described relation. We believe, however, that in the current analyses, the influence of medical treatment is very small. We have shown that only 3.1% of the participants received medical treatment for LUTS, mostly an alpha-blocking agent (16). Moreover, it has been shown that nocturia as a symptom in men with BPH was reduced in only 13.9% of men, using alpha-blocking medication (17).

Our second objective was to evaluate the influence of different patterns of nocturia on the mortality rate. Univariably, men without nocturia had the lowest mortality risk, closely followed by men with incident and transient/resolved nocturia. Although men with persistent nocturia had the highest risk for mortality, the association was not significant. Notwithstanding this result, the higher mortality risk might indicate that men with persistent nocturia need closer attention in the primary care setting.

A limitation of our analysis might be that we only included men with known sleeping hours, even though >20% of all data on "sleeping hours" were missing. We did this because the use of an arbitrary number of sleeping hours would lead to a miscalculation of the prevalence of nocturia (9). This did not result in a selection-bias because we found no difference in the IPSS. However, men with reported sleeping hours were slightly older than those who omitted theirs. Since nocturia prevalence increases with age (10) there might be a slight overrepresentation of nocturics. However, although the difference in age was significant, the clinical relevance (median 60.8 vs. 59.3 years) seems to be limited.

In addition: we cannot distinguish between men who get out of bed at night for other reasons and also happen to void, and men with 'real' nocturia. However, this will apply to both FVCs and IPSS questionnaires. It is possible that 'real' nocturia (and its possible pathophysiological cause) might have a greater influence on the mortality rate (when untreated) than nocturia that is, in reality, a convenience void. The findings in this and other studies need to be confirmed by additional studies that discriminate between 'convenience voids' and nocturia.

CONCLUSION

In contrast to earlier (questionnaire-based) studies we did not find an independently increased risk for nocturia on mortality, regardless of the pattern (i.e. incident, persistent, or transient/resolved nocturia). The effect of nocturia appeared to be largely age-dependent.

REFERENCES

1. Hakkinen JT, Hakama M, Shiri R, et al. J. Incidence of nocturia in 50 to 80-year-old Finnish men. J Urol 2006;176(6 Pt 1):2541-5; discussion 2545.
2. Hernandez C, Estivill E, Prieto M, et al. Nocturia in Spanish patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). Curr Med Res Opin 2008;24(4):1033-8.
3. van Kerrebroeck P, Rezapour M, Cortesse A, et al. Desmopressin in the treatment of nocturia: a double-blind, placebo-controlled study. Eur Urol 2007;52(1):221-9.
4. Lee YS, Lee KS, Jung JH, et al. Prevalence of overactive bladder, urinary incontinence, and lower urinary tract symptoms: results of Korean EPIC study. World J Urol 2009.
5. Asplund R. Mortality in the elderly in relation to nocturnal micturition. BJU Int 1999;84(3):297-301.
6. Bursztyn M, Jacob J, Stessman J. Usefulness of nocturia as a mortality risk factor for coronary heart disease among persons born in 1920 or 1921. Am J Cardiol 2006;98(10):1311-5.
7. Kupelian V, Fitzgerald MP, Kaplan SA, et al. Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. J Urol 2011;185(2):571-7.
8. Nakagawa H, Niu K, Hozawa A, et al. Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. J Urol 2010;184(4):1413-8.
9. Blanker MH, Bohnen AM, Groeneveld FP, et al. Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol 2000;164(4):1201-5.
10. van Doorn B, Blanker MH, Kok ET, et al. Once nocturia, always nocturia? Natural history of nocturia in older men based on frequency-volume charts: The Krimpen study. J Urol 2011 *accepted for publication.*
11. Blanker MH, Groeneveld FP, Prins A, et al. Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. BJU Int 2000;85(6):665-71.
12. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21(2):167-78.
13. Blanker MH, Bernsen RM, Bosch JL, et al. Relation between nocturnal voiding frequency and nocturnal urine production in older men:a population-based study. Urology 2002;60(4):612-6.
14. van Doorn B, Kok ET, Blanker MH, et al. Nocturia: prevalence, incidence and mortality-risk in older men, the Krimpen study. Eur Urol supp 2011;10(2):29.
15. Fitzgerald MP, Litman HJ, Link CL, et al. The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey. J Urol 2007;177(4):1385-9.
16. Kok ET, Bohnen AM, Bosch JL, et al. Patient's quality of life and coping style influence general practitioner's management in men with lower urinary tract symptoms: the Krimpen Study. Qual Life Res 2006;15(8):1335-43.
17. Yoshimura K, Ohara H, Ichioka K, et al. Nocturia and benign prostatic hyperplasia. Urology 2003;61(4):786-90.

PART V

GENERAL DISCUSSION AND SUMMARY

CHAPTER 10

GENERAL DISCUSSION

The main focus of this thesis was to determine the prevalence, incidence and natural history of nocturia when objectified with a frequency-volume chart (FVC). The possible causes and mortality risk were also studied, as was the natural history of voided volumes.

In this chapter, the main findings are summarized and discussed in a broader perspective. Finally, implications for daily practice are addressed and possibilities for future research are discussed.

VALIDITY OF THE DATABASE AND CLINICAL RELEVANCE OF THE ANALYSES

At baseline, the Krimpen study included 1688 men aged 50 to 78 years, which accounted for approximately 50% of all eligible men. This could be considered a high response rate given the fact that most community-based studies on nocturia have comparable response rates, but lack the number of invasive tests [1-4].

A survey conducted among a representative sample of non-responders showed that the participants were representative for the complete population of Krimpen aan den IJssel [5]. Participants were similar to non-responders in educational level, marital status, chronic diseases, and smoking and drinking habits. However, the number of men with moderate to severe lower urinary tract symptoms (LUTS; an IPSS > 7) was slightly lower in the non-response group.

Although the loss to follow-up (LTFU) seems substantial throughout the study rounds, the response rate was 78% and 80% in the first two follow-up rounds, respectively, and was similar in the third and final rounds [6]. However, the LFTU analysis showed (similar to the non-response study) a slight overrepresentation of men with moderate to severe LUTS. Therefore, we have to conclude that LUTS are somewhat more prevalent in our study than in the general population. Furthermore, men who could be included because of complete FVCs with declared sleeping hours were slightly (but not clinically relevant) older (about 59 vs. 60 years). Because nocturia becomes more prevalent with higher age, we have to conclude that the prevalence of nocturia might be somewhat lower in the general population than in our study group. However, we believe that this slight overrepresentation of men with moderate to severe symptoms (including nocturia) has not influenced our results on risk factors for nocturia. Moreover, response bias does not affect analyses, such as analyses on correlates [7].

In our study, none of the participants or their general practitioners received information on the test results, such as prostate volume, urinary flow rate and PSA serum levels. Because of this double blinding our findings are not biased by this

knowledge, and could not influence the decision by the participants to enter into a subsequent round. Information on a PSA level was given to a patient only when it was elevated and there was a need to screen for prostate cancer. Furthermore, men with detected prostate cancer were removed from this study.

Epidemiological studies provide information on the distribution of symptoms, and physiological and anatomical parameters, in the community. The data of the Krimpen study allowed us to describe the natural history of voided volumes (which can be used as reference values), and the natural history of nocturia and nocturnal polyuria. To what extent these data are representative for men seeking medical attention for nocturia remains unclear; none of the investigated men that sought help for LUTS, primarily sought help for nocturia [9].

USE OF FREQUENCY-VOLUME CHARTS

Data on the normal values of voided volumes, the prevalence and incidence rates of nocturia, and the nocturnal urine production were all derived from the FVCs. This is the first study to have collected such a large number of FVCs longitudinally. At baseline 1,597 FVCs were completed. During the three follow-up rounds the number of FVCs was 1,156, 882, and 750, respectively. Unfortunately, a significant proportion of our study population omitted to complete their "sleeping hours". Nevertheless, we decided to still use actual sleeping hours because the use of an arbitrary number of sleeping hours would lead to miscalculation of the prevalence of nocturia [10]. This did not result in selection bias, because we found no difference in the IPSS score or other participant characteristics between men with and men without declared sleeping hours. However, men with reported sleeping hours were slightly older than those who failed to report their hours. Since nocturia prevalence increases with age [11] there might be a slight overrepresentation of nocturics in our study population. Also, although the difference in age was significant, the clinical relevance (median 60.8 vs. 59.3 years) seems to be limited. It is expected that, when used in clinical practice, the percentage of adequately completed FVCs will be higher than in our study as we assume that patients will be even more motivated to be accurate.

At the time of the conception of our study, no clear definition was available as to what a FVC should definitely contain. Retrospectively, our FVCs (which contain frequency data of 3 complete days and information on voided volumes for 1 whole day) comply with the ICS definition of a FVC. The ICS states that a FVC should contain both the frequency and the voided volumes for at least 24 hours [12]. However,

we feel that the manner in which we measured the 24 hours (from 0:00 to 0:00) has some shortcomings. A FVC in which a 'whole day' is measured not starting at 0:00, but with the first morning void and continues until the next morning, might be more useful as this includes a complete night's rest, even if this starts before 0:00. Nonetheless, a recent study showed that in a group of patients with nocturia, the average period between going to sleep and the first nocturnal void was about 145 minutes [13]. Because about 98% our participants went to bed at around or after 22:00, it is possible that not many nocturnal voids went unregistered in our study.

The general consensus is that a 3-day FVC would be optimal in terms of compliance and reliability [14, 15]. Despite the fact that our participants had to complete a 3-day FVC in each round, they only recorded their voided volumes on the last day. During follow-up Round III they also recorded the volumes on the second day; these measurements show no significant differences between the various days. This might indicate that there are no large day-to-day differences in voided volumes when measured within a short period of time (e.g. 3 days). Therefore, we feel that our 1-day measurement gives a good representation of voided volumes. However, we do feel that a FVC with more than one day of voided volumes would provide more insight and might reduce the probability that the measured volumes are coincidental.

Although it sounds intuitively correct to also note the fluid intake on a FVC (because fluid intake can influence urine production) we feel that it is not an asset, especially in a research setting. First, fluid intake registration by a participant is strenuous and might not be noted properly; this might lead to lack of/or incorrect compliance and response rates. Second, many food products (such as fruits and vegetables) contain a lot of water which cannot be registered properly. Third, insensible fluid loss (e.g. fluid loss via breathing or sweating) cannot be accounted for or reliably corrected for because it varies considerably from person to person and is dependent on e.g. climatological circumstances and physical activity. Therefore, we feel it is much more informative to precisely monitor the output rather than to monitor the fluid intake.

FVCs have an important advantage compared with history taking and questionnaires. Whilst history and questionnaires are subject to recall bias, a FVC is not [14]. Therefore, we feel that FVCs are a more reliable way of objectifying voiding patterns.

A FVC is a low-cost, patient-friendly and easy-to-use tool. Based on its information various estimates can be derived, such as voiding frequency (day and/or night), average voided volume, maximum voided volume, and total urine production. Also,

with some additional basic calculations, much more can be derived from a FVC: day/night urine production ratio or an estimation of hourly urine production [16, 17]. These parameters can help in determining the cause of nocturia.

FURTHER CONSIDERATIONS ON METHODOLOGY

Besides the shortcomings related to the FVCs, the 113-item questionnaires used in our study also had some limitations. For instance, no information on possible sleeping disorders (which may be an important cause of nocturia) was collected [18]. It remains unclear whether sleep disorders cause nocturia or nocturia causes sleep disorders, as all studies on this topic are cross-sectional and therefore only show associations and not causality. Another important problem with sleep and nocturia is associated with the ease with which a person can go back to sleep; one study showed that this influences the amount of bother perceived by a patient [19]. Another important subject not included in our study is nocturia-specific perceived bother. A validated questionnaire on this would greatly enhance the value of our study. Basically, we have only shown the prevalence of nocturia in the open population, but could not determine the amount of bother specifically attributed to nocturia.

Although we now have an extensive database, in fact we only have a total of four rounds with relatively long periods of time between the successive rounds. As it turned out, in many men the presence of nocturia fluctuates over time. Further insight into the pattern of this fluctuation is valuable because such information can be used to advise a patient more precisely about the length of a "nocturia episode". Furthermore, it can also be used to initiate the start of temporal treatment for nocturia.

Another point is that people who work in shifts (especially nightshifts) might also have influenced our results. However, we have shown that >90% of our participants were asleep between 1:00 and 6:00. Furthermore, men were only included when they had four or more sleeping hours and 'night time' was calculated for each of the participants individually (i.e. declared sleeping hours). Therefore, the influence on nocturnal urine production calculations was zero, as these men were not asleep. The same applies to the nocturnal voiding frequency.

PART III NATURAL HISTORY OF VOIDED VOLUMES

THE NATURAL HISTORY AND DETERMINANTS OF VOIDED VOLUMES (CHAPTER 5)

This study provides normal values for voided volumes for older men in the community over time and their possible determinants. These normal values can be used in daily practice as reference values in men who seek treatment for their LUTS. If their FVC clearly shows abnormal values (i.e. values outside the range of the 1st and 3rd quartiles), this might help to focus on the possible causes and treatment options in the primary urologic work-up. They might also help to gain insight into the development of LUTS over the course of years for both the physician and patient. Although LUTS fluctuate over time [20, 21], we now see that some determinants of LUTS (e.g. frequency) do not progress over time whilst others decline in volume (e.g. maximum voided volume; MVV) in an open population. Whether or not this is also the case in urologic patients needs to be confirmed in future studies.

The 24-hour voiding frequency (24HVF) increased from 6.0 times at baseline to 6.5 times at the Round III follow-up. The MVV showed a decrease over time. This change was explained by higher age and the passing of time. Alcohol intake slightly increased the MVV. The average voided volume (AVV) also decreased over time. Similar to the MVV, a change in AVV was also explained by higher age and the passing of time. Alcohol intake slightly increased the AVV as well. The 24-hour voided volume showed a slight increase over time and with increasing age. This change was influenced by a post-void residual ≥ 50 ml, alcohol intake, the use of diuretics, and hypertension. It is unclear to us why a post-void residual increases the production of urine.

The increase in 24HVF is explained by the increase in 24-h voiding volume and a decrease in both MVV and AVV. Apart from higher age and the passage of time, we were unable to find other associations with the decrease in MVV and AVV; however, it is suggested that relevant changes take place in bladder function over time. Because our study did not reveal which factors determined the changes in voided volumes, future studies should focus on this topic. Our results seem generalizable because our group has characteristics similar to those in other open populations of older men. Therefore, we feel that these results can be used in daily practice as reference values for men who seek treatment for their lower urinary tract symptoms.

PART IV NOCTURIA AND NOCTURNAL POLYURIA: THEIR DETERMINANTS AND MORTALITY RISK

PREVALENCE, INCIDENCE, AND LONGITUDINAL RISK FACTORS OF NOCTURIA (CHAPTERS 6 AND 7)

Overall, the prevalence of nocturia in older men was high and increased from 34.4% to 44.7% after a period of 6.5 years. The incidence of nocturia after 2.1 years was also high: 23.9%. However, after 2.1 years, 36.7% of the nocturics at baseline no longer had nocturia and therefore had resolved nocturia. This fluctuation was seen throughout the follow-up rounds of our study. Fluctuation in the presence of nocturia in some individuals was found in a questionnaire-based study on nocturia by Hakinnen et al. [22]. Although it is unclear what causes this fluctuation in the presence of nocturia, it indicates that a 'wait and see' policy might be a good first step in the management of nocturia. Nevertheless, this has to be applied with caution: the pattern of presence/absence of nocturia remains unclear, as our two-year gap is considerable and it remains uncertain which nocturics have fluctuating nocturia and which have continuous nocturia.

The relation between questionnaire-derived and FVC-derived nocturnal voiding frequency is only modest [10]. This was shown in the baseline analysis of the Krimpen study. In this longitudinal part of the study, we also showed a clear tendency for men to consistently overestimate or underestimate their NVF. We showed that men who tend to overestimate are generally younger than 65 years; this might indicate that men aged ≤ 65 years experience more bother from their nocturia than men over 65 years.

Our longitudinal analysis of risk factors of nocturia showed that a small MVV (<300 ml), higher age (>60 years), polyuria, nocturnal polyuria and LUTS increased the prevalence of nocturia. Many factors that were cross-sectionally associated with nocturia had no relation with nocturia in the longitudinal analyses. This might be explained by the fact that some of the characteristics that were cross-sectionally associated with nocturia (e.g. hypertension) are chronic conditions, whereas nocturia itself can fluctuate. Therefore, it is possible that the association between hypertension and nocturia disappears in a longitudinal analysis. Furthermore, we showed that two different definitions of nocturnal polyuria were independently associated with nocturia; this is discussed below.

PREVALENCE, INCIDENCE AND RESOLUTION OF NOCTURNAL POLYURIA AND ITS RELATION WITH NOCTURIA (CHAPTER 8)

In our study we used two definitions of nocturnal polyuria: one proposed by the International Continence Society (ICS), which is the definition currently most widely

used in clinics and in research [23]. This definition states that an older person has nocturnal polyuria when >33% of their total 24-hour voided volume is voided during the night. The other definition we used was proposed after studying which definition had the best, but only modest, relation with nocturia, in the cross-sectional part of the Krimpen study [24]. This definition states that nocturnal polyuria is a nocturnal urine production of >90 ml/h (NUP90).

The definition in the consensus statement of the ICS was based on a small group of older men and, although confirmed in a small group of patients, has never been confirmed in the open population [25, 26]. Furthermore, the definition is based on the ratio between day and night urine production, rather than actual nocturnal production. Our study shows that a high proportion of men with nocturia meet this definition (91.9% at baseline); however, am astonishing 70.1% of men without nocturia also meet this definition. Therefore, we believe that this definition is not discriminative enough to determine nocturnal polyuria as a determinant of nocturia. The incidence rate was 60.3% after 2.1 years, much higher than the incidence rate of nocturia after the same period of time. The resolution rate was 17.8%. Nonetheless, the ICS definition for nocturnal polyuria (NUV33) is an independent determinant of nocturia, as well as the NUP90 definition. This might sound counterintuitive as one might expect that an increased nocturnal urine production per hour and a disturbed day-night production ratio are related. However, it might also be explained by the fact that the total 24-hour urine production increases over the years, and the low level of nocturnal urine production disappears when men are aged >65 years. In this way, the natural relation between day and night urine production shifts towards the night. Nevertheless, although the mechanism is not completely clear, the increased urine production is an additional factor in the disturbed ratio of urine production between day and night, or vice versa.

The prevalence of NUP90 was 27.7% at baseline in nocturics and 8.0% in men without nocturia. The incidence rate was 13.6% after 2.1 years, which is only slightly higher than the incidence in nocturia. The resolution rate was 57.0%. It seems that NUP90 is a more discriminative definition of nocturnal polyuria, although it is only a modest predictor of nocturia; this underlines the multi-factorial etiology of nocturia.

MORTALITY RATE IN MEN WITH NOCTURIA (CHAPTER 9)

Studies in men and women with nocturia showed an increase in mortality risk [27-30]. These (questionnaire-based) results could not be confirmed by our study in older men after correction for age. We found no relation between nocturia and an increased mortality rate after 15 years. After analyzing the influence of different nocturia patterns (e.g. persistent or fluctuating prevalence of nocturia throughout

the study rounds), we also found no association. The results of these studies differ from ours, but are not necessarily contradictory: the difference might, in part, be explained by the fact that they all used questionnaires rather than FVCs. Although not discussed in Chapter 9, we also examined whether there was an increased mortality rate in men with nocturia if we used the IPSS instead of the FVC to determine nocturia. After correction for other risk factors, nocturia was a non-significant risk factor (OR: 1.31 95CI: 0.98-1.75, p=0.066) [31]. Furthermore, the populations of the above-mentioned studies differ from ours. The study by Kupelian et al. had one of the most comparable populations [29]. They showed a significant but attenuated increase in mortality risk for older men. However, they included many more participants than in our study (n=3.424 vs. n=1.114, respectively), which might explain their significant association with only a relatively small HR [1.60 (1.06, 2.41), p=0.02].

Another explanation might be the fact that we failed to discriminate between the various etiologies of nocturia. In case of a significant difference in the causes of nocturia, it is possible that the men in the Krimpen study have less potentially life-threatening causes; however, there is no indication that such a difference in causes is problematic. An analysis of the risk of nocturia in specific causes of death was not possible due to the general way of reporting causes of death by the GPs. Thus, whether or not there is a relation between, e.g. cardiac death and nocturia, remains unclear.

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE STUDIES

In addition to extensive data on general health status and LUTS, the Krimpen study database contains longitudinal FVC data, making it a unique study from which the data can be applied in future studies and in daily practice.

Both the average voided volume (AVV) and maximum voided volume (MVV) declined slowly but significantly over the course of the study. Only higher age and the passage of time were found to be related to these changes. This implies that other factors are involved (not measured by us) that influence these changes. Therefore, future studies should focus on additional characteristics, such as kidney function and changes in bladder function due to possible age-related vascular and neurogenic causes. A higher alcohol intake slightly increased both AVV and MVV, which might be explained by a bladder 'getting used to' larger volumes, or by a lower state of arousal.

The 24h-voided volume increased slightly over time. Together with the mildly decreased MVV and AVV this seems to explain the increase in voiding frequency. These normal values can be used in daily practice as reference values for older men. If their FVC shows clearly abnormal values these reference values might help

focus on possible causes and treatment options in the primary urologic work-up. They might also help to gain insight in the development of LUTS over the course of years.

Nocturia is very prevalent in older men. However, our study also showed that about one-third of the men with nocturia, do not have this condition 2.1 years later. Because of this high fluctuation rate a good first step, after excluding habitual nocturia (i.e. nocturia from polydipsia) and imminent cardiac conditions, would be to inform the patient about the high resolution rate. Additional research with shorter a follow-up period is needed to explore whether or not these high resolution rates are present, and to objectify the duration of such a 'nocturic episode'. It is possible that patients with nocturia change their behavior (e.g. less fluid intake in the evening) to stop the nocturia. This might (partly) explain the fluctuation rate. Patient-implemented lifestyle changes, including fluid intake, are therefore an interesting topic to investigate in future studies.

Because of the overestimation/underestimation of nocturia, we recommend to let a patient complete a questionnaire on LUTS (e.g. the IPSS) and a FVC. The questionnaire can be used to make some distinction between the severity of symptoms and the amount of bother experienced, while the FVC can be used to objectify the actual nocturnal voiding frequency.

Future studies should also focus on a validated means to objectify an increase in QoL, with a combination of lifestyle advice and medication to restore the proper balance between nocturnal urine production and the nocturnal bladder capacity. The combination of an anti-diuretic and an anti-muscarinic drug might be an interesting topic for future clinical trials.

Other major points to be addressed in future studies are the patterns of nocturia fluctuation (which should be investigated using shorter follow-up periods than ours) and the effect of sleep disturbance on nocturia. The latter has proven to influence nocturia when using 'snoring' as a proxy for sleep disturbance [32]. A validated questionnaire on sleep disturbances could be a valuable tool to use in a future epidemiological study on nocturia.

When we apply the most widely used definition of nocturnal polyuria (i.e. NP being >33% of the total 24-hour voided volume, or the ICS definition), it appears to be very prevalent in both men with and without nocturia. Although a nocturnal overproduction of urine plays an important role in nocturia, we feel that the ICS definition lacks discriminative value since nocturnal polyuria according to this definition is very prevalent in men with and without nocturia. Furthermore, this definition has not yet been properly validated in a general population. However, when used in our multivariable model to determine risk factors for nocturia, it still turned out to be an independent determinant, even after correction for 24-hour polyuria and

a second definition of NP (NUP90). Therefore, this definition cannot be ignored when investigating nocturia in older men.

Although The NUP90 definition was only a modest predictor of nocturia in the baseline study, it seems to be a useful definition [10]. The fluctuation of this definition of NP seems more in line with the fluctuation in nocturia, indicating that there is a strong association. The disadvantage of using this definition is that the physician has to make more calculations and, therefore, it takes more time. However, in an era where virtually all physicians and their patients in the western world use smartphones and (tablet) computers, it should be easy to develop an application which helps patients to record voids and calculate urine production. Future research has to confirm the usefulness of the NUP90 definition in selected patient populations. Also, studies should focus on applying different definitions of NP and nocturia according to the cause of the nocturia and NP. It seems instinctively wrong to treat patients with a different etiology in the same way, when their conditions are clearly different. Although the symptom of nocturia might be the same, the cause might be urologic, nephrogenic, cardiac, or even behavioral. Most physicians recognize this, but do not investigate the different types of nocturia exhaustively. Why investigate nocturia as if it is all the same, when we treat it differently because we know it is different? This might also explain why the effect of medical treatment of nocturia in trials is relatively small. If the right 'type' of nocturia patient is selected for the right kind of treatment, results might finally become clinically significant instead of merely statistically significant.

Despite the above-mentioned difficulties related to the definitions of NP, these definitions are (together with a small MVV and higher age) a determinant of nocturia. Therefore, we think that both definitions could be used in daily practice. They could be used to find a possible cause of nocturia or may help provide additional insights for patients. Future studies should focus on both definitions and their order of chronicity. For example, a shift in the day/night ratio might be a first step, and an overproduction of urine a second step. i.e. when a patient already produces a relatively large portion of his urine at night, an overproduction might be the final decisive factor which causes nocturia to appear. It is also possible that the urine production per hour affects other mechanisms in the body, other than just the speed with which the bladder is filled. Because detrusor over activity (DO) can be triggered by supplying a patient with furosemide, one could hypothesize that an increased nocturnal urine production has a similar effect on the bladder. Future studies, especially when investigating treatment options for NP, should focus on both definitions of NP. The key to successfully treating nocturia might be found in a drug that treats not only the overproduction per hour but also the day/night ratio. In addition, future studies should focus on the effects of DO in combination with NP and its role in the etiology of nocturia. In men with (benign prostatic

enlargement-related) DO, NP might be an extra trigger which leads to urge and, therefore, to nocturia. This could, for example, be tested by determining the nocturnal bladder capacity and cross-referencing it with the different types of NP. It seems important for future studies to not only examine which factors influence nocturia, but also what combination of factors might contribute to the condition. As nocturia has a highly multi-factorial etiology, certain combinations of factors might significantly increase the probability, as they might be synergetic.

Many of the cross-sectionally determined associations of certain conditions and characteristics with nocturia do not seem to have causality with nocturia. However, our study had a low prevalence of certain conditions (such as diabetes), and included practically only Caucasian men; therefore, these findings need to be confirmed in much larger FVC-based studies.

We found no association between nocturia and an increased mortality rate. However, it remains unclear whether this is an effect of using FVCs (being a more reliable tool to objectify nocturia), or because the exact etiology of the nocturia in the men in the Krimpen study is different from that in other studies. Future studies need to confirm our findings on the mortality risk in FVC-derived nocturia, and also focus on the type of etiology and cause of death, before definitive conclusions can be drawn about the increase in mortality rate based on nocturia.

REFERENCES

1. Hakkinen, J.T., et al., Depressive symptoms increase the incidence of nocturia: Tampere Aging Male Urologic Study (TAMUS). J Urol, 2008. 179(5): p. 1897-901.
2. Kupelian, V., et al., Nocturia and quality of life: results from the Boston area community health survey. Eur Urol, 2012. 61(1): p. 78-84.
3. Tikkinen, K.A., et al., Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol, 2010. 57(3): p. 488-96.
4. Chute, C.G., et al., The prevalence of prostatism: a population-based survey of urinary symptoms. J Urol, 1993. 150(1): p. 85-9.
5. Blanker, M.H., et al., Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. BJU Int, 2000. 85(6): p. 665-71.
6. Blanker, M.H., et al., Loss to follow-up in a longitudinal study on urogenital tract symptoms in Dutch older men. Urol Int, 2005. 75(1): p. 30-7.
7. MacMahon, B., Trichopoulos, D., Epidemiology: principles and methods. 2nd ed. 1996, Boston: Brown & Co. 165-227.
8. Blanker, M.H., Normal values and determinants of urogenital tract (dys)function in older men: the Krimpen study, in department of General Practice. 2002, Erasmus University: Rotterdam. p. 159.
9. Kok, E.T., et al., Determinants of seeking of primary care for lower urinary tract symptoms: the Krimpen study in community-dwelling men. Eur Urol, 2006. 50(4): p. 811-7.
10. Blanker, M.H., et al., Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol, 2000. 164(4): p. 1201-5.
11. van Doorn B, B.M., Kok ET, Westers P, Bosch JLHR, Once nocturia, always nocturia? Natural history of nocturia in older men based on frequency-volume charts: The Krimpen study. J Urol, 2011.
12. Abrams, P., et al., The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Am J Obstet Gynecol, 2002. 187(1): p. 116-26.
13. Weiss, J.P., et al., Efficacy and safety of low-dose desmopressin orally disintegrating tablet in men with nocturia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. J Urol, 2013: p. e-pub ahead of print.
14. Bright, E., M.J. Drake, and P. Abrams, Urinary diaries: evidence for the development and validation of diary content, format, and duration. Neurourol Urodyn, 2011. 30(3): p. 348-52.
15. Yap, T.L., D.C. Cromwell, and M. Emberton, A systematic review of the reliability of frequency-volume charts in urological research and its implications for the optimum chart duration. BJU Int, 2007. 99(1): p. 9-16.
16. van Mastrigt, R. and F. Eijskoot, Analysis of voided urine volumes measured using a small electronic pocket balance. Scand J Urol Nephrol, 1996. 30(4): p. 257-63.
17. Weiss, J.P., et al., Evaluation of the etiology of nocturia in men: the nocturia and nocturnal bladder capacity indices. Neurourol Urodyn, 1999. 18(6): p. 559-65.
18. Cornu, J.N., et al., A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management--a systematic review and meta-analysis. Eur Urol, 2012. 62(5): p. 877-90.
19. Endeshaw, Y., Correlates of self-reported nocturia among community-dwelling older adults. J Gerontol A Biol Sci Med Sci, 2009. 64(1): p. 142-8.
20. Hall, J.C., J.L. Hall, and P.J. McRae, The quality of life of patients on a waiting list for transurethral resection of the prostate. J Qual Clin Pract, 1996. 16(2): p. 69-73.

21. Temml, C., et al., The natural history of lower urinary tract symptoms over five years. Eur Urol, 2003. 43(4): p. 374-80.
22. Hakkinen, J.T., et al., Incidence of nocturia in 50 to 80-year-old Finnish men. J Urol, 2006. 176(6 Pt 1): p. 2541-5; discussion 2545.
23. van Kerrebroeck, P., et al., The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn, 2002. 21(2): p. 179-83.
24. Blanker, M.H., et al., Relation between nocturnal voiding frequency and nocturnal urine production in older men: a population-based study. Urology, 2002. 60(4): p. 612-6.
25. Kirkland, J.L., et al., Patterns of urine flow and electrolyte excretion in healthy elderly people. Br Med J (Clin Res Ed), 1983. 287(6406): p. 1665-7.
26. Weiss, J.P., et al., Nocturia in adults: etiology and classification. Neurourol Urodyn, 1998. 17(5): p. 467-72.
27. Asplund, R., Nocturia in relation to sleep, health, and medical treatment in the elderly. BJU Int, 2005. 96 Suppl 1: p. 15-21.
28. Bursztyn, M., J. Jacob, and J. Stessman, Usefulness of nocturia as a mortality risk factor for coronary heart disease among persons born in 1920 or 1921. Am J Cardiol, 2006. 98(10): p. 1311-5.
29. Kupelian, V., et al., Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. J Urol, 2011. 185(2): p. 571-7.
30. Nakagawa, H., et al., Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. J Urol, 2010. 184(4): p. 1413-8.
31. van Doorn B, K.E., Blanker MH, Westers P, Bosch JLHR, Nocturia: prevalence, incidence, and mortality-risk in older men, the Krimpen study. EUR UROL SUPP, 2011. 10(2): p. 29-29.
32. Tikkinen, K.A., et al., A systematic evaluation of factors associated with nocturia--the population-based FINNO study. Am J Epidemiol, 2009. 170(3): p. 361-8.

CHAPTER 11

SUMMARY AND SUMMARY IN DUTCH

Nocturia, or waking at night to void, is a common problem among both men and women of all ages. It is regarded as one of the most bothersome urinary symptoms, which may lead to sleep disturbance. Although the International Continence Society (ICS) defined nocturia as *waking at night to void one or more times,* only a nocturnal voiding frequency of two or more seems to generate significant bother and decreased quality of life. Furthermore, nocturia is associated with an increase in falls and hip fractures and may even be associated with an increased mortality rate.

Traditionally, urologists have considered nocturia to be an increased urinary frequency at night without paying much attention to urine volume, whereas internists have assumed nocturnal frequency to be the result of an excessive urine production without focus on other lower urinary tract symptoms. Nowadays, both medical disciplines agree that the causes of nocturia can roughly be divided into the following categories: 1) sleep disorders, 2) nocturnal polyuria, 3) 24-hour polyuria, and 4) reduced bladder capacity. Clearly, nocturia is a symptom, rather than a disease. However, regardless of its cause, nocturia appears when the production of urine is greater than the storage capacity of the bladder.

Although earlier studies have provided information on possible causes of nocturia, almost all of these studies were cross-sectional and based their data on self-report questionnaires. Because of this, the information concerning which factors are causally related to nocturia remains unclear.

The Krimpen study was initiated in 1995 to monitor the natural history of lower urinary tract symptoms (LUTS) in the aging male and its burden on the general population of older men. A total of four rounds of data collection were performed. The three follow-up rounds had a planned follow-up time of 2, 4 and 6 years. Data collection ended in 2004. In addition to the original design, the general practitioner's database was checked again after 15 years (2010) for (possible) date of death. In addition to extensive data on health status, the Krimpen study database contains data on longitudinal frequency-volume charts (FVC). These FVC data offer insight into the epidemiology and natural history of both FVC-based nocturia and nocturnal polyuria.

This thesis describes the natural history of nocturia and of voided volumes, as well as that of an important contributor to nocturia, i.e. nocturnal polyuria. The association between nocturia and the mortality rate in older men is also examined. In the first four chapters an introduction and aims of the study, study design, a review of the literature and the specific methodology of FVC analysis are presented.

VOIDED VOLUMES AND ITS DETERMINANTS

In **Chapter 5** we studied how voided volumes change over time and what factors influence this change. During six years, over four rounds, our study showed that the 24-hour voiding frequency increased slightly and significantly from 6.0 to 6.5 voids. Both maximum voided volume and average voided volume decreased. The total 24-hour voided volume increases slightly. All these parameters changed with age and the passage of time. Increase in maximum voided volume and average voided volume were associated with the use of alcohol. The 24-hour voided volume was associated with a post-void residual >50 ml, the use of alcohol, the use of diuretics, and with hypertension. The slight increase in 24-hour voided volume, while the maximum voided volume and average voided volume decreased, could explain the slight increase in 24-hour voiding frequency. In addition to the determinants of changes in voided volumes, this chapter also provides reference values, which can be used in daily practice to determine whether a patient has abnormal values when he uses an FVC.

PREVALENCE, INCIDENCE, AND DETERMINANTS FOR NOCTURIA

Chapter 6 describes the epidemiology of nocturia in older men. Nocturia, defined as two or more voids per night, is very prevalent: at baseline, 34.4% of the participants had nocturia. This prevalence had increased to 44.7% at the last follow-up round. The incidence of nocturia was also high: after 2.1 years the incidence was 23.9%. However, we also observed a resolution rate of 36.7%. This means that, of those men who had nocturia at baseline, 36.7% did not have nocturia after 2.1 years. This fluctuation of nocturia was earlier reported in questionnaire-based research, and is now confirmed in FVC-based nocturia.

The agreement between questionnaire-based and FVC-derived nocturia is only modest. This was previously described in a cross-sectional study, where men aged less than 65 years overestimated their nocturnal voiding frequency more often than men aged over 65 years. We now show that men who overestimate their nocturnal voiding frequency once are likely to repeat this during the follow-up rounds. This might indicate that subjective estimation of nocturia frequency is influenced by the amount of bother perceived by an individual person.

In **Chapter 7** the longitudinal determinants of nocturia were explored. We show that, longitudinally, a smaller maximum voided volume (< 300 ml), a higher age, 24-hour polyuria, nocturnal polyuria (the two definitions), and LUTS are independent determinants for nocturia. This analysis also reveals that many factors cross-sectionally associated with nocturia (such as hypertension, diabetes mellitus, and cardiac symptoms) do not show this association longitudinally.

These insights are of importance in the education of patients and in the management of the possible causes of nocturia. The fact that two definitions of nocturnal

polyuria were independent determinants of nocturia is interesting. Whilst one is based on a urine production per hour (>90 ml/hour between 1 and 6 a.m.), the other is based on a day to night urine production ratio (>33% of the total 24-hour urine production is produced in the night). Although both definitions try to somehow show the same determinant, apparently, they do not. Etiologically, it is possible that a shift in the day/night ratio is the first step and an overproduction of urine the second step, i.e. when a patient already produces a large proportion of urine at night, an hourly overproduction might be the final factor, which causes nocturia. Additionally, it is possible that the increased urine production per hour also has an influence on other mechanisms than only the speed at which the bladder is filled. In this respect, it has been shown that detrusor over activity can be triggered by giving a patient furosemide; thus, one could hypothesize that an increased nocturnal hourly urine production has a similar effect on the bladder.

Prevalence and incidence of nocturnal polyuria and its relation with nocturia

Chapter 8 describes the epidemiology of nocturnal polyuria (NP). In this study we used two definitions of NP. The first is the most widely used definition: NP defined as a nocturnal voided volume being >33% of the total 24-hour voided volume (NUV33). The second definition is an hourly urine production of >90 ml per hour between 1 and 6 a.m. (NUP90). The first definition, NUV33, is highly prevalent in men with nocturia: 91.9%. However, according to this definition, a staggering 70.1% of men without nocturia also have NP. These numbers show that this definition might not be discriminative enough to use in daily practice. Nevertheless, as discussed in Chapter 7, NUV33 is an independent risk factor for nocturia, even after correction for 24-hour polyuria and NUP90 and, therefore, both definitions have a meaningful role in the diagnostic analysis of nocturia.

NUP90 is prevalent in 27.7% of men with nocturia and in 8.0% in men without nocturia; therefore, this definition seems to be more discriminative. Again, we must stress that both definitions of NP are independent risk factors for nocturia, demonstrating the multi-factorial etiology of nocturia.

Mortality risk of men with nocturia

Chapter 9 reports on the mortality analysis based on the Krimpen study long-term data. Previously, several studies postulated that nocturia gives rise to an increased mortality risk in certain populations. All these studies determined nocturia via questionnaires. In our study we found no significant increase in mortality risk after correction for several confounders (such as age) after 15 years of follow-up. Another analysis, in which we divided men with nocturia into several groups with different patterns of nocturia, also showed no increase in mortality. These results imply

that there is no relation between nocturia and mortality in older men. Since we believe that FVCs are a more objective method of assessing nocturia, we feel that the conclusions of the other studies based on questionnaires should be regarded with caution.

The results of this study provide important information on nocturia, nocturnal polyuria, and voided volumes in older men, which can be used in daily practice. In contrast to cross-sectional analyses, the longitudinal analyses of the Krimpen study database provide indications of causal associations between certain factors and nocturia.

We found that nocturia is often a transient symptom, and close attention should be paid to the amount of bother a patient perceives from nocturia. It was also found that in the determination of nocturnal polyuria, the proposed definition by the ICS (NUV33) is not sufficiently discriminative and therefore should be re-evaluated for daily practice. However, nocturnal polyuria, as determined by the definition NUV33 and by the definition NUP90, are both independent determinants of nocturia. This may indicate that the development of nocturia is a two-step process: first the day-night ratio of urine production changes and later the actual volume of nightly urine production per hour increases. We did not find a relation between nocturia and increased mortality in older men. In the management of nocturia, attention should be paid to 24-hour polyuria, nocturnal polyuria, a small functional bladder capacity as well as LUTS with or without benign prostatic obstruction.

NEDERLANDSTALIGE SAMENVATTING (SUMMARY IN DUTCH)

Nycturie, ofwel 's nachts wakker worden om te plassen, is een veel voorkomend probleem bij mannen en vrouwen van alle leeftijden. Het wordt gezien als een van de meest hinderlijke plasklachten. Hoewel de 'International Continence Society' (ICS) nycturie heeft gedefinieerd als "eenmaal of vaker opstaan in de nacht om te plassen met de intentie om daarna weer te gaan slapen" blijkt uit onderzoek dat pas een nachtelijke plasfrequentie van twee of vaker wezenlijke hinder geeft en daardoor een daling van de kwaliteit van leven laat zien. Daarnaast is nycturie in verband gebracht met valincidenten en heupfracturen. Ook zou nycturie met een verhoogd mortaliteitsrisico kunnen samengaan.

Van oudsher beschouwden urologen nycturie als een verhoogde nachtelijke plasfrequentie, terwijl de meeste internisten nycturie als een overproductie van urine beschouwden, zonder stil te staan bij andere plasklachten. Vandaag de dag zijn beide specialismen het er over eens dat de oorzaken van nycturie grofweg kunnen worden ingedeeld in vier categorieën. Deze categorieën zijn: 1) slaapstoornissen, 2) nachtelijke polyurie, 3) 24-uurspolyurie en 4) een kleine blaascapaciteit. Nycturie moet beschouwd worden als een symptoom, ofwel een duiding van een onderliggend lijden, in plaats van als een op zichzelf staande ziekte. Ongeacht de oorzaak is nycturie het resultaat van urineproductie die de maximale (functionele) blaascapaciteit overstijgt.

Hoewel eerdere studies antwoord hebben gegeven op de vraag welke oorzaken mogelijk ten grondslag liggen aan nycturie, waren bijna al deze studies dwarsdoorsnede-onderzoeken, gebaseerd op enquêtes die mensen zelf, zonder hulp moesten invullen. Hierdoor blijft het antwoord op de vraag welke factoren daadwerkelijk een causaal verband hebben met nycturie onduidelijk.

De Krimpenstudie is in 1995 gestart. Deze studie had als doel het natuurlijke beloop van plasklachten bij de ouder wordende man en de ziektelast die hij hiervan ondervond in kaart te brengen. In totaal is er gedurende vier rondes data verzameld. Dit gebeurde tijdens een uitgangsmeting en in drie vervolgrondes (gepland na 2, 4 en 6 jaar). De dataverzameling werd beëindigd in 2004. In aanvulling op dit oorspronkelijke onderzoeksontwerp is de databank in 2010 (15 jaar na start van de studie) opnieuw geopend om overlijdensdata te analyseren. Naast uitgebreide informatie over de gezondheidsstatus van deelnemers bezit de Krimpenstudie-database ook longitudinale plasdagboekdata (PDB). Deze PDB-data geven inzicht in de epidemiologie en in het natuurlijke beloop van met PDB vastgestelde nycturie en nachtelijke polyurie.

Dit proefschrift beschrijft het natuurlijke beloop van nycturie, de algemeen geplaste volumina en van een belangrijke veroorzaker van nycturie: nachtelijke polyurie.

Tevens wordt de relatie tussen nycturie en overlijden beschreven. In de eerste vier hoofdstukken worden achtereenvolgens een introductie gegeven, de doelen van het onderzoek besproken, een overzicht van de literatuur gegeven en de methodologie van PBD-analyse besproken.

GEPLASTE VOLUMINA EN HUN DETERMINANTEN

In **Hoofdstuk 5** beschrijven we hoe geplaste volumina veranderen in de tijd en welke factoren van invloed zijn op deze veranderingen. Onze analyses lieten zien dat gedurende zes jaar, verdeeld over vier rondes, de gemiddelde plasfrequentie per 24 uur licht steeg van 6.0 naar 6.5 keer. Hoewel licht en derhalve klinisch mogelijk niet relevant was deze stijging toch statistisch significant. Zowel het maximaal geplaste volume per 24 uur als het gemiddeld geplaste volume daalden. Het totaal in 24 uur geplaste volume steeg licht. De bovenstaande vier typen volumina veranderden allen onder invloed van de leeftijd en met het verstrijken van de tijd.

Het maximaal geplaste volume en het gemiddeld geplaste volume stegen iets onder invloed van alcoholgebruik (twee of meer eenheden per dag). Het totaal geplaste volume per 24 uur veranderde onder invloed van een residu na mictie dat groter was dan 50 ml, alcoholgebruik, het gebruik van plasmedicatie en hypertensie.

De lichte toename van het 24-uursvolume en de afname in gemiddeld en maximaal geplast volume zou de hogere frequentie kunnen verklaren. Naast een beschrijving van de determinanten van de verandering in plasvolumina, laat dit hoofdstuk ook normaalwaarden zien die in de dagelijkse praktijk toegepast zouden kunnen worden.

Deze waarden kunnen gebruikt worden ter illustratie voor een patiënt die een plasdagboek heeft bijgehouden om deze inzicht te geven in hoeverre zijn volumina en frequenties afwijken van het gemiddelde.

PREVALENTIE, INCIDENTIE EN DETERMINANTEN VAN NYCTURIE

Hoofdstuk 6 beschrijft de epidemiologie van nycturie bij de ouder wordende man. Nycturie, gedefinieerd als twee of meer plassen per nacht, is zeer veel voorkomend: tijdens de uitgangmeting had 34,4% van alle deelnemers nycturie. Deze prevalentie was toegenomen tot 44,7% tijdens de laatste studieronde. De incidentie van nycturie was eveneens hoog; tijdens de eerste vervolgronde, na gemiddeld 2,1 jaar, was deze maar liefst 23,9%. Wel dient daarbij aangetekend te worden dat er ook een resolutiepercentage van 36,7% werd gevonden na 2,1 jaar. Dat wil zeggen dat 36,7% van de mensen die tijdens de uitgangstudie nycturie hadden, dit na 2,1 jaar niet meer hadden. Deze fluctuatie was eerder al beschreven in een studie waarbij vragenlijsten werden gebruikt en is nu bevestigd door ons plasdagboekonderzoek.

De ernst van nycturie zoals deze gemeten wordt met vragenlijsten komt maar matig overeen met de resultaten van plasdagboeken. Dit was al eerder vastgesteld tijdens dwarsdoorsnede-onderzoek. Dat onderzoek liet zien dat mannen onder de 65 jaar in verhouding tot mannen boven de 65 jaar, vaker de neiging hebben hun aantal nachtelijke plassen te overschatten op een vragenlijst in verhouding tot wat gevonden wordt in hun plasdagboek. Dit werd ook gezien in ons longitudinale onderzoek. Verder wees ons onderzoek uit dat mannen die een overschatting gaven van hun nachtfrequentie een grotere kans hadden dit bij herhaling te doen. Dit gegeven lijkt er op te wijzen dat de subjectieve weergave van de nachtelijke plasfrequentie onder invloed staat van het ongemak dat het met zich meebrengt.

In **Hoofdstuk 7** hebben we de longitudinale determinanten van nycturie onderzocht. Uit deze analyse bleek dat een kleiner maximaal geplast volume (<300 ml), een hogere leeftijd, 24-uurspolyurie, nachtelijke polyurie (2 verschillende definities; zie hoofdstuk 8) en plasklachten (zoals nadruppelen en hesitatie) onafhankelijke determinanten zijn van nycturie. Deze analyse wees verder uit dat een aantal karakteristieken die tijdens dwarsdoorsnedeonderzoek onafhankelijke determinanten bleken, zoals hypertensie, diabetes mellitus en hartklachten, niet meer van invloed waren tijdens longitudinale analyse. Deze inzichten zijn van belang, zowel voor het voorlichten van patiënten over nycturie als voor het behandelen van mogelijke oorzaken.

Het feit dat twee definities van nachtelijke polyurie onafhankelijk van elkaar van invloed zijn op nycturie is een zeer interessant gegeven. Terwijl de ene definitie gebaseerd is op een geplast volume per uur (>90 ml/uur tussen 1 en 6 in de nacht), is de andere gebaseerd op een ratio tussen nachtelijk en overdag geproduceerde urine (>33% van het totaal in 24 uur geplaste volume). Hoewel beiden dezelfde determinant lijken aan te geven doen zij dat kennelijk niet. Vanuit een etiologisch standpunt bezien zou het kunnen zijn dat een verandering in de verhouding van de dag-nacht urineproductie de eerste stap is in het ontstaan van nycturie en een hogere urineproductie per uur een tweede. Anders gezegd: bij een patiënt die reeds een relatief grote portie van zijn urine in de nacht produceert kan een hogere productie per uur de doorslaggevende factor zijn voor het ontstaan van nycturie. Daar komt nog bij dat de urineproductie per uur mogelijk ook nog invloed heeft op andere factoren dan alleen het tempo waarin de blaas gevuld wordt. Het is namelijk al eens eerder aangetoond dat blaasoveractiviteit uitgelokt kan worden door een diureticum zoals furosemide. Hieruit zou men af kunnen leiden dat een verhoogde urineproductie per uur een soortgelijk effect kan hebben.

PREVALENTIE EN INCIDENTIE VAN NACHTELIJKE POLYURIE EN DE RELATIE MET NYCTURIE

Hoofdstuk 8 beschrijft de epidemiologie van nachtelijke polyurie (NP). Wij hebben tijdens onze analyses steeds twee definities van NP gebruikt. De eerste en meest toegepaste definitie luidt: een totaal nachtelijk geplast volume dat meer dan 33% van het totaal geplaste volume per 24 uur bedraagt (NUV33). De tweede definitie is een urineproductie van meer dan 90 ml per uur tussen 1 en 6 uur 's nachts (NUP90). De eerste definitie, NUV33, is met een prevalentie van 91,9% bij mannen met nycturie veelvoorkomend. Echter, het is ook zo dat 70,1% van de mannen zonder nycturie voldoen aan deze definitie. Deze percentages laten zien dat deze definitie van NP niet onderscheidend genoeg is om toe te passen in de dagelijkse praktijk. Wel is het zo dat deze definitie van NP een onafhankelijke determinant van nycturie is, ook na correctie voor polyurie en voor NUP90, zoals beschreven in hoofdstuk 7. Daarom hebben wij geconcludeerd dat NUV33 desalniettemin van belang is bij de diagnostische evaluatie van nycturie.

NUP90 komt voor bij 27,7% van de mannen met nycturie en in 8,0% van de gevallen bij mannen zonder nycturie. Deze definitie lijkt dus meer onderscheidend dan NUV33 en heeft mogelijk meer klinische waarde. We willen echter nogmaals benadrukken dat beide definities onafhankelijke determinanten van nycturie zijn en daarmee de multifactoriële etiologie van nycturie benadrukt.

OVERLIJDENSRISICO VAN MANNEN MET NYCTURIE

In **Hoofdstuk 9** laten wij de resultaten van onze mortaliteitsanalyse zien. Een aantal eerdere studies lieten zien dat er mogelijk een verband was tussen nycturie en een hoger overlijdensrisico in geselecteerde populaties. In al deze studies was nycturie vastgesteld met vragenlijsten. Onze op het plasdagboek gebaseerde analyse met een looptijd van 15 jaar liet geen verhoogd overlijdensrisico zien na correctie voor een aantal factoren zoals leeftijd. Deze resultaten zijn dus anders dan die van eerdere studies. Omdat wij ervan overtuigd zijn dat het meten van nycturie met een plasdagboek objectiever is denken wij dat de resultaten van de eerdere studies, gebaseerd op vragenlijsten, met enige terughoudendheid bekeken moeten worden.

De resultaten van onze studie laten belangrijke informatie zien over nycturie, nachtelijke polyurie en geplaste volumina bij de ouder wordende man. Deze informatie kan gebruikt worden in de dagelijkse praktijk doordat het zowel arts als patiënt inzicht geeft in de normaalwaarden, causale verbanden van, en overlijdensrisico's bij nycturie. In tegenstelling tot een dwarsdoorsnedeonderzoek kan deze longitudinale analyse van de Krimpenstudie indicaties van causale verbanden tussen bepaalde factoren en nycturie laten zien.

Wij hebben gezien dat nycturie vaak een tijdelijk symptoom is en dat er goed gekeken moet worden naar de hoeveelheid last die patiënt van zijn nycturie ondervindt. Tevens hebben wij ontdekt dat de definitie van nachtelijke polyurie zoals voorgesteld door de ICS (NUV33) niet onderscheidend genoeg is en mogelijk heroverwogen dient te worden voor gebruik in de dagelijkse praktijk. Echter, zowel NUV33 als NUP90 zijn onafhankelijke determinanten van nycturie. Dit wijst er op dat de etiologie van nycturie mogelijk een tweestapsproces is, waarbij in eerste instantie de verhouding tussen de overdag en 's nachts geproduceerde urine verandert en in tweede instantie de urineproductie per uur stijgt.

Wij hebben geen verband aangetoond tussen nycturie en een verhoogd overlijdensrisico. Tijdens de behandeling van nycturie moet aandacht besteed worden aan polyurie, nachtelijke polyurie, een klein maximaal geplast volume en aan plasklachten.

PART VI

APPENDICES

LIST OF ABBREVIATIONS

24hfreq	24-hour Voiding Frequency
24HVV	24-hour Voided Volume
5-ARI	5-alpha reductase inhibitor
ADAM	Androgen Deficiency in Aging males
ATC	Therapeutical Chemical Classification
AUA	American Urological Association
AUA-SS	American Urological Association Symptom Score
AVV	Average Voided Volume
BII	BPH Impact Index
BL	Baseline
BMI	Body-Mass Index
BPE	Benign Prostatic Enlargement
BPH	Benign Prostatic Hyperplasia
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DAN-PSS	Danish Prostatic Symptom Score
DI	Diabetes Insipidus
DM	Diabetes Mellitus
DOX	Doxazosin
DRE	Digital Rectal Exam
FIN	Finasteride
FINNO	Finnish National Nocturia and Overactive bladder study
FU	Follow-Up
FVC	Frequency-Volume Chart
GP	General Practitioner
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
ICS	International Continence Society
IIEF	International Index of Erectile Function
I-PSS	International Prostate Symptom Score
IQR	Inter-Quartile Range
IRB	Internal Review Board
KM	Kaplan-Meier
LME	Linear Mixed Effect
LUTS	Lower Urinary Tract Symptoms
MMAS	Massachusetts Male Aging Study
MTOPS	Medical Therapy of Prostatic Symptoms

MVV	Maximum Voided Volume
NP	Nocturnal Polyuria
NUP	Nocturnal Urine Production
NUP90	Nocturnal Urine Production >90 ml/h
NUV	Nocturnal voided Volume
NUV33	Nocturnal Voided Volume >33% (of the Total 24-hour voided volume)
NVF	Nocturnal Voiding requency
OAB	Overactive Bladder
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
p	probability
PCP	Primary Care Physician
PLA	Placebo Arm
PSA	Prostate specific Antigen
p-value	probability value
PVR	Post-Void Residual volume
PY	Person-Years
Q1-Q3	1st and 3rd quartile
Qmax	Peak flow rate
QoL	Quality of Life
REM	Rapid Eye Movement
TAMUS	Tampere Aging Male Urologic Study
TER	Terazosin
TRUS	Transrectal Ultrasound
TURP	Transurethral Resection of the Prostate

PUBLICATIONS RELATED TO THE STUDIES PRESENTED IN THIS THESIS

Chapter 3
van Doorn B, Bosch JL. Nocturia in older men. Maturitas. 2012 Jan; 71(1):8-12.

Chapter 4
van Doorn B and Bosch JLHR. Diary-based population analysis of nocturia in older men: the Krimpen study. In: Weiss JP, Blaivas JG, van Kerrebroeck PE, Wein AJ, editors. Nocturia: Causes, Consequences and Clinical Approaches, Springer publishing; 2011. p. 59-76

Chapter 5
van Doorn B, Kok ET, Blanker MH, Martens EP, Bohnen AM, Bosch JLHR. The natural history and predictive factors of voided volume in older men: the Krimpen study. J Urol 2011 Jan; 185(1): 213-218

Chapter 6
van Doorn B, Blanker MH, Kok ET, Westers P, Bosch JLHR. Once nocturia, always nocturia? The natural history of nocturia in a community-based population of older men: the Krimpen study. J Urol 2011 Nov; 186(5):1956-61

Chapter 7
van Doorn B, Blanker MH, Kok ET, Westers P,Bosch JLHR. Prevalence, incidence and resolution of nocturnal polyuria, a longitudinal community-based study in older men: the Krimpen study. Eur Urol. 2013 Mar; 63(3):542-7

Chapter 8
van Doorn B, Kok ET, Blanker MH, Westers P, Bosch JLHR. Determinants of nocturia: a longitudinal analysis of a community-based group of older men: the Krimpen study. J. Urol. 2014 Apr;191(4):1034-9

Chapter 9
van Doorn B, Kok ET, Blanker MH, Westers P, Bosch JLHR. Mortality in older men with nocturia. A 15-year follow-up community-based study in older men: the Krimpen study. J Urol. 2012 May; 187(5):1727-31

AWARDS RELATED TO THE STUDIES PRESENTED IN THIS THESIS

2012 **'Best of AUA meeting'**
For the abstract: 'What predicts incident nocturia? A population-based study in older men: the Krimpen study.'
American Urological Association Congress 2012, Atlanta, Georgia, USA

2012 **'Best poster of poster session'**
For the abstract: 'What predicts the development of nocturia? A population-based study in older men.'
27th European Association of Urology Congress, Paris, France

2011 **'Best poster of poster session'**
For the abstract: 'Nocturia: prevalence, incidence and mortality-risk in older men, the Krimpen study.'
26th European Association of Urology Congress, Vienna, Austria

2009 **ICS Prize for 'Most innovative research on nocturnal voiding problems'**
For the abstract: 'The epidemiology of nocturnal polyuria (incidence and prevalence): a longitudinal community-based study in men between 50 and 78 years of age.'
39th International Continence Society Meeting, San Francisco, CA, USA

2009 **EAU prize for 'Best abstract (non-oncology)'**
For the abstract: 'Frequency-volume charts in older men: changes in parameter values with advancing age and predictive factors: the Krimpen study.'
24th European Association of Urology Congress, Stockholm, Sweden

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CURRICULUM VITAE

Boris van Doorn was born on March 19th, 1984 in Leeuwarden, The Netherlands, where he also spent his childhood. In 2002 he graduated from highschool at Piter Jelles College in Leeuwarden and was admitted to medical school at the University of Groningen. His internships were completed at St Elisabeth's hospital on Curaçao (N.A.) and in Medisch Spectrum Twente, Enschede. The last year of his studies were spent at the University Medical Center Utrecht. During this year he did a research rotation, which was the start of this thesis, and he completed a final clinical rotation in urology. After graduating from medical school in 2009 he started working as a PhD-student under the supervision of prof. dr. J.L.H.R. Bosch. Starting in the winter of 2011, he worked as a resident under the supervision of drs. M.TW.T. Lock at the Central Military Hospital, Utrecht, whilst continuing his research. In May 2013 he started as a resident-in-training at the Rijnland Hospital in Leiderdorp under the Supervision of dr. A.M. Zeillemaker.