# Benign prostatic hyperplasia - management and long-term prognosis

PhD dissertation

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Health

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2023

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# Acknowledgements

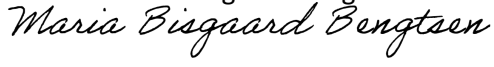
First, I would like to express my sincere gratitude to my main supervisor Mette Nørgaard. Thank you for your guidance and support throughout my PhD journey. Your expert knowledge in epidemiology, dedication, helpfulness, and positive energy has been invaluable to me. Thank you for opening the door to Department of Clinical Epidemiology in the first place, and for giving me the chance to conduct my PhD under your supervision. It has been a true privilege to learn from you. Thank you to my co-supervisor Michael Borre for the clinical inputs and expert knowledge for each study, which have been highly appreciated. A special thanks to my co-supervisor Uffe Heide-Jørgensen. You have a remarkable gift for disseminating advanced biostatistics, which has been truly invaluable to me. Thank for keeping the door open to me, and for answering my many questions with endless patience. Thank you to all collaborators, and to Henrik Toft Sørensen and Jens-Christian Djurhuus for drawing my attention towards acute urinary retention. Also, I wish to thank Bettina Nørby for welcoming me at the Department of Urology, Sygehus Lillebælt, where I was fortunate to spend two months during my PhD.

Thank you to the most incredible colleagues at the Department of Clinical Epidemiology. It has been a pleasure to do my PhD studies in such an inspiring environment. Thank you to the members of the iCURE research team for the weekly meetings. I truly enjoyed our discussions on epidemiological methods. Thank you to all my PhD colleagues at the department, for making the past years joyful and memorable. A special thanks to Cathrine, Rikke, Kristina, Phillip, Malene and Kasper for all the laughs and conversations in the office. Linea, my sincere gratitude for your support and friendship throughout my academic journey, starting from the very first day at medical school. Thank you for your contribution to my PhD.

Last, my warmest thanks go to my family and friends for supporting me. A special thanks to Mads, Eva, Karl, and Aksel, who fill my life with joy and unconditional love every day.

Aarhus, February 2023

Maria Bisgaard Bengtsen



## Grants

This work was made possible with financial support from:

- Health Research Foundation of Central Denmark Region
- The Hede Nielsen Family Foundation

# List of papers

The dissertation is based on the following four original studies that are referred to by their Roman numerals (I-IV).

I. Bengtsen MB, Heide-Jørgensen U, Blichert-Refsgaard LS, Hjelholt TJ, Borre M, Nørgaard M. Positive Predictive Value of Benign Prostatic Hyperplasia and Acute Urinary Retention in the Danish National Patient Registry: A Validation Study. *Clin Epidemiol*. 2020;12:1281-1285. doi:10.2147/CLEP.S278554

II. Bengtsen MB, Heide-Jørgensen U, Borre M, Knudsen JS, Nørgaard M. Acute urinary retention in men: 21-year trends in incidence, subsequent benign prostatic hyperplasia-related treatment and mortality: A Danish population-based cohort study. *Prostate*. 2023;83(1):87-96. doi:https://doi.org/10.1002/pros.24440

III. Bengtsen MB, Heide-Jørgensen U, Borre M, Nørgaard M. Long-term risk of benign prostatic hyperplasia-related surgery and acute urinary retention in men treated with 5-alpha reductase inhibitor versus alpha-blocker monotherapy in routine clinical care. [SUBMITTED]

IV. Bengtsen MB, Farkas DK, Borre M, Sørensen HT, Nørgaard M. Acute urinary retention and risk of cancer: population based Danish cohort study. *BMJ*. 2021;375:2305. doi:10.1136/BMJ.N2305

# Abbreviations

5-ARI: 5-alpha reductase inhibitor

ATC: Anatomical Therapeutic Chemical

AUA: American Urological Association

AUA-SI: American Urological Association Symptom Index

AUR: acute urinary retention

BPE: benign prostatic enlargement

BOO: bladder outlet obstruction

BPH: benign prostatic hyperplasia

BPO: benign prostatic obstruction

CCI: Charlson Comorbidity Index

CI: confidence interval

DAN-PSS: Danish Prostate Symptom Score (mainly used in Denmark and Finland)

DNPR: The Danish National Patient Registry

EAU: European Association of Urology

ICD: International Classification of Diseases

IPSS: International Prostate Symptom Score

ITT: intention to treat

LUTS: lower urinary tract symptoms

LUTS/BPH: LUTS suggestive of BPH

PP: per protocol

PPV: positive predictive value

PSA: prostate-specific antigen

Qmax: maximum urinary flow rate

RCT: randomized controlled trial

SMRW: standardized mortality ratio weighting

# Contents

# 1. Introduction

A paradigm shift has occurred in the management of benign prostatic hyperplasia (BPH).[1] Previously, surgery was the only active treatment option for men with BPH, but in the mid-1990s medical therapy was introduced and rapidly replaced surgery as first-line treatment.[1,2] This shift from surgery to medical therapy transformed BPH from a surgical condition to a chronic medical condition.[1] Despite the high prevalence of BPH in the aging male population, there is limited data on the long-term consequences of this shift. It remains uncertain if the shift to medical therapy has resulted in changes in the incidence of more advanced stages of BPH and late complication such as acute urinary retention (AUR). AUR is a feared complication to BPH, and a previous study demonstrated that AUR was associated with a high mortality in men of all ages.[3] However, the reason for the high mortality in men with AUR is not well understood. Studies have shown that medical treatment with 5-alpha reductase inhibitor (5-ARI), but not alpha-blocker monotherapy, reduces the risk of AUR and surgery for up to 4.5 years of treatment. However, it is not clear whether treatment with 5-ARIs reduces the longer-term risk of surgery and AUR, or if it is simply delaying the inevitable. To address these gaps in knowledge, we wrote this dissertation based on four papers that are referred to by their Roman numerals (I-IV). Study I validated the diagnostic coding of BPH and AUR in the Danish National Patient Registry (DNPR). Study II examined temporal trends in AUR incidence, management, and mortality, as well as causes of death after a first AUR hospitalization. Study III examined the risk of BPH-related surgery and AUR in men treated with 5-ARI versus alpha-blocker monotherapy in routine clinical care for up to 15 years of follow-up. Lastly, Study IV investigated the risk of cancer after a first hospitalization for AUR.

## 1.1 Epidemiology of BPH

The prevalence of BPH and associated lower urinary tract symptoms (LUTS) increases as men age.[4,5] Histological BPH is prevalent in the aging male population, with autopsy studies showing that the age-specific prevalence of histological BPH is 23% in the fifth decade of life, 42% in the sixth decade of life, and 82% in the eighth decade of life and beyond.[5] A systematic review of data from 25 countries reported that the age-specific prevalence of LUTS suggestive of BPH (LUTS/BPH) was 15% in men aged 40-49, 20% in men aged 50-59, and 37% in men aged 70-79.[4] LUTS can cause significant bother and negatively impact daily activities and quality of life.[6,7] Thus, 15-25% of men aged 50-64 years reported LUTS to a degree that had a substantial negative impact on their quality of life.[6,7]

BPH not only affects the individual patient, but it also represents a global burden.[8] Within the past 20 years, the number of prevalent BPH cases has almost doubled globally, and this burden is expected to continue to increase due to aging and growing populations.[8] This highlights the

importance of knowledge about the condition, including information on treatment and long-term prognosis.

## 1.2 Definition of BPH and related conditions

BPH refers to a non-malignant growth of epithelial and stromal cells in the transitional zone of the prostate.[9] In some (but not all) men, this growth can result in benign prostatic enlargement (BPE) which can, in turn, lead to benign prostatic obstruction (BPO). [10] Bladder outlet obstruction (BOO) is a term used to describe obstruction during voiding, characterized by a reduced urinary flow rate and increased pressure in the detrusor muscle.[10] When the cause of BOO is known to be BPE secondary to BPH, the condition is referred to as BPO.[10]

BPH is an important cause of LUTS. In this dissertation, we will refer to LUTS suggestive of BPH as LUTS/BPH.[11] In the 20th century, symptoms of BPH were referred to as "prostatism", but this term is no longer used because it incorrectly implies that the prostate is the sole cause of voiding symptoms in aging males.[12] LUTS is the clinical term used to describe a group of symptoms characterized by bothersome voiding.[13] LUTS can be divided into symptoms related to urinary storage (e.g., urgency, frequency, and nocturia), urinary voiding (e.g., straining to void, urinary intermittency, and hesitancy), and post-micturition symptoms.[10] Male LUTS can be caused by a variety of conditions, of which some are unrelated to the prostate, such as bladder dysfunction (detrusor overactivity, detrusor underactivity), and other structural/functional abnormalities in the urinary tract and its surroundings.[14] The complex relationship between BPH, BOO, BPO, and LUTS is illustrated in Figure 1. This figure demonstrates how BPH can be associated with LUTS with or without BOO, and how BPH can also be associated with BOO with or without LUTS. Additionally, LUTS can occur with BOO with or without BPH.

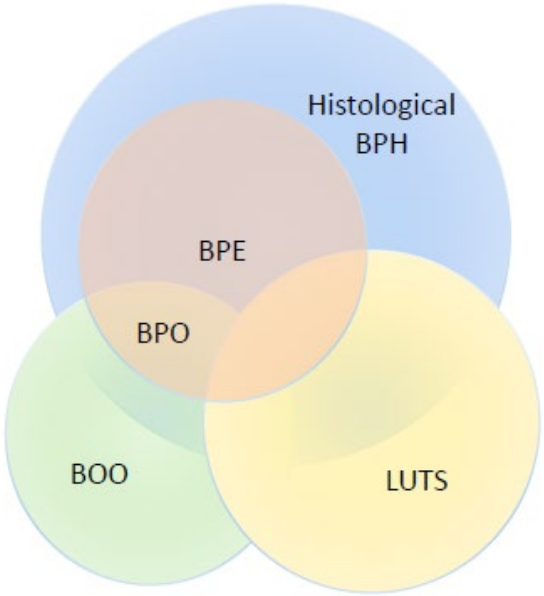



**Figure 1. Illustration of the complex interplay of BPH, BPE, BPO, BOO, and LUTS.**
*Abbreviations: BPH - benign prostatic hyperplasia; BPE - benign prostatic enlargement; BPO - benign prostatic obstruction; BOO - bladder outlet obstruction; LUTS - lower urinary tract symptoms.*

Although the term BPH refers to a histological diagnosis, the diagnostic work-up of men presenting with LUTS does not involve biopsy, unless prostate cancer is suspected. Instead, it typically includes a medical history, a symptom score questionnaire (such as the International Prostate Symptom Score (IPSS), the American Urological

Association Symptom Index (AUA-SI), or the Danish Prostate Symptom Score (DAN-PSS)), frequency-volume charts, bladder diaries, physical examination including digital rectal examination, urinalysis, and measurement of serum-creatinine and sometimes post-void residual urine.[14–16] Since 2004, prostate-specific antigen (PSA) measurement has been recommended as a standard part of the diagnostic work-up for men presenting with LUTS in Denmark.[15] However, the most recent Danish guidelines (published in 2022) do not recommend serum-PSA measurements except in cases with a family history of prostate cancer, digital rectal examination indicating prostate cancer, BRCA mutation, or symptoms of prostate cancer.[17] In Denmark, the initial work-up and treatment of men with LUTS/BPH is most commonly performed by general practioners.[15] In complicated cases (i.e., occurrence of AUR, impaired kidney function, recurrent urinary tract infections, bladder stones, or severe recurrent haematuria), referral to departments of urology is recommended and the diagnostic work-up can be supplemented with other investigations, such as uroflowmetry, ultrasound, and urodynamics.[18]

## 1.3 Pathophysiology of BPH

BPO secondary to BPH can contribute to LUTS through both a direct mechanical obstruction of the urethra caused by the enlarged tissue (static component) as well as an increased tone in the smooth muscle tone and resistance in the enlarged glad (dynamic component).[16] BPO can lead to structural and functional changes of the bladder.[19] Structural changes include muscular hypertrophy, collagen infiltration, and the formation of diverticula in the bladder.[19] The interior wall of an obstructed bladder is typically characterized by bladder trabeculation with saccules and diverticula herniating through the urothelium.[19] These structural changes can affect the bladder function leading to reduced compliance and contractility of the detrusor and storage symptoms.[19] Prolonged BOO can lead to detrusor failure, characterized by an inability to empty the bladder completely, and residual urine.

The presence of residual urine is a risk factor for developing complications, such as urinary tract infections, bladder stones, chronic urinary retention, hydronephrosis, nephropathy, and AUR. The underlying pathophysiology of AUR is primarily attributed to factors related to BOO, infections, medications, neurological impairment, insufficient detrusor muscle, and other.[20,21]

## 1.4 Natural history of BPH and risk factors of progression

In many men, BPH is a progressive disease characterized by a deterioration of symptoms over time, and a worsening of other clinical variables such as health-related quality of life, peak flow rate, and the occurrence of complications such as BPH-related surgery and AUR.[22] AUR is a urologic

emergency characterized by a sudden and painful inability to urinate. In men, the most common cause of AUR is BPH.[21]

Knowledge about the natural history of LUTS/BPH can be obtained from longitudinal community-based studies. The Olmsted County study followed 2,115 randomly selected men aged 40-79 years.[23] The study demonstrated that BPE, peak flow rate, and LUTS are age-dependent and that the disease is slowly progressive with a mean increase in IPSS of 0.18 points per year, mean decrease in peak flow by 2.1% per year, and a mean prostate growth of 2.2-2.5% per year (1-2 mL).[24–28] The risk of BPH-related surgery and AUR was relatively low in the community setting, with a cumulative risk of AUR of 2.7% and 3.0% of BPH-related surgery during a 6-year follow-up period.[29] Similarly, a low incidence of AUR was seen in the Health Professional Follow-up Study, which followed 6,100 health professionals in the United States (US) aged 45-83 for three years.[30] The incidence of AUR was 1% during the 3-year period.

Although the incidence of AUR is relatively low in a community setting, it increases significantly with age and the presence of LUTS.[29] Data from the Olmsted County study showed that one in ten men between the ages of 70 and 79 years developed AUR during a 5-year follow-up period.[29] In the placebo group of the Proscar Long-term Efficacy and Safety Study (PLESS), which included men with clinical BPH and moderate to severe LUTS, 7% developed AUR and 10% underwent BPH-related surgery during a 4-year follow-up period.[31] In the placebo group of the Medical Therapy of Prostatic Symptoms (MTOPS) study, which included men with moderate to severe LUTS, the 4-year risks were 2% for AUR and 5% for surgery.[31]

Several factors have been linked to the risk of BPH progression, such as advanced age, high prostate volume, reduced urinary flow rate, increased post-void residual urine, severe LUTS, and high serum-PSA.[29,32] Some studies indicate that prostate volume and baseline serum-PSA levels are the strongest predictors of BPH-related surgery and AUR,[31,33] and the current guidelines from the European Association of Urology (EAU) and the American Urological Association (AUA) on management of male LUTS recommend using prostate volume or serum-PSA levels to identify patients with an increased risk of progression.[14,16]

## 1.5 Treatment of LUTS/BPH

Current treatment options for LUTS/BPH include watchful waiting, behavioural and dietary modifications, medical therapy, and surgical treatment.

Watchful waiting is recommended for men with mild to moderate LUTS who are minimally bothered by their symptoms.[14] Behavioural and dietary modifications include education of the patient, reassurance, period monitoring, and lifestyle advice.[14]

Medical therapy with alpha-blockers and 5-ARIs remains the cornerstone of medical treatment of LUTS/BPH. Thus, current EAU and AUA guidelines recommend consideration of treatment with alpha-blocker and 5-ARIs alone or in combination in men with moderate to severe LUTS.[14,16] These two medications differ in their mechanism of action, characteristics, and side effects, which will be described more thoroughly below, as they are the exposure investigated in Study III.

Alpha-blockers provide rapid symptom relief by relaxing the smooth muscle in the prostate and bladder neck.[34] Treatment with alpha-blocker versus placebo reduces symptoms by approximately 30-40% versus 10-30% in placebo, and improves the peak urinary flow rate by 15-30% versus 10-15% in placebo.[35] However, alpha-blockers do not reduce prostate volume or prevent BPH-related surgery or AUR.[36–39] The most significant adverse events associated with alpha-blocker treatment are orthostatic hypotension, dizziness, fatigue, retrograde ejaculation, nasal congestion, and intra-operative floppy iris syndrome.[14,34]

In contrast to alpha-blockers, 5-ARIs have a slow onset of action (three to six months).[14] The 5-ARIs finasteride and dutasteride work by inhibiting the 5-alpha-reductase enzyme, which converts testosterone to the more potent dihydrotestosterone: the primary androgen involved in prostate development.[14] This results in a reduction of dihydrotestosterone levels and a 20-25% reduction in prostate volume after one year.[34] Alpha-reductase type I is predominantly expressed in the skin and liver and type II is predominantly expressed in the prostate.[14] Finasteride only targets type II of the enzyme, while dutasteride targets both types. The effect on symptoms depends on prostate volume.[14,34] Treatment with finasteride may not be more effective than placebo in patients with prostate volume less than 40 mL for treatment duration less than one year.[40,41] However, over a 4-year follow-up period dutasteride treatment reduced the IPSS as much as tamsulosin treatment in a trial of men with LUTS, prostate volume larger than 30 mL, and an increased risk of disease progression.[42] The greater the prostate volume, the more and faster effective symptom reduction was seen with dutasteride compared with tamsulosin.[42] Treatment with 5-ARIs alone or in combination with alpha-blockers reduce the risk of BPH-related surgery for up to 4.5 years of follow-up. The literature review for Study III includes a more detailed discussion of this topic. Sexual side effects occur in less than 5%, including reduced libido, erectile dysfunction, ejaculatory problems, and gynecomastia. 5-ARIs reduce serum-PSA by approximately 50%, which should be taken into account when interpreting PSA-levels in patients receiving 5-ARI treatment.[14,16]

## 1.6 Literature review

To review the existing literature, four separate literature reviews were conducted. The reviews examined the positive predictive value (PPV) of BPH and AUR in the DNPR (Study I), temporal trends in the incidence, management, and mortality of AUR in men (Study II), the risk of BPH-related surgery and AUR in men treated with 5-ARIs versus alpha-blockers (Study III), and the risk of cancer after a first-time AUR diagnosis (Study IV). The literature searches were conducted using MEDLINE (PubMed) with search queries utilizing Medical Subject Headings (MeSH) and free text search terms. The searches were limited to studies published in English, with the exception of Study I, which also included studies published in Danish. The database searches were followed by an initial screening of titles and abstracts, and any relevant full-text papers were retrieved. Full text original research, review articles, meta-analyses, and their reference lists were then reviewed. To screen for further relevant publications, I additionally reviewed the reference list and related papers highlighted by MEDLINE for each selected paper. Summaries of the included papers are provided in Tables 1-4, with search queries listed as footnotes.

### 1.6.1 PPV of BPH and AUR in the DNPR

The studies included in this dissertation are registry-based and the validity therefore depends on the quality of data in the registries used. Therefore, the first study in this dissertation (Study I) is a validation study that examined the PPV of the International Classification of Diseases 10$^{th}$ revision (ICD-10) coding for BPH and AUR in the DNPR. The literature search for Study I did not identify any relevant studies on the diagnostic coding of BPH or AUR in the DNPR. However, from review of reference lists, we identified two studies that validated the diagnostic ICD-9, Clinical Modification (ICD-9-CM) coding of AUR.[43,44] In addition, two previous studies, known to us beforehand, validated other benign urological diagnoses in the DNPR,[45,46] but these were not included in the summary of the literature review (Table 1), as they did not pertain the diagnoses of interest.

**Table 1. Summary of the existing literature of validity of the diagnostic coding of BPH and AUR.**

| Study I | | | |
|---|---|---|---|
| **Author, journal, year** | **ICD-codes/algorithm, contact type, diagnosis type** | **Study population, study period, reference standard, outcome** | **Results and comments** |
| Quinlan et al, *Pharmacoepidemiol Drug Saf*, 2016 [43] | - ICD-9-CM: 594.4, 596.53, 596.54, 788.20, 788.21, 788.29 accompanied by a medical claim for catheterization in the 7 days after the diagnosis and no medical claims for UR or catheterization in the preceding six months<br>- N/A | - Epilepsy patients who initiated a new antiepileptic drug with UR, n=20 (retrospective phase) and n=12 (prospective phase)<br>- 2008-2011 (retrospective) and 2012-2013 (prospective)<br>- Medical record review<br>- PPV | Retrospective phase:<br>- PPV (overall) = 85% (75.1-99.9), PPV (788.20) = 100 (80.5-100)<br>Prospective phase:<br>- PPV (overall) = 83.3 (51.6-97.9), PPV (788.20) = 81.8 (48.8-97.7) |
| Vouri et al, *J Clin Transl Sci,* 2017 [44] | - ICD-9-CM: 788.20, 788.21, 788.29, and current procedural terminology, fourth edition (CPT-4): 51701, 51702, 51703 (urinary catheterization)<br>- Emergency department and outpatient urology clinic<br>- N/A | - Men aged 45 years or older, n=333 (ICD-9) and n=245 (CPT-4)<br>- N/A<br>- Medical record review<br>- Sensitivity, specificity | - Emergency department: sensitivity 95%; specificity 91%<br>- Outpatient urology clinic sensitivity 95%; specificity 58% |
| Abbreviations: AUR – acute urinary retention; DNPR – Danish National Patient Registry; ICD – International Classification of Diseases; N/A – not available; PPV – positive predictive value; UR – urinary retention. | | | |
| MEDLINE search query:<br>(((("positive predictive value"[All Fields]) OR ("validity"[All Fields])) AND (((((("danish national patient register"[All Fields]) OR ("danish national patient registry"[All Fields])) OR ("danish national hospital register"[All Fields])) OR ("danish national registry of patients"[All Fields])) OR ("danish national hospital discharge registry"[All Fields])) OR ("danish hospital discharge register"[All Fields])) OR ("danish hospital register"[All Fields]))) AND ((((((((("benign prostatic hyperplasia"[All Fields]) OR ("benign prostatic hypertrophia"[All Fields])) OR ("benign prostatic obstruction"[All Fields])) ) OR ("benign prostatic enlargement"[All Fields])) OR ("bladder outlet obstruction"[All Fields])) OR ("prostatism"[All Fields])) OR ("lower urinary tract symptom"[All Fields])) AND ("positive predictive value"[All Fields])) AND (((((("danish national patient register"[All Fields]) OR ("danish national patient registry"[All Fields])) OR ("danish national hospital register"[All Fields])) OR ("danish national registry of patients"[All Fields])) OR ("danish national hospital discharge registry"[All Fields])) OR ("danish hospital discharge register"[All Fields])) OR ("danish hospital register"[All Fields]))) | | | |

### 1.6.2 AUR: Trends in incidence, management, and mortality

Knowledge of temporal trends of AUR incidence, management, and associated mortality is a cornerstone in improving our understanding of the long-term consequences of the shift in management of BPH. Nevertheless, it remains unclear whether the advent of medical therapy has coincided with an increase in late complications to BPH, such as AUR. The shift away from surgery coincided with a considerable decline in prostatic surgeries performed in Denmark as well as other parts of Europe and the US.[1,6,47–49] In addition, studies have reported an increasing proportion of patients presenting with more advanced stages of BPH including acute and chronic urinary retention upon the time of transurethral resection of the prostate (TURP) in the United Kingdom (UK) (1990-2000)[48] and Canada (1988-2008).[50] Previous studies examining the incidence of AUR have been limited by shorter time frames,[2,51,52] not including data after 2010, not including all types of hospital contacts,[2,51] or required a previous or concomitant BPH diagnosis along with the AUR diagnosis[2,51] (Table 2). However, restricting the study population to men with a previous or concomitant BPH diagnosis may exclude relevant cases, as AUR can be the first presentation of LUTS/BPH in up to 50% of all AUR cases.[53]

The management of AUR has also shifted towards a more conservative treatment. Previously, AUR was considered an absolute indication for surgery.[54] Today, the recommended treatment is initial catheterization, followed by alpha-blocker treatment and a trial without catheter.[14,16] A trial without a catheter is successful in around 23%-40% of cases, and treatment with an alpha-blocker before catheter removal increases the success rate.[55,56] If this approach fails, prostatic surgery will often be considered. We identified one previous study that investigated the impact of implementing the trial without a catheter policy on the use of BPH-related surgery after AUR (1998-2003).[52]

A previous study reported that the overall 1-year mortality was two to three times higher among men hospitalized for AUR, compared with the general population.[3] Although linked to comorbidities, the reason for this excess mortality remains poorly understood.

**Table 2. Summary of the existing literature of the changes in AUR incidence, management, and mortality.**

| Study II | | | |
|---|---|---|---|
| **Author, journal, year** | **Design, setting, year** | **Population, exposure, outcomes** | **Results and comments** |
| Cathcart et al, *J Urol,* 2006 [52] | The UK, Hospitals Episode Statistics Database, 1998-2003 | All men hospitalized with a primary diagnosis of AUR or secondary to BPH, n=165,527 | - Overall AUR incidence decreased during 1998-2003 from 3.17/1,000 to 2.96/1000; spontaneous AUR incidence decreased from 2.09/1000 to 1.91/1000 and precipitated AUR incidence from 1.08/1000 in 1998 and 1.06/1000 in 2003<br>- The 6-month risk of surgery decreased by approximately 20% during 1998-2003, from 32% to 26% for spontaneous AUR and from 7.6% to 5.8% for precipitated AUR<br>- The incidence of recurrent AUR increased by 20%.<br>- Note: postsurgical AUR was included |
| Fitzpatrick et al, *BJU Int.*, 2012 [55] | Clinics in France, Asia, Latin America, Algeria, and the Middle East, Cross-sectional survey, 2004-2008 | Men catheterized for AUR in real-life practice at public, private, and mixed healthcare practices, n=6,074 | - Surgery was performed immediately in 7.2% of all men: 8.4% of men with spontaneous AUR and 4.3% of men with precipitated AUR with considerable variation between countries<br>- Surgery was performed after prolonged catheterization in 13.3% of all men: 15.6% of men with spontaneous AUR and 7.6% of men with precipitated AUR<br>- Note: precipitated AUR included postsurgical AUR. No temporal trends reported |
| Stroup et al, *BJU Int.*, 2012 [2] | The US, cross-sectional, sample from the Nationwide Inpatient Sample (20% sample of US community hospitals), 1998-2008 | Men aged ≥18 years with an inpatient hospitalization for primary or secondary BPH or primary BPH combined with urinary retention, bladder stones, urinary tract infections, acute renal failure, or BPH surgery, n=7,464,730 | - The age-adjusted proportion of discharges of primary BPH with urinary retention and other adverse events (bladder stones, urinary tract infections, and bladder stones) remained stable<br>- The age-adjusted proportion of discharges for BPH with acute renal failure increased<br>- Note: only inpatient diagnoses included. Required a concomitant diagnosis of BPH |
| Groves et al, *Prostate Cancer Prostatic Dis,* 2013 [51] | California, the California Office of Health Planning and Development Emergency rooms database, | All men aged ≥50 years diagnosed with BPH and hospitalized for AUR during 2007-2010 (n=17,023) | - The incidence of BPH-associated AUR increased from 4.0 per 1000 emergency room visits in 2007 to 5.23 in 2010, corresponding to an overall increase of 36%<br>- Primary AUR increased from 3.2/1000 to 3.9/1000 (25% increase) and secondary AUR from 0.4/1000 to 1.4/1000 (80% increase) |

| | | | |
|---|---|---|---|
| | 2007-2010 | | - Note: only emergency room diagnoses included. Required a concomitant diagnosis of BPH. Postsurgical AUR included |
| Armitage et al, *BMJ, 2007* [3] | The UK, Hospitals Episode Statistics Database, 1998-2005 | All men aged >45 years with first AUR hospitalization (n=176,046).<br>Outcomes: 90-day and 1-year mortality and standardized mortality ratio (SMR) | - 90-day mortality was 6.7% after spontaneous AUR and 14.8% after precipitated AUR<br>- 1-year mortality was 14.7% after spontaneous AUR and 25.3% after precipitated AUR<br>- Overall, SMR was 2.2 for spontaneous AUR and 3.5 for precipitated AUR. Mortality increased with age and presence of comorbidity, but an excess mortality was observed in men without previous comorbidity and spontaneous AUR (SMR 1.6) |
| Abbreviations: AUR – acute urinary retention; BPH – benign prostatic hyperplasia; UK – United Kingdom; US – United States of America; SMR – standardized mortality ratio | | | |
| MEDLINE search query:<br>("urinary retention"[MeSH Terms]) AND (((incidence[MeSH Terms]) OR (mortality[MeSH Terms])) OR (disease management[MeSH Terms])) | | | |

### 1.6.3 Risk of BPH-related surgery and AUR in men treated with 5-ARIs versus alpha-blockers

The overall target of treatment of LUTS/BPH is to improve symptoms, enhance quality of life, and reduce the risk of disease progression, including BPH-related surgery and AUR.[57] For many men, the fear of needing BPH-related surgery or developing AUR is a significant concern.[58] Surveys have shown that the risk of having to undergo BPH-related surgery is a greater concern for patients than other factors such as symptoms or quality of life.[59–61] A survey of men with BPH from five European countries found that more than half of patients were concerned about the risk of requiring surgery and developing AUR.[59] Reducing the risk of surgery was considered a more important treatment outcome than rapid symptom relief by more than three-quarters of men.[59] Similarly, in a survey of men taking finasteride, the major preoccupation was that the treatment reduced the risk of major urological complications and the need for surgery, while symptoms and quality of life were considered less important.[61] One study reported that most men preferred a treatment that would provide even a 1% absolute risk reduction of surgery and AUR.[62]

Data from clinical trials have shown that treatment with 5-ARIs alone or in combination with alpha-blockers reduces the risk of BPH-related surgery and AUR (Table 3). However, the existing evidence on the effectiveness of 5-ARIs on the risk of BPH progression has limitations. Importantly, most previous studies had a follow-up of no more than four years.[36,38,39,63–69] However, in the lifespan of a patient with BPH, four years only covers a fraction of the entire duration at which the patient is at risk of BPH-related surgery and AUR. A man presenting with LUTS/BPH in his 60s is potentially facing many years of treatment. Therefore, it is of paramount interest to assess whether 5-ARIs reduce the risk of BPH-related surgery and AUR on a longer term. Previous studies that reported on the effectiveness of 5-ARIs with more than 4.5 years of follow-up[70–75] were limited by small sample sizes (<200),[70,73] lack of a comparison group,[70,72,73] or included patients with no to moderate LUTS, low serum-PSA, and normal digital rectal examination, for whom 5-ARI treatment is not recommended.[71]

In addition, although treatment with 5-ARIs has been shown to decrease the risk of BPH-related surgery and AUR under “ideal” circumstances in clinical trials, there is limited data on its effectiveness in routine clinical care. Trial participants are often highly selected, more closely monitored than patients treated in routine clinical care, and adherence patterns may differ substantially between patients treated in clinical trials and routine clinical care.[76] Therefore, the efficacy of treatment estimated in randomized controlled trials (RCTs) may not accurately reflect the effectiveness of treatment in routine clinical care.

**Table 3. Summary of the existing literature of validity of the risk of BPH-related surgery and AUR in men treated with 5-ARIs compared with placebo or alpha-blockers.**

| Study III | | | |
|---|---|---|---|
| **Author, journal, year** | **Design, year** | **Population, exposure, follow-up, outcomes** | **Results and comments** |
| **Follow-up <=2 years** | | | |
| Nickel et al,<br>*CMAJ,*<br>1996 [63] | Double-blinded, parallel-group, placebo-controlled multicentre study (PROSPECT Study) | - Men aged 45-80 years with moderate BPH, n=613<br>- Finasteride versus placebo<br>- Follow-up: 2 years | 2-year risk<br>Surgery and urinary retention (composite endpoint)<br>Finasteride: 6.1% versus placebo:10.2% |
| Andersen et al,<br>*Urology,*<br>1995 [64] | Double-blinded, placebo-controlled study, Scandinavian multicentre (SCARP) | - Men with moderate symptomatic BPH, n=707<br>- Finasteride compared with placebo<br>- Follow-up: 2 years | 2-year risk<br>Surgery<br>Finasteride: 0% versus placebo: 2.5%<br>AUR<br>Finasteride: 1.1% versus placebo: 4.2% |
| Marberger et al,<br>*Urology*,<br>1998 [38] | Double-blinded, placebo-controlled RCT (PROWESS study) | - Men aged 60-75 years with moderate to severe LUTS and enlarged prostates, etc., n=3,270<br>- Follow-up: 2 years<br>- Finasteride compared with placebo.<br>- Outcomes: symptom score, max urinary flow rate, prostate volume, risks of BPH-related surgery and AUR | 2-year risk<br>Surgery<br>Finasteride: 3.5% versus placebo: 5.9%<br>HR: 0.60 (0.43-0.84)<br>AUR<br>Finasteride 1.0% versus placebo: 2.5%<br>HR: 0.43 (0.43-0.84)<br>Conclusion: finasteride reduced the risk of AUR and surgery compared with placebo during 2 years of follow-up |
| Roehrborn et al,<br>*Urology,*<br>2002 [65] | Three double-blinded, placebo-controlled RCTs (ARIA3001, 3002, and 3003) | - Men with clinical BPH and moderate to severe LUTS, enlarged prostates, PSA 1.5-10, etc., n=4,325<br>- Follow-up: 2 years<br>- Dutasteride compared with placebo<br>- Outcome: AUA-SI, risks of AUR, prostate volume, Qmax, surgical intervention, serum PSA, and the safety and tolerability of the drug | 2-year risk<br>Surgery<br>Dutasteride: 2.2% versus placebo: 4.1%.<br>RR of surgery was 0.52 and risk reduction was 48%.<br>AUR<br>Dutasteride: 1.8% versus placebo: 4.2%<br>RR of AUR was 0.43 and risk reduction was 57%.<br>Conclusion: dutasteride reduced the risk of AUR and surgery compared with placebo during 2 years of follow-up |

| | | | |
|---|---|---|---|
| Tsukamoto et al,<br>*Int J Urol.,*<br>2009 [66] | Double-blinded, placebo-controlled parallel-group study | - Men aged >=50 years, IPSS >=8, PV <=30 mL , etc., n=378<br>- Dutasteride compared with placebo<br>- Follow-up: 52 weeks | During 52 weeks, 5 cases of AUR in the placebo group and one case in the finasteride group<br>No report on surgery |
| **Follow-up <=4 years** | | | |
| McConnell et al,<br>*NEJM*,<br>1998 [36] | Double-blinded, placebo-controlled RCT (PLESS trial), enrolled between 1990-1992 | - Men with moderate to severe LUTS and enlarged prostate, n=3,040<br>- Follow-up: 4 years<br>- Finasteride compared with placebo<br>- Outcomes: Primary outcomes: symptom scores, urinary flow rates, occurrence and prostate volume for a subgroup of men. Secondary outcomes: AUR and surgery for BPH. | Four-year risk<br><u>Surgery</u><br>Finasteride: 5% versus placebo: 10%<br>ARR: 5%, RR (using log-rank test): 55%<br><u>AUR</u><br>Finasteride: 3% versus placebo: 7%<br>ARR: 4%, RR (using log-rank test): 57%<br>Conclusion: finasteride reduced the risk of AUR and surgery compared with placebo for four years of treatment |
| Debruyne et al,<br>*Eur Urol,*<br>2004 [67] | 2-year open-label extension of three RCTs (ARIA3001, 3002, and 3003) | - Men aged ≥50 years with BPH and moderate to severe LUTS, n=2,340<br>- Follow-up: 2-4 years<br>- Dutasteride<br>- Outcomes: AUA-SI, Qmax, prostate volume, AUR and BPH-surgery | AUR and BPH surgery occurred in small percentages (0.3% and 0.1%, respectively) during the open-label phase |
| Gittelman et al,<br>*J Urol,*<br>2006 [77] | Analysis of data from the ARIA3001, 3002, and 3003 and 2-year open-label extension[65,67] | - All men in included in Debruyne et al (2004)[67] with available prostate volume, n=2,332<br>- Follow-up: 4 years<br>- Patients receiving dutasteride in the double-blinded phase and open-label phase (dutasteride/dutasteride) versus patients receiving placebo during double blinded phase and dutasteride in the open-label phase (placebo/dutasteride)<br>- Outcomes: RR | Four-year RR; dutasteride/dutasteride versus placebo/dutasteride group<br><u>Surgery</u><br>Baseline PV 30-<40: 27% (95% CI: 42-63%)<br>PV≥40 $cm^3$: 48% (95% CI: 24-64%)<br><u>AUR</u><br>Baseline PV 30-<40: 60% (95%: CI 3-83%)<br>Baseline PV≥40 $cm^3$: 55% (95% CI: 36-69%)<br>Conclusion: the dutasteride/dutasteride had a decreased risk of BPH-related surgery and AUR compared with the placebo/dutasteride group |
| Roehrborn et al,<br>*Eur Urol,*<br>2010 [39] | Double-blinded, randomized, parallel-group study (CombAT Study) | - Men aged ≥50 years with clinical BPH IPSS≥12, PSA 1.5-10, etc., n=4,844<br>- Follow-up: 4 years<br>- Tamsulosin versus Dutasteride versus combination of both<br>- Outcomes: time to first AUR or BPH-related surgery | Four-year risk<br><u>Surgery</u><br>Tamsulosin: 7.8%<br>Dutasteride: 3.5%<br>Combination therapy: 2.4%<br><u>AUR</u> |

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|---|---|---|---|
| | | | Tamsulosin: 6.8%<br>Dutasteride: 2.7<br>Combination therapy: 2.2%<br>Conclusion: combination therapy was superior to tamsulosin but not dutasteride at reducing the RR of BPH-related surgery or AUR |
| Roehrborn et al,<br>*Urology,*<br>2011 [68] | Post-hoc analysis of REDUCE trial cohort | - Men aged 50-75, PSA 2.5-10, IPSS<25, PV <=80 $cm^3$, n=8122<br>- Dutasteride versus placebo<br>- Follow-up: 4 years | Four-year risk<br><u>Surgery</u><br>Dutasteride 1.4% versus placebo 5.1%. ARR=3.7%, RRR=73%<br><u>AUR</u><br>Dutasteride 1.6% versus placebo 6.7%. ARR=5.1%, RRR=77%<br>Conclusion: dutasteride reduced the risk of AUR and surgery compared with placebo during 4 years of follow-up |
| Toren et al,<br>*BMJ,*<br>2013 [69] | Post-hoc analysis of the 4-year, double-blinded Reduction by Dutasteride of Prostate Cancer Events (REDUCE trial) study | - Men with prostate volume>40 mL and baseline IPSS <8 (mild LUTS), n=1,617<br>- Finasteride compared with placebo<br>- Follow-up: 4 years | Four-year risk<br><u>Surgery</u><br>Dutasteride 0.9% versus placebo 4.7%<br>ARR 3.8%, RRR= 81%<br>OR=0.18 (0.08-0.40)<br><u>AUR</u><br>Dutasteride 1.6% versus placebo 7.6%<br>ARR=6%, RRR=79%<br>OR=0.20 (0.11-0.37)<br>Conclusion: treatment with dutasteride reduced the risk of BPH-related surgery and AUR in men with no or mild symptoms and enlarged prostates |
| **Follow-up >4 years** | | | |
| Hudson et al,<br>*Urology,*<br>1999 [73] | Open-label extension of Phase III North American BPH trial | - Patients who completed the initial 12-month double-blinded, placebo-controlled trial and initially randomized to finasteride, asked to continue open label, n=186<br>- Eligibility criteria initial trial: age 10-83, symptoms of urinary obstruction, enlarged prostate on digital rectal examination, and Qmax<15ml/s, etc.<br>- Follow-up: >1-5 years<br>- Finasteride | During the open-label extension, 0.3-1.0% of patients per year experienced AUR, and 1.3% of patients per year required surgery for BPH |

| | | | |
|---|---|---|---|
| Lam et al,<br>*Urology,*<br>2003 [70] | Additional open-label extension (of open-label extension) of Phase III North American BPH trial | - 43 patients from one single institution in the US who completed the 1-year Phase III North American BPH trial and subsequently completed a 5-year open extension and subsequently another 5-year open label extension (30 completed the 6-10-year extension).<br>- Eligibility criteria initial trial: age 10-83, symptoms of urinary obstruction, enlarged prostate on digital rectal examination, and Qmax<15ml/s, etc.<br>- Finasteride<br>- Follow-up: 6-10 years | 8 of 43 (19%) patients underwent prostatectomy during the 6-10-year open-label extension period. No report on AUR |
| McConnell et al,<br>*NEJM,*<br>2003 [74] | Double-blinded, placebo-controlled RCT (MTOPS study), 1995-2001 | - Men ≥50 years with moderate to severe LUTS, serum PSA<10. A range of exclusion criteria, n = 3,047<br>- Doxazosin, finasteride or combination therapy compared with placebo<br>- Follow-up: mean 4,5 years<br>- Outcomes: crude event rates, cumulative incidence, RR and number needed to treat (NNT) | Four-year risks<br><u>Surgery</u><br>Doxazosin: 3%<br>Finasteride: 2%<br>Combination: 1%<br>Placebo: 5%<br><u>AUR</u><br>Doxazosin: 1%<br>Finasteride: <1%<br>Combination: <1%<br>Placebo: 2%<br>Conclusion: doxazosin and finasteride combination therapy and finasteride monotherapy reduced the risk of AUR and surgery, and combination therapy was superior to monotherapy |
| Souverein et al,<br>*Eur Urol,*<br>*2003* [75] | Population-based cohort study, The Netherlands, 1991-2000 | - Men aged 50 years or above with no history of using alpha-blockers or 5-ARIs and more than one year of database history prior to first date of BPH drug-dispensing who filled at least one prescription for alpha-blockers (alfuzosin, tamsulosin, or terazosin) or 5-ARIs (finasteride), n=5,671<br>- HR (adjusted for age, calendar time, prescriber, and chronic disease score), Kaplan-Meier estimates for BPH-related surgery in the two treatment groups<br>- Follow-up: mean 2.8 years | <u>Surgery</u><br>Alpha-blocker versus 5-ARI users: HR 1.52 (1.24-1.88). Kaplan-Meier curves illustrated, but estimates are not reported |

| | | | |
|---|---|---|---|
| Roehrborn et al,<br>*J Urol,*<br>2004 [72] | 2-year open label extension of PLESS study | - 1,693 men (785 from the original placebo group and 908 from the original finasteride group) of 3,016 patients initially randomized for the PLESS study<br>- Follow-up: 4-6 years<br>- Finasteride<br>- Outcomes: incidence rates of BPH-related surgery and AUR | The decrease in incidence of BPH-related surgery and AUR remained during the 2-year extension period |
| Unger et al,<br>*JNCI J Natl Cancer Inst,*<br>2016 [71] | Post-hoc analysis of the Prostate Cancer Prevention Trial (PCPT) linked to Medicare claims data,<br>1993-1997 | - Men enrolled in the PCPT: men aged 55 years or above with normal digital rectal examination, PSA<=3.0 ng/mL, and AUA-SI <20 (i.e., no to moderate LUTS) and available Medicare claims data, n=13,935<br>- Finasteride versus placebo (during the duration of the trial: 7 years)<br>- Follow-up: median 16 years (from trial registration to end of Medicare claims data) | <u>Surgery</u><br>Five-year risk<br>Finasteride: 0.5% versus placebo: 0.5%<br>10-year risk<br>Finasteride: 1.3% versus placebo: 1.5%<br>HR=0.90 (0.72-1.14)<br>Note: PCPT eligibility criteria: limited generalizability |

Abbreviations: 5-ARI – 5-alpha reductase inhibitor; ARR – absolute risk reduction; AUA-SI – American Urological Association Symptom Index; AUR – acute urinary retention; BPH – benign prostatic hyperplasia; CI – confidence interval; HR= hazard ratio; IPSS – international prostate symptom score; LUTS – lower urinary tract symptoms; OR=odds ratio; PSA – prostate specific antigen; PV – prostate volume; RCT – randomized controlled trial; RR - relative risk; RRR – relative risk reduction; Qmax – maxinum urinary flow rate; US – United States of America

MEDLINE search query

('prostate hypertrophy'/exp OR 'bph (benign prostatic hyperplasia)' OR 'benign hyperplasia, prostate' OR 'benign hyperplasia, prostatic' OR 'benign hypertrophy, prostate' OR 'benign hypertrophy, prostatic' OR 'benign prostate hyperplasia' OR 'benign prostatic hyperplasia' OR 'benign prostatic hypertrophy' OR 'hyperplasia, prostate' OR 'hypertrophy, prostate' OR 'prostate benign hyperplasia' OR 'prostate benign hypertrophy' OR 'prostate enlargement' OR 'prostate gland hypertrophy' OR 'prostate hyperplasia' OR 'prostate hyperthrophy' OR 'prostate hypertrophia' OR 'prostate hypertrophy' OR 'prostatic benign hyperplasia' OR 'prostatic benign hypertrophy' OR 'prostatic hyperplasia' OR 'prostatic hypertrophy' OR 'benign prostatic obstruction'/exp OR 'lower urinary tract symptom'/exp OR 'luts' OR 'lower urinary tract symptom' OR 'lower urinary tract symptoms' OR 'bladder obstruction'/exp OR 'bladder neck obstruction' OR 'bladder outflow obstruction' OR 'bladder outlet obstruction' OR 'obstructio vesicae urinariae' OR 'urinary bladder neck obstruction' OR 'urinary bladder obstruction') AND ('steroid 5alpha reductase inhibitor'/exp OR '5 alpha reductase inhibitor' OR '5 alpha reductase inhibitors' OR '5-alpha reductase inhibitor' OR '5-alpha reductase inhibitors' OR '5-alpha-reductase inhibitor' OR '5-alpha-reductase inhibitors' OR '5alpha reductase inhibitor' OR '5alpha reductase inhibitors' OR 'steroid 5alpha reductase inhibitor' OR 'finasteride'/exp OR 'dutasteride'/exp OR 'alpha adrenergic receptor blocking agent'/exp OR 'adrenergic alpha antagonists' OR 'adrenergic alpha-antagonists' OR 'alpha adrenergic antagonist' OR 'alpha adrenergic blocker' OR 'alpha adrenergic blocking agent' OR 'alpha adrenergic blocking drug' OR 'alpha adrenergic receptor antagonist' OR 'alpha adrenergic receptor blocker' OR 'alpha adrenergic receptor blocking agent' OR 'alpha adrenoceptor antagonist' OR 'alpha adrenoceptor blocker' OR 'alpha adrenoceptor blocking agent' OR 'alpha adrenoceptor blocking drug' OR 'alpha blocker' OR 'alpha blocking agent' OR 'alpha receptor blocker' OR 'alpha receptor blocking agent' OR 'tamsulosin'/exp OR 'alfuzosin'/exp OR 'doxazosin'/exp OR 'terazosin'/exp) AND ('progression'/exp OR 'surgery'/exp OR 'prostate surgery'/exp OR 'urine retention'/exp OR 'retention, urine' OR 'urinary retention' OR 'urine retention' OR 'acute urinary retention'/exp)

### 1.6.4 AUR and risk of cancer

The most common causes of AUR are benign, with obstruction secondary to BPH being the most common cause in men and detrusor failure being the most common cause in women.[20,78–80] However, AUR can also be a presenting symptom of prostate cancer and possibly other types of cancer.[20] The mechanisms through which cancers can cause obstruction leading to AUR can be intrinsic, such as with prostate or bladder cancer, or extrinsic, such as with a pelvic or gastrointestinal mass compressing the bladder neck.[78] A number of case reports suggest that AUR can be the presenting sign of cancers other than prostate cancer, including other urogenital cancers, neurological cancers, and gastrointestinal cancers,[81–92] and these cancers are also suggested causes of AUR in the literature.[20,78,93,94] However, existing knowledge on the risk of these cancers after a first AUR diagnosis is sparse. Previous studies on the association between AUR and cancer were limited by small sample sizes (<400)[21,95–97] or single hospital studies.[21,96,97] Studies on the association of AUR and prostate cancer were carried out before the era of PSA testing,[21,95] and studies reporting on the risk of cancer in women with AUR had strict selective inclusion criteria (Table 4), making the generalizability difficult.[96,97]

**Table 4. Summary of the existing literature of validity of the risk of cancer after a first diagnosis of AUR.**

| Study IV: | | | |
|---|---|---|---|
| **Author, journal, year** | **Design, setting, year** | **Population, exposure, outcomes** | **Results and comments** |
| Moul et al, *J Urol,* 1989[95] | Washington, US, 1984-1988 | - Patients admitted to two institutions with AUR requiring catheterization, n=90 | - Prostate cancer was found in 13.3%<br>- No other cancers were reported |
| Murray, *Br. J. Urol,* 1984[21] | Bristol, UK, 1979-1980 | - Men admitted to the Department of Urology, Southmead Hospital with AUR, n=310 | - Prostate cancer was found in 7%<br>- No other cancers were reported |
| Wheeler et al, *Urology,* 1990[96] | US, retrospective hospital record review, N/A | - Women who presented with urinary retention or symptomatic large urinary residuals and who were referred for urodynamic evaluation, n=68 | - Central nervous system tumour in 6% |
| Ahmad et al, *J. Clin. Urol,* 2009[97] | UK, retrospective hospital record review, 1996-2007 | - Women diagnosed with urinary retention during an inpatient hospital admission to one department of urology, n=300 | - Bladder cancer was detected in 4%, rectal cancer in 1%, ovarian cyst/cancer in 1%, and endometrial cancer in 0.3% |
| Abbreviations: AUR – acute urinary retention; UK – United Kingdom; US – United States of America | | | |
| Medline search query:<br>(urinary retention[MeSH Terms]) AND ((causes[MeSH Terms]) OR (neoplasms[MeSH Terms])) AND (1980/1/1:2022/12/12[pdat]) AND (english[Filter]) **Filters:** English, from 1980/1/1 - 2022/12/12 | | | |

# 2. Objectives and hypotheses

The mid-1990s' introduction of medical therapy has changed the management of BPH and AUR substantially. The overall aim of this dissertation was to improve our understanding of the long-term consequences of this paradigm shift and the prognoses of BPH and AUR.

We conducted four studies with the following objectives:

I. To examine the PPVs of BPH and AUR in the DNPR.

II. To examine 21-year trends in AUR incidence, subsequent BPH-related treatment, and mortality. Additionally, to compare all-cause and cause-specific mortality with mortality in the general population.

III. To examine the 15-year risk of BPH-related surgery and AUR in men treated with 5-ARI versus alpha-blocker monotherapy in routine clinical care.

IV. To examine the risk of cancer after a first hospitalization for AUR.

We hypothesized that a) the PPVs of AUR and BPH in the DNPR were high (Study I), b) the shift in management of BPH and AUR coincided with changes in AUR incidence, management, and mortality (Study II), c) treatment with 5-ARIs versus alpha-blocker monotherapy was associated with a reduced risk of BPH-related surgery and AUR for up to 15 years of follow-up (Study III), and d) AUR was a marker of occult urogenital, colorectal, and neurological cancers (Study IV).

# 3. Methods

The following sections describe the methods used in Studies I-IV and Table 5 provides a summary.

## 3.1 Setting

All studies were conducted in Denmark, which had a population of 5.8 million residents in 2018.[98] The country is administratively divided into five regions, each of which is representative of the Danish population in terms of sociodemographic characteristics, healthcare utilization, and medication usage.[99] Study I was carried out in the Central Denmark Region, which has a source population of 1.3 million residents, while Studies II-IV were nationwide population-based cohort studies.

The Danish healthcare system offers tax-funded healthcare to all residents, which includes free access to primary care physicians and hospitals, as well as reimbursement for prescription medications.[100] The healthcare system is divided into primary care, provided by general practitioners, and secondary care, which includes inpatient, outpatient, and emergency room hospital visits. Except for emergencies, patients must first visit a primary care physician to access secondary care.[101] A unique personal identification number is assigned to all residents at birth or upon immigration, which allows for accurate linkage of individual-level data across registries and complete follow-up.[101]

## 3.2 Data sources

We have used the following data sources.

### *Medical records*

In Study I, data were gathered from the medical records of patients sampled from two hospitals in the Central Denmark Region.

### *The Danish Civil Registration System*

The Danish Civil Registration System holds information on sex, date of birth, emigration and vital status and date of death since 1968, allowing for complete follow-up of all patients.[102]

### *The Danish National Patient Registry (DNPR)*

The DNPR contains information on all inpatient hospital contacts in Denmark since 1977 and all emergency room and outpatient clinic visits since 1995.[103] This registry contains information on date of admission and discharge, and of primary and secondary diagnoses classified according to the ICD 8$^{th}$ revision until 1993, and the 10$^{th}$ revision thereafter. Since 1996, surgical procedures have been coded according to the Danish version of the Nordic Medico-Statistical Committee Classification of

Surgical Procedures (NOMESCO).[104] Each hospital contact has one primary diagnosis (the main reason for hospital visit) and, when relevant, one or more secondary diagnoses.

*The Danish National Prescription Registry*

The Danish National Prescription Registry contains information on all prescriptions dispensed by community pharmacies in Denmark since January 1, 1995.[105] This registry contains information on medication classification code (Anatomical Therapeutic Chemical (ATC) classification system product code), date of dispensing, package size, tablet strength, and amount (expressed in "defined daily doses" (DDD)). Prescription duration and indications are not recorded.[105]

*The Danish Cancer Registry*

The Danish Cancer Registry contains data on the incidence of cancer in Denmark since 1943, classified according to ICD-10 and ICD Oncology codes (ICD-0-1-3) for topography and morphology. Since 1987, the reporting of cancer incidents to this registry is mandatory.[106]

*The regional Clinical Laboratory Information System database*

The regional Clinical Laboratory Information System database contains laboratory information from two (Central and North Denmark Regions) of five Danish regions. The registry is complete since 2005 but contains data from smaller geographical areas from the late 1990s.[107]

*The nationwide Register of Laboratory Results for Research*

The nationwide Register of Laboratory Results for Research contains nationwide laboratory test results with data from all five Danish regions since July 2015.[108]

*The Danish Register of Causes of Death*

The Danish Register of Causes of Death contains data on causes of death on all deaths among Danish residents dying in Denmark since 1971.[109]

*Statistics Denmark*

From online published data from Statistics Denmark, we obtained information on the annual sex and age distribution as well as data on all-cause and cause-specific mortality of the Danish population.[98]

## 3.3 Study designs

We conducted a validation study (Study I) and three population-based cohort studies (Studies II-IV). In Studies II and IV, we used the general population as reference population, comparing the rates of mortality (Study II) and cancer (Study IV) in men with AUR with the rates in the general population.[98,106] Study III was an active comparator, new user study, in which we used patients

treated with alpha-blocker monotherapy as an active comparator. A brief introduction of the active comparator, new user study design is provided below.

### 3.3.1. Active comparator, new user study design

The active comparator, new user study design aims to emulate the design of a head-to-head RCT.[110] In this design, a cohort of new drug users are assembled and followed over time for the outcomes of interest.[111] The active-comparator group serves as a control group and ensures that the drug of interest is compared with another drug that is used for the same indication rather than no treatment.[110] This restricts the study population to patients with an indication for treatment and reduces both measured and unmeasured confounding (such as confounding by indication, healthy initiator, and frailty).[110] The new-user component ensures that all patients are anchored at a uniform time point, the date of treatment initiation, which ensures the correct temporality between covariate and exposure assessment, and reduces the risk of immortal time bias.[111]

**Table 5. Summary of methods.**

| | Study I | Study II | Study III | Study IV |
|---|---|---|---|---|
| **Objectives** | Examine the PPV of BPH and AUR in the DNPR | Examine trends in AUR incidence, subsequent BPH-related treatment, and mortality. Compare all-cause and cause-specific mortality with the general population | To examine whether treatment with 5-ARI versus alpha-blocker monotherapy reduces the 15-year risk of BPH-related surgery and AUR | To examine the risk of urogenital, colorectal, and neurological cancers after a first diagnosis of AUR. |
| **Design** | Validation study | Nationwide cohort study | Nationwide population-based active comparator, new user study | Nationwide cohort study |
| **Study period** | January 2011-December 2017 | January 1997-December 2017 | January 1997-December 2017 | January 1995-December 2017 |
| **Setting** | Central Denmark Region | Denmark | Denmark | Denmark |
| **Data sources** | DCRS, DNPR, medical charts | DCRS, DNPR, NPR, DRCD | DCRS, DNPR, NPR, LABKA, RLRR | DCRS, DNPR, DCR |
| **Study population** | A random sample of 100 men aged ≥50 years diagnosed with BPH and 100 men diagnosed with AUR | All men aged ≥45 years with a first hospitalization for AUR (n=70,775) | All men who filled at least two prescriptions for 5-ARI or alpha-blocker (BPH-specific only) within 6 months of first prescription | All patients aged ≥50 years with a first hospitalization for AUR (n=75,983) |
| **Exclusion criteria** | - | History of AUR, prostate cancer, multiple sclerosis, Parkinson's disease, and postsurgical AUR | See Figure 3 | History of AUR, cancer, postsurgical AUR |
| **Exposure** | Diagnosis of BPH or AUR in the DNPR | Calendar year (incidence), AUR hospitalization (mortality) | 5-ARI versus alpha-blocker monotherapy | AUR hospitalization |
| **Outcomes** | PPV | AUR incidence, 1-year CI of BPH-related surgery and BPH medications, all-cause and cause-specific mortality | wHR and wCI of BPH-related surgery and AUR | Absolute and excess cancer risk compared with the general population |
| **Adjustment strategy** | - | Direct and indirect standardization | Propensity score SMRW | Indirect standardization |
| **Statistical analysis** | PPV with corresponding 95% confidence intervals using the Wilson Score method | Incidence rates, 1-year CI of BPH-related surgery and BPH-medications, mortality rates (Kaplan-Meier), all-cause and cause-specific SMRs compared with mortality in the general population | MI for missing values of baseline PSA. SMRW analyses using alpha-blocker group as an active comparator. wHR using Cox regression analysis and wCI (Aalen-Johansen) using intention to treat and per protocol approach | CI, SIRs, and excess cancer risk among patients with AUR compared with the general population |
| **Stratification** | Age, calendar period, type of hospital, type of hospital contact, and department | Age, type of AUR, CCI score | - | Age, sex, calendar period, type of AUR, CCI score, urogenital disease, neurological disease, diabetes |
| **Sensitivity analysis** | | | Altering inclusion criteria to men who redeemed at least 3 prescriptions within 12 months of first prescription | Exclusion of patients with a diagnosis of concomitant haematuria |

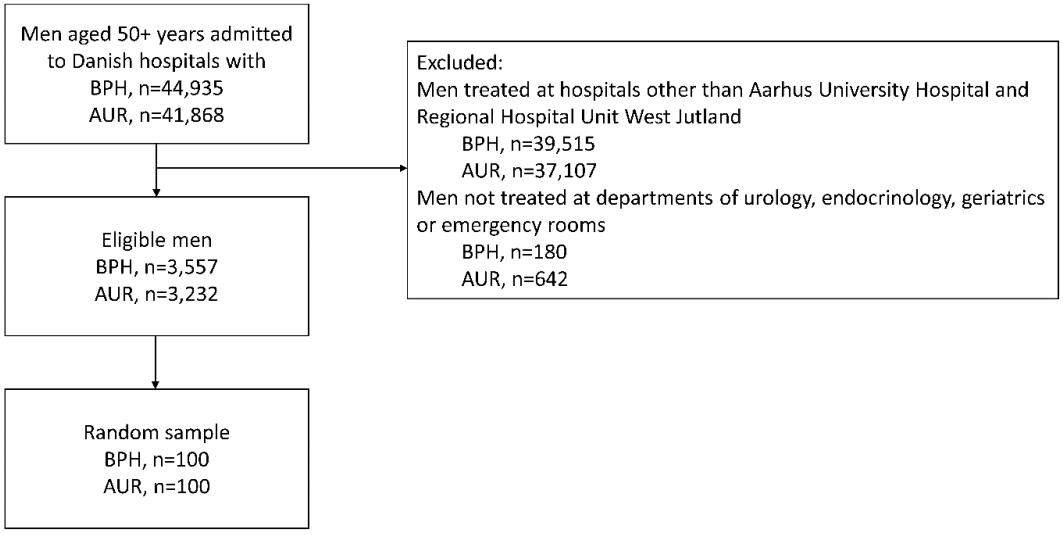
Abbreviations: AUR – acute urinary retention; BPH – benign prostatic hyperplasia; CCI score – Charlson Comorbidity Index score; CI – cumulative incidence; DRCD – The Danish Register of Causes of Death; DCRS – The Danish Civil Registration System; DCR – The Danish Cancer Registry; DNPR – Danish National Patient Registry; LABKA - The regional Clinical Laboratory Information System database; MI – multiple imputation; NPA – Then Danish National Prescription registry; PPV – positive predictive value; RLRR - The nationwide Register of Laboratory Results for Research; SMR – standardized mortality ratio; SMRW– standardized mortality ratio-weighting; 5-ARI – 5-alpha-reductase inhibitor; wCI – weighted Cumulative Incidence; wHR – weighted Hazard Ratio

## 3.4 Study populations

The Central Denmark Region has departments of urology at two hospitals: Aarhus University Hospital and Regional Hospital Unit West Jutland.

In Study I, we used the DNPR to randomly sample 100 men diagnosed with BPH and 100 men diagnosed with AUR at Aarhus University Hospital and Regional Hospital Unit West Jutland. We sampled patients diagnosed at departments of urology, acute medicine/emergency room, geriatrics, and endocrinology. We included these departments, because they were the departments where patients with BPH and AUR were most frequently diagnosed. Combined, they covered ~90% of all BPH and AUR diagnoses at the included hospitals. A flow chart depicting the selection of the study population for Study I is provided in Figure 2.

***Figure 2. Flow chart depicting study population selection for Study I.***




*Modified Figure from Bengtsen MB, Heide-Jørgensen U, Blichert-Refsgaard LS, Hjelholt TJ, Borre M, Nørgaard M. Positive predictive value of benign prostatic hyperplasia and acute urinary retention in the danish national patient registry: A validation study. Clin Epidemiol. 2020;12:1281-1285.[126] Appendix I.*

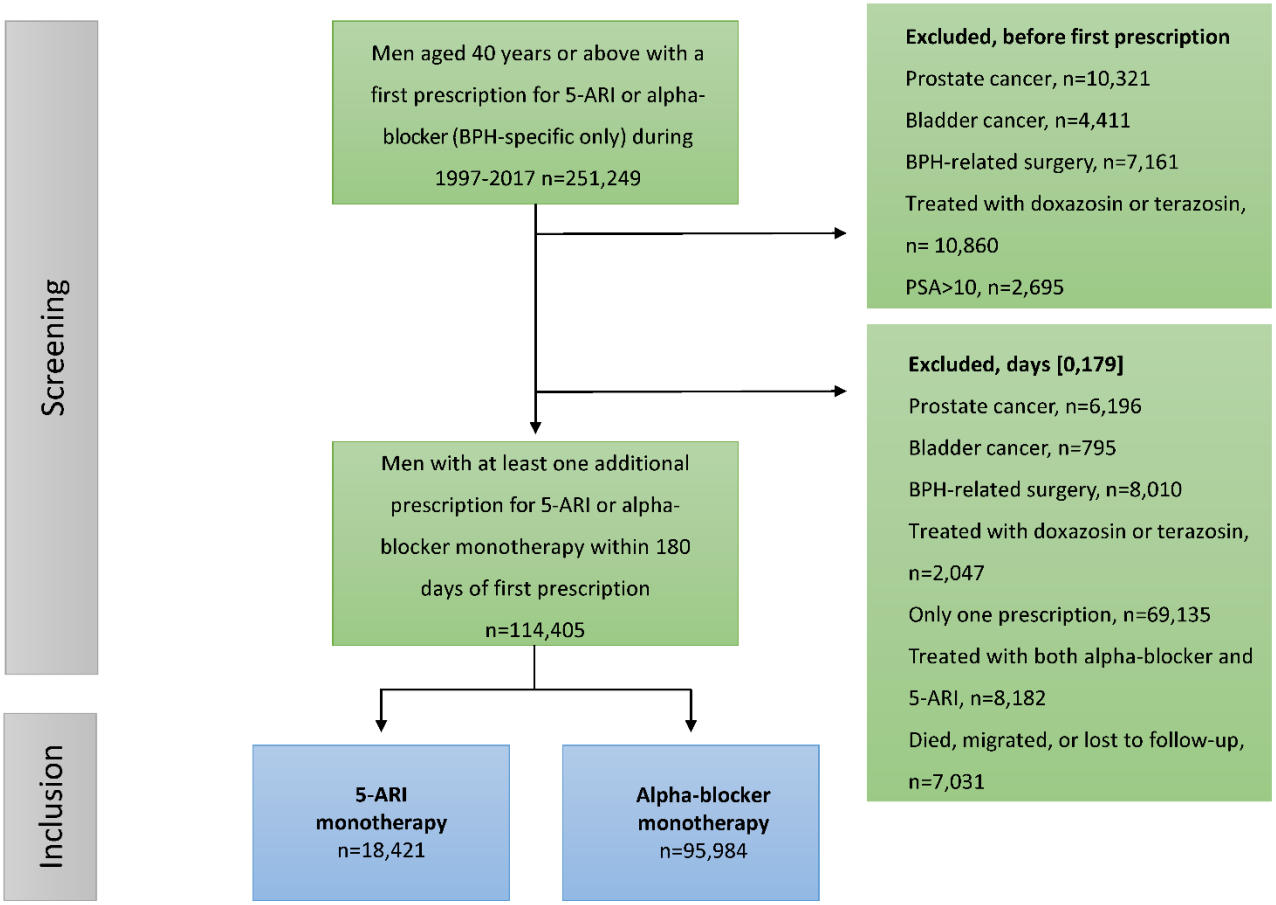
The study populations of Studies II and IV included patients with a first hospitalization for AUR; however, the study periods and exclusion criteria varied.

In Study II, we excluded patients with conditions related to AUR other than BPH (i.e., prostate cancer, multiple sclerosis, and Parkinson's disease) as well as men with postsurgical AUR (defined as AUR occurring within one week after surgery).[20] Given the fact that AUR can be the first presenting sign of BPH in up to 50% of cases, we did not require a concomitant diagnosis of BPH or use of BPH medications prior to AUR hospitalization.[53]

In Study IV, we excluded patients with postsurgical AUR as well as patients with a previous diagnosis of any cancer (except non-melanoma skin cancer) because our primary outcome was a first cancer diagnosis.

In Study III, we first identified all men with a first prescription for 5-ARI or alpha-blocker in Denmark from 1997 to 2017. To identify men receiving 5-ARI or alpha-blocker monotherapy, we set an index date 180 days after the first prescription. We disregarded men who did not redeem at least one additional prescription before the index date. We also excluded men who switched treatment, initiated combination therapy, or underwent BPH-related surgery before the index date. By setting an index date 180 days after the first prescription, we wanted to avoid including patients who discontinued treatment early due to side effects or insufficient efficacy. In addition, we did not want to include patients who initiated alpha-blocker monotherapy only as symptomatic relief while waiting for BPH-related surgery. Similarly, we did not want to include patients treated with 5-ARI prior to surgery to reduce the risk of bleeding. The study population selection for Study III is illustrated in Figure 3 and the underlying time scale and covariate assessment are illustrated in Figure 4.

***Figure 3. Flow chart depicting study population selection for Study III.***




Abbreviations: 5-ARI - 5-aplha reductase inhibitor; BPH - benign prostatic hyperplasia

*Figure from Bengtsen MB, Heide-Jørgensen U, Borre M, Nørgaard M. Appendix III.*

***Figure 4. Graphical depiction of underlying time scale and covariate assessment for Study III.***

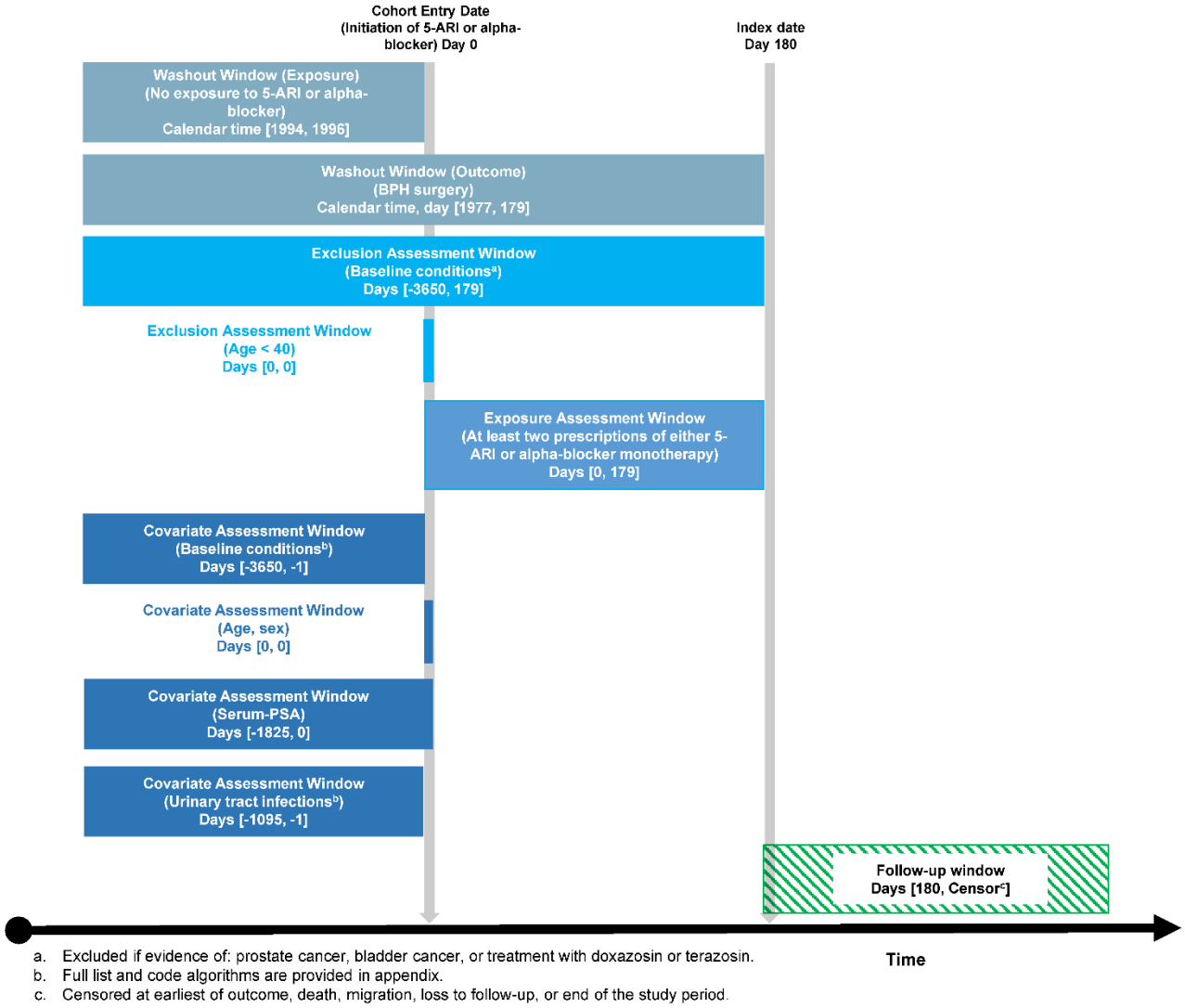



*Figure from Bengtsen MB, Heide-Jørgensen U, Borre M, Nørgaard M. Appendix III.*

## 3.5 Exposures

A first hospital diagnosis of AUR was the exposure in Study II (when studying mortality) and Study IV. We used the DNPR to identify AUR hospitalization, using ICD-10 coding, and included both primary and secondary AUR diagnoses. From a clinical and prognostic perspective, spontaneous AUR differs from precipitated AUR.[19] Precipitated AUR is preceded by a triggering event other than BPH (such as surgical procedures, anaesthesia, medications, and infections), and may occur in the presence or absence of BPH.[19] All other cases can be characterized as spontaneous AUR.[19]

In Study II, we defined AUR as spontaneous if it was recorded as a primary diagnosis or if it was recorded as a secondary diagnosis with BPH as the primary diagnosis.[3] All other cases of AUR were categorized as precipitated. The same definition was used in Study IV (that also included women),

but instead of spontaneous and precipitated AUR, we used the terms primary and secondary AUR, respectively.

In Study III, we used the Danish National Prescription Registry to identify all patients with a first prescription for alpha-blocker monotherapy and 5-ARI between January 1, 1997 and December 31, 2017. We included the alpha-blockers tamsulosin and alfuzosin and the 5-ARIs finasteride and dutasteride. We did not include the alpha-blockers doxazosin and terazosin, as they are non-specific alpha-blockers, used for treatment of hypertension as well as BPH.[112] Nor did we include use of finasteride 1 mg, used for treatment of male-pattern baldness.[112]

## 3.6 Outcomes

In Study I, we used medical record review as the reference standard to evaluate the PPV of BPH and AUR in the DNPR. The medical record review was performed by three physicians and information was entered into a standardized form developed for the purpose. For each patient, we evaluated if the diagnosis could be confirmed by medical record review. We considered the presence of BPH confirmed if men received BPH-specific medication, had a history of LUTS and no other causes of LUTS were specified, or if BPH was confirmed by biopsy. AUR was considered confirmed in the presence of an inability to urinate that required immediate catheterization.

In Studies II and III, data on AUR hospitalization were retrieved from the DNPR (including both primary and secondary diagnoses). We obtained data on BPH-related surgery from the DNPR (Studies II and III) and on prescription for BPH medications from the Danish National Prescription Registry within 1 year after the AUR diagnosis (Study II). In Study II, data on all-cause mortality were retrieved from the Danish Civil Registration System. Data on cause-specific mortality were retrieved from the Danish Register of Causes of Death for the AUR cohort. Data on all-cause and cause-specific mortality of the general population were obtained from Statistics Denmark.[98] Data on cause-specific mortality in the general population were only available in the period 2007-2016.

In Study IV, we obtained data on selected cancer incidents from the Danish Cancer Registry.[106] We categorized cancers by location: urinary tract cancers, genital cancers, colorectal cancers, and neurological cancers. We categorized urogenital cancers further into those located in the prostate, bladder (invasive cancer and non-invasive cancer), kidney, renal pelvis, and genitals in women. Data on cancer in the general population were obtained from the Danish Cancer Registry.

## 3.7 Statistical analysis

In this section, I will provide a brief overview of the applied statistical methodology and the reasoning behind its utilization. The statistical analyses performed for Studies I-IV are summarized in Table 5 and described in detail in each paper in the Supplementary.

Data management, statistical analyses, and visualizations were performed using R version 4.1 (The R Foundation for Statistical Computing, *www.R-project.org*. Studies I-III) and SAS statistical software package, v. 9.4 (SAS Institute, Cary, NC. Study IV).

### 3.7.1 Standardization (Studies II and IV)

Standardization of rates is a common epidemiological technique that eliminates the confounding effect of variables that vary between populations being compared.[113] There are two main standardization methods, distinguished by whether the standard used is a population distribution (direct method) or a set of specific rates (indirect method).[113] The direct standardization method calculates the rate that would be expected in the populations under study if they all had the same composition with respect to the variable for which the effect is being adjusted or controlled.[113] We used this method in Study II to adjust for age when studying temporal trends in incidence and mortality rates. The indirect standardization method uses specific rates from the standard population and applies them to the populations under comparison.[113] This allows for the calculation of the expected number of cases. The standardized mortality ratio (SMR) or standardized incidence ratio (SIR) are then computed by dividing the observed number of cases by the expected number. We used indirect standardization to compute the SMR (Study II) and the SIR (Study IV), to compare the risk of dying (Study II) and cancer (Study IV) in patients with AUR with that expected if they had the same risk as the general population. In Study IV, we computed the excess risk of cancer in patients with AUR compared with the general population, defined as the difference between the observed and expected number of cancers divided by the total follow-up period.

### 3.7.2 Cumulative incidence and competing risks (Studies II-IV)

We calculated the cumulative incidence of outcomes in Studies II-IV using the Kaplan-Meier[114] method (Study II) and cumulative incidence function[115] (Studies II-IV). Both methods handle time-to-event data, where follow-up can be censored. A key assumption of censoring is that it is independent (or non-informative), meaning individuals being censored have the same chance of the outcome as those who are uncensored.[116] The Kaplan-Meier estimator denotes the probability of surviving time t[116] and does not consider competing risks.[117] A competing risk is an event that precludes the occurrence of the primary event of interest.[117] In any study in which the outcome is not all-cause mortality, death will act as a competing risk. In the presence of competing risks, the

Kaplan-Meier estimator will overestimate the incidence of the outcome, because the Kaplan-Meier estimator assumes that competing risks do not occur and censors patients upon the time of death, even when the outcome is not all-cause mortality.[117] Thus, estimates from the Kaplan-Meier estimator pertain to a population in which individuals cannot die, a setting of questionable clinical relevance.[117] We therefore used the Kaplan-Meier estimator when the outcome was all-cause mortality (Study II) and the cumulative incidence function in the presence of competing risks (Studies II-IV). In the presence of competing risk, we followed each patient from index date until first occurrence of outcome, competing risk, emigration, or end of follow-up. In Study III, we analysed data using both intention to treat (ITT) and per protocol (PP) analyses.[76] In the ITT analysis, men were followed from the index date until first occurrence of an outcome event, competing risk, emigration, or death. In the PP analysis, men were further censored when they switched treatment or discontinued treatment for more than 90 days. For evaluation of treatment switch and discontinuation, treatment with the non-BPH-specific alpha-blockers (doxazosin and terazosin) were also considered alpha-blocker exposure. Discontinuation of treatment defined as days covered by a redeemed prescription plus a 90-day grace period. In the PP analysis, when studying BPH-related surgery as an outcome, men were followed for additionally 180 days after treatment discontinuation to allow for waiting time for surgery after treatment discontinuation.

### 3.7.3 Cox proportional hazards regression (Study III)

While the Kaplan-Meier estimator and cumulative incidence function provide measures of the absolute risk, the Cox regression model provides a measure of the rate ratio, specifically the hazard ratio (HR). In Study III, we used cause-specific Cox regression to compute HRs. The HR is calculated as the ratio between the hazard rate (or instantaneous rate) of the event in the exposed group and the hazard of the event in the unexposed group. In the cause-specific Cox-model, patients are censored upon time of death or other competing events, implicitly assuming that censored patients would have had the same rate of the outcome as those that remain uncensored. Thereby, it pertains to a population in which individuals cannot die or experience other competing events before experiencing the outcome of interest. Although this may be a setting of questionable clinical relevance, it still provides useful information. If the risk of the competing events group was different in the two treatment groups (5-ARI versus alpha-blocker groups), an observed risk difference of BPH-related surgery/AUR could potentially be explained by differences in survival or occurrence of other competing risks. In that case, the HR would complement the cumulative incidence estimates, by taking into account the accrued person-time.

### 3.7.4 Propensity score standardized mortality ratio weighting (Study III)

The propensity score is a balance score that can be used to reduce or eliminate the effects of confounding when using observational data.[118] The propensity score is defined as patients' predicted probability of receiving a certain treatment given their characteristics and can be computed using logistic regression.[118] Several methods can be used to balance the exposed and non-exposed individuals. The propensity score targets causal inference in observational studies in a manner that resembles randomised experiments.[118] However, an important difference is that randomized experiments can achieve exchangeability with respect to both measured and unmeasured confounding, whereas the propensity score method only achieves exchangeability with respect to measured confounders. In Study III, we estimated the propensity of being in the observed treatment groups using a logistic regression model, including the following variables: age, calendar year, baseline serum-PSA, presence of previous urogenital comorbidity (AUR, urinary tract infection, recurrent urinary tract infection, bladder stones, bladder disease, haematuria, incontinence, and hydronephrosis) and other comorbidity (chronic pulmonary disease, diabetes, hypertension, Charlson Comorbidity Index score (CCI score)). Considered covariates were all covariates associated with the outcomes.[119] Continuous variables (age, calendar year, and serum-PSA) were included in the model as natural cubic splines with five knots. We used standardized mortality ratio weighting (SMRW) to reweight the alpha-blocker users so that the distribution of covariates resembles that of the 5-ARI users. Thus, we assigned the 5-ARI users a weight of 1 and the alpha-blocker users the odds of treatment probability (propensity score/(1-prosensity score)).[120] We chose the SMRW approach to measure the average treatment effect in the treated (ATT) because of the differential indications for treatment with 5-ARI versus alpha-blockers. Thus, while alpha-blocker treatment should be considered in men with moderate to severe LUTS, 5-ARI treatment is reserved to men with moderate to severe LUTS *and* an increased risk of progression, i.e., prostate volume >30-40mL or serum-PSA>1.4-1.6 ng/mL.[14,16] Moreover, the effectiveness of 5-ARIs depends on prostate volume and may not be more effective than placebo in men with prostate <40mL.[40,41] When it is not feasible to treat everyone in the eligible population but only patients with certain characteristics who actually received the treatment, the relevant target of interest is the ATT.[120] The ATT can be interpreted as the effect of the treatment when patients receiving treatment in the study population were treated versus the reference treatment.[118] Covariate balance between the two treatment groups was assessed using standardized mean differences.[120]

### 3.7.5 Multiple imputation (Study III)

In Study III, data on missing baseline serum-PSA were missing. Missing data are often classified as being: missing completely at random (i.e., the probability of data being missing does not depend on

observed or unobserved data), missing at random (i.e., the probability of data being missing does not depend on unobserved data, conditional on the observed data), and missing not at random (i.e., the probability of data being missing does depend on the unobserved data, conditional on the observed data).[121] If data are missing completely at random, the complete case analysis is unbiased.[122] However, when data are not missing completely at random, the complete case analysis can be biased.[122] In Study III, we used multiple imputation with chained equations to replace missing values of serum-PSA to avoid bias due to the complete case analysis and to avoid excluding a substantial part of the study population due to missing data.[122] Standard implementation of multiple imputation assumes that the missing data are missing at random.[123] In Study III, missing serum-PSA was expected due to the incomplete coverage of laboratory databases during the study period. PSA testing has been recommended as a standard part of the work-up of men with LUTS in Denmark during the study period.[15] Still, the patient and physician sometimes refrain from measuring serum-PSA, e.g., due to advanced age and comorbidity. This would, however, also most likely lead to data missing at random, because we do have data on patient-related factors, such as age and comorbidity. Based on these considerations, we found it reasonable to assume that serum-PSA was missing at random and performed multiple imputation using data from the 29,753 men with available serum-PSA.[124] The multiple imputation model included all variables included in the analysis models (listed above) and the analysis models outcome variables: the Nelson Aalen estimates of the cumulative hazard function and censoring indicators.[121] A rule of thumb is that the number of imputations should be similar to the percentage of cases that are incomplete,[121] and therefore we created 70 imputed datasets. All analyses were performed for each imputed dataset and then combined using Rubin's Rule.[121,125]

## 3.8 Ethical aspects

All studies were approved by the Danish Data Protection Agency (Studies I-III: record number 2016-051-000001; Study IV: KEA-2017-36/812). Study I was additionally approved by the Danish Patient Safety Authority (reference number: 3-3013-2925/1) and by the Head of each of the involved departments. In accordance with Danish law governing analysis of registry data, no Ethics Committee approval was required.

# 4. Results

The main findings from Studies I-IV are presented below and in detail in the appendices.

## 4.1 Study I

Medical records were available for all 200 sampled patients. Outpatient diagnoses comprised 92% of BPH diagnoses and 59% of AUR diagnoses.[126] Overall, medical record review could confirm 95 out of 100 BPH cases, resulting in a PPV of 95% (95% confidence interval (CI): 89%-98%). The overall PPV for AUR was 98% (95% CI: 93%-99%). The PPVs stratified by age, type of hospital, type of hospital contact, calendar year group, and department were consistent with the main results (Table 6).[126]

**Table 6. Positive predictive value (PPV) of benign prostatic hyperplasia (BPH) and acute urinary retention (AUR) in the Danish National Patient Registry.**

| | BPH | | AUR | |
|---|---|---|---|---|
| | Verified/Total | PPV (95% CI) | Verified/Total | PPV (95% CI) |
| **Overall** | 95/100 | 95 (89–98) | 98/100 | 98 (93–99) |
| **Age** | | | | |
| 50–69 years | 44/47 | 94 (83–98) | 23/23 | 100 (86–100) |
| 70–79 years | 28/29 | 97 (83–100) | 35/35 | 100 (90–100) |
| 80+ years | 23/24 | 96 (80–100) | 40/42 | 95 (84–99) |
| **Type of hospital** | | | | |
| University Hospital | 48/48 | 100 (93–100) | 65/67 | 97 (90–99) |
| Regional Hospital | 47/52 | 90 (79–96) | 33/33 | 100 (90–100) |
| **Type of hospital contact** | | | | |
| Inpatient | 7/8 | 88 (53–99) | 34/34 | 100 (90–100) |
| Outpatient | 88/92 | 96 (89–98) | 57/59 | 97 (88–99) |
| Emergency room | 0/0 | - | 7/7 | 100 (65–100) |
| **Year group** | | | | |
| 2011–2013 | 42/44 | 95 (85–99) | 44/45 | 98 (88–100) |
| 2014–2017 | 56/56 | 100 (94–100) | 51/55 | 93 (83–97) |
| **Department** | | | | |
| Urology | 88/93 | 95 (88–98) | 71/73 | 97 (91–99) |
| Emergency room | 0/0 | - | 6/6 | 100 (61–100) |
| Endocrinology | 1/1 | 100 (5–100) | 8/8 | 100 (68–100) |
| Geriatrics | 6/6 | 100 (61–100) | 13/13 | 100 (77–100) |

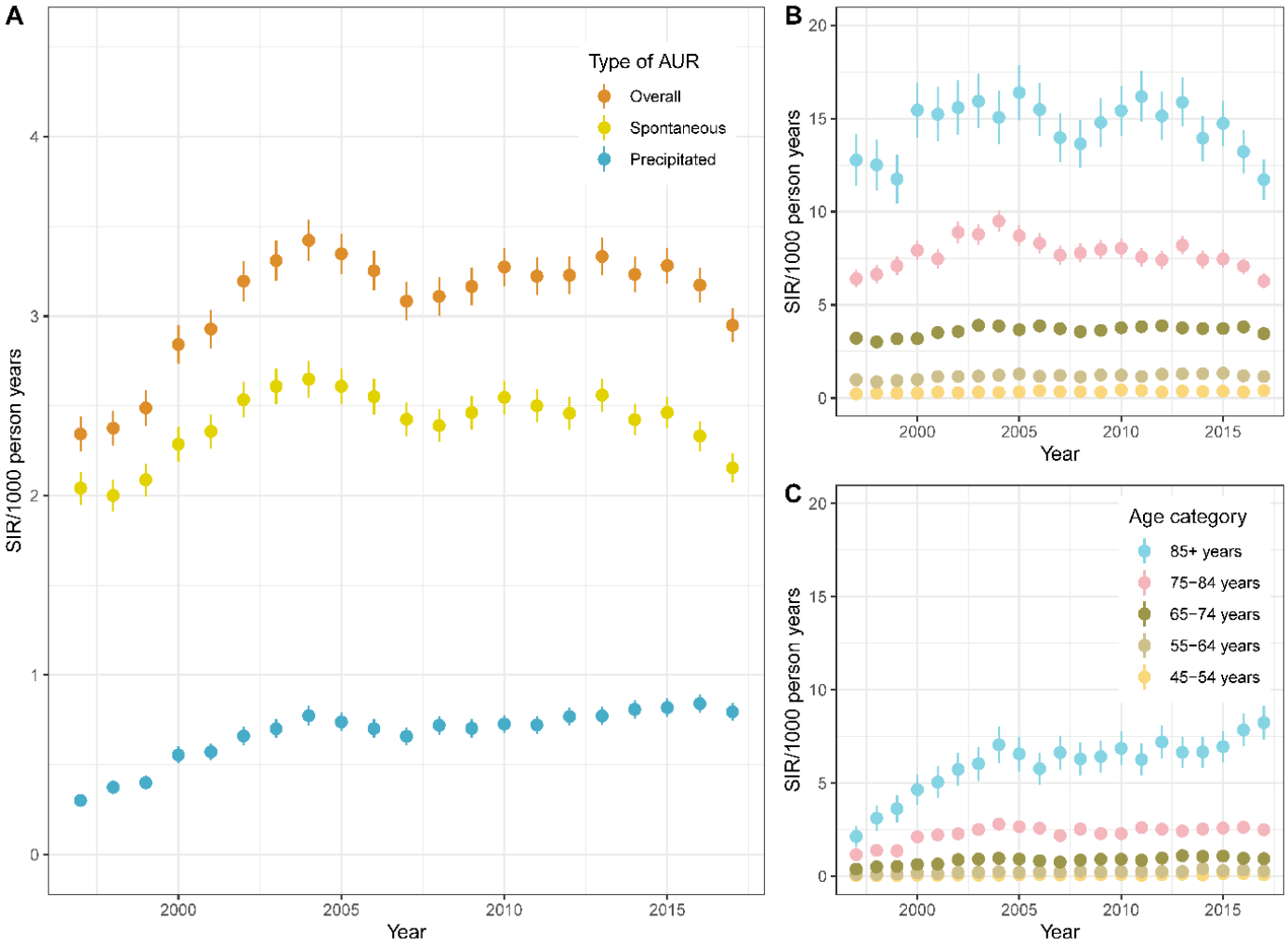
*Modified Figure from Bengtsen MB, Heide-Jørgensen U, Blichert-Refsgaard LS, Hjelholt TJ, Borre M, Nørgaard M. Positive predictive value of benign prostatic hyperplasia and acute urinary retention in the danish national patient registry: A validation study. Clin Epidemiol. 2020;12:1281-1285.[126] Appendix I.*

## 4.2 Study II

We identified 70,775 men aged 45 years or above with a first hospital diagnosis of AUR in Denmark during 1997-2017. Of these, most had spontaneous AUR (77.8%).[127]

The standardized incidence rate of AUR per 1,000 person-years increased transiently from 2.34 (95% CI: 2.24-2.44) in 1997 to 3.42 (95% CI: 3.30-3.54) in 2004 and then gradually declined to 2.95 (95% CI: 2.86-3.04) in 2017 (Figure 5A). [127] The transient increase observed during 1997-2004 was observed for both spontaneous and precipitated AUR, and it was mainly driven by men aged 75 years or above (Figure 5A-C). After 2004, the standardized incidence rate of spontaneous AUR gradually declined to 2.15 (95% CI: 2.07-2.33) in 2017, while it continued to increase for precipitated AUR in men aged 85 years or above (Figure 5C).[127]

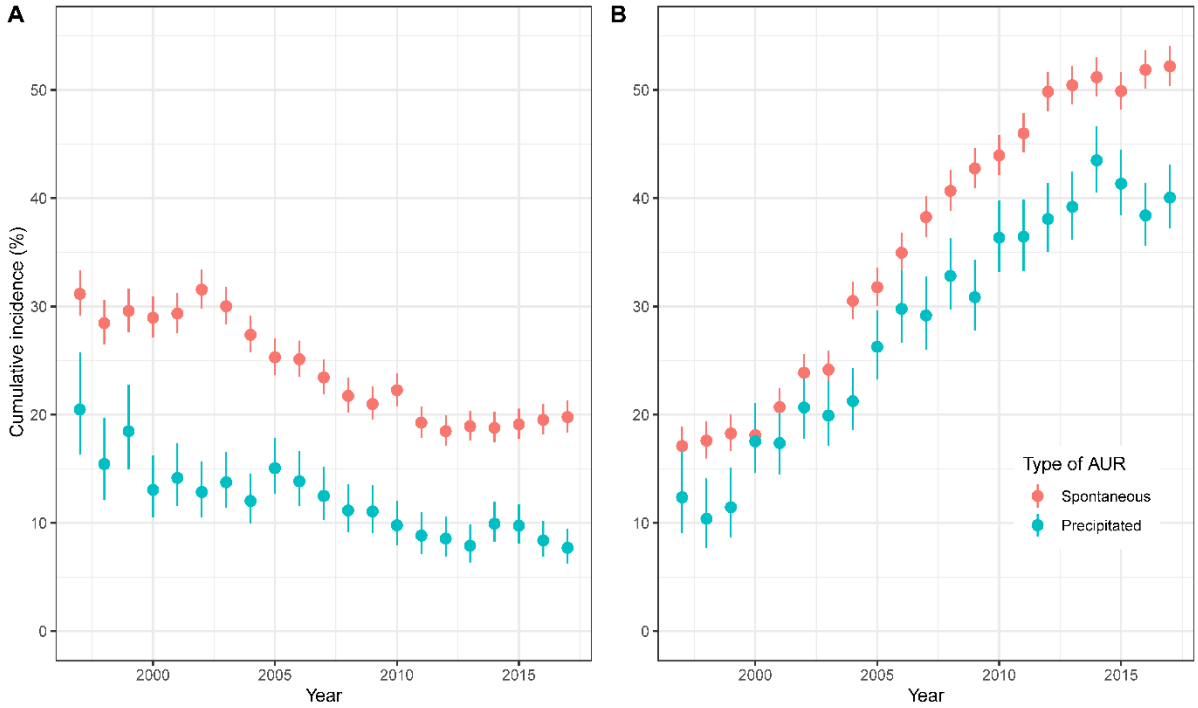
***Figure 5. Standardized incidence rates (SIRs) of first hospitalization for acute urinary retention (AUR) overall (A), within age groups for spontaneous (B) and precipitated AUR (C), 1997–2017***




*Modified Figure from Bengtsen MB, Heide-Jørgensen U, Borre M, Knudsen JS, Nørgaard M. Acute urinary retention in men: 21-year trends in incidence, subsequent benign prostatic hyperplasia-related treatment and mortality: A Danish population-based cohort study. Prostate. 2023;83(1):87-96.[127] Appendix II.*

The cumulative incidence of patients who underwent BPH-related surgery within one year of AUR declined from 31.2% (95%CI: 29.2%–33.3%) in 1997 to 19.8% (95% CI: 18.4%–21.3%) in 2017 after spontaneous AUR and from 20.5% (95% CI: 16.3%–25.8%) to 7.7% (95% CI: 6.3%–9.5%) after precipitated AUR (Figure 6A). A concurrent increase in patients receiving BPH medication within a year after AUR diagnosis was observed (Figure 6B).[127]

***Figure 6. Trends in 1–year cumulative incidence of benign prostatic hyperplasia-related surgery (A) and medication (B) after first hospitalization for acute urinary retention (AUR), 1997-2017.***




*Modified Figure from Bengtsen MB, Heide-Jørgensen U, Borre M, Knudsen JS, Nørgaard M. Acute urinary retention in men: 21-year trends in incidence, subsequent benign prostatic hyperplasia-related treatment and mortality: A Danish population-based cohort study. Prostate. 2023;83(1):87-96.[127] Appendix II.*

During 1997-2017, the standardized 1-year mortality declined from 22.2% (95% CI: 20.1%-24.2%) to 17.5% (95% CI: 16.2%-18.9%), but the SMRs were stable across calendar periods (Appendix II).[127]

The 3-month and 1-year SMRs compared with the general population were 3.6 (95% CI: 3.5-3.7) and 2.2 (95% CI: 2.2-2.3) for men with spontaneous AUR and 5.4 (95% CI: 5.2-5.7) and 2.8 (95% CI: 2.7-2.9) for men with precipitated AUR, respectively (Table 7).[127]

**Table 7. Three-month and one-year mortality rates in men with spontaneous and precipitated acute urinary retention and standardized mortality ratios against the general population by age group.**

| | | Mortality | | | | | |
|---|---|---|---|---|---|---|---|
| | | 3 months | | | 1 year | | |
| | Total | Rate (95% CI) | O/E | SMR (95% CI) | Rate (95% CI) | O/E | SMR (95% CI) |
| **Spontaneous AUR** | | | | | | | |
| 45-54 years | 2,412 | 2.7 (2.0-3.3) | 65/3 | 21.2 (16.7-27.1) | 5.9 (4.9-6.8) | 141/12 | 11.5 (9.8-13.6) |
| 55-64 years | 7,993 | 2.8 (2.5-3.2) | 225/25 | 9.1 (8.0-10.3) | 7.1 (6.5-7.6) | 562/99 | 5.7 (5.2-6.2) |
| 65-74 years | 16,188 | 4.1 (3.8-4.4) | 662/118 | 5.6 (5.2-6.1) | 10.3 (9.8-10.8) | 1,655/472 | 3.5 (3.3-3.7) |
| 75-84 years | 18,828 | 7.0 (6.6-7.4) | 1,304/369 | 3.5 (3.4-3.7) | 18.7 (18.1-19.2) | 3,496/1,474 | 2.4 (2.3-2.5) |
| 85+ years | 9,615 | 14.4 (13.7-15.1) | 1,370/494 | 2.8 (2.6-2.9) | 33.5 (32.6-34.5) | 3,204/1,976 | 1.6 (1.6-1.7) |
| Total | 55,036 | 6.6 (6.4-6.8) | 3,626/1,009 | 3.6 (3.5-3.7) | 16.6 (16.3-16.9) | 9,058/4,034 | 2.2 (2.2-2.3) |
| **Precipitated AUR** | | | | | | | |
| 45-54 years | 526 | 4.0 (2.3-5.7) | 19/1 | 29.4 (18.7-46.1) | 8.6 (6.2-10.9) | 45/3 | 17.4 (13.0-23.3) |
| 55-64 years | 1,606 | 4.9 (3.8-5.9) | 77/5 | 15.8 (12.6-19.8) | 10.8 (9.3-12.4) | 174/20 | 8.9 (7.7-10.4) |
| 65-74 years | 3,796 | 6.8 (6-7.6) | 252/28 | 9.2 (8.1-10.4) | 16.5 (15.3-17.6) | 620/110 | 5.6 (5.2-6.1) |
| 75-84 years | 5,649 | 12.4 (11.5-13.2) | 693/111 | 6.2 (5.8-6.7) | 26.5 (25.3-27.6) | 1,486/445 | 3.3 (3.2-3.5) |
| 85+ years | 4,102 | 22.4 (21.1-23.7) | 913/217 | 4.2 (3.9-4.5) | 42.2 (40.7-43.7) | 1,719/868 | 2.0 (1.9-2.1) |
| Total | 15,679 | 12.6 (12.1-13.1) | 1,954/361 | 5.4 (5.2-5.7) | 26.0 (25.3-26.6) | 4,044/1,445 | 2.8 (2.7-2.9) |

Abbreviations: AUR – acute urinary retention; CI – confidence interval; O – observed; E – expected; SMR – standardized mortality ratio.

*Modified Table from Bengtsen MB, Heide-Jørgensen U, Borre M, Knudsen JS, Nørgaard M. Acute urinary retention in men: 21-year trends in incidence, subsequent benign prostatic hyperplasia-related treatment and mortality: A Danish population-based cohort study. Prostate. 2023;83(1):87-96.[127] Appendix II.*

**Table 8. One-year mortality rates in men with spontaneous and precipitated acute urinary retention and standardized mortality ratios against the general population by presence of comorbidity.**

| | | Mortality | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Men without comorbidity* | | | Men with comorbidity* | | | |
| | Total | Rate (95% CI) | O/E | SMR (95% CI) | Total | Rate (95% CI) | O/E | SMR (95% CI) |
| **Spontaneous AUR** | | | | | | | | |
| 45-54 years | 1,655 | 2.2 (1.5-3.0) | 37/8 | 4.4 (3.2-6.1) | 757 | 13.7 (11.3-16.2) | 104/4 | 27.0 (22.3-32.7) |
| 55-64 years | 5,141 | 2.5 (2.1-3.0) | 128/64 | 2.0 (1.7-2.4) | 2,852 | 15.2 (13.9-16.5) | 434/36 | 12.2 (11.1-13.4) |
| 65-74 years | 8,916 | 4.1 (3.7-4.5) | 362/258 | 1.4 (1.3-1.6) | 7,272 | 18.0 (17.1-18.8) | 1,293/215 | 6.0 (5.7-6.4) |
| 75-84 years | 8,489 | 10.9 (10.3-11.6) | 922/669 | 1.4 (1.3-1.5) | 10,339 | 25.0 (24.2-25.9) | 2,574/814 | 3.2 (3-3.3) |
| 85+ years | 4,216 | 27.0 (25.6-28.3) | 1,131/891 | 1.3 (1.2-1.3) | 5,399 | 38.6 (37.3-39.9) | 2,073/1,086 | 1.9 (1.8-2.0) |
| Total | 28,417 | 9.1 (8.8-9.5) | 2,580/1,880 | 1.4 (1.3-1.4) | 26,619 | 24.5 (24.0-25.0) | 6,478/2,154 | 3.0 (2.9-3.1) |
| **Precipitated AUR** | | | | | | | | |
| 45-54 years | 309 | 2.9 (1.0-4.8) | 9/2 | 6.0 (3.1-11.5) | 217 | 16.6 (11.6-21.5) | 36/1 | 33.1 (23.9-45.8) |
| 55-64 years | 872 | 4.9 (3.5-6.4) | 43/11 | 4.1 (3.0-5.5) | 734 | 17.8 (15.1-20.6) | 131/9 | 14.6 (12.3-17.3) |
| 65-74 years | 1,749 | 9.0 (7.7-10.4) | 158/51 | 3.1 (2.7-3.6) | 2,047 | 22.8 (21.0-24.6) | 462/59 | 7.8 (7.1-8.6) |
| 75-84 years | 2,235 | 18.3 (16.7-19.9) | 404/176 | 2.3 (2.1-2.5) | 3,414 | 31.9 (30.3-33.4) | 1,082/268 | 4.0 (3.8-4.3) |
| 85+ years | 1,816 | 35.5 (33.3-37.7) | 641/392 | 1.6 (1.5-1.8) | 2,286 | 47.5 (45.5-49.6) | 1,078/476 | 2.3 (2.1-2.4) |
| Total | 6,981 | 18.1 (17.2-19) | 1,255/631 | 2.0 (1.9-2.1) | 8,698 | 32.3 (31.3-33.3) | 2,789/813 | 3.4 (3.3-3.6) |

Abbreviations: AUR – acute urinary retention; CI – confidence interval; O – observed; E – expected; SMR – standardized mortality ratio.

*Presence of comorbidity was measured by Charlson Comorbidity Index score.

*Modified Table from Bengtsen MB, Heide-Jørgensen U, Borre M, Knudsen JS, Nørgaard M. Acute urinary retention in men: 21-year trends in incidence, subsequent benign prostatic hyperplasia-related treatment and mortality: A Danish population-based cohort study. Prostate. 2023;83(1):87-96.[127] Appendix II.*

Mortality was generally higher after precipitated AUR and increased with age and presence comorbidity according to CCI score (Tables 7 and 8).[127] The main cause of death within a year of AUR diagnosis was malignancy (n=1,849, 28%. Table 9).[127] Cause-specific SMRs were particularly high for urogenital disease (6.0), diabetes (5.1), certain infections (4.7, mainly sepsis, which accounted for 91 of 166 cases), malignancies (4.2), and chronic pulmonary disease (3.6. Table 9). Of 283 deaths attributable to urogenital disease, the most important causes of death were urinary tract infections (n=99), kidney failure (n=92), and BPH (n=47).[127]

**Table 9. Causes of death occurring within one year after first hospitalization for acute urinary retention.***

| | Overall | | Spontaneous AUR | | Precipitated AUR | |
|---|---|---|---|---|---|---|
| **Cause of death** | **O/E** | **SMR (95% CI)** | **O/E** | **SMR (95% CI)** | **O/E** | **SMR (95% CI)** |
| Urogenital disease | 283/478 | 6.0 (5.4-6.8) | 188/33 | 5.8 (5.0-6.7) | 95/14 | 6.6 (5.4-8.1) |
| Malignancies | 1,849/439 | 4.2 (4.0-4.4) | 1,323/317 | 4.2 (4.0-4.4) | 526/123 | 4.3 (3.9-4.7) |
| Prostate cancer | 271/100 | 2.7 (2.4-3.1) | 192/71 | 2.7 (2.4-3.1) | 79/30 | 2.7 (2.2-3.3) |
| Neurological disease | 176/669 | 2.7 (2.3-3.1) | 121/46 | 2.6 (2.2-3.1) | 55/20 | 2.8 (2.1-3.6) |
| Certain infectious diseases | 166/35 | 4.7 (4.1-5.5) | 98/24 | 4.0 (3.3-4.9) | 68/11 | 6.4 (5.1-8.2) |
| Respiratory disease | 920/254 | 3.6 (3.4-3.9) | 572/178 | 3.2 (3.0-3.5) | 348/76 | 4.6 (4.1-5.1) |
| COPD and asthma | 571/127 | 4.5 (4.2-4.9) | 354/89 | 4.0 (3.6-4.4) | 217/37 | 5.8 (5.1-6.7) |
| Cardiovascular disease | 1,476/586 | 2.5 (2.4-2.7) | 964/411 | 2.3 (2.2-2.5) | 512/175 | 2.9 (2.7-3.2) |
| Stroke | 379/140 | 2.7 (2.4-3.0) | 260/98 | 2.6 (2.3-3.0) | 119/42 | 2.8 (2.4-3.4) |
| Diabetes | 248/49 | 5.1 (4.5-5.7) | 165/35 | 4.7 (4.1-5.5) | 83/14 | 5.9 (4.7-7.3) |

Abbreviations: AUR – acute urinary retention; CI – confidence interval; COPD – chronic obstructive pulmonary disease; O – observed; E – expected; SMR – standardized mortality ratio.

*Restricted to calendar period 2007-2016 due to limitations in data availability.

*Modified Table from Bengtsen MB, Heide-Jørgensen U, Borre M, Knudsen JS, Nørgaard M. Acute urinary retention in men: 21-year trends in incidence, subsequent benign prostatic hyperplasia-related treatment and mortality: A Danish population-based cohort study. Prostate. 2023;83(1):87-96.[127] Appendix II.*

## 4.3 Study III

In total, we included 18,421 and 95,985 men who initiated 5-ARI and alpha-blocker monotherapy, respectively. Before SMRW, men in the 5-ARI group had higher age (median age 71 versus 69 years) and baseline serum-PSA (2.6 versus 1.9) compared with men in the alpha-blocker group. After SMRW, all standardized differences were below 10% indicating that groups were comparable (Appendix III). The weighted median age was 71 years and median serum-PSA was 2.7 ng/mL.

Overall, treatment with 5-ARI versus alpha-blocker monotherapy was associated with a reduced risk of BPH-related surgery (ITT weighted hazard ratio (wHR)=0.73 (95% CI: 0.68-0.78); PP wHR=0.77 (95% CI: 0.70-0.84)) and AUR (ITT wHR=0.73 (95% CI: 0.67-0.78); PP wHR=HR=0.75 (95% CI: 0.66-0.84)).

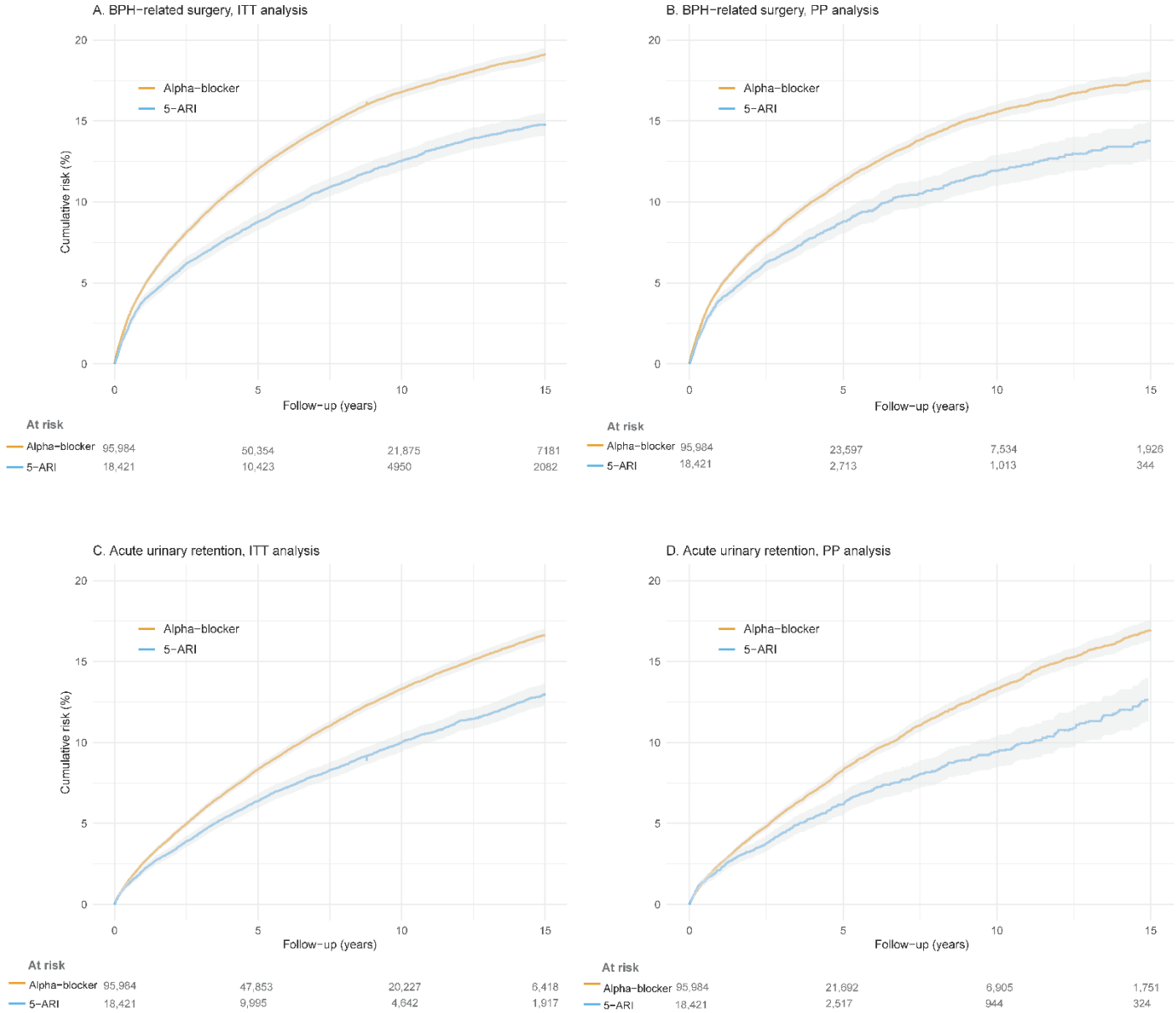
In the ITT analysis, the 15-year weighted cumulative incidence (wCIs) of BPH-related surgery were 14.8% (95% CI: 14.1-15.5%) in the 5-ARI group versus 19.1% (95% CI: 18.7-19.5%) in the alpha-blocker group, corresponding to a relative risk reduction (RRR) of 22.5% and an absolute risk reduction (ARR) of 4.3%. (Figure 7A and Table 10). In the PP analysis, the wCIs of BPH-related surgery in men receiving 5-ARI versus alpha-blocker monotherapy were 13.8% (95% CI: 12.6-17.5%) versus 17.5% (95% CI: 16.9-18.0%) after 15 years of follow-up (RRR=21.1%; ARR=3.7%. Figure 7B).

In the ITT analysis, the 15-year wCIs of AUR were 13.0% (95% CI: 12.3-13.6%) versus 16.6% (95% CI: 16.3-17.0%) in the 5-ARI versus alpha-blocker group (RRR=27.7%; ARR=3.6%. Figure 7C). In the PP analysis, the 15-year wCIs of AUR were 12.6% (95% CI: 11.3-14.0%) versus 16.9% (95% CI: 16.3-17.6%) in men receiving 5-ARI versus alpha-blocker monotherapy, respectively (RRR=25.4%; ARR=4.3%. Figure 7D).

The RRR was stable after 5, 10, and 15 years of follow-up for both BPH-related surgery (23-27% in the ITT analysis and 21-24% in the PP analysis) and AUR (22-25% in the ITT analysis and 25-29% in the PP analysis).

A more pronounced difference in the risk of BPH-related surgery and AUR was seen in the sensitivity analysis, where we restricted to men who redeemed three rather than two prescriptions and started follow-up after one year (Appendix III).

***Figure 7. Cumulative risk of BPH-related surgery (A-B) and acute urinary retention (C-D) associated with 5-ARI versus alpha-blocker monotherapy after SMRW.***




Abbreviations: 5-ARI - 5-alpha reductase inhibitor; BPH - benign prostatic hyperplasia; ITT - intention to treat; PP - per protocol; SMRW - standardized mortality ratio weighting.

*Figure from Bengtsen MB, Heide-Jørgensen U, Borre M, Nørgaard M. Appendix III.*

**Table 10. Cumulative risk of BPH-related surgery and acute urinary retention in men treated with 5-ARI versus alpha-blocker monotherapy after SMRW.**

| | Intention to treat | | | | Per protocol | | | |
|---|---|---|---|---|---|---|---|---|
| | Cumulative risk % (95% CI) | | RRR % | ARR % | Cumulative risk % (95% CI) | | RRR % | ARR % |
| | 5-ARI | Alpha-blocker | | | 5-ARI | Alpha-blocker | | |
| **5-year risk** | | | | | | | | |
| BPH-related surgery | 8.8 (8.3-9.3) | 12.0 (11.7-12.3) | 26.7 | 3.2 | 8.8 (8.1-9.5) | 11.3 (10.9-11.6) | 22.1 | 2.5 |
| AUR | 6.4 (6.0-6.8) | 8.3 (8.1-8.6) | 22.9 | 1.9 | 6.2 (5.5-6.8) | 8.3 (8.0-8.6) | 25.3 | 2.1 |
| **10-year risk** | | | | | | | | |
| BPH-related surgery | 12.5 (11.9-13.1) | 16.8 (16.4-17.2) | 25.6 | 4.3 | 11.9 (11.0-12.9) | 15.6 (15.1-16.0) | 23.7 | 3.7 |
| AUR | 10.0 (9.5-10.5) | 13.3 (13.0-13.6) | 24.8 | 3.3 | 9.4 (8.5-10.4) | 13.3 (12.9-13.8) | 29.3 | 3.9 |
| **15-year risk** | | | | | | | | |
| BPH-related surgery | 14.8 (14.1-15.5) | 19.1 (18.7-19.5) | 22.5 | 4.3 | 13.8 (12.6-14.9) | 17.5 (16.9-18.0) | 21.1 | 3.7 |
| AUR | 13.0 (12.3-13.6) | 16.6 (16.3-17) | 21.7 | 3.6 | 12.6 (11.3-14) | 16.9 (16.3-17.6) | 25.4 | 4.3 |

Abbreviations: BPH – benign prostatic hyperplasia; 5-ARI – 5-alpha reductase inhibitor; SMRW – standardized mortality ratio weighting; CI – confidence interval; RRR – relative risk reduction; ARR – absolute risk reduction; AUR – acute urinary retention

*Table from Bengtsen MB, Heide-Jørgensen U, Borre M, Nørgaard M. Appendix III.*

## 4.4 Study IV

We identified a total of 75,082 patients aged 50 years or above with a first AUR hospitalization and no previous cancer diagnosis during 1995-2017.[128] Patients had a median age of 76 (interquartile range 68-83 years) and most were men (n=62,753, 82.6%).

The absolute risk of prostate cancer was 5.1% (95% CI: 4.9%-5.3%) at three months, 6.7% (95% CI: 6.6% to 6.9%) at one year, and 8.5% (95% CI: 8.3% to 8.7%) at five years after first AUR hospitalization.[128] The excess risk of prostate cancer per 1,000 person-years was 218 (95% CI: 214-221) during less than three months of follow-up, and 21 (95% CI: 20-23) during three to less than 12 months of follow-up, while no elevated risk of prostate cancer was observed after more than one year of follow-up (SIR=1.1 (95% CI: 1.0-1.2), Table 11).[128]

The absolute risk of urinary tract cancers was 1.3% (95% CI: 1.3-1.4%) at three months, 1.8% (1.7-1.9%) at one year, and 2.5% (2.4-2.7%) after five years of follow-up.[128] An excess risk of urinary tract cancers per 1,000 person-years was observed within the first three months of follow-up (45 (95% CI: 54-58)) and three to less than twelve months of follow-up (5 (95% CI: 4-6). Table 12). Invasive and non-invasive bladder cancer accounted for the majority of urinary tract cancers detected in patients with AUR. While the risk of bladder cancer did not differ substantially from that of the general population in men after more than one year of follow-up, women had a sustained increased risk of invasive bladder cancer during one to five years of follow-up (SIR=3.0 (95% CI: 2.0-4.4)). Exclusion of patients with a concomitant diagnosis of haematuria (n=3,938, 5.2%) reduced the 0-<3-month risk estimates, but the SIR for the first three months and during three to less than 12 months of follow-up remained elevated for almost all investigated urinary tracts cancers (Appendix IV).[128]

Within three months after AUR diagnosis, the excess risk per 1,000 person-years was 24 (95% CI: 21-27) for female genital cancer, 12 (95% CI: 11-13) for colorectal cancer (7 (95% CI: 5-9) for women, 13 (95% CI: 12-14) for men), and 2 (95% CI: 2-2) for neurological cancers. After three months of follow-up, no excess risk of female genital, colorectal, and neurological cancers was observed, and the absolute risk of these cancers were low (<1% at one year of follow-up).[128]

**Table 11. Excess risk and standardized incidence ratios of prostate cancer in 62,753 men with acute urinary retention, stratified by patient characteristics.**

| | Follow-up period | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0 - < 3 months | | | 3 - < 12 months | | | 1 - 5 years | | |
| Patient characteristics | O/E | Excess risk per 1,000 PY (95% CI) | SIR (95% CI) | O/E | Excess risk per 1,000 PY (95% CI) | SIR (95% CI) | O/E | Excess risk per 1,000 PY (95% CI) | SIR (95% CI) |
| **Overall** | 3,198/93 | 218 (214-221) | 34.5 (33.3-35.7) | 1,035/24 | 21 (20-23) | 4.2 (4.0-4.5) | 984/896 | 1 (0-2) | 1.1 (1.0-1.2) |
| **Age (years)** | | | | | | | | | |
| 50-64 | 448/6 | 163 (156-170) | 74.5 (67.8-81.8) | 138/19 | 16 (13-18) | 7.4 (6.2-8.8) | 149/113 | 1 (-1-3) | 1.3 (1.1-1.5) |
| 65-79 | 1,772/48 | 256 (251-261) | 37.0 (35.3-38.7) | 544/132 | 23 (21-25) | 4.1 (3.8-4.5) | 497/532 | -1 (-2-1) | 0.9 (0.9-1.0) |
| >80 | 978/39 | 194 (189-200) | 25.2 (23.7-26.9) | 353/94 | 22 (19-25) | 3.8 (3.4-4.2) | 338/251 | 3 (0-5) | 1.3 (1.2-1.5) |
| **Calendar period** | | | | | | | | | |
| 1995-1998 | 411/7 | 249 (239-259) | 57.3 (51.9-63.1) | 128/19 | 26 (21-31) | 6.8 (5.7-8.1) | 115/83 | 2 (-1-5) | 1.4 (1.2-1.7) |
| 1999-2003 | 664/16 | 233 (225-240) | 42.3 (39.2-45.7) | 231/42 | 26 (22-30) | 5.5 (4.8-6.3) | 226/190 | 1 (-1-4) | 1.2 (1.0-1.4) |
| 2004-2008 | 782/24 | 234 (227-241) | 31.9 (29.7-34.2) | 245/64 | 22 (18-25) | 3.8 (3.4-4.3) | 235/250 | -0 (-3-2) | 0.9 (0.8-1.1) |
| 2009-2013 | 725/25 | 197 (190-203) | 29.2 (27.2-31.5) | 244/64 | 19 (16-22) | 3.8 (3.3-4.3) | 279/254 | 1 (-1-3) | 1.1 (1.0-1.2) |
| 2014-2017 | 616/21 | 194 (187-201) | 30.0 (27.7-32.4) | 187/54 | 16 (13-19) | 3.4 (3.0-4.0) | 129/119 | 1 (-2-3) | 1.1 (0.9-1.3) |
| **Type of urinary retention** | | | | | | | | | |
| Primary AUR | 2,469/72 | 212 (208-216) | 34.2 (32.8-35.6) | 856/193 | 22 (20-24) | 4.4 (4.2-4.8) | 830/734 | 1 (-0-2) | 1.1 (1.1-1.2) |
| Secondary AUR | 729/20 | 239 (232-246) | 35.6 (33.1-38.3) | 179/51 | 17 (14-21) | 3.5 (3.0-4.1) | 154/162 | -0 (-3-2) | 0.9 (0.8-1.1) |
| **Urogenital disease** | | | | | | | | | |
| No | 1,936/44 | 273 (268-278) | 44.1 (42.2-46.2) | 545/114 | 24 (22-26) | 4.8 (4.4-5.2) | 424/413 | 0 (-1-2) | 1.0 (0.9-1.1) |
| Yes | 1,262/49 | 165 (161-169) | 25.8 (24.4-27.3) | 490/130 | 19 (17-21) | 3.8 (3.5-4.1) | 560/483 | 1 (-0-3) | 1.2 (1.1-1.3) |
| **Neurological disease** | | | | | | | | | |
| No | 2720/67 | 253 (249-257) | 40.8 (39.3-42.3) | 856/177 | 25 (23-26) | 4.8 (4.5-5.2) | 800/686 | 1 (-0-2) | 1.2 (1.1-1.3) |
| Yes | 478/26 | 119 (114-124) | 18.4 (16.8-20.1) | 179/67 | 11 (9-14) | 2.7 (2.3-3.1) | 184/211 | -1 (-3-1) | 0.9 (0.8-1.0) |
| **Diabetes** | | | | | | | | | |
| No | 2,945/80 | 231 (227-235) | 36.9 (35.6-38.2) | 945/211 | 23 (21-24) | 4.5 (4.2-4.8) | 890/792 | 1 (-0-2) | 1.1 (1.1-1.2) |
| Yes | 253/13 | 128 (120-136) | 19.7 (17.4-22.3) | 90/33 | 12 (8-16) | 2.7 (2.2-3.4) | 94/104 | -1 (-4-2) | 0.9 (0.7-1.1) |
| **CCI score** | | | | | | | | | |
| 0 | 1,964/39 | 292 (286-297) | 49.9 (47.8-52.2) | 578/108 | 26 (24-29) | 5.4 (4.9-5.8) | 585/462 | 2 (0-3) | 1.3 (1.2-1.4) |
| 1-2 | 1,007/37 | 179 (174-184) | 27.0 (25.4-28.7) | 363/97 | 19 (17-22) | 3.8 (3.4-4.2) | 324/327 | -0 (-2-2) | 1.0 (0.9-1.1) |
| ≥ 3 | 227/16 | 93 (87-99) | 14.1 (12.3-16.1) | 94/39 | 10 (7-13) | 2.4 (1.9-2.9) | 75/108 | -2 (-5-0) | 0.7 (0.5-0.9) |

Abbreviations: AUR – acute urinary retention; CI – confidence interval; CCI – Charlson Comorbidity Index; E - expected; PY – person-years; O – observed; SIR – standardized incidence ratio.

*Modified Table from Bengtsen MB, Farkas DK, Borre M, Sørensen HT. Acute urinary retention and risk of cancer: population based Danish cohort study. BMJ. 2021;375:2305.[128] Appendix IV.*

**Table 12. Excess risk and standardized incidence ratios of urogenital, gastrointestinal, and neurological cancers in 75,983 patients with acute urinary retention.**

| | Follow-up period | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0 - < 3 months | | | 3 - < 12 months | | | 1 - 5 years | | |
| Cancer site | O/E | Excess risk per 1,000 PY (95% CI) | SIR (95% CI) | O/E | Excess risk per 1,000 PY (95% CI) | SIR (95% CI) | O/E | Excess risk per 1,000 PY (95% CI) | SIR (95% CI) |
| **Urinary tract cancers** | 1,025/49 | 56 (54-58) | 21.1 (19.9-22.5) | 354/127 | 5 (4-6) | 2.8 (2.5-3.1) | 497/454 | 0 (0-1) | 1.1 (1.0-1.2) |
| Women | 114/3 | 36 (32-39) | 40.5 (33.4-48.7) | 32/8 | 3 (2-4) | 4.2 (2.9-5.9) | 52/28 | 1 (0-2) | 1.9 (1.4-2.5) |
| Men | 911/46 | 61 (59-63) | 19.9 (18.7-21.3) | 322/119 | 5 (5-6) | 2.7 (2.4-3.0) | 445/426 | 0 (-1-1) | 1.0 (1.0-1.2) |
| **Invasive bladder cancer** | 434/20 | 24 (23-25) | 22.2 (20.1-24.3) | 149/51 | 2 (2-3) | 2.9 (2.5-3.4) | 228/181 | 0 (0-1) | 1.3 (1.1-1.4) |
| Women | 62/1 | 20 (17-22) | 63.2 (48.5-81.1) | 14/3 | 1 (1-2) | 5.3 (2.9-8.9) | 29/10 | 1 (0-1) | 3.0 (2.0-4.4) |
| Men | 372/19 | 25 (23-26) | 20.0 (18.0-22.1) | 135/48 | 2 (2-3) | 2.8 (2.4-3.3) | 199/171 | 0 (0-1) | 1.2 (1.0-1.3) |
| **Non-invasive bladder cancer** | 413/18 | 23 (22-24) | 22.4 (20.3-24.7) | 129/48 | 2 (1-2) | 2.7 (2.2-3.2) | 140/172 | 0 (-1-0) | 0.8 (0.7-1.0) |
| Women | 30/1 | 9 (8-11) | 38.3 (25.8-54.7) | 10/2 | 1 (0-2) | 4.7 (2.2-8.6) | 5/8 | 0 (0-0) | 0.6 (0.2-1.5) |
| Men | 383/18 | 26 (24-27) | 21.7 (19.6-24.0) | 119/46 | 2 (1-3) | 2.6 (2.2-3.1) | 135/164 | 0 (-1-0) | 0.8 (0.7-1.0) |
| **Kidney cancer** | 130/8 | 7 (6-8) | 16.3 (13.6-19.4) | 57/21 | 1 (0-1) | 2.7 (2.0-3.5) | 108/77 | 0 (0-0) | 1.4 (1.2-1.7) |
| Women | 15/1 | 5 (3-6) | 19.2 (10.7-31.7) | 6/2 | 0 (0-1) | 2.8 (1.0-6.1) | 13/8 | 0 (0-1) | 1.7 (0.9-2.9) |
| Men | 115/7 | 8 (7-8) | 16.0 (13.2-19.2) | 51/19 | 1 (0-1) | 2.7 (2.0-3.5) | 95/69 | 0 (0-1) | 1.4 (1.1-1.7) |
| **Renal pelvic cancer** | 23/1 | 1 (1-2) | 17.2 (10.9-25.9) | 12/3 | 0 (0-0) | 3.5 (1.8-6.1) | 7/12 | 0 (0-0) | 0.6 (0.2-1.2) |
| **Genital cancers** | | | | | | | | | |
| Women | 80/5 | 24 (21-27) | 15.9 (12.6-19.8) | 19/14 | 1 (0-2) | 1.4 (0.8-2.2) | 42/50 | 0 (-1-1) | 0.8 (0.6-1.1) |
| Men | 3,216/94 | 219 (215-222) | 34.0 (32.9-35.2) | 1,039/248 | 21 (20-23) | 4.2 (3.9-4.5) | 1,005/913 | 1 (0-2) | 1.1 (1.0-1.2) |
| **Gastrointestinal cancers** | 412/100 | 18 (17-19) | 4.1 (3.7-4.5) | 299/264 | 1 (0-2) | 1.1 (1.0-1.3) | 887/951 | 0 (-1-1) | 0.9 (0.9-1.0) |
| Women | 43/13 | 10 (7-12) | 3.4 (2.5-4.6) | 51/34 | 2 (0-4) | 1.5 (1.1-2.0) | 111/123 | 0 (-2-1) | 0.9 (0.7-1.1) |
| Men | 369/88 | 20 (18-21) | 4.2 (3.8-4.7) | 248/230 | 0 (0-1) | 1.1 (1.0-1.2) | 776/828 | 0 (-1-1) | 0.9 (0.9-1.0) |
| **Neurological cancers** | 46/10 | 2 (2-2) | 4.7 (3.4-6.2) | 29/26 | 0 (0-0) | 1.1 (0.7-1.6) | 114/97 | 0 (0-0) | 1.2 (1.0-1.4) |
| Women | 11/2 | 3 (2-4) | 6.2 (3.1-11.2) | 7/5 | 0 (0-1) | 1.4 (0.6-2.9) | 19/18 | 0 (-1-1) | 1.0 (0.6-1.6) |
| Men | 35/8 | 2 (1-2) | 4.3 (3.0-6.0) | 22/21 | 0 (0-0) | 1.0 (0.6-1.6) | 95/79 | 0 (0-0) | 1.2 (1.0-1.5) |

Abbreviations: E - expected; CI – confidence interval; CCI – Charlson Comorbidity Index; PY – person-years; O – observed; SIR – standardized incidence ratio;

*Modified Table from Bengtsen MB, Farkas DK, Borre M, Sørensen HT. Acute urinary retention and risk of cancer: population based Danish cohort study. BMJ. 2021;375:2305.[128] Appendix IV.*

# 5. Discussion

## 5.1 Summary of main findings

We found high PPVs for BPH and AUR in the DNPR. During 1997-2017, only a transient increase in the standardized incidence rate of spontaneous AUR occurred, while precipitated AUR became an increasingly important part of AUR, particularly in men aged 85 years or above. The use of BPH-related surgery after a first AUR hospitalization decreased substantially. Mortality in men after AUR continued to be high, and the excess mortality risk was particularly high for deaths attributed to malignancies, urogenital disease, infections, and pre-existing comorbidity. We found AUR to be a clinical marker of urogenital, colorectal, and neurological cancers. For most cancers, the excess risk was confined to the first three months after AUR diagnosis.

Medical treatment with 5-ARI versus alpha-blocker monotherapy in routine clinical care was associated with a reduced risk of BPH-related surgery and AUR for up to 15 years of follow-up. After 15 years of follow-up, the ARR for both BPH-related surgery and AUR was 4%.

## 5.2 Comparison to the existing literature

### 5.2.1 Study I

Previous data on the validity of the diagnostic coding of AUR and BPH are sparse. We found no studies investigating the validity of these diagnoses in the DNPR. Still, in agreement with our results, previous studies investigating the validity of other benign urogenital diseases in the DNPR found PPVs ranging between 77% and 100%.[45,104,129] Two studies evaluated the ICD-9-CM coding of urinary retention (788.20) in the US. Vouri et al reported a 95% sensitivity of ICD-9-CM coding of AUR in an emergency department and an outpatient clinic.[44] Among patients with epilepsy who initiated a new antiepileptic drug and were diagnosed with AUR, the PPV was also high, ranging from 82%-100%.[43]

We acknowledge that we only considered one aspect of data quality (the PPV) in Study I, thereby not assessing other important measures of data quality including sensitivity, specificity, and negative predictive values.

### 5.2.2 Study II

Previous studies have investigated changes in the incidence of AUR in the era of medical therapy but with the previously discussed limitations. Importantly, the studies were conducted over shorter time periods and several of the studies did not include all types of hospital contacts.[2,51]

A study from the UK reported a decrease in the incidence of spontaneous AUR and a stable incidence of precipitated AUR during 1998-2003.[52] In the US, inpatient discharges of men with primary BPH and AUR were stable during 1998-2008,[2] while a study from California reported an increasing incidence of BPH-associated spontaneous and precipitated AUR among Californian men during 2007-2010.[51] Overall, our results supported most previous studies,[2,52] reporting that the introduction of medical therapy for BPH did not coincide with an increasing incidence of AUR overall or of spontaneous AUR. Still, while we observed an only transient increase of spontaneous AUR, the incidence of precipitated AUR increased, particularly in men aged 85 years or above. Men hospitalized with precipitated AUR were characterized by high age and a high degree of comorbidity, and precipitated AUR was yet another marker of comorbidity. Most western countries experience a demographic shift towards an elderly population.[130] The fact that people (including those with comorbidity) generally live longer, is likely to affect the occurrence of diseases that are associated with other systemic disease, such as precipitated AUR. Possibly, the increasing incidence of precipitated AUR is the result of an ageing population.

Cathcart et al reported a decline in the use of BPH-related surgery performed within six months after spontaneous AUR (from 32% to 26%) and precipitated AUR (from 7.6% to 5.8%) in the UK after the implementation of the trial without a catheter policy after AUR (1998-2003).[52] In contrast to our study, the authors included postsurgical AUR as precipitated AUR, which may explain the lower proportion of patients undergoing BPH-related surgery compared with our findings. The estimates of BPH-related surgery after spontaneous AUR strongly agrees with our findings. Our results demonstrated that the use of BPH-related surgery continued to decline in Denmark until 2011, where it stabilized at approximately 20% and 8-10% after spontaneous and precipitated AUR, respectively.

Only one previous study provided data on the mortality in men with AUR, and the reason for the high mortality was not entirely clear. In accordance with Armitage et al, we found that the one-year mortality was two to three times higher than in the general population and increased with presence of comorbidity and precipitated AUR. Our study confirmed that men hospitalized with AUR continued to have a high mortality compared with the general population and extended previous research by investigating causes of death occurring within one year of AUR diagnosis. Thus, the excess mortality risk observed in men with AUR was related to malignancies, infections, urogenital disease (mainly urinary tract infections and kidney failure), infections, and pre-existing comorbidity (diabetes and chronic pulmonary disease). The aim of Study IV was to investigate the association between AUR and cancer. While infections such as prostatitis, urethritis, and vulvovaginitis (in women) can cause AUR, hospitalization for AUR may also predispose to the risk of nosocomial and

catheter-related infections.[20] The link between AUR and diabetes (possibly mediated through diabetic neuropathy) has been described previously.[20] Likewise, the association between AUR and chronic pulmonary disease has been reported in previous studies where the use of inhaled anticholinergics was associated with an increased risk of AUR, particularly in men with BPH.[131]

In summary, our results indicated that precipitated AUR is an increasingly important part of AUR. In accordance with most previous studies, we found that the shift away from surgical to medical management of BPH did not coincide with an increased incidence of spontaneous AUR or AUR overall. The use of BPH-related surgery after AUR stabilized after a considerable decline initially after the introduction of medical BPH therapy. In alignment with Armitage et al,[3] our study confirmed that men hospitalized with AUR had a high mortality compared with men in the general population, and we extended previous knowledge with data on causes of death.

### 5.2.3 Study III

A number of RCTs have demonstrated that treatment with 5-ARI alone or in combination with alpha-blockers reduce the risk of BPH-related surgery and AUR for up to four years of follow-up (Table 4).[36,38,39,63–69] A COCHRANE review estimated that the absolute risk reduction observed with finasteride treatment was 3% for AUR and 3% for surgery over four years of follow-up.[132]

As previously described, limited data exist on the efficacy of 5-ARI treatment on the risk of BPH-related surgery and AUR for follow-up periods of more than four years and with the previously described limitations. Our study contributes to the existing literature by demonstrating a sustained reduction in the risk of BPH-related surgery and AUR among men treated with 5-ARI versus alpha-blocker monotherapy for up to 15 years of follow-up in routine clinical care.

The literature search identified six previous studies that reported absolute risks of BPH-related surgery and AUR in men that were treated with 5-ARI versus alpha-blocker or placebo for at least four years of follow-up,[36,37,39,68,69,71] of which four studies included men with enlarged prostate and LUTS.[36,37,39,68] A summary of baseline characteristics of participants in these studies and Study III is provided in Supplementary Table 1. The 5-year risk of BPH-related of surgery (11-12%) and AUR (8%) in the alpha-blocker group in Study III strongly agrees with most previous research,[36,39,68,69] where the 4-year risks of BPH-related surgery in the alpha-blocker or placebo group ranged between 5-10% for BPH-related surgery and 7-8% for AUR (Table 3). In the 5-ARI group, however, the 4-year risks ranging from 0.9-5% for BPH-related surgery and 1.6-3% for AUR observed in previous studies [36,37,39,68,69] were almost half of the 5-year risks of BPH-related surgery (9%) and AUR (6%) observed in our study. Men treated with 5-ARIs in routine clinical care were older than men participating in RCTs (mean age 71 versus 63-66 years) while the mean PSA was 3.4 versus 2.3-5.9 ng/mL (Supplementary

Table 1). Whether men treated with 5-ARI in routine clinical care had higher prostate volume or more severe LUTS than men participating in RCTs remains unclear, but such a difference could explain this difference in the risk of progression. Nevertheless, the risk of BPH-related surgery and AUR was considerably higher among men receiving 5-ARI treatment in routine clinical care compared to men participating in RCTs, resulting in a smaller risk difference between the two treatment groups in our study compared to the findings from RCTs.

In the Combination of Avodart and Tamsulosin (CombAT) study, combination therapy with dutasteride and tamsulosin was superior to tamsulosin but not dutasteride monotherapy in reducing the risk of BPH-related surgery and AUR.[39] In the MTOPS trial, combination therapy with doxazosin and finasteride was superior to either drug alone in reducing the risk of AUR and surgery.[37] In this study, we aimed at assessing a head-to-head comparison of 5-ARI or alpha-blocker monotherapy, and not combination therapy. Still, since guidelines recommend that men who initiate combination therapy of 5-ARI and alpha-blocker attempt alpha-blocker discontinuation after six months of treatment,[14,15] the long-term effectiveness of 5-ARI monotherapy is highly relevant to patients who initiate combination therapy as well.

In summary, using population-based data from routine clinical care, we found a reduced risk of BPH-related surgery and AUR in men treated with 5-ARI versus alpha-blocker monotherapy for up to 15 years of follow-up.

### 5.2.4 Study IV

To the best of our knowledge, no previous studies have quantified the absolute and relative risk of cancer (other than prostate cancer) after a first hospital diagnosis of AUR. The association between AUR and prostate cancer was examined in two previous studies carried out before the era of PSA.[21,95] One study reported a 7% risk of prostate cancer after initial diagnostic work-up of 310 men admitted with AUR to one hospital in Bristol, UK during 1979-1980,[21] which agrees with our finding of a 5.1% absolute risk of prostate cancer at three months of AUR diagnosis. Moul et al reported a slightly higher risk of prostate cancer (13.3%) among 90 men admitted with AUR at two institutions in Washington, US during 1984-1988.[95] In contrast to previous studies, we excluded patients with a previous cancer diagnosis, because they are known to be at increased risk of developing a secondary cancer.[133] Consequently, this exclusion likely led to a lower cancer incidence compared with studies that did not exclude these patients. As mentioned, previous studies were carried out before the implementation of PSA testing in men with LUTS,[134] which resulted in a rapid increase in the incidence of prostate cancer.[135] Of note, during the study period in Denmark, no systematic screening for prostate cancer occurred. Thus, only individual-based testing for PSA initiated by the

patient or doctor for case-specific reasons occurred. Nevertheless, our data pointed towards a slight decrease in the risk of prostate cancer after a first AUR diagnosis over calendar time (from 5.7% in 1995-1998 to 4.6% in 2014-2017). The reason for this is not entirely clear, but if prostate cancer is increasingly being detected early because of systematic PSA-testing as part of the diagnostic investigations for LUTS, rather than for AUR, this might explain the decreasing risk of prostate cancer after a first diagnosis of AUR over calendar time.

Data on the risk of cancer in women with AUR were reported in two previous studies, but with the previously mentioned limitations. Importantly, the small study sizes and strict selective inclusion criteria limited the generalizability. Wheeler et al found central nervous tumour in 6% of 68 women who presented with AUR and were referred for further urodynamic evaluation.[96] Among 300 women diagnosed with AUR during an inpatient hospital admission to one department of urology in the UK, underlying cancer was reported in the bladder (4%), rectum (1%), ovaries (1%), and endometrium (0.3%).[97] In our study, the absolute risks of these cancers were small (<1% during 0-<3 months of follow-up) compared with those reported in previous studies, probably due to the strict selective inclusion criteria of previous studies.

In summary, we found an association between AUR and urogenital, colorectal, and neurological cancers suggesting that AUR may be a marker of occult cancer.

## 5.3 Methodological considerations

Studies II-IV presented in this dissertation were based on large-scale nationwide registry data. These studies, therefore, relied on secondary data, i.e., administrative data collected for other purposes than these studies.[101] Registry-based studies offer numerous benefits, such as the ability to conduct large-scale, nationwide research using prospectively collected data.[101] In Denmark, this is particularly advantageous due to the country's universal healthcare system, which ensures that all citizens have free access to primary and secondary care, and virtually complete follow-up.[101] The data collected in these registries is prospectively recorded, as the information on exposures and covariates were recorded before the information on the outcome. Still, registry-based studies may be subject to random and systematic error.[113] Additionally, registry-based studies depend on the quality of the data, which can be assessed through validation studies.

In the following, I discuss the potential sources of error in the studies included in this dissertation. First, I briefly discuss random error before focusing on the three main sources of systematic error encountered in epidemiological studies: selection bias, information bias, and confounding.

### 5.3.1 Statistical precision and random error

Random error, or variation, is the result of chance or random variation.[113] Random error can occur in the process of sampling the study population (i.e., sampling variation). In Study I, we reviewed 100 medical records for each diagnosis to ensure appropriate precision of the estimated PPVs. However, in the stratified analysis, the precision was lower. This could have been avoided with larger sample sizes. In Studies II-IV, we used large population-based cohorts resulting for the most in estimates with high statistical precision that are unlikely to be caused by chance. In all studies, we measured the magnitude of random error using statistical estimation, expressed by the CIs. CIs encapsulate both the estimates of the effect size and its precision.[136] We did not use significance testing (such as P-values) to avoid fostering the frequent misinterpretations in which inferences are reduced to dichotomy based on statistical rather than clinical significance.[136]

### 5.3.2 Selection bias

Selection bias originates from the way study participants were selected or from factors that influenced study participation.[113] Selection bias occurs when the study population is not representative of the target population (i.e., the population of interest) regarding the association between the exposure and disease.[137] In cohort studies, selection bias also occurs if continued participation depends on exposure and risk of outcome (differential loss to follow-up or competing risks). Studies II-IV were nationwide population-based studies, conducted in a country with universal and free access to healthcare, with individual level linkage of data and virtually complete follow-up, thereby minimizing the risk of selection bias due to selective inclusion of specific hospitals, health insurance systems, socioeconomic factors, or ethnicities.[101]

For feasibility reasons, Study I was limited to two different hospitals in the Central Denmark Region with urological departments. We considered this restriction to be reasonable due to the homogeneity of Denmark in regard to demographic composition, socioeconomic characteristics, and healthcare utilization.[99] The study included both a university hospital and a regional hospital to reflect the Danish regions' healthcare structure.[99] We included the five departments that in total covered ~90% of all diagnoses at the investigated hospitals. Moreover, the study period was restricted to the years 2011-2017, due to the availability of electronic medical records within this timeframe. Therefore, the results may not necessarily be applicable to other departments or time periods. However, the consistency observed in the PPVs across departments and calendar year groups suggests that they may have wider applicability.

The study populations of Studies II and IV were restricted to patients with a hospital diagnosis with AUR. As a result, we missed patients with AUR managed in primary care without hospital referral.

Although current Danish guidelines recommend hospital referral of all patients presenting with AUR and residual urine >100 mL,[15] general practitioners may have treated patients with an obvious benign underlying condition without hospital referral. These patients might have a lower mortality (Study II) and lower cancer risk (Study IV) than patients without hospital referral. Moreover, we might not have captured all patients hospitalized with AUR if patients with an obvious underlying benign cause of AUR (such as urinary tract infections) only received a diagnosis code for the underlying condition. Consequently, our results are not necessarily generalizable to patients presenting with AUR in primary care settings. Nevertheless, our data are likely to be complete for patients with a hospital diagnosis of AUR and no obvious underlying cause.

Informative censoring occurs when the censoring is related to the occurrence of the outcome of interest. The PP analysis in Study III may be subject to informative censoring, because patients who adhere to the protocol differ from those who do not adhere to the protocol. Patients that adhere to the protocol through 15 years of follow-up are likely to be those with the most beneficial treatment effect, whereas patients with no or insufficient treatment effect are likely to censored before reaching the end of the study in the PP analysis. We did not include any method to deal with informative censoring, because we lacked data on time-varying confounders, such as clinical data that are prognostic of treatment failure and censoring, which is a limitation of the study. For these reasons, we found it is essential to consider the results from both the ITT and PP analyses and the results were presented together.

### 5.3.3 Information bias

Information bias occurs when systematic error is present in the measurement of information about study participants, resulting in misclassification of exposure, outcome, or covariates. Broadly, misclassification can be non-differential (i.e., the misclassification does not depend on other study variables) or differential (i.e., the misclassification depends on the other study variables).[137] Non-differential misclassification of dichotomous exposures biases an effect towards the null.[137] If the exposure is not dichotomous, bias can be towards or away from the null, depending on the categories to which individuals get misclassified.[137] Differential misclassification can thus lead to over- or underestimation of an effect.[137]

All studies in this dissertation were based on prospectively collected data that eliminate the risk of recall bias and thereby reduce the risk of differential misclassification. In the following, I discuss potential misclassification of exposures and outcomes in Studies II-IV.

***Misclassification of exposure***

*Misclassification of AUR (Studies II and IV)*

Study I demonstrated that the PPV of hospital-diagnosed AUR was high, however, we did not investigate the sensitivity of the diagnosis. As previously mentioned, patients with an obvious cause of AUR may not receive the AUR diagnosis. Still our data are likely to be complete for patients who received a hospital diagnosis of AUR. In agreement with previous research in the field, we distinguished between spontaneous and precipitated AUR (in Study IV referred to as primary or secondary AUR).[3,51,52] These definitions were not validated, which is a limitation. Nevertheless, we did observe substantial differences in relation to subsequent BPH-related treatment and mortality, in accordance with previous studies.[3,51,52]

*Misclassification of 5-ARI and alpha-blocker monotherapy users (Study III)*

Data on redeemed prescriptions were obtained from the Danish National Prescription Registry, which is virtually complete with respect to redeemed medications in the primary sector.[105] In contrast to other larger databases, the Danish National Prescription Registry is based on redeemed prescriptions rather than on issued prescriptions, making it a more accurate representation of the actual drug intake.[105] One limitation is that in-hospital treatment is not included in this registry.[105]

A limitation to the ITT approach is that non-adherence causes a discrepancy between the assigned treatment and the treatment received. In the ITT analyses, we required patients to redeem at least two prescriptions within the first 6 months of treatment to reduce the risk of including patients who discontinued treatment early due to side effects, insufficient treatment effect, or other. In addition, we performed a sensitivity analysis where follow-up started 12 months after first prescription and where three rather than two redeemed prescriptions were required to define the treatment groups. Still, the ITT principle estimates the effect of the assigned treatment and should be interpreted as such.

*Misclassification of outcomes*

*AUR (Studies II and III)*

In Study II, it is probable that the incidence rate of AUR is underestimated due to the restriction to hospitalized cases. During the study period, no changes occurred in the coding classification (ICD-10 throughout the entire study period), and we have not found reason to believe that any changes occurred in the diagnostic criteria or coding practice of AUR. Therefore, we did not consider misclassification of AUR a major threat to the findings in Study II. In Study III, any potential misclassification of AUR is most likely non-differential, provided that the misclassification is independent of the exposure, which would result in an underestimation of the difference between the two treatment groups.

*Mortality (Study II)*

In Study II, we used the Danish Civil Registration System to obtain data on all-cause mortality. This registry contains daily updated data on vital status, ensuring virtually complete follow-up regarding all-cause mortality.[102] Therefore, misclassification of all-cause mortality is unlikely.[102] Data on all-cause mortality were extracted from the Danish Registry of Causes of Death. The reporting of causes of death is mandatory in Denmark. Causes of death are registered based on subjective clinical judgement, rather than autopsy, and therefore may be prone to measurement error.[109] Any misclassification of causes of death is most likely to be non-differential.

*BPH-related surgery (Studies II and III)*

The procedure codes used to identify BPH-related surgery have not previously been validated in the DNPR, which is a study limitation of Studies II and III. Nevertheless, the diagnostic coding in the DNPR is generally high, and previous studies validated other surgical procedure codes of the urinary system, male genital organs, and retroperitoneal space, reporting PPVs ranging between 99-100%.[104] The decision to undergo BPH-related surgery may be influenced by patient- or physician-related factors. Some patients, for instance, may prefer intermittent catheterization or indwelling urinary catheters over surgery. Moreover, in benign conditions like BPH, the decision to undergo surgery might be taken with a considerable delay, especially since many men fear having to undergo prostatic surgery.[62] In contrast, the sudden onset of AUR makes less susceptible to patient- or physician-related factors, and AUR therefore provides a useful addition as a more objective measure of the risk of progression. Any misclassification of BPH-related surgery in our study would most likely be non-differential, i.e., unrelated to the exposure, and therefore bias the results towards the null.[137]

*Cancer (Study IV)*

Reporting of cancer has been mandatory in Denmark since 1987. Data on cancer were obtained from the Danish Cancer Registry, containing high validity data on all cancers diagnosed in Denmark.[106,138] Patients hospitalized with AUR are in closer contact with the hospital than people in the general population, potentially leading to detection bias and differential misclassification of the outcome in Study IV (cancer), which, in this case, would tend to overestimate the risk of cancer in patients with AUR compared with the general population. This is likely to be part of the explanation for the short-term increased risk of cancer. However, if the increase in cancer risk solely occurred due to enhanced diagnostic effort, we would expect a subsequent compensatory decrease which the 1- to 5-year SIRs did not support.

### 5.3.4 Confounding

A simple definition of confounding is distortion of effects.[139] Thus, confounding occurs when the effect of the exposure is distorted with the effect of another variable, leading to confounding bias.[137]

To act as a confounder, a factor must be associated with both the exposure and the outcome, without being an intermediate step between the exposure and outcome on the causal pathway. [137] Confounders can be controlled for by design (e.g., restriction or matching) and by statistical analysis (e.g., standardization, stratification, or adjustment). The overall aim of Study II was to extend the knowledge of epidemiological aspects of AUR with emphasis on description rather than causation. Although we did adjust for some covariates (age and calendar year) in this study, adjustment was kept to a minimum. Similarly, in Study IV, we adjusted for sex, age, and calendar year, but not other lifestyle factors or comorbidities. The aim of Study IV was, as such, not to investigate the causal effect between cancer and AUR, but rather to investigate if AUR was associated with an increased risk of cancer, regardless of potential underlying shared risk factors, such as lifestyle factors or comorbidity.

In Study III, we addressed confounding by design (active comparator, new-user design) and analysis phase (SMRW). Nevertheless, the observational nature of our study leaves it vulnerable to residual and unmeasured confounding. In Study III, we lacked data on clinical variables predictive of the outcome, such as prostate volume, symptom score, maximum urinary flow rate, and post-void residual urine volume, which is a limitation of the study. Still, a study investigated clinical predictors of AUR based on pooled data from placebo-treated patients in several clinical trials and found that the predictive ability of a classification and regression decision tree including PSA was similar to that of a model including serum-PSA, urinary frequency, hesitancy, flow rate parameters, and symptom problem index.[33] In addition, serum-PSA strongly correlates with prostate volume and can be used as a proxy hereof, when prostate cancer is ruled out.[140,141] Data from the PLESS trial further demonstrated that PSA was a strong predictor for prostate growth as well as long-term changes in LUTS, maximum urinary flow rates, and the risk of BPH-related surgery and AUR in men treated with finasteride relative to placebo.[142] In that study, neither symptom score nor bothersomeness of symptoms predicted the BPH-related surgery or AUR in patients treated with finasteride.[142] Nevertheless, we cannot rule out residual (or unmeasured) confounding. Since 5-ARI treatment is recommended to patients with an increased risk of progression, residual confounding would most likely lead to an underestimation of the association.

# 6. Conclusions and perspectives

The studies in this dissertation add to the existing knowledge on the prognosis of BPH and AUR regarding the incidence, management, and prognosis of AUR (Studies II and IV) and the long-term risk of BPH-related surgery and AUR associated with 5-ARI versus alpha-blocker monotherapy in routine clinical care (Study IV).

Study II adds to most previous evidence suggesting that the shift from surgical to medical management of BPH did not coincide with an increasing incidence of one of the most significant complications of the disease. Study II demonstrated that the management of AUR has changed over the past two decades, with only one in five patients with spontaneous AUR and one in ten with precipitated AUR requiring BPH-related surgery during the first year of AUR diagnosis in 2017. Moreover, Study II adds to the existing evidence that AUR warranted a high mortality among men of all ages and provided new evidence on the underlying causes of death, which may provide evidence for the underlying mechanism.

Study III provides new evidence of the long-term risk of progression in men treated with 5-ARI versus alpha-blocker monotherapy. In routine clinical care, treatment with 5-ARI was associated with a reduced risk of BPH-related surgery and AUR for up to 15 years of follow-up. However, our results suggested a 20-25% RRR and a 4% ARR after 15 years of treatment, which is less than observed in RCTs over shorter follow-up periods. Our results may assist in determining the appropriate treatment for the individual patients, which should optimally reflect the individual patient's values and preferences.[58]

Study IV provides evidence that AUR is a marker for cancer, not only in the prostate, but also for other urogenital, colorectal, and neurological cancers. As such, our data suggest that occult cancer should possibly be considered in patients hospitalized with AUR and no obvious cause. For most cancers, an excess risk of cancer was confined to the first three months of diagnosis, but an excess risk of prostate cancer and urinary tract cancer persisted for up to one year after the AUR diagnosis. Whether this represents an opportunity for earlier cancer detection remains to be elucidated. The association between AUR and cancer could, in part, explain the high mortality observed in men with AUR, as also indicated in Study II, where malignancies accounted for most deaths occurring within one year of an AUR diagnosis. Whether AUR in women also warrants high mortality could be the aim of future research.

# 7. Summary

Benign prostatic hyperplasia (BPH) is a prevalent condition in the ageing male population. It is a progressive disease with the risk of requiring BPH-related surgery and developing acute urinary retention (AUR). AUR is a severe complication to BPH associated with high mortality among men of all ages. In the mid-1990s, medical therapy for BPH was introduced and rapidly replaced surgery as the first choice of treatment. Despite the high prevalence of BPH in older men, there is limited data on the long-term effects of this shift in the treatment approach. Moreover, the reasons for the high mortality observed in men with AUR are not well understood. To explore this further, we used Danish health registries to investigate trends in AUR incidence, management, and mortality (Study II), the 15-year risk of BPH-related surgery and AUR in men treated with 5-alpha-reductase inhibitor (5-ARI) versus alpha-blocker monotherapy in routine clinical care (Study III), and the risk of cancer after a first AUR hospitalization (Study IV). The studies were preceded by a validation study including the positive predictive value of BPH and AUR coded in the DNPR (Study I).

In Study I (2011-2017), we reviewed a total of 200 medical records from one university hospital and one regional hospital in the Central Denmark Region. Using medical record review as the reference standard, we found a high positive predictive value of BPH (95 (95% (89-98%)) and AUR (98 (95% CI: 93-99%)) encoded in the DNPR.

In Study II (1997-2017), we found an only transient increase in the standardized incidence rate of AUR overall, while an increasing trend was observed for precipitated AUR in men aged 85 years or above. The use of BPH-related surgery declined substantially in the study period, while the mortality remained high in men hospitalized with AUR compared with the general population. The excess mortality was mainly attributed to death related to malignancies, urogenital disease, infections, and pre-existing comorbidity.

In Study III (1997-2017), we found an overall reduced risk of BPH-related surgery and AUR in men treated with 5-ARI versus alpha-blockers in routine clinical care for up to 15 years of follow-up. After 15 years of follow-up, the absolute risk reduction was 4% and the relative risk reduction was 21-25%.

In Study IV (1995-2017), we found AUR to be a clinical marker for prostate cancer as well as urogenital cancer, colorectal cancer, and neurological cancer. The excess risk of cancer was particularly high for prostate and bladder cancer in men and for bladder and genital cancer in women. For most cancers, an excess risk of cancer was observed only within the first three months of follow-up.

# 8. Dansk resumé (summary in Danish)

Benign prostata hyperplasi (BPH) er en hyppig tilstand blandt ældre mænd. BPH kan progrediere og medføre risiko for kirurgi og udvikling af komplikationer såsom akut urinretention (AUR). AUR er en alvorlig komplikation til BPH, som er forbundet med betydelig overdødelighed blandt mænd i alle aldre. I midten af 1990'erne blev medicinsk behandling for BPH introduceret og erstattede hurtigt kirurgi som førstevalgsbehandling. Imidlertid mangler en række spørgsmål at blive besvaret for at kunne vurdere langtidseffekterne af dette behandlingsskift. Desuden er årsagen til den høje dødelighed blandt mænd med AUR fortsat ukendt. For at undersøge dette nærmere, brugte vi landsdækkende danske registre med det formål at beskrive tendenser i forekomst, behandling og dødeligheden af AUR (studie II), 15-års risikoen for BPH-relateret kirurgi og AUR blandt mænd behandlet med 5-alfa-reduktasehæmmere (5-ARI) versus alfa-blokker monoterapi (studie III) og risikoen for kræft efter et førstegangstilfælde af AUR (studie IV). Disse studier blev forudgået af et valideringsstudie, hvor vi undersøgte den positive prædiktive værdi af diagnoserne BPH og AUR i Landspatientregistret (studie I).

I studie I (2011-2017) gennemgik vi 200 patientjournaler fra et universitetshospital og et regionshospital i Region Midtjylland. Vi anvendte gennemgang af patientjournaler som referencestandard og fandt en høj positiv prædiktiv værdi af diagnoserne BPH (95% konfidensinterval (KI): (89%-98%) og AUR (98% (95% KI: 93%-99%) i Landspatientregistret.

I studie II (1997-2017) fandt vi en kun forbigående stigning i den standardiserede incidensrate af alle tilfælde af AUR, mens incidensen af AUR udløst af anden årsag end BPH var stigende blandt mænd i alderen 85 år og derover. Brugen af BPH-relateret kirurgi efter et førstegangstilfælde af AUR faldt betydeligt i studieperioden, mens dødeligheden forblev høj blandt mænd med AUR sammenlignet med den danske baggrundbefolkning. Denne overdødelighed var særligt høj for dødsårsager relateret til maligne sygdomme, urogenitale sygdomme, infektioner og anden komorbiditet.

I studie III (1997-2017) fandt vi en nedsat risiko for BPH-relateret kirurgi og AUR blandt mænd som blev behandlet med 5-ARI versus alfa-blokker monoterapi i klinisk praksis i op til 15 års opfølgning. Efter 15 års opfølgning var den absolutte risikoreduktion 4% og den relative risikoreduktion 21-25%.

Studie IV (1995-2017) viste, at hospitalsdiagnosticeret AUR var en markør for prostatakræft og andre former for urogenital kræft, kolorektalkræft og kræft i centralnervesystemet. Den øgede risiko for kræft var særligt høj for prostata- og blærekræft blandt mænd og blære- og genitalkræft blandt kvinder. For de fleste typer af kræft, fandt vi kun en øget kræftrisiko inden for de første tre måneders opfølgning.

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# 10. Supplementary

**Supplementary Table 1. Comparison of baseline characteristics and absolute risks of previous studies* and Study III.**

| | Age | Symptom score (mean) | PV ($cm^3$) | PSA (ng/mL) | 4-year risk | |
|---|---|---|---|---|---|---|
| | | | | | **BPH-related surgery** | **AUR** |
| Roehrborn, 2011[68] | Mean: 63 years | IPSS: 8.6-8.7 | Mean: 46 | Mean: 5.9 | Dutasteride: 1.4%<br>Placebo: 5.1% | Dutasteride: 1.6%<br>Placebo: 6.7% |
| McConnell, 1998[36] | Mean: 64 years | AUA-SI: 15 | Mean: 54-55 | Mean: 2.8 | Finasteride: 5%<br>Placebo: 10% | Finasteride: 3%<br>Placebo: 7% |
| McConnell, 2003[37] | Mean: 63 years<br>Median: 63 years | AUA-SI: 17 | Mean: 35-36<br>Median: 31 | Mean: 2.3-2.4<br>Median: 1.5-1.6 | Doxazosin: 3%<br>Finasteride: 2%<br>Combination therapy: 1%<br>Placebo: 5% | Doxazosin: 1%<br>Finasteride: <1%<br>Combination therapy: <1%<br>Placebo: 2% |
| Roehrborn, 2010[39] | Mean: 66 years | IPSS: 16.4-16.6 | Mean: 55-56<br>Median: 48-50 | Mean: 3.9-4.0 | Tamsulosin: 7.8%<br>Dutasteride: 3.5%<br>Combination therapy: 2.4% | Tamsulosin: 6.8%<br>Dutasteride: 2.7<br>Combination therapy: 2.2% |
| | | | | | **5-year risk** | |
| Study III, weighted population | Mean: 71 years<br>Median: 71 years | N/A (recommended for men with moderate to severe LUTS, measured by DAN-PSS) | N/A | Mean: 3.4<br>Median: 2.7 | ITT analysis<br>5-ARI: 8.8%<br>Alpha-blocker: 12.0%<br>PP analysis<br>5-ARI: 8.8%<br>Alpha-blocker: 11.3% | ITT analysis<br>5-ARI: 6.4%<br>Alpha-blocker 13.3%<br>PP analysis<br>5-ARI: 6.2%<br>Alpha-blocker 8.3% |

*Including previous studies that estimated absolute risk estimates of BPH-related surgery and AUR in men treated with 5-ARIs versus alpha-blockers or placebo, enlarged prostates, presence of LUTS, and at least 4 years of follow-up. The studies were identified through literature review for Study III which is summarized in Table 3.

Abbreviations: PV – prostate volume; PSA – prostate specific antigen; AUA-SI – American Urological Association Symptom Index; IPSS – International Prostate Symptom Score; DAN-PSS – Danish Prostate Symptom Score; LUTS – lower urinary tract symptoms; ITT – intention to treat; PP – per protocol; 5-ARI – 5-alpha-reductase inhibitor

# 11. Appendices

Full versions of Paper I-IV are provided in the Appendices I-I:

**Appendix I** Paper I

**Appendix II** Paper II

**Appendix III** Paper III

**Appendix IV** Paper IV

*The papers have been removed from the file due to copyright issues*