Acute urinary retention in men: 21-year trends in incidence, subsequent benign prostatic hyperplasia-related treatment and mortality: A Danish population-based cohort study

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Abstract

Objective: To examine trends in incidence of acute urinary retention, subsequent benign prostatic hyperplasia-related treatment and mortality in the era of medical therapy for benign prostatic hyperplasia. Additionally, to compare mortality with the general population.

Materials and Methods: We conducted a Danish nationwide registry-based study including 70,775 men aged 45 years or older with a first hospitalization for acute urinary retention during 1997–2017. We computed annual standardized incidence rates, subsequent 1-year cumulative incidence of benign prostatic hyperplasia-related surgical and medical treatment, and standardized 3-month and 1-year mortality rates. Finally, we compared standardized all-cause and cause-specific mortality ratios with the general population.

Results: The standardized incidence rate of acute urinary retention per 1000 person-years increased transiently from 2.34 to 3.42 during 1997–2004, but gradually declined to 2.95 in 2017. The 1-year cumulative incidence of benign prostatic hyperplasia-related surgery declined from 31.2% to 19.8% and 20.5% to 7.7% after spontaneous and precipitated acute urinary retention, respectively. During 1997–2017, the standardized 1-year mortality declined from 22.2% to 17.2%. Compared with the general population, mortality was 4–5 times higher after 3 months and 2–3 times higher after 1 year of acute urinary retention. The cause-specific standardized mortality ratios were particularly high for deaths attributable to malignancies, urogenital disease, certain infections, chronic pulmonary disease, and diabetes.

Conclusion: During 1997–2017, we observed a transient increase in the incidence of acute urinary retention. The subsequent use of benign prostatic hyperplasia-related surgery declined considerably and mortality continued to be high, mainly...
1 | INTRODUCTION

Acute urinary retention (AUR) is a urological emergency associated with high mortality among men in all ages. It is one of the most significant complications to benign prostatic hyperplasia (BPH), which affects more than half of men aged 50 years or older. In recent decades, substantial changes have occurred in the management of BPH as well as AUR. In the mid-1990s, medical therapy for BPH was introduced and rapidly replaced surgery as first-line treatment. This resulted in a 21% decline in prostatic surgeries performed in Denmark between 1993 and 2003, despite a growing number of elderly in the same period. The management of AUR in men with BPH also shifted towards more conservative treatment. Previously, AUR was considered an absolute indication for surgery. Today, the recommendation is initial bladder decompression and initiation of alpha-blocker treatment followed by trial without a catheter. If this fails, prostatic surgery will often be considered.

Although treatment with 5-alpha reductase inhibitors reduces the risk of AUR compared with placebo, alpha-blockers do not reduce the risk of progression to AUR or surgery. Therefore, the shift away from surgery, could potentially lead to an increasing incidence of late complications to BPH, such as AUR.

Mortality among men hospitalized with AUR has been reported to be high in one previous study. Even in men without previous comorbidity, mortality within a year of AUR diagnosis was at least 60% greater than that observed in men of similar age in the general population. Although linked to preexisting comorbidity, the reason for the high mortality in men hospitalized with AUR remains unclear. To improve our understanding of the high mortality in men with AUR it is necessary to examine causes of death occurring within one year of AUR diagnosis.

In this population-based cohort study, we examined 21-year trends in AUR incidence, subsequent BPH-related surgical and medical treatment, and mortality. We also compared all-cause and cause-specific mortality in men with AUR with men in the general population.

2 | MATERIALS AND METHODS

2.1 | Setting

We conducted a population-based cohort study in Denmark (5.8 million residents in 2018). The Danish National Health Services provides tax-funded medical care to all residents including free access to treatment at general practitioners and hospitals and reimbursement for prescription medications. Danish health care registries can be linked at an individual level using the civil personal registration number.

2.2 | AUR

We used the Danish National Patient Registry (DNPR) to identify all men aged 45 years or older with a first hospital diagnosis of AUR during 1997–2017. The DNPR contains data on all inpatient hospital contacts in Denmark since 1977 and emergency room and outpatient clinics since 1995. Diagnoses are classified according to the International Classification of Diseases 8th revision until 1993, and 10th revision thereafter. Each hospital contact has one primary diagnosis (the main reason for hospital contact) and, when relevant, one or more secondary diagnoses.

From a clinical and prognostic perspective, spontaneous AUR (AUR with no precipitating factors other than BPH) differs from precipitated AUR (AUR precipitated by a triggering event other than BPH). We categorized 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. All other cases of AUR were categorized as precipitated AUR. We excluded men previously diagnosed with prostate cancer, multiple sclerosis, and Parkinson’s disease, and men with postsurgical AUR (i.e., AUR occurring within one week after surgery).

2.3 | BPH-related treatment and mortality

We obtained information on BPH-related surgery from the DNPR and prescription of BPH medication within 1 year after the AUR diagnosis from the Danish National Prescription Registry. This registry contains information on all prescriptions for medications redeemed at community pharmacies in Denmark since January 1, 1995. Information on all-cause mortality was obtained from the Danish Civil Registration System through January 17, 2019. This registry records daily updated changes in vital status and migration for all residents in Denmark since 1968.

From the Danish Registry of Causes of Death we obtained information on the underlying causes of deaths occurring within 1 year after AUR diagnosis. This registry contains information on all causes of death in Denmark since 1943. Data on underlying causes of...
| Age group (years) | Overall (n = 70,775) | Spontaneous AUR (n = 55,088) | Precipitated AUR (n = 15,687) |
|------------------|----------------------|-----------------------------|-----------------------------|
| 45–54            | 2945 (4.2%)          | 2417 (4.4%)                 | 528 (3.4%)                  |
| 55–64            | 9616 (13.6%)         | 8009 (14.5%)                | 1607 (10.2%)                |
| 65–74            | 20,004 (28.3%)       | 16,204 (29.4%)              | 3800 (24.2%)                |
| 75–84            | 24,491 (34.6%)       | 18,841 (34.2%)              | 5650 (36.0%)                |
| 85+              | 13,719 (19.4%)       | 9617 (17.5%)                | 4102 (26.1%)                |

**Urogenital medical history**

|                         | Overall (n = 70,775) | Spontaneous AUR (n = 55,088) | Precipitated AUR (n = 15,687) |
|-------------------------|----------------------|-----------------------------|-----------------------------|
| BPH                     | 33,318 (47.1%)       | 26,994 (49.0%)              | 6324 (40.3%)                |
| BPH medication          | 29,636 (42%)         | 24,012 (44%)                | 5624 (36%)                  |
| Alpha-blocker           | 26,880 (38.0%)       | 21,839 (39.6%)              | 5041 (32.1%)                |
| 5-ARI                   | 9720 (13.7%)         | 7859 (14.3%)                | 1861 (11.9%)                |
| Previous urinary tract  | 12189 (17.2%)        | 9507 (17.3%)                | 2682 (17.1%)                |
| infection              |                      |                             |                             |
| Hydronephrosis          | 213 (1.4%)           | 779 (1.4%)                  | 992 (1.4%)                  |
| Bladder stones          | 600 (0.8%)           | 480 (0.9%)                  | 120 (0.8%)                  |

**Other comorbidity**

|                | Overall (n = 70,775) | Spontaneous AUR (n = 55,088) | Precipitated AUR (n = 15,687) |
|----------------|----------------------|-----------------------------|-----------------------------|
| Diabetes       | 11364 (16.1%)        | 8531 (15.5%)                | 2833 (18.1%)                |
| Chronic pulmonary disease | 8819 (12.5%) | 6353 (11.5%)                | 2466 (15.7%)                |
| Hypertension   | 21,941 (31.0%)       | 16,397 (29.8%)              | 5544 (35.3%)                |

**Comorbidity category**

| Category           | Overall (n = 70,775) | Spontaneous AUR (n = 55,088) | Precipitated AUR (n = 15,687) |
|--------------------|----------------------|-----------------------------|-----------------------------|
| No comorbidity     | 35,449 (50.1%)       | 28,461 (51.7%)              | 6988 (44.5%)                |
| Moderate           | 13,405 (18.9%)       | 10,122 (18.4%)              | 3283 (20.9%)                |
| Severe             | 9638 (13.6%)         | 7293 (13.2%)                | 2345 (14.9%)                |
| Very severe        | 12,283 (17.4%)       | 9212 (16.7%)                | 3071 (19.6%)                |

**Medications associated with AUR**

| Medication                          | Overall (n = 70,775) | Spontaneous AUR (n = 55,088) | Precipitated AUR (n = 15,687) |
|-------------------------------------|----------------------|-----------------------------|-----------------------------|
| Opioids                             | 12,502 (17.7%)       | 9403 (17.1%)                | 3099 (19.8%)                |
| Tricyclic antidepressants           | 1398 (2.0%)          | 1072 (1.9%)                 | 326 (2.1%)                  |
| Benzodiazepines                     | 11,715 (16.6%)       | 8978 (16.3%)                | 2737 (17.4%)                |
| Antipsychotics                      | 3128 (4.4%)          | 2367 (4.3%)                 | 761 (4.9%)                  |
| Antihistamines                      | 1837 (2.6%)          | 1394 (2.5%)                 | 443 (2.8%)                  |
| NSAIDs                              | 8787 (12.4%)         | 6712 (12.2%)                | 2075 (13.2%)                |
| Calcium channel antagonists         | 10,702 (15.1%)       | 8165 (14.8%)                | 2537 (16.2%)                |
| Adrenergic and anticholinergic agents used for chronic pulmonary disease | 8708 (12.3%) | 6297 (11.4%) | 2411 (15.4%) |

Abbreviations: 5-ARI, 5-alpha-reductase inhibitor; AUR, acute urinary retention; BPH, benign prostatic hyperplasia; NSAIDs, nonsteroidal anti-inflammatory drugs.

*Recent use of medications known to increase the risk of AUR, defined as at least one reimbursement of relevant drugs within 3 months before AUR diagnosis.
death for the general population were obtained from online published data from The Danish Health Data Authority, currently available in the period 2007–2016.17

2.4 | Comorbidity

We retrieved information on comorbidity associated with AUR18 (as listed in Table 1) based on diagnoses recorded in the DNPR and prescription data recorded within 10 years before the AUR diagnosis. As a measure of general comorbidity burden, we computed the Charlson Comorbidity Index (CCI) score for each patient,19 and defined four levels of comorbidity: a total score of 0: no comorbidity, 1: low comorbidity, 2: moderate comorbidity, 3+: severe comorbidity.

Finally, we retrieved information on recent—within 3 months before AUR diagnosis—reimbursement of medications known to increase the risk of AUR.20

Codes used to define variables are provided in Supporting Information: Table 1.

2.5 | Statistical analysis

We computed the annual incidence rate of AUR, standardized to the age distribution of the Danish male population in year 2000 (1-year age groups), and the subsequent 3-month and 1-year mortality rate, standardized to the age distribution in the AUR cohort in the year 2000 (1-year age groups). Confidence intervals (CIs) were computed using the gamma method.21

We examined the annual 1-year cumulative incidences of BPH-related surgery and prescription of BPH medication after AUR diagnosis, respectively, treating death as a competing risk. For cumulative incidence of BPH medication, we also considered BPH-related surgery as a competing risk.

We used the Kaplan–Meier method to estimate 3-month and 1-year mortality, stratified by age group and comorbidity. We calculated all-cause and cause-specific standardized mortality ratios (SMRs) as the ratio of observed deaths in the AUR cohort and expected number of deaths, using age- and calendar year-specific mortality rates (all-cause and cause-specific) in the Danish male population (1-year age groups). We stratified analyses for men with

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**Figure 1** Standardized incidence rates (SIRs) of first hospitalization for acute urinary retention (AUR) overall (A) and within age groups for spontaneous (B) and precipitated (C) AUR, 1997–2017. [Color figure can be viewed at wileyonlinelibrary.com]
and without comorbidity. We performed a sensitivity analysis, estimating all-cause mortality SMRs stratified by calendar periods: 1997–2002, 2003–2007, 2008–2012 and 2013–2017.

All statistical analyses were performed using R v. 3.5.2.

3 | RESULTS

3.1 | Patient characteristics

We identified 70,775 men aged 45 years or older with a first hospitalization for AUR during 1997–2017 (Table 1). Most men had spontaneous AUR (77.8%). Half of all men had at least one CCI comorbidity before the AUR diagnosis. Frequent comorbidities included previously diagnosed BPH (47.1%), diabetes (16.1%), chronic pulmonary disease (12.5%), and hypertension (31.0%).

Within 3 months before AUR diagnosis, 17.7% of all men filled a prescription on opioid, 16.6% on benzodiazepines and 15.1% on calcium channel antagonists.

3.2 | Incidence

Although there was a transient increase in the standardized incidence rate of AUR per 1000 person-years during 1997–2004, from 2.34 (95% CI: 2.24–2.44) in 1997 to 3.42 (95% CI: 3.30–3.54) in 2004, it gradually declined to 2.95 (95% CI: 2.86–3.04) in 2017 (Figure 1A). The 1997–2004 increase was observed for both spontaneous AUR (from 2.04 (95% CI: 1.95–2.13) in 1997 to 2.65 (95% CI: 2.55–2.75) in 2004) and precipitated AUR (from 0.30 (95% CI: 0.27–0.34) in 1997 to 0.77 (95% CI: 0.72–0.83) in 2004), and was mainly driven by patients aged 75 years or older (Figure 1B,C). However, while the standardized incidence rate of spontaneous AUR gradually declined to 2.15 (95% CI: 2.07–2.33) in 2017, the standardized incidence rate of precipitated AUR continued to increase—particularly in men aged 85 years or older (Figure 1C).

3.3 | BPH-related treatment

During 1997–2017, the use of BPH-related surgery within the first year after AUR declined from 31.2% (95%CI: 29.2%–33.3%) to 19.8% (95% CI: 18.4%–21.3%) 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 2A). Concomitantly, the use of BPH medication within the first year after AUR increased during 1997–2017; from 17.1% (95% CI: 15.5%–18.9%) to 52.2% (95% CI: 50.4%–54.1%) after spontaneous AUR and 12.4% (95% CI: 9.1%–16.9%) to 40.1% (95% CI: 37.2%–43.1%) after precipitated AUR (Figure 2B).
3.4 | Mortality

The 1-year standardized mortality declined slightly from 22.2% (95% CI: 20.1%–24.2%) in 1997 to 17.5% (95% CI: 16.2%–18.9%) in 2017 (Figure 3). However, SMRs yielded similar estimates across all calendar periods (Supporting Information: Table 2). Thus, men hospitalized with AUR continued to have a high mortality compared with the general population.

Compared with men of same age in the general population, men hospitalized with AUR had an excess mortality in all investigated age

![FIGURE 3 Standardized 1-year mortality rates after first hospitalization for acute urinary retention (AUR), 1997–2017. [Color figure can be viewed at wileyonlinelibrary.com]](image)

### TABLE 2 Three-month and 1-year mortality rates in men with spontaneous and precipitated acute urinary retention and standardized mortality ratios against the general population by age group

| Type of AUR | Total | Mortality 3 months | 1 year |
|-------------|-------|-------------------|--------|
|              | Rate (95% CI) | O/E | SMR (95% CI) | Rate (95% CI) | O/E | SMR (95% CI) |
| Spontaneous AUR (years) | | | | | | |
| 45–54       | 2412  | 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       | 7993  | 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       | 16,188| 4.1 (3.8–4.4)     | 662/118| 5.6 (5.2–6.1)  | 10.3 (9.8–10.8)| 1655/472| 3.5 (3.3–3.7)   |
| 75–84       | 18,828| 7.0 (6.6–7.4)     | 1304/369| 3.5 (3.4–3.7)| 18.7 (18.1–19.2)| 3496/1474| 2.4 (2.3–2.5)   |
| 85+         | 9615  | 14.4 (13.7–15.1)  | 1370/494| 2.8 (2.6–2.9)| 33.5 (32.6–34.5)| 3204/1976| 1.6 (1.6–1.7)   |
| Total       | 55,036| 6.6 (6.4–6.8)     | 3626/1009| 3.6 (3.5–3.7)| 16.6 (16.3–16.9)| 9058/4034| 2.2 (2.2–2.3)   |
| Precipitated AUR (years) | | | | | | |
| 45–54       | 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       | 1606  | 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       | 3796  | 6.8 (4–7.6)       | 252/28 | 9.2 (8.1–10.4)  | 16.5 (15.3–17.6)| 620/110 | 5.6 (5.2–6.1)   |
| 75–84       | 5649  | 12.4 (11.5–13.2)  | 693/111| 6.2 (5.8–6.7)  | 26.5 (25.3–27.6)| 1486/445| 3.3 (3.2–3.5)   |
| 85+         | 4102  | 22.4 (21.1–23.7)  | 913/217| 4.2 (3.9–4.5)  | 42.2 (40.7–43.7)| 1719/868| 2.0 (1.9–2.1)   |
| Total       | 15,679| 12.6 (12.1–13.1)  | 1954/361| 5.4 (5.2–5.7)| 26.0 (25.3–26.6)| 4044/1,445| 2.8 (2.7–2.9)   |

Abbreviations: AUR, acute urinary retention; CI, confidence interval; O, observed; E, expected; SMR, standardized mortality ratio.
groups—irrespective of type of AUR and presence of comorbidity (Tables 2 and 3). The all-cause SMRs after spontaneous and precipitated AUR were 3.6 (95% CI: 3.5–3.7) and 5.4 (95% CI: 5.2–5.7) at 3 months and 2.2 (95% CI: 2.2–2.3) and 2.8 (95% CI: 2.7–2.9) at 1 year, respectively (Table 2). Although the highest 1-year SMRs was observed for men with comorbidity and precipitated AUR, mortality in men without comorbidity and spontaneous AUR was still 40% higher than that in men of same age in the general population (SMR 1.4 [95% CI 1.3–1.5], Table 3).

3.5 Causes of death

Malignancy was the main cause of death, accounting for 28% of the deaths occurring in the first year after AUR diagnosis (SMR 4.2 [95% CI: 4.0–4.4], Table 4). The highest SMR was observed for deaths attributable to urogenital disease (6.0 [95% CI: 5.4–6.8]). Of 283 deaths attributable to urogenital disease, the most frequently recorded causes of death were urinary tract infections (n = 99) and kidney failure (n = 92).
The SMR was also particularly high for deaths attributable to diabetes (5.1 [95% CI: 4.5–5.7]), certain infectious diseases (4.7 [95% CI: 4.1–5.5]), mainly sepsis which accounted for 91 of 166 cases), and chronic pulmonary disease (4.5 [95% CI: 4.2–4.9]).

4 | DISCUSSION

During 1997–2017, we found a transient increase in the annual standardized incidence rate of AUR. Use of BPH-related surgery within the first year after AUR declined considerably during the study period and mortality after AUR hospitalization continued to be high—even in men without comorbidity. The excess mortality risk was particularly high for deaths attributable to malignancies, urogenital disease (mainly urinary tract infections and kidney failure), certain infections, diabetes, and chronic pulmonary disease.

Previous studies on time trends in AUR incidence were conducted over shorter time periods. AUR-related surgery continued to decline until 2011, from 32% to 26% after spontaneous AUR and from 7.6% to 5.8% after precipitated AUR. This study included postsurgical AUR, which may explain the lower use of BPH-related surgery after precipitated AUR compared with our study. Our data demonstrated that the use of BPH-related surgery continued to decline until 2011, where it stabilized at approximately 20% for spontaneous AUR and 8%–10% after precipitated AUR.

Mortality among men hospitalized for AUR continued to be high, and—in accordance with Armitage et al.—we observed an overall 1-year mortality two to three times higher than in the general population. We confirmed that patients with AUR are a vulnerable group of patients characterized by high age, high comorbidity burden, and high mortality. This is further emphasized by our finding of a surprisingly frequent use of AUR associated drugs, particularly opioids and benzodiazepines. Moreover, we demonstrated that precipitated AUR has become an increasingly important part of AUR, particularly in men aged 85 years or older. Possibly, this is the result of an ageing population. Precipitated AUR was characterized by lower rates of subsequent BPH-related surgery, higher comorbidity burden and higher mortality—emphasizing that these patients are particularly vulnerable and may require special attention.

Although preexisting comorbidity most likely explains part of the excess mortality risk in men with AUR, mortality was still at least 40% higher than expected in men with spontaneous AUR and no previous comorbidity. To the best of our knowledge, no previous study has investigated causes of death in men with AUR, which may provide evidence for underlying mechanisms of the excess mortality risk observed in men hospitalized for AUR.

Our results suggest that that the excess mortality is related to malignancies, urogenital disease (mainly urinary tract infections and kidney failure), infections and preexisting comorbidity (chronic pulmonary disease and diabetes). Since we excluded patients with previous prostate cancer, previously diagnosed prostate cancer could not explain the excess risk of dying from malignancies. We previously examined the association between AUR and cancer in a Danish nationwide cohort study, and found AUR to be a marker of occult urogenital, colorectal, and neurological cancer. While infections can directly cause AUR, AUR hospitalization is also associated with a potential risk of nosocomial and catheter-related infections. Due to the design of our study, causation cannot be inferred. The association between AUR and chronic pulmonary diseases has previously been established. Accordingly, in two observational studies and a pooled analysis of randomized controlled trials, use of inhaled anticholinergics increased the risk of AUR, particularly in men with BPH. Likewise, the association between AUR and diabetes has previously been described, and is most likely mediated through diabetic bladder dysfunction secondary to diabetic neuropathy.

Our study has several strengths and limitations. Strengths include access to prospectively collected population-based data in a country with universal health care. The positive predictive value of diagnoses and surgical procedure codes in the DNPR are generally high, and the positive predictive value is 98% for AUR, 95% for BPH and 98% for the diagnoses used for the CCI. A potential limitation is that we only included patients with a hospital diagnosis (i.e., inpatient, outpatient, and emergency room hospital contacts) of AUR, thus patients treated at general practitioners without referral to hospital, were not included. However, national guidelines recommend referral to hospital for evaluation by a urologist of all men presenting with AUR and residual urine >100 ml. We therefore expect the proportion of men treated solely at general practitioners to be relatively low. These patients may be patients with advanced disease making hospital referral and further evaluation futile. However, we do not expect this to substantially influence our time trends in incidence, subsequent BPH-related treatment and mortality. Another limitation is that cause of deaths were based on a subjective clinical judgment rather than autopsy, and may
consequently not be entirely accurate. Still, we do not expect such misclassification to explain the excess mortality that we observed for specific causes of death.

5 | CONCLUSIONS

The shift from surgical to medical first-line treatment of BPH was only transiently followed by an increase in the incidence of AUR. The use of BPH-related surgery after AUR stabilized at 10%–20% after a considerable decline, following implementation of the trial without catheter policy. The high mortality observed in men with AUR was related to deaths attributable to malignancies, urogenital disease, infections and preexisting comorbidity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used in the current study are not freely available owing to national regulations. Interested researchers may apply for data access through the Research Service at the Danish Health Data Authority.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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