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The Reduction of Male Lower Urinary Tract Symptoms Is Associated With a Decreased Risk of Death

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Study Need and Importance: Male urinary symptoms are common and may be bothersome. Despite this, men generally seek treatment only when symptoms are significantly bothersome. While research has established the negative medical complications associated with male urinary symptoms, the connection between these symptoms and mortality has not been well studied.

What We Found: We used data from the MTOPS (Medical Treatment of Prostate Symptoms) randomized study which had the following arms: placebo, alpha blocker (doxazosin), 5-alpha reductase inhibitor (finasteride), and combination therapy (doxazosin and finasteride). Among the 3,046 men, we found that reducing urinary symptoms (as measured by the AUA Symptom Score) resulted in a statistically significant reduction in the risk of mortality. This effect was quite pronounced: the hazard of death decreased by 12% if the AUA Symptom Score decreased by 3 points. This effect persisted in sensitivity analyses when we censored men at the time of transurethral prostatectomy, adjusted for confounders, and shortened the observation period after the last study visit. Importantly, the reduced risk of mortality was seen with both the storage and the voiding domains independently (see Table). The mechanism of this effect is not clear and may be from direct nonurinary benefits from the medications, or it may represent a causal relationship with unresolved urinary symptoms increasing the risk of falls, poor sleep, and impaired mental health.

Limitations: This is still a historical cohort, and the impact of changes in clinical care and the predominance of newer alpha blockers are not clear. This effect needs to be further studied in other treatment areas for male urinary symptoms (such as overactive bladder medications or procedural interventions) to better understand this relationship.

Interpretation for Patient Care: It is possible that medical interventions for male urinary symptoms may help reduce mortality risk for men.

Table. *Exploratory Analysis of the Individual Components of the AUA Symptom Score on the Risk of Death*

	Hazard ratio	*P* value
Model 1: Quality-of-life question score change (per 1-point improvement)	0.84 (0.73-0.95)	< .01
Model 2: Storage symptom score change (per 1-point improvement)	0.94 (0.88-0.99)	.04
Model 3: Voiding symptom score change (per 1-point improvement)	0.95 (0.91-0.99)	.03
Model 4: Nocturia score change (per 1-point improvement)	0.90 (0.76-1.06)	.2

All models were adjusted for age and treatment assignment. A hazard ratio less than 1 indicates a lower risk of death.

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The Reduction of Male Lower Urinary Tract Symptoms Is Associated With a Decreased Risk of Death

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Purpose: Male lower urinary tract symptoms have been correlated with an increased risk of death; however, it is unclear if treatment will reduce this risk. Our objective was to determine whether a reduction in lower urinary tract symptoms is associated with a reduced risk of mortality.

Materials and Methods: We conducted a secondary analysis of the MTOPS (Medical Treatment of Prostate Symptoms) randomized trial of placebo, doxazosin, finasteride, or doxazosin and finasteride. Men in the United States between 1993 and 1998 who were >50 years of age with moderate to severe lower urinary tract symptoms were included. We used various Cox regression models to assess the relationship between AUA Symptom Score (modeled as a time-varying exposure) and death.

Results: A total of 3,046 men (median age 62, quartiles 57-68) were randomized and had a baseline AUA Symptom Score. For each 1-point improvement in the AUA Symptom Score, the hazard ratio for death was 0.96 (0.94-0.99, $P = .01$). Our sensitivity analyses found a similar significant reduction in the hazard ratio for death within men who had active treatment, but not among men who were randomized to the placebo arm; our results did not change when men were censored at the time of transurethral prostate resection, with adjustment for potential confounders, or with a shorter observation period after the last study visit. A comparable significant reduction in death was seen with 1-point improvements in the storage (HR 0.94, 95% CI 0.88-0.99, $P = .04$) and voiding (HR 0.95, 95% CI 0.91-0.99, $P = .03$) subscales individually.

Conclusions: Improvement in male lower urinary tract symptoms was associated with a reduced risk of death. Further study is warranted to determine if the male treatment paradigm should shift toward symptom treatment independent of bother.

Key Words: prostatic hyperplasia, mortality, lower urinary tract symptoms

BENIGN prostatic hyperplasia (BPH) is a pathological diagnosis that is often used to refer to a set of symptoms (frequently termed lower urinary tract symptoms [LUTS]) in older men. LUTS commonly include storage symptoms such as urinary frequency and nocturia, and voiding symptoms such as weak stream. While the prostatic enlargement from BPH is a considerable contributor to LUTS, age-related bladder changes, metabolic syndrome, and vascular disease also play a role.[1] Globally, approximately 1 in 4 men will have BPH-related LUTS in their lifetime, and the prevalence increases with age.[2] There is a considerable risk of worsening LUTS with time, and men usually seek treatment only when their symptoms cause significant bother.[3,4] Current treatment guidelines suggest initiating treatment based on the degree of symptom bother.[5,6]

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Conflict of Interest: BW is a consultant for Becton, Dickinson, and Company (outside of this work). JAM has no conflicts of interest to disclose.

Ethics Statement: This study received Western University Research Ethics Board approval (REB No. 121296).

Author Contributions: Both Authors contributed to the conception and design of the work. JAM performed the statistical analysis. BW drafted the manuscript, JAM revised it critically for important intellectual content. Both Authors gave final approval and agreed to be accountable for all aspects of the work.

Data Availability: Data from the Medical Therapy of Prostatic Symptoms [(V2)/https://doi.org/10.58020/b3ns-nq56] reported here are available for request at the NIDDK Central Repository (NIDDK-CR) website, Resources for Research (R4R), https://repository.niddk.nih.gov/

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Studies have reported a significantly increased risk of mortality with worse LUTS; while most of the research has focused on nocturia,[7] male LUTS in general may also be associated with an increased risk of death.[8] However, this observed relationship may be due to the confounding effects of frailty or cardiovascular disease (which are associated with both mortality and LUTS).[9] Additional study examining the association between LUTS and mortality is necessary. Our objective was to determine if the improvement of male LUTS in the setting of medical treatment is associated with a reduction in the risk of mortality.

METHODS

We conducted a secondary analysis of the existing clinical trial data from the Medical Treatment of Prostate Symptoms (MTOPS) study. The trial design[10] and primary outcomes[11] of the MTOPS study have been previously published. Briefly, the MTOPS study was designed to determine whether medical therapy with an alpha blocker or a 5-alpha reductase inhibitor, alone or in combination, would prevent the progression to clinically relevant consequences of BPH. A total of 4391 men were screened, and 3,047 men were randomized into one of 4 arms: placebo, doxazosin, finasteride, or a combination of doxazosin and finasteride. The planned follow-up period was 5 years. Men 50 years of age or older with an AUA Symptom Score for BPH (AUASS) of 8-30 out of 35 (representing moderate to severe LUTS), a flow rate of 4-15 mL/s, and a PSA of <10 were eligible for enrollment. The original study showed that AUASS improved significantly for all treatment groups compared to placebo.[11] For this secondary analysis of the MTOPS clinical trial data, we excluded men missing an AUASS measurement at baseline. A total of 17 centers recruited men between 1993 and 1998. Loss to follow-up was less than 5% per year. All original study sites obtained Institutional Review Board approval, and all participants provided written consent. Western University's Research Ethics Board approved the current secondary data analysis (REB No. 121296).

Primary Outcome and Exposure for the Present Study

The primary outcome for the current study was all cause mortality. This was collected prospectively throughout the clinical trial. The primary exposure was the change in the AUASS from baseline. The AUASS is a well-studied, simple, and psychometrically valid 7-question patient reported outcome measure (Supplementary Appendix 1, https://www.jurology.com).[12] AUASS groups range from 0-7 (mild), 8-19 (moderate), and 20-35 (severe), and there is an additional question that assesses the symptom bother. The AUASS was completed by study participants at each of the protocolized quarterly trial visits and was the primary outcome of the original clinical trial. Our a priori study hypothesis was that the reduction in LUTS (as measured by a lower AUASS) would be associated with a lower risk of death.

Baseline Characteristics

These included basic demographics (age, race, marital status, education level), medical history (such as diabetes, liver disease, heart disease, hypertension), urological history (prior urinary infection, retention, or gross hematuria), and some basic physical and laboratory parameters (such as height, weight, supine heart rate and blood pressure, and creatine level).

Statistical Analysis

We used a marginal Cox model extended to allow for time-dependent variables (with a robust sandwich covariance matrix estimate to account for intracluster independence[13]) to determine the association between AUASS change from baseline and death, adjusted for age and treatment assignment. We tested for the interaction treatment assignment $\times$ AUASS. Follow-up started on the first study visit (at the time of randomization), and men were censored after their last study visit plus 2 years. The AUASS was modeled as a time-varying covariate and the change from baseline was recalculated at each follow-up visit. The change in AUASS was carried forward in time until the next AUASS score was available at which point the change from baseline AUASS was recalculated. There was minimal missing data (there were 26 visits with missing AUASS). In cases where the AUASS was not assessed at a given visit, scores from the previous visit were carried forward. Participants were censored 2 years after their last visit.

We conducted 4 sensitivity analyses. First, we looked at 2 subgroups individually: the placebo group, and those in an active treatment arm (doxazosin, finasteride or combination). Second, to see if perioperative mortality from a transurethral prostate resection in patients with worse LUTS could be confounding the relationship between AUASS and mortality, we censored patients on the date of transurethral prostate resection. Third, we adjusted our primary analysis with 3 available baseline covariates which could act as confounders: diabetes, hypertension, and history of kidney disease. Finally, we repeated our primary analysis with a shorter censoring time of 6 months after their last study visit. We also conducted an exploratory analysis with the individual domains of the AUASS (quality-of-life question), storage symptoms (questions 2, 4, 7, previous referred to as irritative symptoms), voiding symptoms (questions 1, 3, 5, 6), and the nocturia question). Medians and quartiles (25th-75th percentile) are reported. Hazard ratios with 95% confidence intervals and P values are reported for the marginal Cox model ($P < .05$ was considered significant). SAS EG 8.3 was used for statistical analysis.

RESULTS

Of the 3,047 men randomized in MTOPS, 3,046 had an AUASS at baseline. Details on patient flow in the trial has been previously published.[11] The median age was 62 (quartiles 57-68). The median baseline AUASS was 17 (quartiles 13-21), and the scores of the entire cohort over time is shown in the Figure 1. Median follow-up time of the survivors was 6.6 (quartiles 6.1-7.3) years, and 2,729/3,046 men remained in the study at 5 years. The measured baselines reported by randomization status are shown in Supplementary Appendix 2 (https://www.jurology.com). There was no significant difference in the risk of death by randomization assignment (Supplementary Appendix 3, https://www.jurology.com). The baseline characteristics are shown

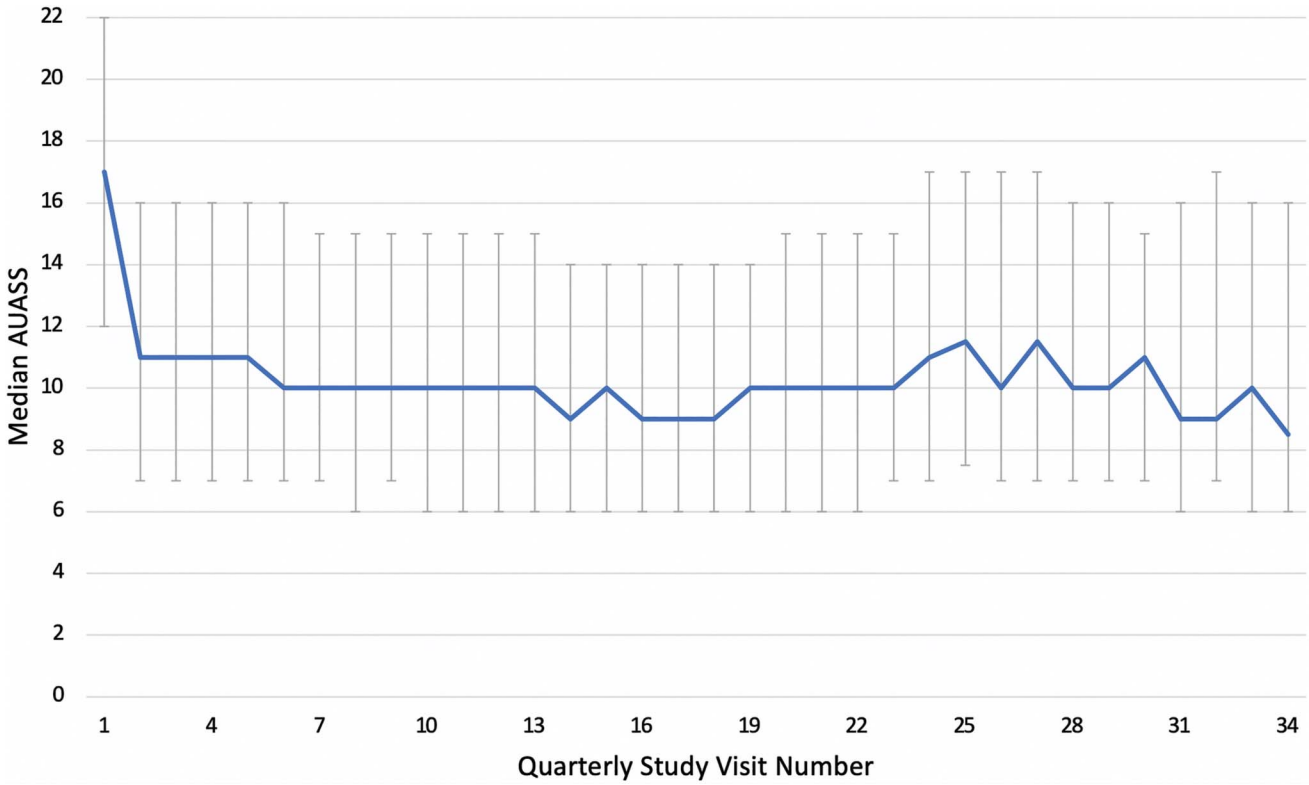

Figure. The median AUA Symptom Score (AUASS) is shown over time based at each of the quarterly study visits. The error bars show the 25th-75th quartiles.

in Table 1. A total of 127 men died during or after the study from cancer (49), cardiovascular disease/stroke (45), pulmonary conditions (11), and "other" causes (22). Potentially BPH relevant causes of death within the "other" category included 1 person who died of renal failure and 2 who died of sepsis. Only 117/127 of these deaths occurred during the at-risk period (within 2 years of the end of the study) and were counted as outcome events.

In our primary analytic model, each 1-point improvement in the AUASS was associated with a HR for death of 0.96 (0.94-0.99, $P = .01$, Table 2); a 3-point improvement in the AUASS resulted in a HR for death of 0.88 (95% CI 0.81-0.95), and a 10-point improvement in the AUASS had a HR for death of 0.65 (95% CI 0.51-0.83). Our sensitivity analyses are shown in Table 3, with a similar reduction in the HR for death within men who had active treatment, but not among men who were randomized to the placebo arm (although the interaction term for AUASS × treatment assignment was not significant, $P = .09$). Our results did not change when men were censored at the time of transurethral prostate resection or when we adjusted the primary model for 3 potential confounders (Table 3 and Supplementary Appendix 4, https://www.jurology.com). When we changed the at-risk period to 6 months from their last follow-up visit (instead of 2 years), 98/117 deaths were included, and our results were not materially changed (Table 3 and Supplementary Appendix 4, https://www.jurology.com).

The results of our exploratory analysis of the AUASS quality-of-life question, storage symptoms, voiding symptoms, and single nocturia question are shown in Table 4 (with further details in Supplementary Appendix 4, https://www.jurology.com). A significant reduction in the HR for death was seen with improvements in the quality-of-life question, and the storage and voiding subscales individually.

DISCUSSION

We used existing and well-known randomized trial data from MTOPS to evaluate whether an improvement in urinary symptoms is independently associated with the risk of mortality among men with BPH. We found that there was a statistically significant decrease in the risk of mortality of 4% per 1-point improvement in the AUASS. While this is a small decrease, it is clinically quite meaningful given the significance of the outcome. A similar, statistically significant decrease in the risk of mortality was seen when looking at a 1-point improvement in storage symptoms alone (6%) or voiding symptoms alone (5%). The point estimate for the single nocturia question was in a similar direction (10% reduction in mortality per 1-point improvement), however was

Table 1. *Baseline Characteristics of the Study Cohort of 3,046 Men*

Age, median (IQR), y	62	(57-68)
Race, No. (%)		
White	2,508	(82)
Black	270	(8.9)
Asian	41	(1.4)
Hispanic/Native American	227	(7.4)
Marital status, No. (%)		
Single	218	(7.2)
Married	2,336	(77)
Separated	48	(1.6)
Divorced	334	(11)
Widowed	110	(3.6)
Education completed, median (IQR), y	15	(12-17)
History, No. (%)		
Congenital disease	100	(3.3)
Lung disease	335	(11)
Heart disease	593	(19)
Hypertension	871	(29)
Renal disease	217	(7.1)
Rheumatic/vascular disease	707	(23)
Diabetes	259	(8.5)
Endocrinopathy	135	(4.4)
Liver disease	105	(3.5)
Gastrointestinal tract disease	806	(26)
Skin disease	633	(21)
Organic CNS disease	123	(4.0)
Neoplastic disease	152	(5.0)
Anemia	69	(2.3)
Hematological disease	56	(1.8)
Urinary tract infection	321	(11)
Urinary retention	111	(3.6)
Gross hematuria	236	(7.8)
Creatinine, median (IQR), mg/dL	1.00	(0.90-1.20)
Physical exam, median (IQR)		
Height (in)	70	(68-72)
Weight (lbs)	188	(170-210)
Supine heart rate	68	(60-76)
Supine bp, systolic	132	(122-146)
Supine bp, diastolic	80	(76-88)

Abbreviations: bp, blood pressure; CNS, central nervous system; IQR, interquartile range.

not statistically significant, possibly as a result of decreased discriminatory power as there was only a single question measuring nocturia in the AUASS. We did not show an effect in the placebo group, which may mean that active treatment is necessary to reduce the risk of mortality, or this may be a result of a lower rate of improvement in the AUASS in this group and reduced statistical power; it is important to also remember this is a subgroup analysis, and therefore should not be overly emphasized.

Table 2. *Primary Analysis of the Effect of AUA Symptom Score Change on the Risk of Death*

	HR	*P* value
AUASS change (per 1 point)	0.96 (0.93-0.99)	.01
Patient age (per y)	1.07 (1.05-1.10)	< .01
Treatment		
Doxazosin vs placebo	0.69 (0.39-1.25)	.22
Finasteride vs placebo	1.26 (0.77-2.08)	.35
Combination vs placebo	1.31 (0.78-2.19)	.31

Abbreviations: AUASS, AUA Symptom Score; HR, hazard ratio.

Our results are unique as this is the first study, to our knowledge, to look at whether an improvement in male LUTS is associated with a lower risk of death, rather than showing an association between the degree of LUTS and mortality. Our results are consistent with the other studies in this area. A large longitudinal Finnish study found that among 3,143 men >50 years who were repeatedly surveyed over 15 years, an increased magnitude of either storage or voiding LUTS increased the risk of death by 10%-20%.[8] The individual symptoms of frequency, nocturia, and urgency incontinence were most relevant to the risk of mortality. Nocturia specifically has been well studied in relation to mortality risk. A recent meta-analysis of 11 studies found that ≥2 episodes of nocturia was associated with a 27% increased risk of mortality (or a 1.6% absolute risk increase in those >60 years of age). Similarly, a secondary analysis of the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial showed that nocturia, defined as ≥3 voids per night, was associated with a 72% increased risk of death.[14]

The relationship between urinary symptoms and mortality could be an association, whereby urinary symptoms are a marker of cardiovascular disease, obesity, sleep apnea, diabetes, or early neurological disease with urinary symptoms. However, this would seem to be less likely in the context of our study results as it is not clear why improvement of LUTS through treatment would reduce the risk of mortality if these mortality risks are due to an underlying disease. It is also possible that the medications used to treat urinary symptoms may directly decrease the risk of mortality through nonurological effects. For example, alpha-1 blockers may decrease the risk of mortality in adults with respiratory infections (perhaps by altering cytokine release),[15] and finasteride may decrease the risk of bladder cancer.[16] However, in this situation we would expect death to be significantly different based on randomization, and this was not the case in either the analysis based on randomization (Supplementary Appendix 3, https://www.jurology.com), or in our adjusted models. Finally, it could be a causal relationship, whereby urinary symptoms impair sleep, increase the risk of falls and fractures, and negatively impair quality of life and mental health.[17] This would mean that successful treatment of these symptoms directly decreases the risk of death. The above causal mechanisms are plausible, given the causes of death that we saw among the MTOPS participants; for example, poor sleep is strongly correlated with cardiovascular disease, and minor depression is correlated with cardiovascular death in older men.[18,19]

This study has direct implications on clinical practice. Currently, urinary symptoms are generally viewed as a benign condition and patients are treated if they have significant bother. However, symptom bother is not perfectly correlated with the degree of

Table 3. *Sensitivity Analyses*

AUASS change per 1-point improvement	HR	*P* value
Treatment group		
Placebo (n = 737)[a]	1.02 (0.96-1.08)	[b]
Active treatment (n = 2,309)[a]	0.95 (0.92-0.98)	[b]
Censoring on date of transurethral prostate resection (n = 3,046; 77 men were censored due to transurethral prostate resection)[a]	0.96 (0.94-0.99)	< .01
Primary model with additional confounder adjustment[c]	0.96 (0.94-0.99)	.01
Primary model with a 6-mo buffer period after last follow-up visit[a]	0.96 (0.93-0.99)	.02

Abbreviations: AUASS, AUA Symptom Score; HR, hazard ratio.
The primary adjusted analysis was repeated separately in men randomized to placebo or active treatment (either doxazosin, finasteride, or combination), with censoring on the date of transurethral prostate resection to account for possible confounding, adjusted with covariates which may have been confounders, and with different criteria for time after last visit to look for the outcome of death.
[a] Models were adjusted for age and treatment assignment. Full details are shown in Supplementary Appendix 4 (https://www.jurology.com).
[b] In keeping with statistical guidelines, *P* values are not reported for subgroup analyses.
[c] Model was adjusted for age, treatment assignment, hypertension, diabetes, and history of kidney disease. Full details are shown in Supplementary Appendix 4 (https://www.jurology.com).

symptoms (the correlation between the AUASS total and the bother question is 0.78[12]); it is therefore possible that if there is a causal association between LUTS and mortality, earlier intervention based on symptom level alone would be appropriate. This would be analogous to the primary care approach to control of systolic blood pressure, where there is a linear increased risk mortality with increasing systolic blood pressure that starts even at 125-129 mm Hg, but is reduced with treatment.[20] Our research is especially timely given the wide range of conservative options, medications, and minimally invasive surgical options that are now available to treat male LUTS.[6,21] Although the magnitude of decrease in the risk of death was low, for an outcome such as mortality this is very relevant.

Strengths

Strengths of our study are the use of high-quality clinical trial data in which interventions were randomly assigned to men to reduce LUTS (which resulted in men randomized to combination therapy having the best chance of having an improvement in their LUTS[11]). This partially addresses residual confounding that is found in observational studies, where men with worse urinary symptoms at baseline may be more likely to have diagnosed or undiagnosed conditions associated with both mortality and LUTS. We censored people on the date of transurethral prostate resection to evaluate for potential confounding by this intervention, and did not see a significant difference in our results. Our primary exposure was a validated and well-recognized instrument to assess LUTS, and we accounted for changes over time in the AUASS by modelling this as a time varying covariate.

Limitations

Limitations of our study must also be acknowledged. The use of doxazosin as a treatment for male LUTS is now uncommon, due the availability of other more contemporary alpha-blockers that do not need dose titration, and due to its increased risk of congestive heart failure, stroke and cardiovascular disease.[22,23] However, this would potentially bias our results toward the null and underestimate the hazard ratio, as we still found that independent of treatment assignment, improvement in the AUASS resulted in a reduced risk of death. A beneficial effect on mortality may be more pronounced with newer selective alpha blockers which have a lower risk of heart failure.[24] We could not assess all factors which might be related to mortality in middle-aged men and we could not ascertain if men developed new medical conditions over time that could confound the results. Other treatment of male LUTS (such as with overactive bladder medications, surgery, or lifestyle changes) need to be investigated. Our study population was exclusively male, so this relationship may not be generalizable to women with LUTS. It is important to remember the patient population all had at least moderate LUTS, so these findings are not generalizable to men with mild urinary symptoms. Finally, it is still possible that LUTS are a marker of other systemic disease, and improvement due to lifestyle changes or

Table 4. *Exploratory Analysis of the Individual Components of the AUA Symptom Score*

	HR	*P* value
Model 1: Quality-of-life question score change (per 1-point improvement)	0.84 (0.73-0.95)	< .01
Model 2: Storage symptom score change (per 1-point improvement)	0.94 (0.88-0.99)	.04
Model 3: Voiding symptom score change (per 1-point improvement)	0.95 (0.91-0.99)	.03
Model 4: Nocturia score change (per 1-point improvement)	0.90 (0.76-1.06)	.2

Abbreviations: HR, hazard ratio.
All models were adjusted for age and treatment assignment. Full model results are shown in Appendix 4 (https://www.jurology.com).

other interventions are the common intermediary factor. However, we did not see a significant effect on mortality among men in the placebo group alone, therefore medical therapy may be required to cause a significant enough improvement to realize a mortality benefit.

CONCLUSIONS

An improvement in the AUASS of older men with BPH is associated with a decreased risk of mortality over 6 years. Improvements in both storage and voiding symptoms are significantly associated with a lower risk of death. Further study is necessary to see if early LUTS treatment independently decreases the risk of mortality.

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EDITORIAL COMMENT

The days of always delaying definitive treatment for benign prostatic hyperplasia (BPH) until men fail medications are over. The pitfalls in nontreatment or undertreatment of urinary symptoms due to BPH are becoming more apparent with studies demonstrating worsening presurgical and postsurgical outcomes in men with delayed treatment of BPH.[1] In a study looking at BPH surgery utilization based

on age groups, men in the oldest cohort (85 years and older) had among the highest rates of BPH surgery utilization. This cohort would of course also have the highest perioperative risk due to age and increasing comorbidity.[2]

The pitfalls of undertreated BPH are numerous. Men undergo irreversible changes to the detrusor with ongoing obstruction making it both weaker and overactive. Nocturia leads to broken hips as men wander through the dark to find the bathroom. While the renal failure seen with acute obstruction is generally reversible with bladder drainage, men don't always return to baseline levels of kidney function.

I applaud the authors for linking improvements in urinary symptoms to mortality—an obviously important finding.[3] Many previous studies have demonstrated the association of worsening lower urinary tract symptoms and mortality, but the opposite has not previously been demonstrated. Use of this well-known cohort and standardized symptom scores only strengthens the findings.

I caution the urological community not to wait for BPH treatment to become salvage procedures in men with neurogenic/atonic bladders after years to decades of underwhelming medication response. With the data presented here we may also be saving lives with timely and appropriate BPH treatment.

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