Association of Frailty with Clinical Benign Prostatic Hyperplasia Progression and Serious Adverse Drug Events: the MTOPS Study

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Introduction

- Benign prostatic hyperplasia (BPH) is common among older men and can cause bladder outlet obstruction.
- Lower urinary tract symptoms due to suspected BPH are increasingly treated with medications.
- Frailty may shift the balance of benefits and harms of medical therapy for BPH.
- We examined prospective associations between frailty and clinical BPH progression or adverse drug events.

Methods

Study Population

- 3047 men enrolled in the Medical Therapy of Prostatic Symptoms (MTOPS) Study randomized to placebo, doxazosin, finasteride, or combination therapy.

Exposure Assessment

- Frailty index (FI; range: 0-1) using 69 items collected at baseline, including medical history, vitals, laboratory values, self-reported QOL and functional status.
- Men were categorized as fit (≤0.1), less fit (0.1-<0.25), or frail (≥0.25) based on prior studies.

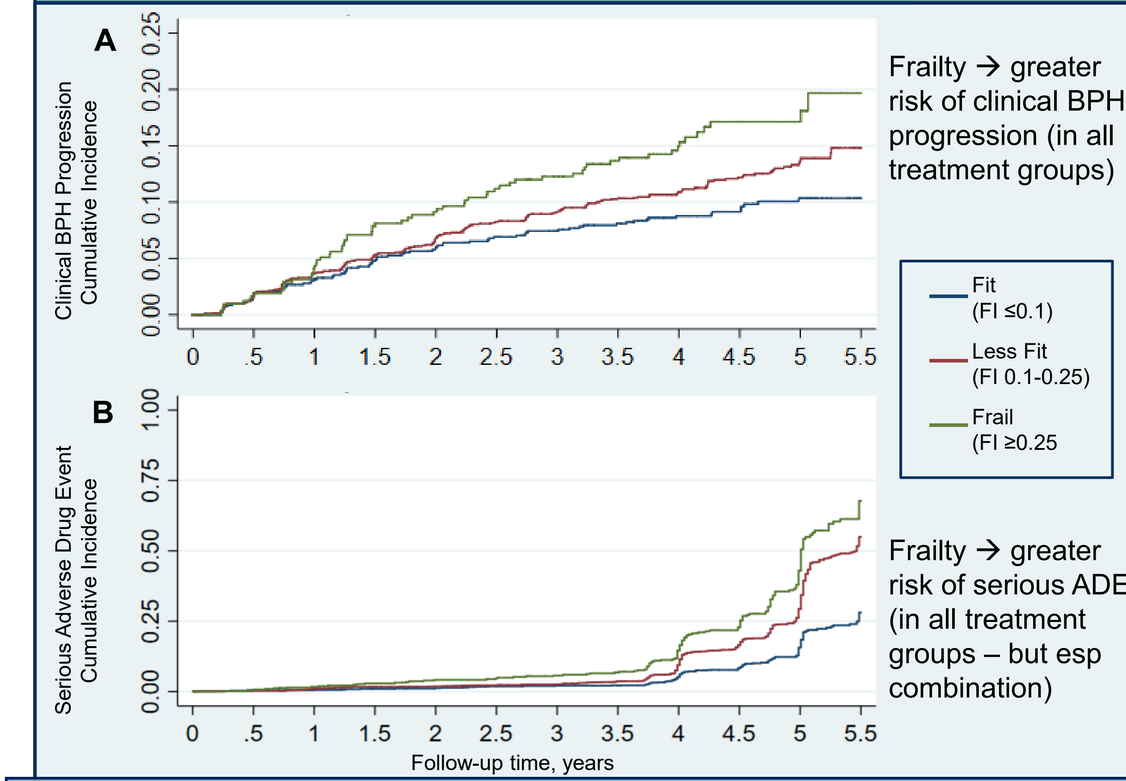
Outcome Assessment

- Clinical BPH progression was defined as an increase of ≥4 in the American Urological Association Symptom Score (AUASS), acute urinary retention, urinary incontinence, renal insufficiency, or recurrent UTI.
  - 78% of events were due to increased AUASS
- Serious adverse drug events (ADE) were defined and adjudicated by a data and safety monitoring board.

Statistical Analysis

- The 2 primary outcomes as defined in the original trial were time to first progression event or serious ADE.
- Cox proportional hazards regression models were adjusted for demographics, treatment group, measures of obstruction, health behaviors, and comorbidities.

Kaplan-Meier curves for A) Clinical BPH Progression and B) Serious Adverse Drug Event (ADE) among MTOPS Participants, by Frailty Status



Frailty → greater risk of clinical BPH progression (in all treatment groups)

Frailty → greater risk of serious ADE (in all treatment groups – but esp combination)

Risk of Clinical BPH Progression and Serious Adverse Drug Event, by Frailty Status

	Clinical BPH Progression HR (95% CI)*		Serious ADE HR (95% CI)*	
	Unadjusted	Multivariable**	Unadjusted	Multivariable**
Fit (Ref.)	1.00	1.00	1.00	1.00
Less Fit	1.34 (1.03, 1.75)	1.33 (0.98, 1.81)	2.41 (2.00, 2.90)	1.45 (1.16, 1.77)
Frail	1.84 (1.32, 2.57)	1.82 (1.16, 2.85)	3.70 (2.96, 4.62)	1.65 (1.22, 2.22)
P value	0.001	0.02	<0.001	0.001

* Hazard ratios (HR) and 95% CI calculated using proportional hazards model. *P* value calculated using FI as continuous variable.
** Adjusted for age, race, marital status, education, treatment group, prostate volume, post-void residual, maximum urinary flow rate, BMI, vigorous activity, hypertension, diabetes, heart disease, depression.

Baseline Characteristics of Participants, by Frailty Status

N (%) or mean ±SD	Fit (≤0.1)	Less Fit (0.1-0.25)	Frail (≥0.25)
Total Participants	845 (28)	1776 (58)	426 (14)
Age, years	61 ± 7	63 ± 7	65 ± 8
Non-White	115 (14)	300 (17)	123 (29)
Education <12 years	39 (5)	138 (8)	82 (19)
BMI, kg/m^2	26.5 ± 3	28.0 ± 4	29.0 ± 5
# of Medications	1.3 ± 2	2.1 ± 2	3.1 ± 2
AUASS	16.5 ± 6	16.8 ± 6	18.5 ± 6
Prostate vol., ml	35 ± 20	37 ± 20	37 ± 22
PVR, ml	66 ± 80	72 ± 87	57 ± 71
Max urinary flow rate, ml/sec	10.3 ± 3	10.5 ± 3	10.6 ± 3

Limitations

- Men were not randomized to their frailty status, therefore unmeasured confounding is possible.
- Unknown generalizability to older, sicker, or more racially diverse populations of men with BPH.
- Limited power to test for interactions.

Conclusion

- Frailty is independently associated with greater risk of clinical BPH progression and serious ADE among men randomized to placebo or medical BPH therapy.
- Prior to initiating medical BPH therapy among frail men, a discussion of both potential benefits and harms via shared decision making is needed.
- Future studies should evaluate potential mechanisms of frailty contributing to clinical BPH progression, which are likely not targeted by current therapeutics.

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