College of Osteopathic Medicine

What's in a p-value? A fragility analysis of AUA guidelines on BPH

Reece Anderson M.P.H., Andriana Peña B.S., Bradley Johnson D.O., Ross Nowlin B.S., Tillman Hudson, M.D., Matt Vassar Ph.D.

INTRODUCTION

Randomized controlled trials (RCTs) underpin clinical practice guidelines (CPGs) utilized by physicians to direct management of care. Evidence shows that physicians often interpret significant p-values to be "real-world probability" which is not accurate, as p-values can be skewed by confounding variables such as sample size and loss to follow-up. Therefore, there is a need to assess the robustness of endpoints within RCTs that underpin CPGs, specifically for benign prostatic hyperplasia (BPH). This study uses the Fragility Index (FI) and Fragility Quotient (FQ) to assess the strength of statistically significant findings for RCTs cited in the American Urological Association (AUA) guidelines for benign prostatic hyperplasia.

METHODS

Two investigators independently screened the AUA guidelines for management of BPH for RCTs cited as evidence for recommendations. In order to be included in this analysis, RCTs needed to 1) report a statistically significant ($p \leq 0.05$) dichotomous outcome as a primary or secondary endpoint, 2) have a parallel or two-by-two factorial design, 3) be randomized in approximately a 1:1 ratio, and 4) be available in English. Investigators extracted data related to event rate per group (e.g. incidence of acute urinary retention in each group) and loss to follow-up which was compared against the FI. Stata was used to calculate the FI and FQ which was then summarized and reported according to primary or secondary endpoints.

RESULTS

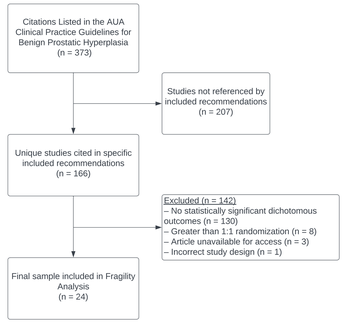

Figure 1. PRISMA Flow Diagram for Study Selection

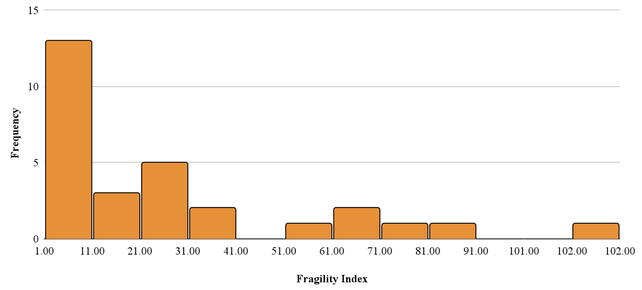

Figure 2. Relative Frequency of Fragility Indices for Included Studies

Table 1. Characteristics of Included Primary Outcomes with FI and FQ

Intervention Category	Article Title	Outcome Description	Fragility Index	Fragility Quotient	Number Lost to Follow-up
Pharmaceutical	Alfuzosin 10 mg Once Daily in the Management of Acute Urinary Retention of Benign Prostatic Hyperplasia: A Double-Blind, Placebo-Controlled Study	Successful TWOC (Cumulative)	26	0.116	21
Pharmaceutical	Alfuzosin 10 mg once daily increases the chances of successful trial without catheter after acute urinary retention secondary to benign prostate hyperplasia	Successful TWOC	2	0.031	3
Surgical	Combination of channel-TURP and ILC versus standard TURP or ILC for elderly with benign prostatic hyperplasia: a randomized prospective trial	UTI incidence in TURP group vs ILC alone	12	0.126	8
Surgical	Combination of channel-TURP and ILC versus standard TURP or ILC for elderly with benign prostatic hyperplasia: a randomized prospective trial	UTI incidence in Channel- TURP + ILC vs. ILC	11	0.115	8
Pharmaceutical	Effect of Dutasteride on the Risk of Prostate Cancer	Incidence of prostate cancer	102	0.015	109
Pharmaceutical	Effect of Dutasteride on the Risk of Prostate Cancer	Incidence of prostate cancer	102	0.015	109
Pharmaceutical	Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (Dutasteride) in men with benign prostatic hyperplasia	Incidence of AUR	27	0.006	119
Pharmaceutical	Incidence and severity of sexual adverse experiences in finasteride and placebo-treated men with benign prostatic hyperplasia	≥ 1 sexual side effects at 1 year	78	0.026	89
Pharmaceutical	Is the double dose alpha-blocker treatment superior than the single dose in the management of patients suffering from acute urinary retention caused by benign prostatic hyperplasia?	Successful TWOC	1	0.014	0
Pharmaceutical	Prospective randomized placebo-controlled study to assess the safety and efficacy of silodosin in the management of acute urinary retention	Successful TWOC	5	0.083	0
Education and Training	Self management for men with lower urinary tract symptoms: randomized controlled trial	Treatment failure	18	0.129	25
Pharmaceutical	Sustained-release alfuzosin and trial without catheter after acute urinary retention: a prospective, placebo-controlled	Successful voiding after catheter removal	2	0.025	1
Pharmaceutical	Tadalafil Administered Once Daily for Treatment of Lower Urinary Tract Symptoms in Korean men with Benign Prostatic Hyperplasia: Results from a Placebo-Controlled Pilot Study Using Tamsulosin as an Active Control	≥ 1 TEAE	4	0.040	5
Pharmaceutical	The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group	Four-year incidence of Acute Urinary Retention or Surgery for BPH	67	0.022	88
Pharmaceutical	The influence of finasteride on the development of prostate cancer	Incidence of prostate cancer	189	0.021	1256
Pharmaceutical	The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia	Doxazosin vs placebo	25	0.017	Not reported
Pharmaceutical	The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia	Doxazosin vs placebo	25	0.017	Not reported
Pharmaceutical	The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia	Finasteride vs placebo	22	0.015	Not reported
Pharmaceutical	The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia	Finasteride vs placebo	22	0.015	Not reported
Pharmaceutical	The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia	Combination (Doxazosin and Finasteride) vs placebo	58	0.039	Not reported
Pharmaceutical	The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia	Combination (Doxazosin and Finasteride) vs placebo	58	0.039	Not reported
Pharmaceutical	Tolterodine and Tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial	Subjective Benefit Reported	21	0.049	68
Pharmaceutical	Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (Dutasteride) in men with benign prostatic hyperplasia	Incidence of AUR	27	0.006	119

CONCLUSION

Among the 373 citations in the AUA guidelines, twenty-four RCTs met inclusion criteria with 29 distinct outcomes analyzed. The median fragility index was 15 (IQR = 4 – 38), indicating that twelve alternative events to either study arm would nullify statistical significance. Six studies had a FI of ≤ 2, indicating that only 1-2 outcomes would need to be changed in order to render non-significance of results. In 10/24 RCTs, the number of patients lost to follow-up was greater than the FI.

The AUA clinical practice guidelines for management of BPH cite RCTs with more robust findings when compared to previous studies assessing fragility in the field of urology. While several included studies had high fragility, the median FI in our analysis was approximately 4-5 times higher than comparable studies of urological RCTs. However, there are areas where improvement is necessary to support the highest quality of evidence-based medicine.

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