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Effect of Increasing Doses of Saw Palmetto on Lower Urinary Tract Symptoms: A Randomized Trial

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Appendix (Online only). Supplemental Product Information.

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Abstract

Context—Saw palmetto fruit extracts are widely used for treating lower urinary tract symptoms attributed to benign prostatic hyperplasia. However, recent clinical trials have questioned their efficacy, at least at standard doses (320 mg daily).

Objective—To determine the effect of a saw palmetto extract at up to three times the standard dose on lower urinary tract symptoms attributed to benign prostatic hyperplasia.

Design—Multicenter placebo-controlled randomized trial conducted from June, 2008 through October, 2010.

Setting—Eleven North American clinical sites.

Participants—Were men at least 45 years old, with a peak urinary flow rate ≥ 4 ml/sec, an AUA Symptom Index (AUASI) score ≥ 8 and ≤ 24, and no exclusions.

Interventions—One, two, and then three 320 mg daily doses of saw palmetto extract or placebo, with dose increases at 24 and 48 weeks.

Main Outcome Measures—Primary outcome was the difference in AUASI score from baseline to 72 weeks. Secondary outcomes were measures of urinary bother; nocturia; uroflow; postvoid residual; prostate-specific antigen; participants' global assessments; and indices of sexual function, continence, sleep quality, and prostatitis symptoms.

Results—From baseline to 72 weeks, mean AUASI scores decreased from 14.4 to 12.2 points with saw palmetto and from 14.7 to 11.7 points with placebo. The group mean difference in AUASI score change from baseline to 72 weeks between the saw palmetto and placebo groups was 0.79 points favoring placebo (bound of the 95% confidence interval most favorable to saw palmetto was 1.77 points, one-sided P=0.91). Saw palmetto was no more effective than placebo for any secondary outcome. No attributable side effects were identified.

Conclusions—Increasing doses of a saw palmetto fruit extract did not reduce lower urinary tract symptoms more than placebo. (CAMUS study number NCT00603304 http://www.ClinicalTrials.gov)

Introduction

Benign prostatic hyperplasia (BPH) is a common cause of bothersome lower urinary tract symptoms (LUTS) among older men,[1] and may be treated with medications, minimally invasive therapies, or surgery.[2, 3] Plant extracts are also widely used for LUTS in the United States and Europe. [4] The most common are extracts of the fruit of the saw palmetto dwarf palm tree. In a 2007 U.S. survey, 17.7% of adults reported use of a natural product in the last 30 days, and 5.1% of users had taken saw palmetto[5]; undoubtedly, the frequency would be higher among older men. A variety of mechanisms for saw palmetto have been proposed including anti-androgenic, anti-inflammatory, and anti-proliferative effects, but none have been conclusively proven. [6–9]

In a 2002 Cochrane meta-analysis of the efficacy of saw palmetto extracts for men with LUTS attributed to BPH, 21 clinical trials were identified. Compared to placebo, saw palmetto significantly reduced nocturia, increased self-rated improvement, and improved peak uroflow.[10] Adverse effects were infrequent.

However, subsequent more rigorous trials have yielded less positive results. In 2009, an updated Cochrane review identified nine new trials. Though the effect on nocturia remained significant, there was no significant effect on American Urological Association Symptom Index (AUASI) scores or peak uroflow. [11] The most common dose was 160 mg twice daily.

The largest trial was the Saw palmetto Treatment for Enlarged Prostates (STEP) study. Two hundred twenty-five men ≥50 years old with baseline AUASI score ≥8 were randomized at one center to saw palmetto extract 160 mg BID or placebo. No improvement over placebo was found over one year in symptom scores or any secondary endpoints.[12] No important toxicity was observed.[13]

Following publication of STEP we conducted a randomized clinical trial to determine if a standard daily dose of a saw palmetto extract increased to a double and then a triple daily dose over 72 weeks would improve LUTS attributed to BPH. [14]

Methods

Trial Design

This study was a randomized, placebo-controlled double-blind multicenter trial of increasing doses of saw palmetto fruit extract. Enrollment began in June, 2008 and follow-up was completed in October, 2010.

Participants

We purposefully recruited a broad spectrum of men into the trial, as in the United States men do not need an evaluation by a health care provider or a prescription to buy and take a saw palmetto extract for lower urinary tract symptoms. Men were eligible for enrollment if they were ≥45 years old, had a peak uroflow rate ≥4 ml/sec, an AUASI score ≥ 8 and ≤ 24 at two screening visits, and signed informed consent. Men were ineligible if they had: prior invasive treatment for BPH; recent alpha blocker (1 month), 5-alpha reductase inhibitor (3 months), or phytotherapy including saw palmetto extract (3 months) treatment; recent treatment with other medications affecting LUTS; creatinine > 2.0 mg/dL; liver function tests more than 3 times normal; coagulopathy or anticoagulation; recent unstable medical conditions; neurologic conditions affecting urination; recent prostatitis or repeated urinary tract infections; prostate or bladder cancer or a prostate-specific antigen level >10 ng/mL; recent or planned genitourinary instrumentation; severe incontinence; recent diuretic initiation or dose change; or medical conditions likely to prevent completion. [14] Participants were non-paid volunteers recruited at 11 North American sites (see Acknowledgments); the study was approved by their and the Data Coordinating Center's institutional review boards. An independent data and safety monitoring board established by the National Institutes of Health periodically reviewed the progress and safety of the study.

Interventions

Participants were randomly assigned equally to receive one, two, and then three 320 mg chocolate-colored gelcaps daily containing a standardized saw palmetto fruit extract with dose escalations at 24 and 48 weeks; or an identical number of placebo gelcaps escalated similarly. The two batches of saw palmetto extract used were standardized to a reference chromatogram (with 85–95% fatty acids as marker substances), 30 mg glycerol, 25 mg sorbitol, 10 mg purified water, and 90 mg gelatin. The placebo contained 375 mg polyethylene glycol, 25 mg glycerol and 75 mg gelatin (matched weight of 475 mg). Participants were asked to take the gelcaps together at a convenient time. Participants with unacceptable side effects could split the dose or be maintained on lower doses. The phytotherapy used in this trial was a proprietary lipidic ethanolic extract of ripe, dried saw

palmetto berries, *Serenoa repens* (W.Bartram) Small (Arecaceae), manufactured by Rottapharm/Madaus, Cologne, Germany and sold as PROSTA-URGENIN UNO capsules (see Appendix). Identification, extraction, and phytochemical content are described in the Saw Palmetto extract monograph published in USP33-NF28 S1 Reissue. [15]

Outcomes

The primary outcome was the change in AUASI score from baseline to 72 weeks. The AUASI is a self-administered 7 item index assessing frequency of LUTS (range 0–35 points).[16] Secondary analyses on the AUASI were a comparison of the proportion of participants achieving a 3 point score decrease and a repeated measures analysis of scores over time. Secondary outcomes included participants' global assessments of improvement and satisfaction at end-of-study (both Likert scales) ; as well as change from baseline to 72 weeks in: the BPH Impact Index[17], the Quality of Life item from the International Prostate Symptom Score[18], the nocturia item from the AUASI [16], peak uroflow, postvoid residual volume, prostate specific antigen (PSA) level, indices of erectile and ejaculatory function[19, 20], the ICSmaleIS incontinence scale [21], the Jenkins Sleep Dysfunction Scale[22], and the NIH Chronic Prostatitis Symptom Index.[23] All questionnaires were available in English and Spanish.

Participants were seen at baseline and at 12, 24, 36, 48, 60, and 72 weeks for outcome assessments. They were assessed for side effects including with blood counts, basic blood chemistries, coagulation tests, electrocardiograms and urinalyses 4 weeks after each dose increase and at end of study, including a query about adverse effects occurring within 30 days of treatment discontinuation. Compliance was estimated by pill counts at each visit, and attendance at protocol-specified visits was tracked.

Sample Size

To detect a hypothetical two-point group mean difference in AUASI score change between saw palmetto extract and placebo groups with a two-sample t-test at a one-sided significance level of 0.05 assuming a common standard deviation of 6 points, a sample size of 157 participants per group was estimated to provide 90% power. A two-point difference approximates the mean drop in AUASI score among men with baseline scores of 8–19 points who report "slight" improvement. [24] To allow for 10% dropouts, a total sample size of 350 participants was planned. During recruitment, the sample size was increased to 369 to allow for dilution of any therapeutic effect among participants unable to take the triple dose. Given that the clinical implications for use of the extract in the "real world" would be the same whether it proved no better or worse than placebo, an *a priori* decision was made to use one-sided statistical testing. [25]

Randomization

Randomization was performed centrally using an internet accessible, password-protected, computer-based system that generated group assignments. Randomization was stratified by baseline AUASI score (8–15 or 16–24 points) and clinical center with randomly permuted blocks in each stratum.

Blinding

Study staff and participants were blinded to treatment assignment. Because of a mild odor of the saw palmetto extract, gelcaps were blister packaged to avoid unblinding during compliance assessments. To test the blind, participants were asked to guess their treatment assignment at end of study.

Statistical Methods

The treatment arms were compared with respect to demographic and baseline measures using Pearson's chi-square test, the t-test for independent samples and the Wilcoxon rank sum test. The primary analysis was based on the modified intention to treat (MITT) population that included all eligible participants who took at least one dose of study drug and had at least one follow-up assessment. For participants who discontinued prior to 72 weeks, multiple imputations were used to estimate their AUASI at week 72, and other secondary outcome measures. There were 23 participants (12 on saw palmetto and 11 on placebo) who had all secondary outcome measures for week 72 imputed. For an additional 14 participants (4 on saw palmetto and 10 on placebo), 1–2 secondary outcomes at week 72 were imputed. At baseline, secondary measures were missing for 7 participants (2 on saw palmetto, 5 on placebo) and were estimated using multiple imputation. Baseline measures for AUA-SI were obtained from all participants.

Results of the MITT analysis were confirmed in the per-protocol population which included all participants who received treatment for 72 weeks. An unpaired t-test was used to compare the two treatment arms with respect to change in AUASI score from baseline to 72 weeks, using a one-sided P value of 0.05 as the threshold for statistical significance. Prespecified secondary analyses on the primary outcome included a comparison of the proportion of participants achieving at least a 3 point AUASI score decrease at 72 weeks using Fisher's exact test, and a mixed models repeated measures analysis comparing change in AUASI scores from baseline between the two groups over time. A single prespecified subgroup analysis was based on participants' race and ethnicity; post hoc subgroup analyses were also conducted by dichotomizing baseline age, AUASI score, BPH Impact Index score, peak uroflow, post-void residual volume, and PSA level at the medians of their distributions; education was dichotomized as college graduate or less. The interaction term of the two-way analysis of variance was used to determine the effect of subgroups on the primary outcome measure. Statistical testing in secondary analyses was not adjusted for multiple comparisons to avoid sacrificing sensitivity for specificity. Analyses were conducted in SAS version 9.2

Finally, to explore for any dose-response, the changes in AUASI score between baseline and 24, 24 and 48, and 48 and 72 weeks were compared, with plans to use the Hochberg step-up method to deal with multiple comparisons, if necessary. Secondary outcomes were assessed using two sample t-tests with one-sided 0.05 significance levels. Rates of occurrence of adverse events and abnormal laboratory values were estimated using the Poisson distribution and compared using a normal approximation.

Results

A total of 1032 men were prescreened, usually by telephone; interested and preliminarily eligible men were invited to a screening visit.[26] Figure 1 provides a CONSORT diagram for the 470 men attending a first screening visit. A total of 369 men were randomized, between 19 and 52 per site. Table 1 compares the baseline characteristics of the 357 participants randomized and included in the modified intention to treat analysis. Participants had a mean age of about 61 years, and were predominantly well-educated non-Hispanic whites with a mean AUASI score of 14.4 points.

Compliance with scheduled visits excluding visits after dropouts was 97.0%. Median pill count across attended visits was 98.2%.Of the 306 participants who completed 72 weeks on treatment, all were successfully increased to triple dose and included in the per-protocol analysis. At end of study, of participants randomized to saw palmetto extract who were still on study drug and responded, 45/149 (30.0%) thought they were on saw palmetto, 67/149 (45.0%) thought they were on placebo, and 37/149 (24.8%) said they weren't sure. Of

similar participants randomized to placebo, 66/154 (42.9%) thought they were on placebo, 39/154 (25.3%) thought they were on saw palmetto, and 49/154 (31.8%) said they weren't sure. The responses were not significantly different (P=0.36).

Figure 2 displays the mean AUASI scores during follow-up. Table 2 provides the group mean changes in AUASI scores from baseline to 72 weeks. The AUASI score decreased a mean of 2.20 points with saw palmetto and 2.99 points with placebo, a group mean difference of 0.79 points favoring placebo (upper bound of the one-sided 95% confidence interval most favorable to saw palmetto was 1.77 points, one-sided P=0.91). The per-protocol analysis comparing the mean decrease in AUASI score among 151 participants on saw palmetto extract to 155 participants on placebo who completed 72 weeks on triple dose yielded a group mean difference of 0.82 points favoring placebo (upper bound of the one-sided 95% confidence interval most favorable to saw palmetto extract was 1.91 points, one-sided P= 0.89). The proportion of participants achieving a 3 point decrease in AUASI score at 72 weeks was 42.6% in the saw palmetto group and 44.2% in the placebo group (one-sided Fisher's exact test P=0.66). The results of the mixed models repeated measures analysis showed no greater improvement with saw palmetto extract versus placebo (P=0.22). Finally, the analysis of dose response also showed no greater improvement with saw palmetto extract versus placebo at any dose level. Saw palmetto extract was no better than placebo for any secondary outcome (Table 2).

Figure 3 presents the group mean difference in AUASI score decrease by treatment group stratified by race and ethnicity, as well as the exploratory subgroup analyses for other baseline parameters. These analyses did not reveal any subgroup with a clinically important differential response to saw palmetto compared to placebo. At week 72, the two subjective assessment measures did not differ significantly between the two treatment arms. Participant assessments of urinary symptoms compared to baseline averaged 3.6 and 3.5 for saw palmetto and placebo, respectively, which is between "a little better" and "about the same." Satisfaction with current status of urinary symptoms averaged 3.1 and 3.0 for saw palmetto and placebo, respectively, which corresponds to "neither satisfied nor dissatisfied."

Table 3 presents the number of adverse events by treatment group, and Table 4 describes all serious adverse events reported among participants for those adverse events that occurred in at least 5% of study participants. There were no significant differences between groups in the rates of occurrence of any adverse events. The saw palmetto extract appeared to have no attributable side effects, even up to triple doses.

Discussion

Saw palmetto extracts have been widely used by men with LUTS, but more recent rigorously conducted trials, particularly the STEP trial[12], have not proven superiority to placebo at standard doses of 320 mg daily. We designed this trial to determine whether saw palmetto extract at daily doses up to 960 mg would prove superior to placebo at improving LUTS and other BPH-related outcomes.

We found that the saw palmetto extract tested in this study had no greater effect than placebo on LUTS attributed to BPH or a broad range of secondary outcomes, though small decreases in AUASI scores were seen in both groups. Superiority to placebo was not demonstrated despite using a saw palmetto preparation prepared with an ethanolic extraction procedure as opposed to the CO_2 extraction procedure used in preparing the STEP product, and increasing to three times the standard dose. Increasing to these higher doses was not associated with a greater attributable risk of side effects.

The strengths of our trial, which distinguish it from earlier studies, included the use of a well-characterized saw palmetto extract, an adequate sample size (our one-sided confidence intervals make any clinically important benefit relative to placebo extremely unlikely), recruitment from multiple centers to increase generalizability, an adequate dose of the extract, an adequate duration of treatment (24 weeks at each dose level), excellent compliance with study medication and visits, a comprehensive set of outcome measures, and documentation of adequate blinding of participants.

Do our findings apply to other saw palmetto preparations? We studied just one extract, and because the potential active ingredients and mechanisms are unknown, our findings may not be generalizable. Nevertheless, a recent series of negative trials using different saw palmetto preparations makes it increasingly unlikely a dose of some preparation will be identified that is superior to placebo. [11, 12]

The eligibility criteria for this study were intentionally broader than for many previous trials of prescription medications for LUTS attributed to BPH; such as the Medical Therapy of Prostatic Symptoms (MTOPS) study comparing doxazosin, finasteride, and combination therapy to placebo[3]; in part because of our desire to recruit men who might typically chose to take phytotherapy for LUTS. As a result, participants in this study were slightly younger (mean age 61 versus 63 years), less symptomatic (mean AUASI score 14.5 versus 17 points), with lower PSA levels (mean PSA 2.1 versus 2.4 ng/mL) and substantially higher peak uroflow rates (15 versus 10.5 mL/sec) than men enrolled in MTOPS.[3] As a result, a greater percentage of men in this study compared to MTOPS may have had LUTS due to causes other than BPH.[27, 28] Nevertheless, the exploratory subgroup analyses did not suggest a differential effect of saw palmetto extract on men more likely to have LUTS due to BPH, such as men with higher PSA levels or lower peak uroflow. Not surprisingly, this study population was demographically and clinically more similar to the STEP population.[12]

In conclusion, we found that a saw palmetto extract used at up to three times the standard daily dose, while safe and with no attributable side effects we could identify, had no greater effect than placebo on improving lower urinary symptoms or other outcomes related to BPH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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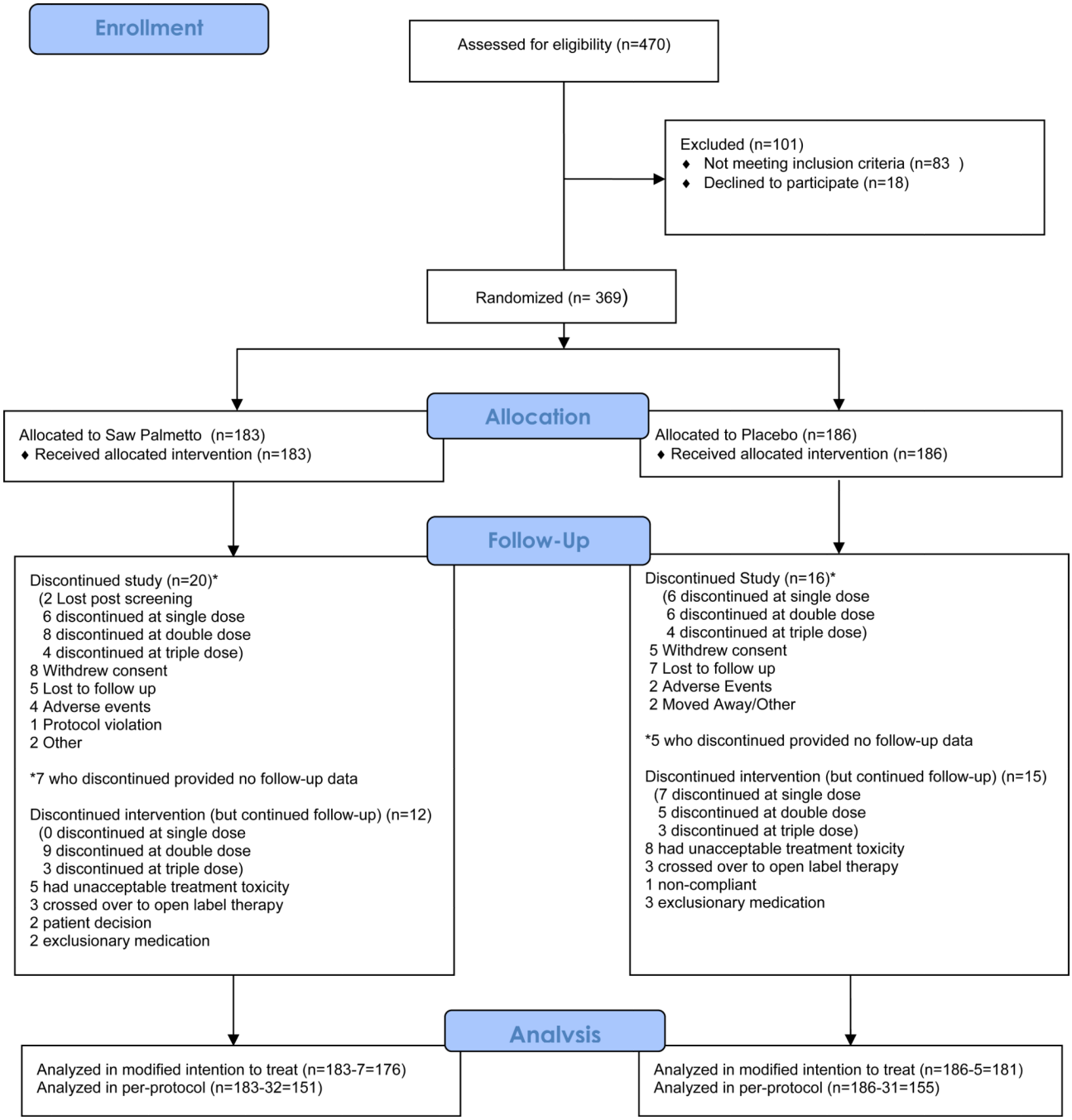

Figure 1.
CONSORT diagram for the trial

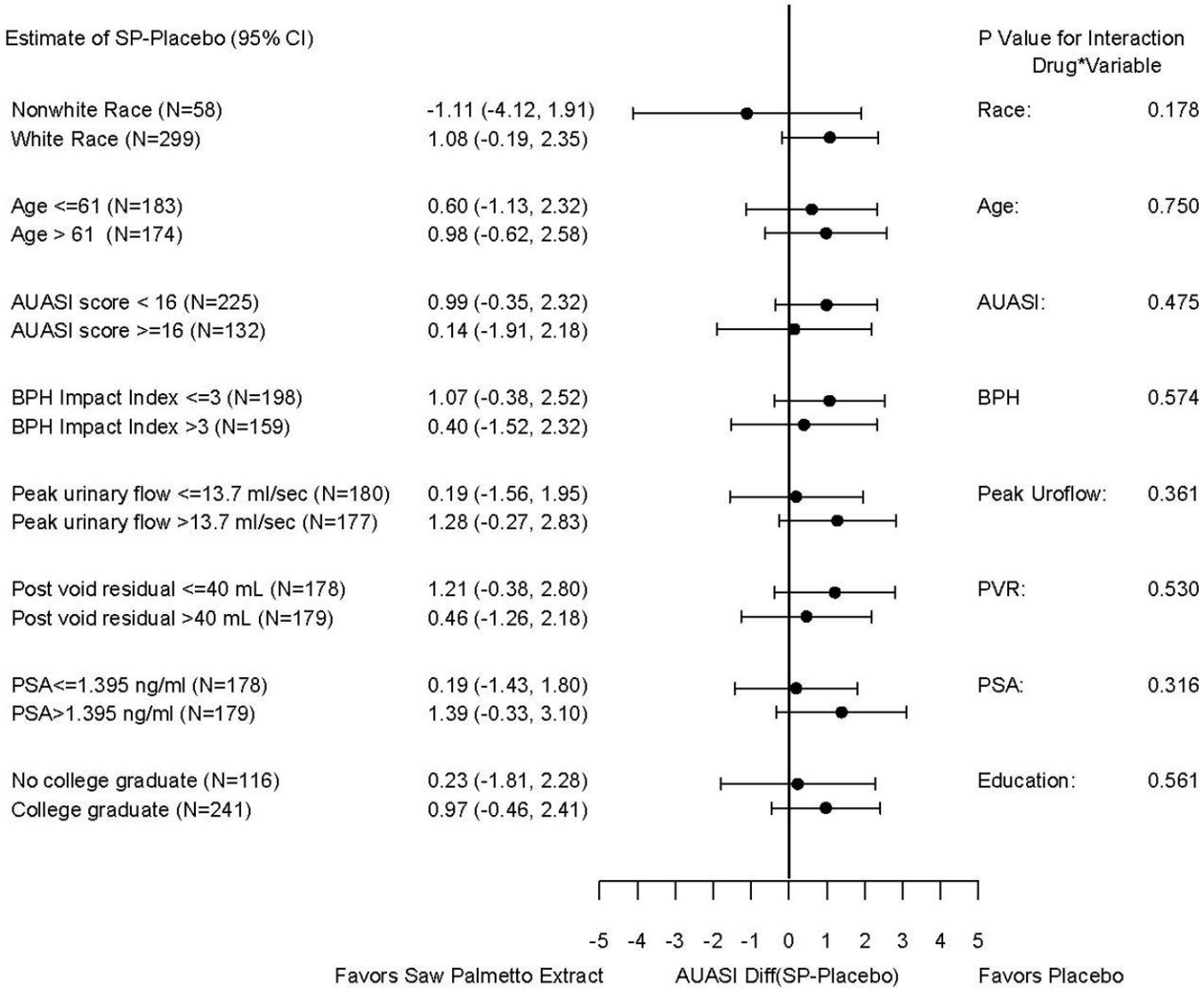

Figure 3.

Comparisons of the difference between group mean AUASI score changes from baseline to 72 weeks for the saw palmetto and placebo groups stratified by select baseline variables (continuous variables dichotomized at the median) in the modified intention to treat population. The subgroup analysis by race was prespecified in the study protocol; the rest are exploratory post hoc analyses. (P values based on a test for interaction in the primary analysis.)

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Table 1

Baseline characteristics of participants included in the modified intention to treat analysis. For all scales except as noted higher scores indicate greater dysfunction. (P values from two sample t tests.)

Variable (units/total score range)	**Total (N=357)**		**Saw palmetto (N=176)**		**Placebo (N=181)**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P value**
Age (years)	60.97	8.40	61.25	8.72	60.7	8.08	0.54
AUASI score (8–24)	14.55	4.52	14.42	4.29	14.69	4.75	0.58
BPH Impact Index score (0–13)	3.55	2.51	3.39	2.24	3.71	2.72	0.30
IPSS QOL score (0–6)	3.21	1.20	3.2	1.2	3.23	1.21	0.83
AUA nocturia item (0–5)	2.17	1.11	2.09	1.08	2.26	1.13	0.14
Peak uroflow (mL/sec)	14.90	6.92	15.03	7.15	14.78	6.71	0.74
Post-void residual (mL)**	41.0	13.0, 90.0	37.5	13.5, 88.0	43.0	12.0, 92.0	0.88
PSA level (ng/mL)	2.07	1.78	2.20	1.95	1.93	1.59	0.16
IIEF erectile function scale (1–30)*	19.38	9.87	18.79	10.36	19.93	9.43	0.29
MSHQ-EjD scale (1–20)*	10.87	4.16	10.56	4.27	11.18	4.03	0.16
ICSmale IS score (0–24)	3.81	2.75	3.44	2.3	4.17	3.08	0.01*
Jenkins Sleep Scale score (0–20)	7.36	4.62	6.95	4.28	7.72	4.93	0.11
NIH-CPSI							
Pain scale (0–21)**	0	0, 2	0	0, 2	0	0, 3	0.17
Urinary symptom scale (0–10)	4.15	2.20	4.02	2.31	4.27	2.08	0.28
QOL scale (0–12)	4.51	2.13	4.45	2.00	4.57	2.24	0.61
Race			N (%)		N (%)		
Non Hispanic white	284 (79.6%)		145 (82.4%)		139 (76.8%)		0.42
African American	41 (11.5%)		17 (9.7%)		24 (13.3%)		
Hispanic/Latino/Other	32 (9.0%)		14 (8.0%)		18 (9.9%)		
Education							
Less than high school	13 (3.6%)		6 (3.4%)		7 (3.9%)		0.64**
High school graduate	38 (10.6%)		20 (11.4%)		18 (9.9%)		

Variable (units/total score range)	Total (N=357)		Saw palmetto (N=176)		Placebo (N=181)		
	Mean	SD	Mean	SD	Mean	SD	P value
Some college	60 (16.8%)		26 (14.8%)		34 (18.8%)		
College graduate	99 (27.7%)		48 (27.3%)		51 (28.2%)		
Post college	142 (39.8%)		75 (42.6%)		67 (37.0%)		
No response	5 (1.4%)		1 (0.6%)		4 (2.2%)		

* Higher scores on these scales indicate *less* dysfunction

** Median and interquartile range shown, P-value based on Wilcoxon rank sum test

Table 2

Change in Primary and Secondary Outcome Measures from Baseline to Week 72

Outcome Measure	Saw Palmetto (N=176)			Placebo (N=181)			
	Baseline Mean	Week 72 Mean	Change - Mean (95% CI)	Baseline Mean	Week 72 Mean	Change - Mean (95% CI)	P-value (1-sided)
Primary							
AUASI score	14.42	12.22	−2.20 (−3.04, −0.36)	14.69	11.70	−2.99 (−3.81, −2.17)	0.91
Secondary							
BPH Impact Index	3.43	2.62	−0.81 (−1.16. −0.46)	3.70	2.47	−1.23 (−1.60, −0.87)	0.95
AUASI QOL	3.20	2.86	−0.34 (−0.52, −0.16)	3.23	2.74	−0.49 (−0.67, −0.31)	0.87
AUA Nocturia	2.09	1.84	−0.36 (−0.72, 0)	2.26	1.78	−0.15 (−0.44, 0.13)	0.19
Peak flow rate (mL/sec)	15.03	14.84	−0.18 (−1.07, 0.70)	14.78	13.99	−0.79 (−1.58, 0)	0.84
Post-void residual (mL)*	37.5	44.5	4.78 (−30.00, 52.00)	43.00	42.00	1.17 (−33.00, 34.00)	0.31*
PSA level (ng/ml)	2.20	2.41	0.32 (−0.08, 0.73)	1.93	2.07	−0.19 (−0.53, 0.14)	0.97
IIEF erectile scale	18.81	18.29	−0.52 (−1.63, 0.59)	19.92	18.86	−1.06 (−2.11, −0.02)	0.76
MSHQ-EjD scale	10.56	10.18	−0.38 (−1.04, 0.28)	11.18	11.09	−0.09 (0.63, 0.45)	0.25
ICSmaleIS score	3.44	2.96	−0.48 (−0.80, −0.16)	4.17	3.32	−0.84 (−1.17, −0.51)	0.94
Jenkins sleep scale	6.96	6.15	−0.80 (−1.34, −0.27)	7.75	6.12	−1.63 (−2.25, −1.01)	0.98
NIH-CPSI scales							
Pain*	0	0	0 (−0.08, 0)	0	0	0 (−1.00, 0)	0.20*
Urinary symptom	4.02	3.67	−0.35 (−0.67, −0.03)	4.27	3.41	−0.86 (−1.22, −0.49)	0.98
QOL	4.45	3.61	−0.85 (−1.16, −0.53)	4.57	3.49	−1.08 (−1.39, −0.77)	0.85

* Median and interquartile range shown, P-value based on Wilcoxon rank sum test.

Table 3

Number of adverse events by treatment group in the modified intention to treat population.

Type of Adverse Event	No. Adverse Events			No. Participants		
	Saw Palmetto	Placebo	P-value*	Saw Palmetto	Placebo	P-value**
All Adverse events	530	476	0.17	136	137	0.80
Arrythmia	8	10	0.72	8	10	0.81
Elevated blood pressure	14	6	0.21	13	6	0.10
Upper respiratory	54	60	0.72	39	34	0.43
Flu-like symptoms	19	15	0.77	16	12	0.43
Ophthalmic	11	11	0.95	8	9	1.00
Oral/dental	26	14	0.19	21	12	0.10
Musculoskeletal	81	72	0.46	53	46	0.35
Genitourinary	58	59	0.96	41	42	1.00
Elevated PSA	15	15	0.95	14	13	0.84
Gastrointestinal	52	58	0.71	38	39	1.00
Dermatologic	17	26	0.33	12	20	0.20
Physical injury/trauma	28	11	0.11	24	10	0101
Abnormal serum chemistry	11	10	0.80	11	7	0.34

* based on comparison of Poisson rates

** based on Fisher's exact test