

Five-year outcomes for Aquablation therapy compared to TURP: results from a double-blind, randomized trial in men with LUTS due to BPH

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Introduction: To determine if Aquablation therapy can maintain long term effectiveness in treating men with moderate to severe lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) with a baseline prostate volume between 30 and 80 mL at 5 years compared to TURP.

Materials and methods: In a double-blinded, multicenter prospective randomized controlled trial, 181 patients with moderate to severe LUTS secondary to BPH underwent TURP or Aquablation. The primary efficacy endpoint was reduction in International Prostate Symptom Score (IPSS) at 6 months. The primary safety endpoint was the occurrence of Clavien-Dindo persistent Grade 1 or Grade 2 or higher operative complications at 3 months. The assessments included IPSS, Male Sexual Health Questionnaire (MSHQ), International Index of Erectile Function (IIEF) and uroflow (Qmax). The patients were followed for 5 years.

Results: The primary safety endpoint was successfully

achieved at 3 months where the Aquablation group had a lower event rate than TURP (26% vs. 42%, $p = .0149$ for superiority). Procedure-related ejaculatory dysfunction was lower for Aquablation (7% vs. 25%, $p = .0004$). The primary efficacy endpoint was successfully achieved at 6 months, where the mean IPSS decreased from baseline by 16.9 points for Aquablation and 15.1 points for TURP; the mean difference in change score at 6 months was 1.8 points larger for Aquablation ($p < .0001$ for non-inferiority, $p = .1346$ for superiority).

At 5 years, IPSS scores improved by 15.1 points in the Aquablation group and 13.2 points in TURP ($p = .2764$). However, for men with larger prostates (≥ 50 mL), IPSS reduction was 3.5 points greater across all follow up visits in the Aquablation group compared to the TURP group ($p = .0123$). Improvement in peak urinary flow rate was 125% and 89% compared to baseline for Aquablation and TURP, respectively. The risk of patients needing a secondary BPH therapy, defined as needing BPH medication or surgical intervention, up to 5 years due to recurrent LUTS was 51% less in the Aquablation arm compared to the TURP arm.

Conclusions: The improvement in net health outcomes from Aquablation therapy outweigh those offered by a TURP when considering the efficacy benefit along with the lower risk of needing a secondary BPH therapy and avoiding retrograde ejaculation. Following Aquablation therapy, symptom reduction and uroflow improvement at 5 years have shown to be durable and consistent across all years of follow up compared to TURP. Larger prostates (≥ 50 mL) demonstrated a larger safety and efficacy benefit for Aquablation over TURP.

Key Words: Aquablation, LUTS, BPH

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Introduction

Moderate to severe lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) affects 30% of men aged over 50 years^{1,2} and the incidence is as high as 90% by age 85.³ Patients often fail medical treatment and seek surgical treatments.

Transurethral surgical approaches include tissue resective treatments, such as transurethral resection of the prostate with electrocautery (TURP), photovaporization, and laser enucleation, and non-tissue resective techniques such as microwave thermotherapy, water vapor therapy, Rezum, or a mechanical device, UroLift. Although non-tissue resective techniques are gaining adoption, it is generally accepted, that resection of tissue is more efficient and leads to better long term improvement as compared to non-resective techniques.⁴ While TURP remains the reference standard for treatment, it carries risks of bleeding, clot retention, bladder neck contracture or urethral stricture, urinary incontinence, erectile dysfunction, and retrograde ejaculation.⁵⁻⁹ Retrograde ejaculation is especially common after TURP (more than 60%).¹⁰ Non-TURP tissue resective techniques have similarly high efficacy rates (exceeding those of non-tissue resective techniques) but still suffer from certain risks, while those risks are less common with minimally invasive therapies at the cost of a reduced efficacy.

The AUA guidelines for BPH recommend a prostate volume estimate study prior to intervention. This recommendation is based in part on the concept that different surgical treatment options may be efficacious for men with different shaped and sized prostates. All the transurethral BPH procedures noted above, except laser enucleation, are noted in the guidelines for treatment of prostates ≤ 80 mL. Only a limited number of technologies are appropriate for men with large (80-150 mL) and very large prostates (> 150 mL).¹¹ Aquablation has demonstrated in numerous studies it can achieve consistent and reproducible outcomes across all sizes and anatomical shapes of prostates.¹²⁻¹⁴ The following manuscript will focus on long term outcomes following Aquablation.

Materials and methods

Trial design and participants

WATER (NCT02505919) is a prospective, double-blind, multicenter, international clinical trial comparing the safety and efficacy of the Aquablation and TURP in the surgical treatment of LUTS secondary to BPH in men 45 to 80 years of age with a prostate size between 30 and 80 mL (measured with transrectal ultrasound),

moderate-to severe symptoms as indicated by an International Prostate Symptom Score (IPSS¹⁵) ≥ 12 , and a maximum urinary flow rate (Qmax) of < 15 mL/s. The WATER trial is the first FDA study to randomize a new therapy against the gold standard TURP procedure for men with LUTS due to BPH. Men were excluded if they had a history of prostate or bladder cancer, neurogenic bladder, bladder calculus or clinically significant bladder diverticulum, active infection, treatment for chronic prostatitis, diagnosis of urethral stricture, meatal stenosis or bladder neck contracture, damaged external urinary sphincter, stress urinary incontinence, post void residual > 300 mL or urinary retention, use of self-catheterization, or prior prostate surgery. Men taking anticoagulants or on bladder anticholinergics or with severe cardiovascular disease were also excluded. TURP was chosen as the control group as it represents the gold standard for the surgical treatment of moderate to severe BPH. Each center obtained institutional review board/ethics committee approval prior to study start. All participants provided informed consent using study-specific forms before any test beyond standard care.

Randomization and intervention

Subjects were randomized in a 2:1 ratio to either Aquablation or TURP. Randomization was obtained through a web-based system and stratified by study site and baseline IPSS score category with random block sizes to assure a prerequisite number of patients with both moderate and severe symptoms for preplanned subset analyses.

TURP was performed according to standard practice using monopolar or bipolar technology. Post-TURP, a urinary catheter was inserted, and subjects received continuous bladder irrigation. Choice of catheter and duration of bladder irrigation was done in accordance with local preferences at each site.

Aquablation was performed using the AQUABEAM Robotic System (PROCEPT BioRobotics, Redwood City, California, USA).¹⁶ A 24F handpiece probe similar to a rigid cystoscope is inserted into the prostatic urethra and locked into place using a bed-mounted rigid arm. Under real-time prostate visualization using transrectal ultrasound, the surgeon uses a console to mark the target resection contour. Under the surgeon's control, the ablation of tissue is robotically executed using a high-velocity waterjet to resect adenomatous tissue while avoiding the verumontanum and the ejaculatory ducts. After Aquablation is complete, hemostasis is achieved using either focal, non-resective electrocautery or low-pressure inflation of a Foley balloon catheter in the prostatic fossa.¹⁷ Use

of catheter and bladder irrigation was left to the local investigator's discretion. Otherwise, post-treatment management, which included continuous bladder irrigation in all subjects, was similar across groups.

Blinding and follow up

Patients and follow up assessors were blinded to the treatment assignment up to 3 years. Once the patient was discharged, a separate blinded team (coordinator and physician) conducted the follow up visits. All patients were unblinded after the 3-year visit. The 4 and 5-year follow up windows occurred during the pandemic caused by COVID-19.

Data and study monitoring

Independent study monitors verified all study data in electronic case report forms prior to analysis. All adverse events were adjudicated by an independent clinical events committee blinded to treatment assignment. A data monitoring committee reviewed safety data periodically.

Study endpoints and statistical analysis

The study sample size was set to establish 80% power to demonstrate superiority for the primary safety endpoint. Both primary endpoints were analyzed using a typical methodology to first test for non-inferiority then subsequently test for superiority.

The study's primary safety endpoint was the proportion of subjects with adverse events rated by the clinical events committee as possibly, probably, or definitely related to the study procedure classified as Clavien-Dindo¹⁸ Grade 2 or higher or any Grade 1 event resulting in persistent disability (ejaculatory or erectile dysfunction or incontinence) evidenced through 3 months post-treatment. Sample size calculation for the safety endpoint assumed rates of 65% in TURP and 40% in Aquablation, with a 12% estimated loss to follow up rate and a standard comparison of proportions test. A sample size of 177 subjects yielded a power of 80% for possible demonstration of superiority for the safety endpoint under the assumptions described previously. The primary safety endpoint with this sample size displays over 99% power at a one-sided alpha level of 0.025 to demonstrate non-inferiority within a margin of 10% under an assumption of a true rate of events in the Aquablation group of 40% and an expected rate of 65% in the TURP. Non-inferiority testing was performed using the approach of Miettinen and Nurminen;¹⁹ once non-inferiority was determined, subsequent superiority testing, including within subgroups, was performed using a one-sided Fisher's test. Pre-planned subgroup analysis included baseline IPSS (< 20 vs. ≥ 20),

prostate size (< 50 vs. ≥ 50 mL) and age (< 65 vs. ≥ 65 years).

The study's primary efficacy endpoint was the change in IPSS from baseline to 6 months. The difference in IPSS change was evaluated using a t-test; additional models controlled for baseline IPSS. Non-inferiority was declared if the lower 95% two-sided confidence limit of the difference in score change at 6 months exceeded -4.7 points. A sample size of 177 randomized subjects had > 80% power to detect non-inferior change scores with a margin of 4.7 points assuming a 16-point improvement in IPSS, an effect size of 1.5 points worse in the Aquablation group, a standard deviation of 6 points, and estimated 12% lost to follow up.

Secondary endpoints included: resection time and total operative time, length of hospital stay, reoperation or re-intervention rate (defined as any invasive procedure [e.g., cystoscopy] on the lower urinary tract to treat problems potentially related to BPH; the definition excluded required study evaluations and bladder catheterization only without surgical intervention), the proportion of sexually active subjects reporting a worsening of sexual function through 6 months on either International Index of Erectile Function (IIEF-5, 6-point drop²⁰) or the Male Sexual Health Questionnaire (MSHQ-EJD-SF, 2-point drop²¹) questionnaires, and the proportion of subjects with a serious device- or procedure-related adverse event. Since both IIEF and MSHQ assume that a man is sexually active, men who were not sexually active at baseline or the study visit were excluded from this analysis. Additional endpoints included change in uroflowmetry, incontinence measured with Incontinence Severity Index,²² pelvic pain, quality of life using EuroQoL-5D,²³ duration of bladder catheterization, WPAI,²⁴ relationship between prostate size reduction (measured with transrectal ultrasound) and change in symptoms scores (to be reported elsewhere). Patients were followed for 5 years.

Results

A total of 275 subjects were evaluated at 17 sites in the United States, United Kingdom, Australia, and New Zealand, between October 2015 and December 2016. Excluding 72 screen failures and 19 roll-in subjects, 184 were randomized. Three subjects (2 TURP, 1 Aquablation) voluntarily withdrew before treatment, leaving 181 in the intent-to-treat population, Figure 1. Baseline characteristics were well balanced across groups and were consistent with moderate-to-severe BPH, Table 1. Approximately one-third of patients were

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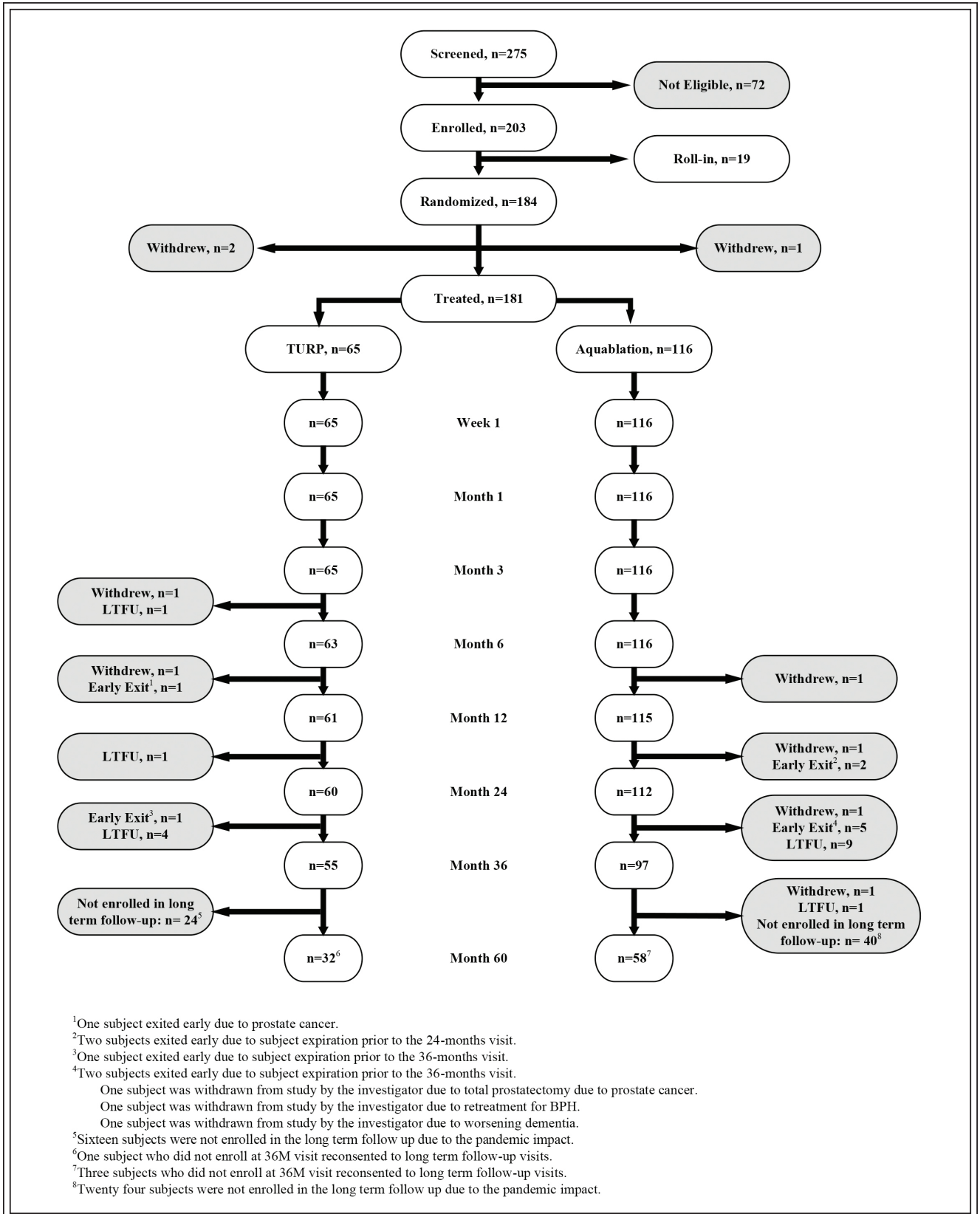


Figure 1. CONSORT diagram for patient randomization and follow up.

TABLE 1. Baseline characteristics

Characteristic	Aquablation n = 116	TURP n = 65
Age, years, mean (SD)	66.0 (7.3)	65.8 (7.2)
Body mass index, mean (SD)	28.4 (4.1)	28.2 (4.5)
Prostate size (TRUS), mL; mean (SD)	54.1 (16.2)	51.8 (13.8)
Obstructive median lobe, %	50%	52%
Prostate-specific antigen, g/dL; mean (SD)	3.7 (3.0)	3.3 (2.3)
Baseline questionnaires		
IPSS score, mean (SD)	22.9 (6.0)	22.2 (6.1)
IPSS QoL, mean (SD)	4.8 (1.1)	4.8 (1.0)
Sexually active, n (%) [MSHQ-EjD]	93 (80.2%)	54 (83.1%)
MSHQ-EjD, mean (SD)*	8.1 (3.7)	8.8 (3.6)
IIEF-5, mean (SD)*	17.2 (6.5)	18.2 (7.0)
Antithrombotic use		
Anticoagulant, n (%)	2 (1.7%)	2 (3.1%)
Antiplatelet/NSAID, n (%)	15 (12.9%)	6 (9.2%)
Aspirin (\leq 100 mg), n (%)	24 (20.7%)	11 (16.9%)
Any of above, n (%)	41 (35.3%)	19 (29.2%)
BPH medication use		
Alpha blocker, n (%)	48 (41.4%)	23 (35.4%)
5-ARI, n (%)	2 (1.7%)	2 (3.1%)
Alpha blocker/5-ARI, n (%)	23 (19.8%)	14 (21.5%)
Any of above, n (%)	73 (62.9%)	39 (60.0%)

*sexually active men
 IPSS = International Prostate Symptom Score; QoL = quality of life; MSHQ-EjD = Male Sexual Health Questionnaire - ejaculatory dysfunction; IIEF-5 = International Index of Erectile Function

on antithrombotic medication at baseline. Any patient on anticoagulant or antiplatelet was required to stop before surgery. Approximately two-thirds of patients were on an alpha blocker or 5-ARI at baseline. Mean prostate size was 53 mL, and 81% were sexually active.

The procedure times, defined as first instrument introduction to insertion of catheter, were similar at 40 minutes for Aquablation and 36 minutes for TURP. Mean resection time was lower in the Aquablation group (4 vs. 27 minutes, $p < .0001$). One Aquablation subject and zero TURP subjects required a blood transfusion. There were no late bleeding events requiring transfusion for either arm. Mean hospital length of stay was 1.4 days in both groups and the urinary catheter was removed a median of 1 day after surgery in both groups. At 3 months, dysuria frequency was similar, but less severity favored Aquablation ($p = .1277$). Pelvic pain levels were low and similar throughout follow up, and time off from work was brief in most cases. The change in

incontinence severity index (ISI) at 3 and 6 months for Aquablation was improved compared to baseline ($p = .0008$ and $p < .0001$, respectively). Aquablation showed a better improvement in ISI than TURP at month 3, $p = .0386$.

The primary safety endpoint was successfully achieved at 3 months where the Aquablation group had a lower event rate compared to TURP (26% vs. 42%, $p = .0149$ for superiority). Urinary complications from 3 to 5 years did not differ between groups. The tabular details of these events were previously published.^{25,26} The rate of persistent grade 1 events at month 3 was lower (7% vs. 25%, $p = .0004$) after Aquablation, and the rate of Grade 2 and above events was similar across groups (20% for Aquablation vs. 23% for TURP, $p = .3038$). There were zero de novo erectile dysfunction events or incontinence events requiring a pad in either arm. However, procedure-related anejaculation was less common after Aquablation, 7%, versus TURP, 25%, $p = .0004$.

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The MSHQ-EjD-SF (MSHQ-EjD) instrument is comprised of three questions with a max score of 15. At all postoperative time points out to 5 years, changes in ejaculatory function, MSHQ-EjD, were close to 0 for the Aquablation group. Changes in MSHQ-EjD score at all follow up visits through 5 years averaged 2.7 points lower, worse, for the TURP group compared to the Aquablation group (repeated measures analysis of variance, $p = .0015$). The IIEF-5 instrument is comprised of five questions with a max score of 25. Erectile function, as measured by IIEF-5, showed no statistically significant changes in either group or across groups through 5 years.

The primary efficacy endpoint was successfully achieved at 6 months where the mean IPSS decreased from baseline by 16.9 points for Aquablation and 15.1

points for TURP; the mean difference in change score at 6 months was 1.8 points larger for Aquablation ($p < .0001$ for non-inferiority, $p = .1346$ for superiority).

The baseline IPSS average for the study was 22.6 and did not differ between treatment groups. Mean (SD) IPSS reduction at 5 years was 15.1 (6.6) in the Aquablation group and 13.2 (8.2) in the TURP group ($p = .2764$ for difference), Figure 2. At 5 years, the median IPSS score was 5.5 for Aquablation and 6 for TURP. For men with larger prostates (≥ 50 mL), IPSS reduction was 3.5 points greater in the Aquablation group compared to the TURP group ($p = .0123$, repeated measures analysis of variance). There was no difference in IPSS changes when analyzing the other pre-specified subgroups of age (< 65 vs. ≥ 65) and LUTS severity as measured by IPSS (< 20 vs. ≥ 20). The IPSS

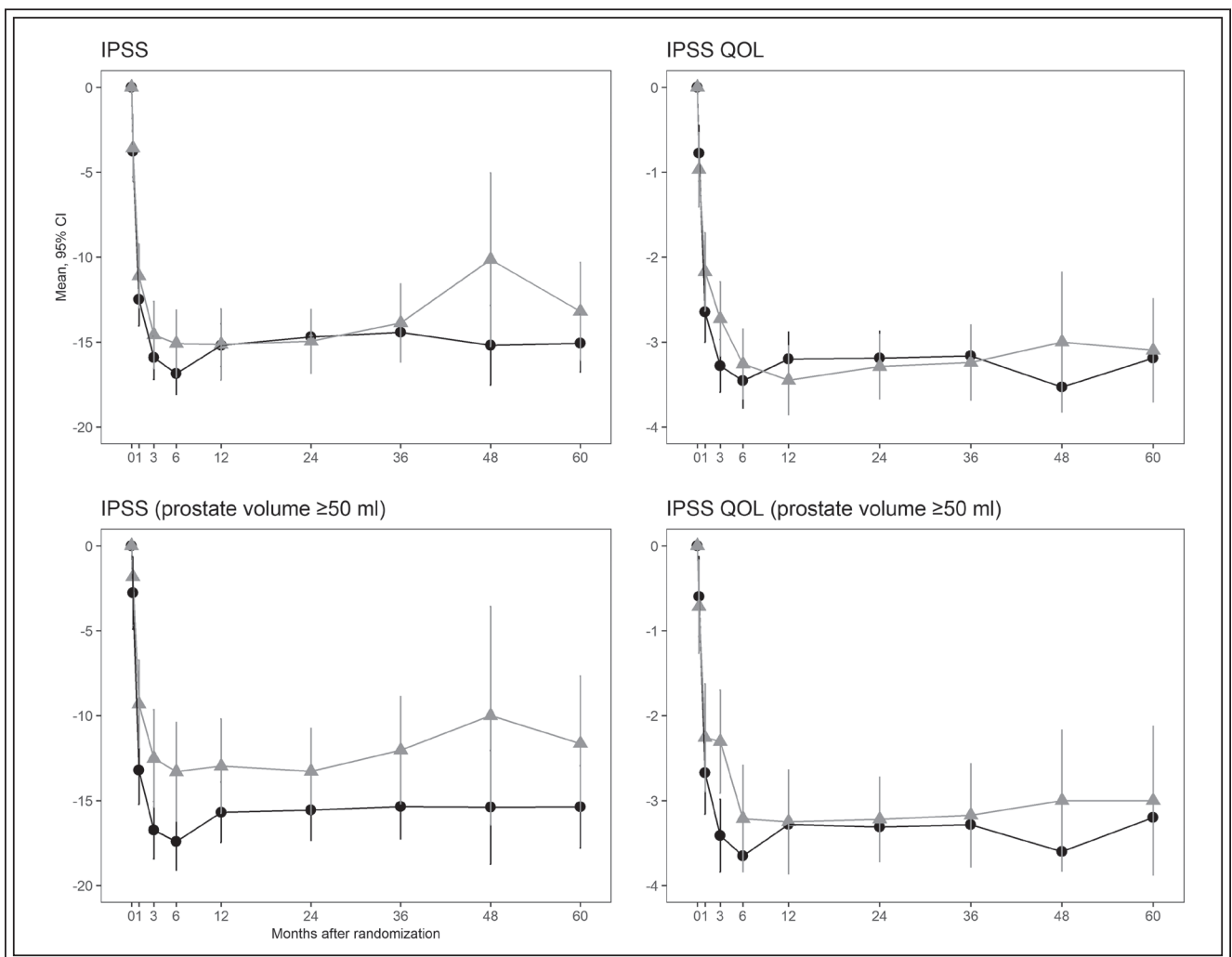


Figure 2. Change in International Prostate Symptom Score (IPSS, top left), IPSS quality of life (top right) for the total study population; Change in IPSS for the subgroup where baseline prostate volumes were 50-80 mL. Aquablation – black line with circle data points; TURP – grey line with triangle data points.

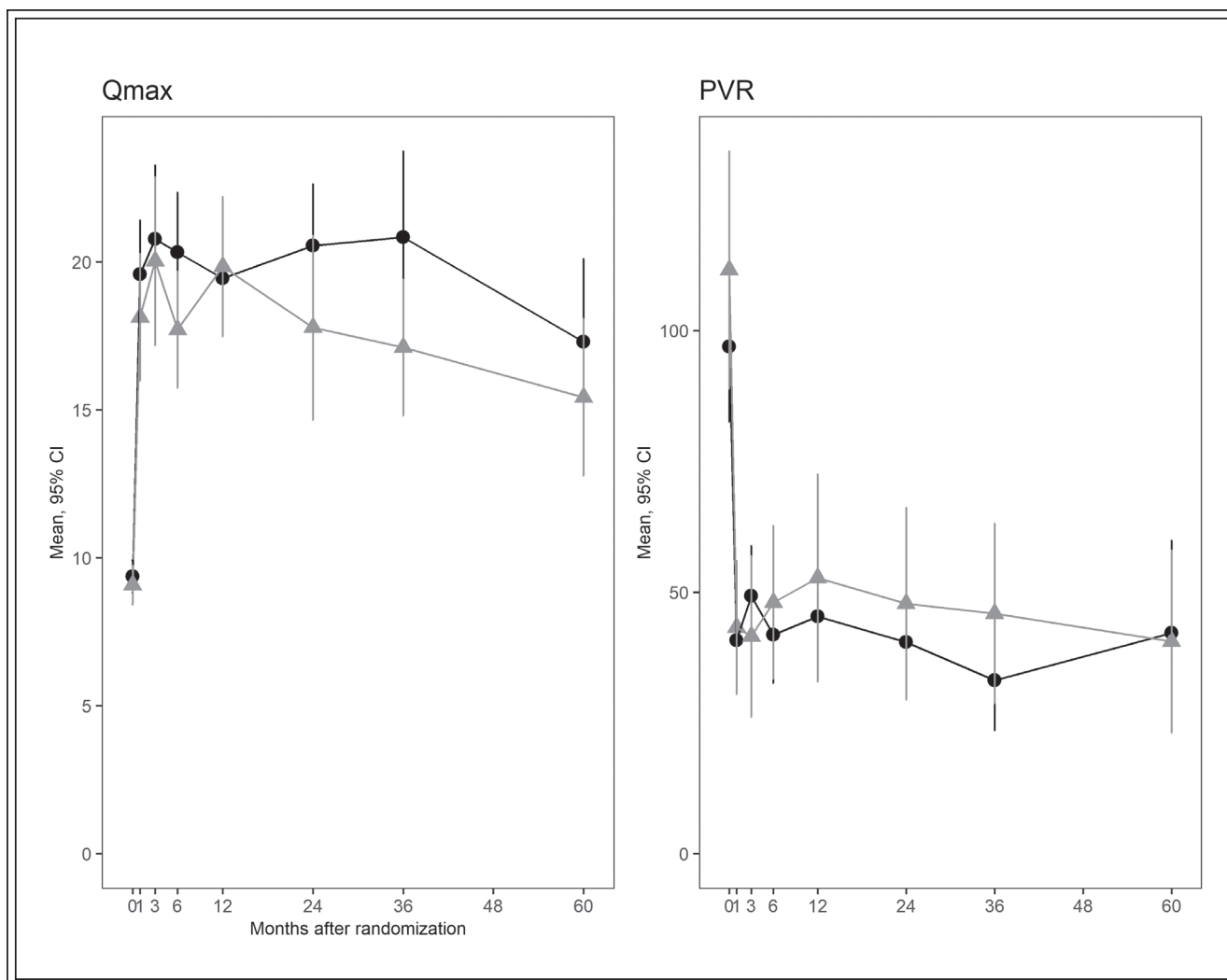


Figure 3. Uroflowmetry for Qmax and PVR. Aquablation – black line with circle data points; TURP – grey line with triangle data points.

quality of life score can range from 0 to 6. The baseline IPSS quality of life average for the study was 4.8 and did not differ between treatment groups. At 5 years, the IPSS QoL score was 1.6 for both arms and showed no statistical difference in change scores, $p = .8009$.

In both groups, 5-year peak urinary flow rates (Qmax) increased markedly within 1 month after surgery and were maintained at 5 years. Mean 5-year improvements in Qmax were 8.7 (9.1) mL/s, or 125% improvement, for the Aquablation group versus 6.3 (7.5) mL/s, or 89% improvement, for TURP, Figure 3. The mean 5-year reduction in post-void residual was 62 (86) and 82 (94) mL ($p = .3960$).

At 5-year follow up for Aquablation, 6.0% of patients needed an additional BPH therapy (started BPH medication anew and continued to study exit or

TABLE 2. Additional BPH therapy details per treatment group

	Aquablation n = 116	TURP n = 65
Year 1	1 BPH medication 2 TURP, 1 Laser	3 BPH medications 1 TURP
Year 2	2 TURP	2 BPH medications
Year 3		
Year 4		1 BPH medication
Year 5	1 TURP	1 BPH medication
Total	7 (6.0%)	8 (12.3%)

intervention) due to recurrent LUTS, which was 51% less than the TURP arm. In the TURP arm, 12.3% of patients needed additional BPH therapy, Table 2. The average IPSS score before the additional BPH therapy was similar in both arms, 14 for Aquablation and 15 for TURP, and did not differ whether the patient chose to undergo another intervention or start medication.

Prostate specific antigen (PSA) was reduced at 5 years compared to baseline (by 1.0 [p = .0658] and 0.5 [p = .2969] ng/dL in the Aquablation and TURP groups, respectively); the difference in PSA reduction was not statistically significant between groups (p = .4650).

Discussion

In this trial, prostate resection using robotically executed, ultrasound guided, surgeon-controlled waterjet improved BPH-related urinary symptoms compared to the reference standard surgical treatment (TURP) and maintained the improvement over 5 years. These improvements were seen across study sites that, in most cases (14/17 sites), had no previous experience with Aquablation. Retrograde ejaculation after TURP is a common and accepted side effect caused by heat-related damage to the ejaculatory ducts.¹⁰ We observed a reduced rate of anejaculation after Aquablation compared to TURP.

Improvements in objective urinary flow measures (maximum flow rate, post-void residual) were in line with expectations for prostate-resecting procedures and sustained for 5 years. Other assessments of the acute impact of surgery (hospital length of stay, work indices, quality of life measurements) showed Aquablation to be well-tolerated.

The avoidance of a secondary BPH intervention over 5 years for both arms in the study had comparable results with open simple prostatectomy, TURP, and laser enucleation with the data reported by Gilfrich et al on 43,041 men undergoing.²⁷ Comparing the 5-year risk of needing a secondary BPH therapy (medication or intervention) across the most recent contemporary BPH FDA clinical trials, the Aquablation and TURP results from this study of 6.0% and 12.3%, respectively, compared favorably to Rezum at 15.5%²⁸ and UroLift (study excluded obstructive median lobe anatomy) at 33.6%²⁹.

Advantages of our study include its randomized, multicenter, and blinded design, with confirmed preservation of blinding, all of which likely minimized bias related to patient-reported outcomes. There was no evidence of variation in degree of effect across study sites or geographies. Additionally, as reflected by both symptom score and uroflow improvements, efficacy

in the TURP control group was large and consistent with expectations extending out to 5 years, adding overall validity to the trial's outcomes. Limitations of the study must acknowledge the impact from the global pandemic caused by COVID-19 on the overall follow up percentages at year 4 and 5, and it did not measure cost effectiveness directly. While the study ended up with a reasonable cohort at 5 years compared to other contemporary BPH studies,²⁸ the study was on track to have much higher follow up based upon the success at 3 years.

Conclusions

The improvement in net health outcomes from Aquablation therapy outweigh those offered by a TURP when considering the efficacy benefit along with the lower risk of needing a secondary BPH therapy and avoiding retrograde ejaculation. Following Aquablation therapy, symptom reduction and uroflow improvement at 5 years have shown to be durable and consistent across all years of follow up compared to TURP. Larger prostates (≥ 50 mL) demonstrated a larger safety and efficacy benefit for Aquablation over TURP.

Disclosures

The clinical study was funded by PROCEPT Biorobotics. Drs. Neil Barber, Mohammed Bidair, Eugene Kramolowsky, Mihir Desai, Alexis E. Te, and Claus G. Roehrborn have had in the past or currently have a consulting agreement with PROCEPT Biorobotics. All authors on the manuscript were involved with recruiting, treating patients, data collection, and manuscript development and review. □

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