Author/s:
Plante, M;Gilling, P;Barber, N;Bidair, M;Anderson, P;Sutton, M;Aho, T;Kramolowsky, E;Thomas, A;Cowan, B;Kaufman, RP;Trainer, A;Arther, A;Badlani, G;Desai, M;Doumanian, L;Te, AE;DeGuenther, M;Roehrborn, C

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Date:
2019-04-01

Citation:
Plante, M., Gilling, P., Barber, N., Bidair, M., Anderson, P., Sutton, M., Aho, T., Kramolowsky, E., Thomas, A., Cowan, B., Kaufman, R. P., Trainer, A., Arther, A., Badlani, G., Desai, M., Doumanian, L., Te, A. E., DeGuenther, M. & Roehrborn, C. (2019). Symptom relief and anejaculation after aquablation or transurethral resection of the prostate: subgroup analysis from a blinded randomized trial. BJU International, 123 (4), pp.651-660. https://doi.org/10.1111/bju.14426.

Symptom Relief and Anejaculation after Aquablation or TURP: Subgroup Analysis from a Blinded Randomized Trial

Mark Plante (corresponding author), Peter Gilling, Neil Barber, Mohamed Bidair, Paul Anderson, Mark Sutton, Tev Aho, Eugene Kramolowsky, Andrew Thomas, Barrett Cowan, Ronald P. Kaufman, Jr., Andrew Trainer, Andrew Arther, Gopal Badlani, Mihir Desai, Leo Doumanian, Alexis E. Te, Mark DeGuenther, Claus Roehrborn

Corresponding Author
Mark Plante
Office of Clinical Trials Research
1 South Prospect Street
Arnold 3434
Burlington, VT 05401
802-598-9641
Mark.plante@med.uvm.edu

Word count = 2,079

Author	Affiliation
Mark Plante	University of Vermont Medical Center, Burlington, VT, US
Peter Gilling	Tauranga Urology Research, Tauranga, New Zealand
Neil Barber	Frimley Park Hospital, Frimley Health Foundation Trust, Surrey, UK
Mo Bidair	San Diego Clinical Trials, San Diego, CA, US
Neil Barber	Frimley Park Hospital, Frimley Health Foundation Trust, Surrey, UK
Paul Anderson	Royal Melbourne Hospital, Melbourne, Australia
Mark Sutton	Houston Metro Urology, Houston, TX, US
Tev Aho	Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, UK
Eugene Kramolowsky	Virginia Urology, Richmond, VA, US
Andy Thomas	Princess of Wales Hospital, Bridgend, Wales, UK
Barrett Cowan	Urology Associates, P.C., Englewood, CO, US

Ronald P. Kaufman, Jr.	Albany Medical College, Albany, NY, US
Andrew Trainer	Adult Pediatric Urology & Urogynecology, P.C., Omaha, NE, US
Andrew Arther	Adult Pediatric Urology & Urogynecology, P.C., Omaha, NE, US
Gopal Badlani	Wake Forest School of Medicine, Winston-Salem, NC, US
Mihir Desai	University of Southern California, Institute of Urology, Los Angeles, CA, US
Leo Doumanian	University of Southern California, Institute of Urology, Los Angeles, CA, US
Alexis E. Te	Weill Cornell Medical College, New York, NY, US
Mark DeGuenther	Urology Centers of Alabama, Birmingham, AL
Claus Roehrborn	UT Southwestern Medical Center, Department of Urology, University of Texas Southwestern, Dallas, TX, US

DR. MARK K PLANTE (Orcid ID : 0000-0002-8874-9483)
PROF. PETER J GILLING (Orcid ID : 0000-0002-3118-1655)
MR. J. ANDREW THOMAS (Orcid ID : 0000-0003-2096-9612)

Article type : Original Article

ARTICLE CATEGORY: ROBOTICS AND LAPAROSCOPY

ABSTRACT

Background

Aquablation, a waterjet-based prostate resection, has been used for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. The hypothesis that BPH surgery standardized with robotic execution may have a more pronounced benefit in certain subgroups such as subjects with more challenging anatomies (e.g., large prostates, large middle lobes) and subjects with moderate BPH has not yet been determined.

Methods

We conducted prespecified and post-hoc exploratory subgroup analyses from a double-blind, multicenter prospective randomized controlled trial comparing transurethral resection of the prostate using either standard electrocautery (TURP) or robotic waterjet (Aquablation) to determine whether certain baseline factors predicted more marked responses after Aquablation as compared to TURP. 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.

Results

For men with larger prostates 50-80g, mean IPSS reduction was 4 points larger after Aquablation compared to TURP (p=.0099), a larger difference than the overall result (1.8 points, p=.1347). Similarly, the primary safety endpoint difference (20% vs. 46% [26% difference, p=.0082]) was larger for men with large prostate compared to the overall result (26% vs. 42% [16% difference, p=.0149]).

Postoperative anejaculation was also less common after Aquablation compared to TURP in sexually active men with large prostates (2% vs. 41%, p=.0001) vs. the overall results (10% vs. 36%, p=.0003)

Exploratory analysis showed larger IPSS changes after Aquablation in men with enlarged middle lobes, men with severe middle lobe obstruction, men with a low baseline Qmax, and men with elevated (>100) post-void residual.

Conclusions

In patients with moderate-to-severe LUTS due to BPH and larger, more complex prostates, Aquablation was associated with both superior symptom score improvements and a superior safety profile, with a significantly lower rate of postoperative anejaculation. The standardized, robotically executed, surgical approach with Aquablation may overcome the increased outcome variability in more complex anatomy that result in superior symptom score reduction. (ClinicalTrials.gov number, NCT02505919)

INTRODUCTION

Surgical approaches to the management of moderate-to-severe LUTS due to BPH include non-resective and resective techniques. While resective techniques generally have higher rates of symptom relief, they also carry a higher risk of adverse events. Moreover, it is generally accepted that increased operative times associated with larger prostate volumes increases the risk of adverse events (1). Less well understood is the relationship between patient or procedure factors (e.g., prostate size, amount of tissue removed) and symptom reduction efficacy and adverse effects.

Aquablation is a novel treatment for LUTS in which prostate tissue is resected under surgeon supervision using a robotically controlled waterjet executing a preplanned resection contour. Early studies of Aquablation showed efficacy levels similar to those observed in TURP (2,3). Initial results from WATER, a randomized trial of Aquablation vs. TURP, showed similar overall improvements in IPSS scores and a superior safety profile with a lower risk of postoperative anejaculation (4). Aquablation was designed to standardize BPH surgery through robotic execution following image-guided resection contours, potentially resulting in superior results compared to freehand resection, especially in patients

with challenging anatomies (large prostates, large middle lobes). We tested this hypothesis through preplanned and exploratory subgroup analyses from the WATER study. Preplanned subgroups of interest specifically focused on men with moderate disease (baseline IPSS < 20), men in the Medicare population (65 years and older), and men with large prostates. Exploratory analyses examined other aspects of challenging anatomy or pathophysiology (enlarged middle lobe, degree of median lobe obstruction and impaired bladder function related to chronic obstruction).

METHODS

TRIAL DESIGN AND PARTICIPANTS

WATER (NCT02505919) is a prospective, double-blind (both subjects and postoperative assessors blinded to treatment assignment) multicenter, international randomized clinical trial comparing the safety and efficacy of Aquablation and TURP in the surgical treatment of LUTS due to BPH (4). The trial enrolled adult men if they had an International Prostate Symptom Score (IPSS (5)) ≥ 12, prostate size between 30-80 g, and a maximum urinary flow rate (Qmax) < 15 mL/s. Ethics committee or institutional review board approval was obtained at all sites prior to study start. Middle lobe obstruction was determined (presence and severity) by preoperative cystoscopy by the surgeon prior to randomization assignment. Uroflow measurements were performed per standard clinical practices.

RANDOMIZATION AND INTERVENTION

Eligible subjects were randomized in a 2:1 fashion to either Aquablation or TURP; randomization was obtained through a web interface and was stratified by study site and baseline IPSS score category (≥20 or <20) using random block sizes.

TURP was performed according to the standard practice with monopolar or bipolar electrocautery loops and isosmolar irrigation fluid. Aquablation was performed using the AQUABEAM® System (PROCEPT BioRobotics, Redwood Shores, California, USA) as previously described (2). After Aquablation was complete, hemostasis was achieved using either focal, non-resective electrocautery (first 40% of enrollment) or low-pressure tamponade with a Foley balloon catheter in the prostatic fossa (last 60% of enrollment) (6). Postoperatively, all subjects received continuous bladder irrigation.

BLINDING AND FOLLOW-UP

The subject and postoperative care were blinded to the treatment. Trial subjects will remain blinded until study end (3 years). Visits were scheduled at 1 week and at 1, 3, and 6 months, 12, 24 and 36 months. Herein we report 6-month (primary efficacy endpoint timing) follow-up.

DATA AND STUDY MONITORING

All study data were monitored and source-verified by independent study monitors. All adverse events, including those related to sexual dysfunction, were adjudicated by an independent clinical events committee blinded to treatment assignment.

STUDY ENDPOINTS AND STATISTICAL ANALYSIS

The study's primary efficacy endpoint (6-month change in IPSS from baseline), and primary safety endpoint (the proportion of subjects with adverse events classified as Clavien-Dindo (7) (C-D) Grade 2 or higher or any Grade 1 event resulting in persistent disability (ejaculatory or erectile dysfunction or incontinence) by month 3 rated as possibly, probably, or definitely related to the study procedure) were previously reported (4). The protocol specified three preplanned subgroup analyses: baseline IPSS (<20 vs. ≥20), prostate size (<50 vs. ≥50 g) and age (<65 vs. ≥65 years). Exploratory analysis focusing on challenging prostate anatomy included the following: baseline Qmax (above or below median), presence of middle lobe and degree of middle lobe obstruction and bladder neck obstruction (all observed on preoperative cystoscopy), and baseline post-void residual. For any subgroup showing marked differences in IPSS change scores, further exploration included analysis of IPSS voiding and storage subscores change differences. Differences in 6-month change scores across groups were evaluated using two-sided t tests; p-values <.05 were considered statistically significant. Differences in primary safety endpoint rates were evaluated using a Fisher's test. For anejaculation rates, only subjects who were sexually active at baseline were included.

RESULTS

275 subjects were enrolled at 17 sites in the U.S., United Kingdom, Australia, and New Zealand, between October 2015 and December 2016. Of these, 72 patients failed screening and a further 19 underwent Aquablation as part of a roll-in training phase. The remaining 184 patients were randomized to either Aquablation or TURP. Accounting for three subjects who withdrew prior to treatment, 116 were treated with Aquablation and 65 TURP. Baseline characteristics were balanced across treatment assignment (not shown, see previously reported data (4)) as well as by prostate size (**Error! Reference source not found.**) with the exception of the presence of middle lobe obstruction, which was unsurprisingly more prevalent in larger prostates compared to smaller prostates. Baseline IPSS scores were similar across treatment groups (22.9 [Aquablation] vs. 22.2 [TURP], p=.4276) and prostate size, consistent with moderate-to-severe LUTS due to BPH. 178 (98.3%) and 175 (96.7%) subjects completed 3- and 6-month follow-up, respectively. Blinding questionnaires at each study visit confirmed no evidence of unblinding.

Symptom scores. Overall, IPSS change scores at 1, 3 and 6 months were numerically but not statistically significantly higher after Aquablation compared to TURP (**Error! Reference source not found.**). For men with larger prostates (>50g), IPSS change scores were 4 points larger (p=.0197, **Error! Reference source not found.**) after Aquablation compared to TURP. Men with larger prostates also showed superior improvements after Aquablation for both IPSS voiding and storage subscores. IPSS improvements were larger in both treatment groups for men with higher (≥20) vs. lower (<20) baseline IPSS scores; in the group with baseline IPSS scores <20, slightly larger responses (p=.0491) were seen after Aquablation compared to TURP. No statistically significant treatment response differences were seen related to subject age.

Exploratory analyses (**Error! Reference source not found.**) showed larger 6-month IPSS score improvements in men with a middle lobe (p=.0050), men with severe middle lobe obstruction (p=.0767), men with baseline Qmax <9 cc/sec (p=.0289), men without bladder obstruction at baseline (p=.0321) and men with an elevated post-void residual (p=.0058). Both voiding and/or storage score improvements after Aquablation were numerically larger than after TURP within these subgroups.

Uroflow. Maximum urinary flow rates (Qmax) in the pre-planned subgroups showed no statistically significant differences in Qmax improvements across treatments. In patients with a middle lobe present, Qmax improvement after Aquablation was 4.4 points larger than for TURP (p=.0482).

Post void residual (PVR). In men with elevated PVR at baseline, no pre-planned or exploratory analysis showed statistically significant differences in PVR improvement across treatments within subgroups.

Prostate-specific antigen (PSA). The 6-month changes in PSA were similar across groups (p=.6975) with no statistically significant differences across treatment arms within individual subgroup levels.

Safety. For pre-planned subgroups, the largest difference in the primary safety endpoint rate was in men with prostate size >50 mL (20% Aquablation vs. 46% TURP, p=.0011, **Error! Reference source not found.**, **Error! Reference source not found.**). The proportion of subjects experiencing of CD grade 2 or above events was numerically but not statistically lower in men overall, with minor differences across pre-planned subgroups. In exploratory analyses, the primary safety endpoint was numerically lower in all subgroups, with statistical significance seen for men with middle lobes and men with low baseline Qmax. Amongst sexually active men, anejaculation rates were lower with Aquablation in all subgroups, especially in men with large prostates (2% vs. 41%, p=.0001).

DISCUSSION

Previously we reported that robotically executed, ultrasound-guided, waterjet-based prostate resection (Aquablation) resulted in similar improvements in symptom scores compared to the reference surgical treatment, TURP, with a reduced rate of postoperative anejaculation (4). In this report, we further explore the relative value of Aquablation in preplanned and exploratory subgroup analysis.

Preplanned subgroup analysis showed superior IPSS changes (by about 4 points) for men with larger prostates; superior improvements were seen in both voiding and storage scores. Exploratory analysis showed larger IPSS change scores in men with markers for complex anatomy or flow measurements indicating chronic obstruction, namely large middle lobes, severe middle lobe obstruction, lower Qmax and and elevated baseline PVR. IPSS subscore improvements appeared to correlate with abnormal baseline physiology, with improvements in voiding subscores in groups with large middle lobes and high degrees of middle lobe obstruction (indicating obstructive symptoms), and improvements in storage subscores in patients with no baseline bladder neck obstruction and high baseline PVR values (indicating poor baseline bladder function). Men with low baseline flow rates had superior improvements in both voiding and storage subscores. These findings suggest that robotically executed, physiologically relevant prostate tissue removal may be more effective and consistent in removing obstructing tissue and improving bladder function, especially in the setting of more complex anatomy, compared to TURP, a procedure that, with large prostates, requires substantial experience and expertise as well as longer operative times. For men without bladder neck obstruction, Aquablation showed superior IPSS changes. This may be explained by the previously stated rationale that Aquablation resects a consistent opening even in patients where the obstruction is not obvious.

Larger IPSS score changes after Aquablation were seen in men both < and >65 years old, demonstrating Aquablation's ability to deliver TURP-like symptomatic relief in the young and the Medicare populations. These findings confirm that Aquablation is suitably effective in the rapidly growing and higher-prevalence Medicare population.

Retrograde ejaculation after TURP, a common finding (63% in one key study (8)), is likely due to heat-related damage to the ejaculatory ducts. The reduced rate of anejaculation in our study is likely due to enhanced resection precision through image guidance and robotic execution, which avoids damage to the ejaculatory ducts around the verumontanum and lack of heat-related damage. The relatively lower observed anejaculation rate in our study in the TURP group compared to other studies is likely due to adjudication of this endpoint as anejaculation (after evaluation by a clinical events committee) as opposed to patient reports of reduced ejaculation. Lower rates of postoperative anejaculation after Aquablation were significant in men with large prostates (2% vs. 41%) and statistically lower rates were seen in most

subgroups (preplanned and exploratory). Clavien-Dindo grade 2 and above complications trended in favor of Aquablation with larger prostates (19% vs. 29%), though this difference did not reach statistical significance.

Subgroup analyses from this randomized trial lend support to a shift in the treatment of BPH, using image guidance and robotic execution to improve targeting and precision of tissue removal, potentially producing superior symptom score improvements while avoiding structures whose heat-related "collateral damage" commonly causes retrograde ejaculation.

Advantages to our study include its prospective, multicenter, international, blinded design as well as observed TURP IPSS score changes in the same range as those reported in prior similar studies.(9) Our findings are especially noteworthy given that the trial involved surgeons with substantial TURP expertise but no experience in 14 of 17 sites with Aquablation. Although the study's sample size was large enough to detect moderate size effects in subgroups, study power was limited for some analyses. Additionally, this study cannot answer whether Aquablation brings similar benefits for even larger (>80 g) prostates; a study of this large prostate population is currently under way (NCT03123250).

LIMITATIONS

We interpret these findings cautiously as, except for prostate size, age, and baseline IPSS, most were exploratory (not preplanned), sample sizes were limited, and the follow-up is 6 months. The relative symptom relief advantage of Aquablation could not be demonstrated in men with smaller prostates, in which case TURP may more easily and consistently remove offending tissue yielding similar results as compared to larger prostates.

CONCLUSION

The prespecified subgroup analysis from a blinded randomized clinical trial showed that in men with larger (>50 g) prostates, resection using Aquablation provided higher symptom score reduction and a reduced rate of postoperative complications (especially anejaculation) compared to TURP. In men with larger prostates, the rate of Clavien-Dindo grade 2 and above complications trended in favor of Aquablation (19% vs. 29%). The advantages to a standardized, robotically executed BPH surgery are confirmed as the treatment complexity increases.

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Table 1. Baseline characteristics

	Prostate volume			Age group			Baseline IPSS			
	<50 (n=82)	≥50 (n=102)	P value	<65 (n=78)	>65 (n=106)	P value	<20 (n=59)	≥20 (n=122)	P value	All (n=184)
Prostate volume	38.7 (6.1)	65.0 (9.5)	<.0001	52.2 (15.8)	54.1 (15.1)	.3958	54.2 (15.9)	52.8 (15.4)	.5627	53.3 (15.4)
Age	65.2 (7.6)	66.5 (7.0)	.2490	58.8 (3.8)	71.1 (4)	<.0001	64.6 (6.3)	66.5 (7.6)	.0805	65.9 (7.3)
Body mass index	28.2 (4.4)	28.5 (4.1)	.6480	28.7 (4.6)	28.1 (3.9)	.3038	28.1 (4.5)	28.5 (4.1)	.5261	28.4 (4.2)
Lobes										
Both lateral and middle	30 (36.6%)	58 (56.9%)		43 (55.1%)	45 (42.5%)		30 (50.8%)	56 (45.9%)		88 (47.8%)
Lateral lobe	45 (54.9%)	36 (35.3%)	.0185	32 (41%)	49 (46.2%)	.0898	25 (42.5%)	55 (45.1%)	.9075	81 (44%)
Middle lobe	5 (6.1%)	7 (6.9%)		2 (2.6%)	10 (9.4%)		4 (6.8%)	8 (6.6%)		12 (6.5%)
NA	2 (2.4%)	1 (1.0%)		1 (1.3%)	2 (1.9%)		0 (0.0%)	3 (2.5%)		3 (1.6%)
Lobes touching	77 (81.9%)	95 (87.2%)	.5439	64 (82.1%)	91 (85.8%)	.6239	49 (83.1%)	103 (84.4%)	.2805	172 (84.7%)
Degree of middle lobe obstruction										
None	29 (30.9%)	16 (14.7%)		17 (21.8%)	21 (19.8%)		11 (18.6%)	26 (21.3%)		45 (22.2%)
Mild	19 (20.2%)	24 (22.0%)	.0281	16 (20.5%)	24 (22.6%)	.9357	14 (23.7%)	26 (21.3%)	.9526	43 (21.2%)
Moderate	27 (28.7%)	34 (31.2%)		26 (33.3%)	31 (29.2%)		20 (33.9%)	36 (29.5%)		61 (30.0%)
Severe	6 (6.4%)	18 (16.5%)		9 (11.5%)	12 (11.3%)		7 (11.9%)	13 (10.7%)		24 (11.8%)
NA	11 (11.7%)	16 (14.7%)		9 (11.5%)	16 (15.1%)		7 (11.9%)	18 (14.8%)		27 (13.3%)
Bladder neck obstruction	29 (30.9%)	34 (31.2%)	1.0000	27 (34.6%)	27 (25.5%)	.2512	15 (25.4%)	38 (31.1%)	.4871	63 (31%)
Urethral strictures	2 (2.1%)	1 (0.9%)	.5972	2 (2.5%)	1 (0.9%)	.5750	0 (0%)	3 (2.5%)	.5520	3 (1.5%)
Bladder trabeculation										
None	12 (12.8%)	9 (8.3%)		14 (17.9%)	5 (4.7%)		5 (8.5%)	14 (11.5$)		21 (10.3%)
Mild	42 (44.7%)	52 (47.7%)	.7406	36 (46.2%)	50 (47.2%)	.0266	23 (39%)	62 (50.8%)	.1986	94 (46.3%)
Moderate	33 (35.1%)	42 (38.5%)		24 (30.8%)	44 (41.5%)		27 (45.8%)	39 932%)		74 (36.9%)
Severe	5 (5.3%)	5 (4.6%)		3 (3.8%)	5 (4.7%)		4 (6.8%)	4 (3.3%)		10 (4.9%)
NA	2 (2.1%)	1 (0.9%)		1 (1.3%)	2 (1.9%)		0 (0%)	3 (2.5%)		3 (1.5%)
Bladder stone	0 (0%)	0 (0%)	1.0	0 (0%)	0 (0%)	1.0	0 (0%)	0 (0%)	1.0	0 (0%)
Bladder diverticulum	6 (6.4%)	1 (0.9%)	.0507	3 (3.8%)	2 (1.9%)	.6518	2 (3.4%)	3 (2.5%)	.6615	7 (3.4%)
Baseline questionnaires										
IPSS	22.8 (6.0)	22.5 (6.2)	.7135	21.9 (5.7)	23 (6.2)	.2303	15.6 (2.4)	25.9 (3.9)	<.0001	22.6 (6.1)
IPSS QOL	4.7 (1.1)	4.9 (1.0)	.3321	4.7 (1)	4.8 (1)	.3160	4.4 (1.1)	5 (1)	.0002	4.8 (1)
MSHQ-Ejd*	8.4 (3.3)	8.4 (4.0)	.9135	9.1 (3.6)	7.7 (3.6)	.0343	9.2 (3.2)	8 (3.8)	.0638	8.4 (3.7)
IIEF-5 (SHIM)*	18 (6.4)	17.2 (6.9)	.5025	18.8 (6.5)	16.4 (6.7)	.0359	18.8 (5.3)	16.9 (7.2)	.0812	17.2 (6.9)

Table 1. Primary safety endpoint event rates by treatment and subgroups. Primary safety endpoint was defined as CD grade 2 or higher and persistent CD grade 1 events.

	N with event / N (rate)		
	Aquablation	**TURP**	**P-Value***
Baseline IPSS			
<20	6/36 (17%)	9/23 (39%)	.0530
≥20	24/80 (30%)	18/42 (43%)	.1118
Age, years			
<65	10/50 (20%)	11/27 (41%)	.0578
>65	20/66 (30%)	16/38 (42%)	.1159
Prostate volume, mL			
<50	17/52 (33%)	11/30 (37%)	.4481
≥50	13/64 (20%)	16/35 (46%)	.0082

*Fisher test

Table 1. Anejaculation (at risk denominator) by treatment and subgroups.

	N with event / N (rate)		
	Aquablation	**TURP**	**P-Value**
Baseline IPSS			
<20	2/30 (7%)	7/16 (44%)	.0049
≥20	6/48 (12%)	9/29 (31%)	.0467
Age, years			
<65	3/37 (8%)	8/24 (33%)	.0159
>65	5/41 (12%)	8/21 (38%)	.0224
Prostate volume, mL			
<50	7/34 (21%)	7/23 (30%)	.2947
≥50	1/44 (2%)	9/22 (41%)	.0001

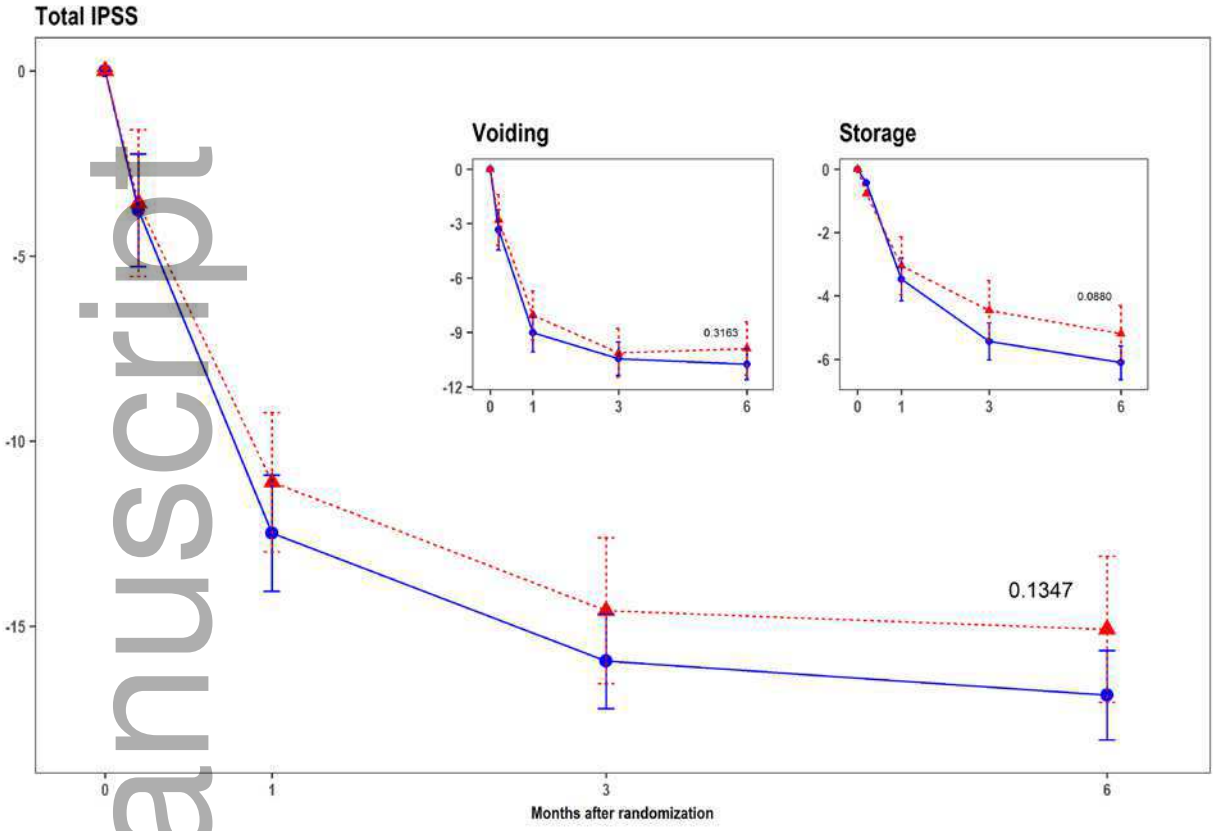
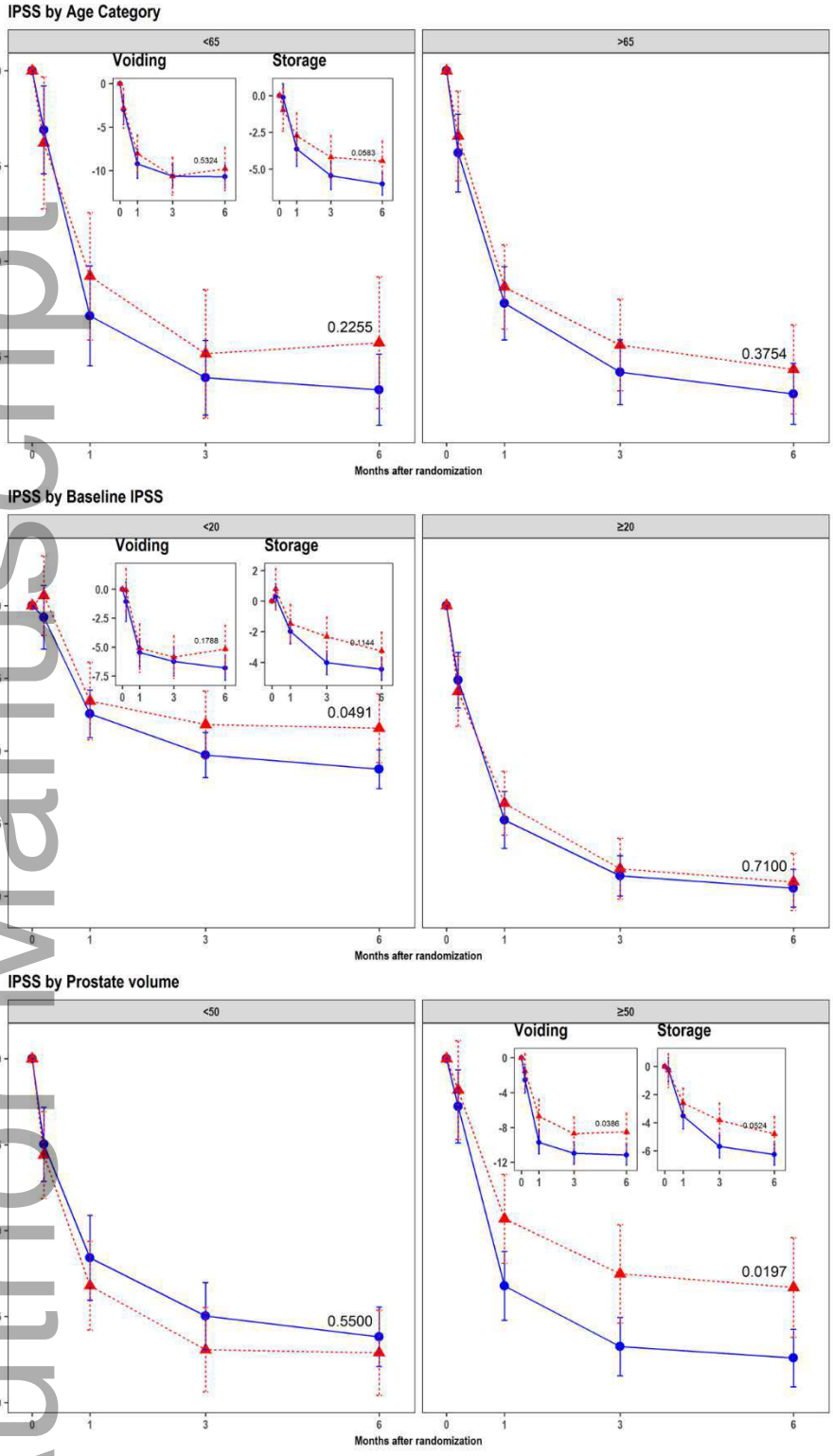


Figure 1. Change in IPSS score by time, treatment and preplanned subgroups. Solid blue = Aquablation; dotted red = TURP. In this and subsequent figures, numbers show p-values for 6-month change score comparisons across treatments and inset plots show voiding and storage subscore changes from baseline with 6-month change score p-values.



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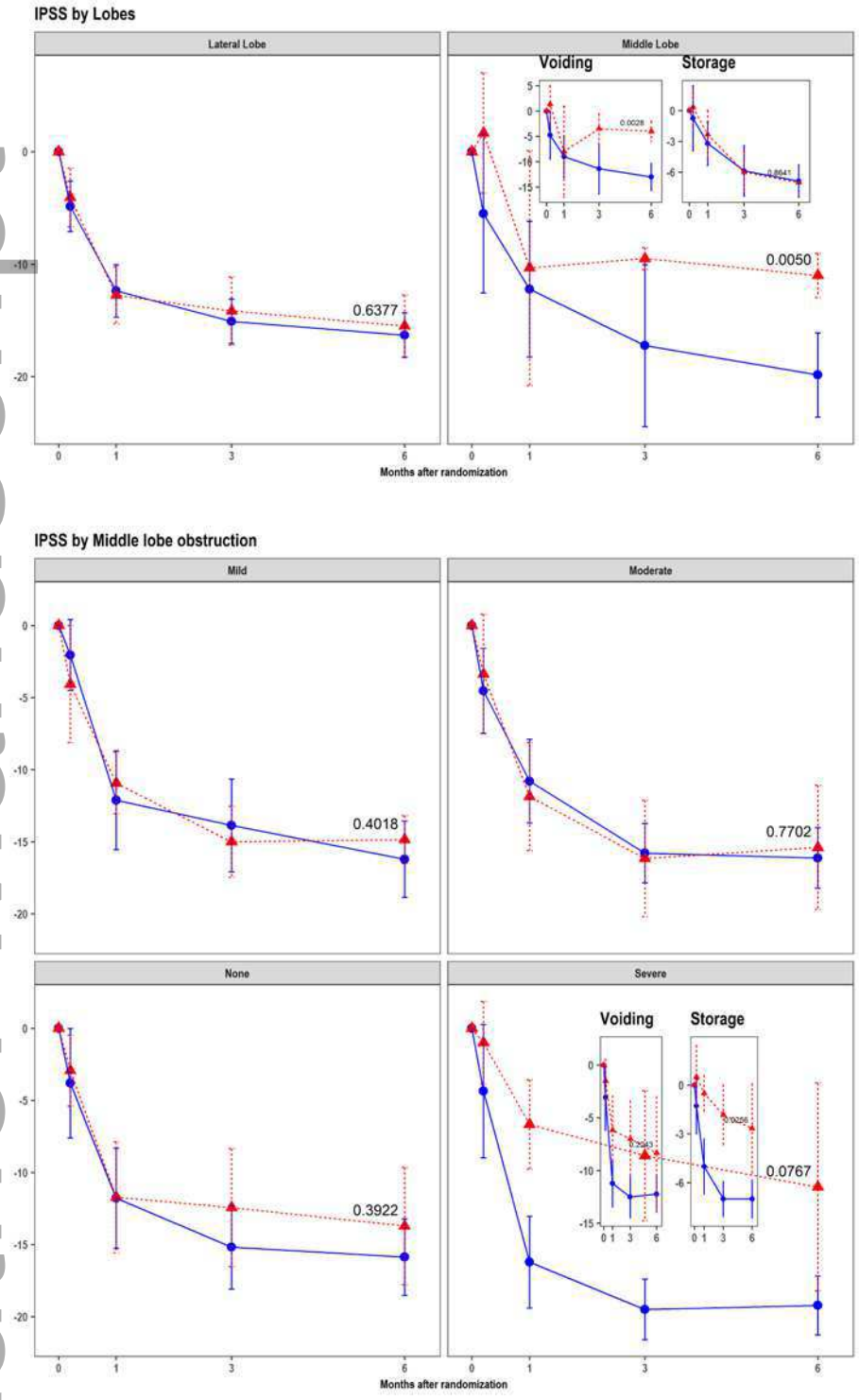

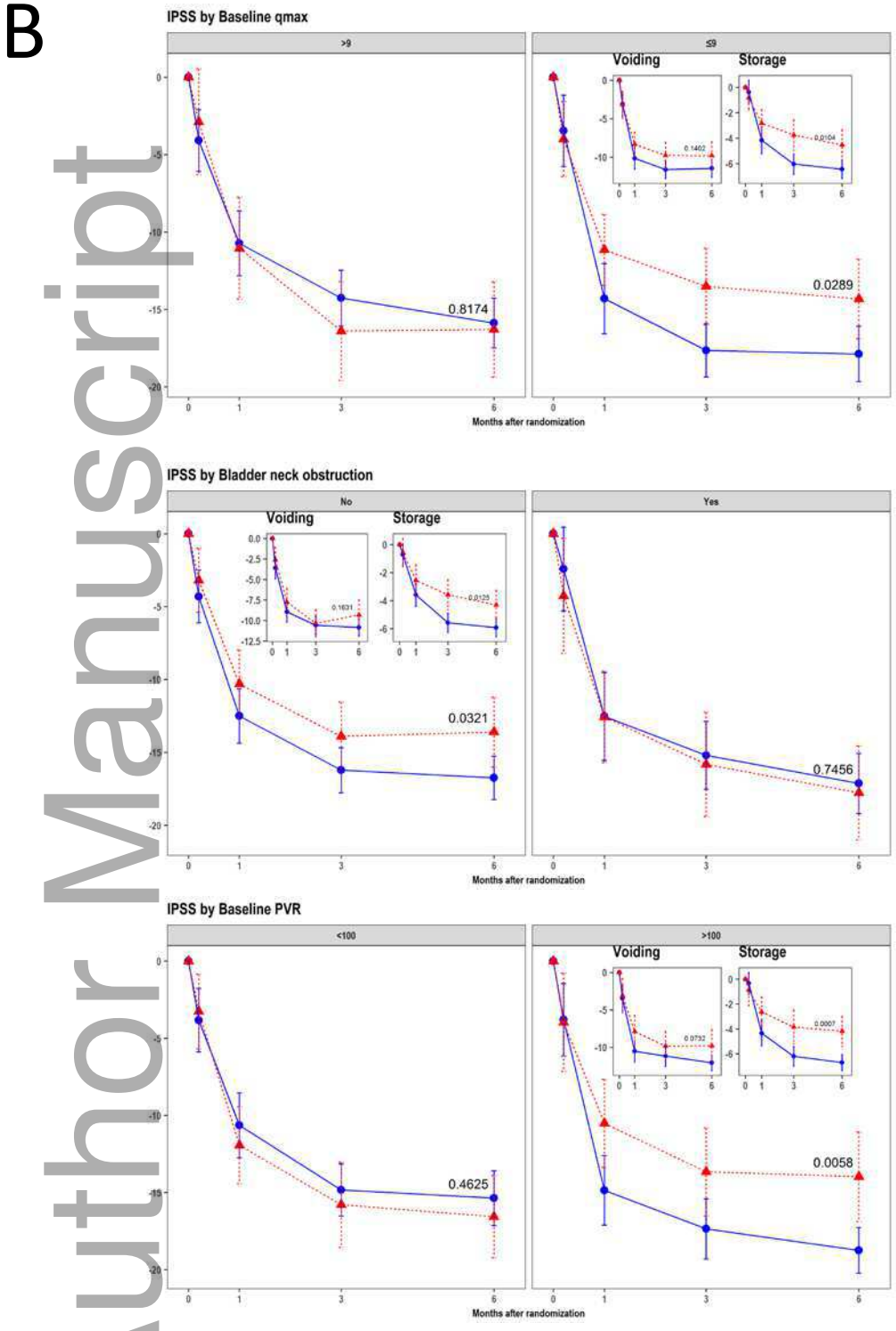

Figure 1. Change in IPSS score by time, treatment and exploratory subgroups. A) presence of middle or lateral lobe and degree of middle lobe obstruction; B) baseline Qmax > or < median value of 9 cc/sec, bladder neck obstruction and baseline PVR < or >100 cc. Solid blue = Aquablation; dotted red = TURP.

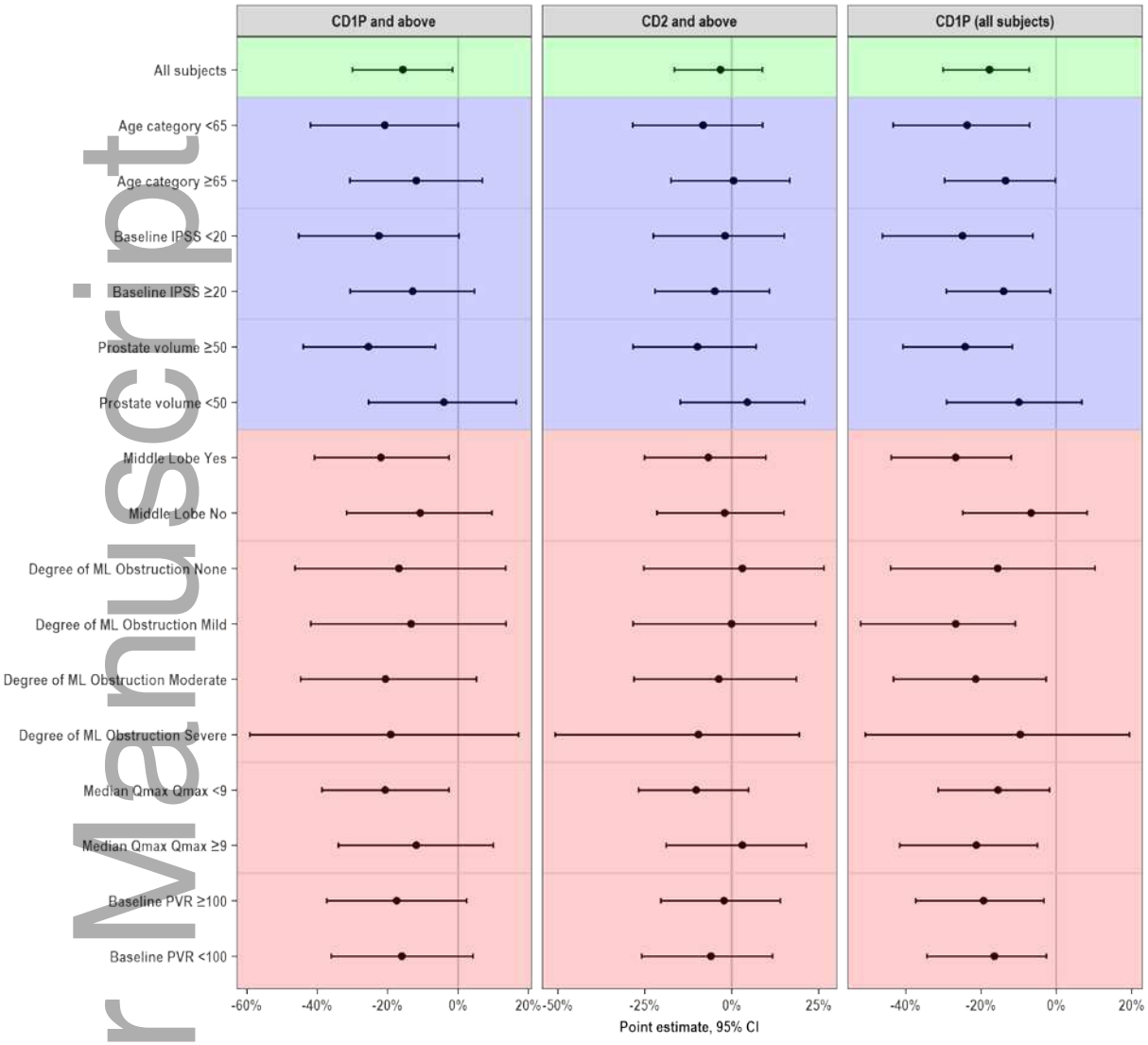

Figure 1. Forest plot of differences in Clavien-Dindo complication rates across treatments by preplanned and exploratory subgroups. CD1P and above refers to persistent CD1 events and CD2-5 events. CD2 and above refers to CD2-5 events. CD1P (all subjects) refers to persisnt CD1 events only. Green background = main results; blue = preplanned subgroup analysis; pink = exploratory analyses.