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REVIEW

Benign Prostatic Obstruction Relief in Patients with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Enlargement Undergoing Endoscopic Surgical Procedures or Therapy with Alpha-Blockers: A Review of Urodynamic Studies

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ABSTRACT

Benign prostatic obstruction (BPO) contributes to the genesis of lower urinary tract symptoms as well as to pathologic remodeling of the lower and upper urinary tract in patients with benign prostate enlargement. Urodynamic studies demonstrate that both medical therapy with alpha-blockers (ABs) and endoscopic surgical procedures provide BPO relief. However, the magnitude of improvement is higher after surgery. Among ABs, silodosin is associated with the highest improvement of bladder outlet obstruction index (BOOI). A complex relationship exists between BOOI improvement and variations of both maximum urinary flow (Q_{max}) and detrusor pressure. When the reduction of BOOI is small, the improvement of Q_{max} is clinically irrelevant and the BOOI is mainly influenced by a decrease of detrusor pressure. In contrast, when the magnitude of BOOI reduction is robust, a meaningful improvement of both detrusor pressure and urinary flow is evident. When clustering ABs according to their receptor pharmacologic selectivity and urodynamic efficacy, three subgroups can be identified,with silodosin being the only member of a subgroup characterized by the highest levels of BOOI improvement and α-1A/α-1B receptor affinity ratio.

Keywords: Alpha-blockers; Benign prostatic obstruction; Surgery; Urodynamics

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INTRODUCTION

Historically, bladder outlet obstruction (BOO) has been considered the key pathophysiological link between benign prostate enlargement (BPE) and lower urinary tract symptoms (LUTS) [1, 2]. Benign prostatic obstruction (BPO) can be attributed to static and/or dynamic factors and, if untreated, may be responsible for both structural and functional pathological remodeling of the lower urinary tract, with potential negative consequences on the upper urinary tract [1, 2]. Consequently, BPO relief is one of the main goals of LUTS/BPE therapy [3]. Although uroflowmetry is commonly accepted as a proxy

of BPO in trials and in clinical practice, its diagnostic accuracy is suboptimal, and invasive urodynamic investigations represent the gold standard to diagnose BPO, which is defined by a high-pressure/low-flow micturition pattern [4, 5]. Treatment strategies for LUTS/BPE patients include medical and surgical options [5, 6]. In recent years, medical therapy has revolutionized the care of LUTS/BPE patients, with a dramatic reduction in the number of patients requiring surgical treatment. Alpha-blockers have been evaluated for the treatment of LUTS/BPE for about 40 years, from early trials with the nonselective α-inhibitor phenoxybenzamine to short-acting then long-acting selective α_1-blockers (ABs) [1]. Nowadays, ABs represent the first-line option and the most frequently prescribed medical therapy in the treatment of patients with moderate to severe LUTS/BPE [6]. Surgical options are recommended as second-line therapy when conservative medical therapy fails [6]. ABs aim to interfere with the dynamic component of BPO by inhibiting the effect of endogenously released noradrenaline on smooth muscle cells in the lower urinary tract [6]. Currently, six ABs have been approved for the treatment of LUTS/BPE: terazosin, doxazosin, tamsulosin, naftopidil, alfuzosin, and silodosin [5]. All ABs are effective in improving LUTS/BPE [5]. However, these drugs are heterogeneous in terms of pharmacologic selectivity with respect to the three distinct α_1-adrenergic receptors (AR) subtypes cloned and characterized: α_1A, α_1B, and α_1D [6]. ABs, although able to significantly improve symptoms and bladder outlet obstruction index (BOOI), exhibit a statistically and clinically irrelevant effect on uroflowmetry parameters. Indeed, a recent meta-analysis of urodynamic studies showed a net, albeit variable, improvement of BOOI after ABs therapy in LUTS/BPE patients but only a small improvement in terms of peak urinary flow (Q_{max}) [5]. Of note, the magnitude of the urodynamic effect varied according to the type of AB [5]. On the other hand, surgical procedures have been proved to improve, in a statistically and clinically significant manner, symptoms and Q_{max} as well as the BOOI. The rationale behind the difference between surgical procedures and ABs is unknown. The existence of pharmacologic differences among ABs may potentially contribute to explain the observed urodynamic differences in terms of obstruction relief. The aim of the present analysis was to summarize the evidence about the urodynamic effects of endoscopic surgical procedures and ABs in LUTS/BPE patients in order to identify possible factors for their different impact on Q_{max}. Furthermore, we investigated the relationship between urodynamic efficacy of ABs and their pharmacological selectivity profile in order to explain the variable effect of ABs in improving the BOOI.

METHODS

We performed a literature review by using the National Library of Medicine's PubMed search engine to search for published studies evaluating urodynamic measurement of BOOI in LUTS/BPE patients both before and after therapy with ABs or endoscopic surgical procedures. The following search strings were used: tamsulosin AND urodynamics; silodosin AND urodynamics; alfuzosin AND urodynamics; doxazosin AND urodynamics; naftopidil AND urodynamics; terazosin AND urodynamics; transurethral resection of the prostate (TURP) AND urodynamics; holmium laser enucleation of the prostate (HOLEP) AND urodynamics; photo-selective vaporization of the prostate (PVP) AND urodynamics; transurethral electro-vaporization of the prostate (TUVP) AND urodynamics; transurethral needle ablation (TUNA) AND urodynamics; and transurethral microwave thermotherapy (TUMT) AND urodynamics. We included full paper publications that met the following criteria: reporting original research; English language; human studies; enrolling LUTS/BPE patients; and reporting Q_{max} and detrusor pressure at maximum urinary flow ($P_{det}Q_{max}$) evaluated by pressure flow studies (PFS) before and after treatment with an AB or surgery. The following data were extracted from the included studies: type of AB or surgical procedure used, and $P_{det}Q_{max}$ and Q_{max} values at baseline and after the treatment. BOOI was calculated using the formula $BOOI = P_{det}Q_{max} - 2Q_{max}$ [7]. A curve estimation procedure was performed to investigate the relationship between the

independent variable (BOOI variation) and the dependent variables ($P_{det}Q_{max}$ and Q_{max} change from baseline). Linear, quadratic and cubic models for the relationship between BOOI variations and $P_{det}Q_{max}$ or Q_{max} changes were examined. The $P_{det}Q_{max}$ and Q_{max} change values were corrected for the baseline. Moreover, we performed a κ-mean cluster analysis to identify subgroups of ABs based on their pharmacological receptor affinities and urodynamic outcomes. The *k*-means statistical algorithm is a partitioning classification system which iteratively regroups into *K* clusters a set of *n* elements characterized by *m* variables [8]. The cluster centers are chosen to minimize the intra-cluster distances. Each cluster is centered around a point, called the centroid, which represents the average coordinate of the cluster's elements. In detail, the following variables were used to classify ABs: α_1A/α_1B affinity ratio, α_1A/α_1D affinity ratio, mean change of BOOI from baseline, and mean change of $P_{det}Q_{max}$ from baseline. The α_1A/α_1B and α_1A/α_1D ratios were calculated from the appropriate ratio after converting the concentration, specifically using 10^M, where $M = pK_i$ (α_1A) − pk_i(α_1B or α_1D). Pk_i values were extracted from published studies [9–12]. Comparisons between clusters were made using the most appropriate test: one-way analysis of variance (ANOVA) for normally distributed data, χ^2 test for proportional data, and the Kruskal–Wallis test for non-normally distributed variables. Univariate regression analysis was performed comparing the cluster centers relative to BOOI change from baseline to the cluster centers relative to the α_1A/α_1B ratio. All tests were two-sided. Statistical analyses were performed by using SAS package (v.9.2).

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

We identified 17 studies related to ABs and 26 related to endoscopic surgical procedures published between 1994 and 2013 [13–55]. Mean values of $P_{det}Q_{max}$, Q_{max} and BOOI change from baseline for each treatment are reported in Table 1. In patients taking ABs, mean $P_{det}Q_{max}$ change from baseline ranged from −9.7 to −34.4%, mean Q_{max} change from baseline ranged from 15.3 to 51.4%, and mean BOOI change from baseline ranged from 11.9 to 32.2 (Table 1). The greatest variations of $P_{det}Q_{max}$, Q_{max} and BOOI were reported after therapy with silodosin. Variations of $P_{det}Q_{max}$, Q_{max} and BOOI after endoscopic surgery ranged from −23.6 to −64.2%, from 76.7 to 179.3% and from 33.5 to 77.8, respectively. HOLEP was associated with the greatest variations of all the three parameters (Table 1).

Curve Estimation Procedure

Results from the curve estimation procedure are depicted in Fig. 1. The adjusted quadratic equation was considered the best fit to explain the relationship between variations of BOOI and $P_{det}Q_{max}$ as well as between variations of BOOI and Q_{max}.

κ-Means Cluster Analysis

A three-cluster model was chosen as it allowed the best discrimination between clusters. Results from the κ-means cluster analysis are showed in Table 2 and Fig. 2.

The following variables showed a significant difference between clusters: α_1A/α_1B ratio, α_1A/α_1D ratio, and BOOI change (Table 2). Cluster 1 included alfuzosin, doxazosin, naftopidil and terazosin. It described a subgroup of ABs characterized by low α_1A/α_1B ratio, low α_1A/α_1D ratio, and BOOI improvement in the lower range. The second cluster included tamsulosin and was characterized by slightly higher α_1A/α_1B and α_1A/α_1D ratios and a BOOI improvement comparable to the previous cluster. The third cluster included silodosin and was characterized by greater α_1A/α_1B and α_1A/α_1D ratios as well as greater BOOI improvement. As shown in Fig. 3, the univariate analysis showed positive correlation between BOOI change from

Table 1 $P_{det}Q_{max}$, Q_{max} and BOOI change from baseline according to treatment modality

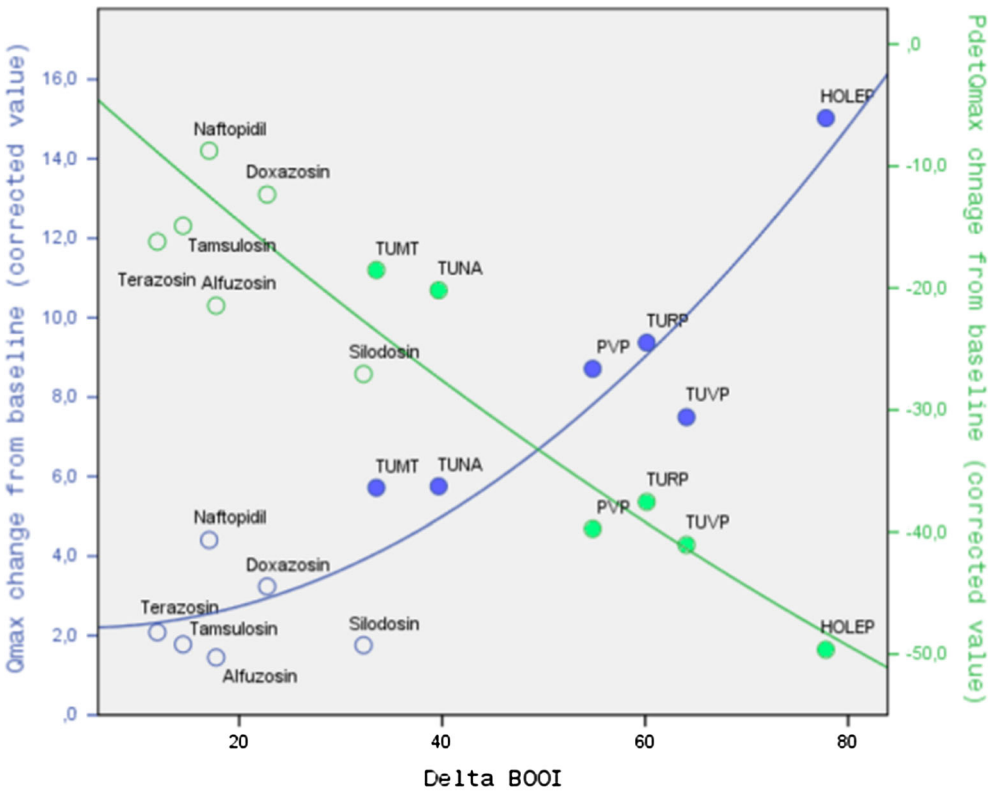
Treatment	$P_{det}Q_{max}$ at baseline Mean (cmH_2O)	$P_{det}Q_{max}$ post-treatment Mean (cmH_2O)	$P_{det}Q_{max}$ change Mean %	Q_{max} change Mean %	BOOI change Mean
α1-blockers					
Alfuzosin	67.5	52.3	−20.9	15.3	17.7
Doxazosin	86.9	68.4	−22.0	21.1	22.7
Naftopidil	78.9	69.1	−12.4	37.0	17.0
Silodosin	76.5	50	−34.4	51.4	32.2
Tamsulosin	70.2	59.8	−12.3	26.5	14.4
Terazosin	63.8	56.2	−9.7	29.1	11.9
Endoscopic surgical procedures					
TURP	82.9	41.8	−49.1	123.0	60.1
HOLEP	74.6	26.7	−64.2	179.3	77.8
PVP	74.9	36.7	−50.8	99.4	54.8
TUVP	89	40.4	−53.4	106.8	64.0
TUNA	88.8	61.3	−30.7	80.2	39.6
TUMT	81.7	60.3	−23.6	76.7	33.5

BOOI Bladder outlet obstruction Index, *HOLEP* holmium laser enucleation of the prostate, $P_{det}Q_{max}$ detrusor pressure at Q_{max}, *PVP* photoselective vaporization of the prostate, Q_{max} maximum urinary flow rate, *TUVP* transurethral electro-vaporization of the prostate, *TURP* transurethral resection of the prostate, *TUNA* transurethral needle ablation, *TUMT* transurethral microwave thermotherapy

baseline and α1A/α1B, although not statistically significant.

DISCUSSION

BPO has been called in cause in the genesis of LUTS. Moreover, high bladder pressures and mechanical bladder tension typical of BPO lead to the activation of molecular pathways leading to progressive histological remodeling of both lower and upper urinary tract with subsequent functional impairment [56]. A timely relief of obstruction may improve symptoms and potentially interrupt or reverse the natural history of obstructive uropathy [55]. Results from published studies demonstrate that both endoscopic surgical procedures and medical therapy with ABs improve BOOI in patients suffering from for LUTS/BPE. However, the magnitude of BOOI reduction varies according to the treatment modality with endoscopic surgical procedures providing greater BOOI reduction if compared to ABs. The rationale behind this difference is unknown. However, some potential explanations may be postulated. First is the different mechanism of action that characterizes the two treatments. Indeed, surgery mainly acts by reducing prostate volume and thus the static component of BPO while ABs act on the dynamic component of BPO by blocking the motor sympathetic adrenergic nerve supply to the prostate. Moreover, patients receiving surgical therapy are commonly characterized by higher prostate volumes and likely higher degree of BPO at baseline with respect to those receiving ABs. In a previous meta-analysis of urodynamic studies we showed that the magnitude of BOOI improvement is influenced by



	Equation	Adjusted R^2	p
PdetQmax change	**Quadratic model**	**0.865**	**0.00**
Qmax change	**Quadratic model**	**0.855**	**0.00**

Fig. 1 Curve estimation plot and statistics describing the relationship between the independent variable (Delta BOOI) and the dependent variables ($P_{det}Q_{max}$ change from baseline, *green line* and *circles*, and Q_{max} change from baseline, *blue line* and *circles*). $P_{det}Q_{max}$ and Q_{max} change values were corrected for the baseline

Table 2 Cluster features

Cluster membership	Cluster 1 ADNT	Cluster 2 Tamsulosin	Cluster 3 Silodosin	*p*
α1A/α1B ratio (cluster center)	0.3	9.5	162.0	0.00
α1A/α1D ratio (cluster center)	0.6	2.5	55.0	0.00
$P_{det}Q_{max}$ change (cluster center)	−13.4	−9.7	−24.9	0.10
BOOI change (cluster center)	−15.5	−14.2	−30.4	0.05

ADNT alfuzosin, doxazosin, naftopidil, terazosin

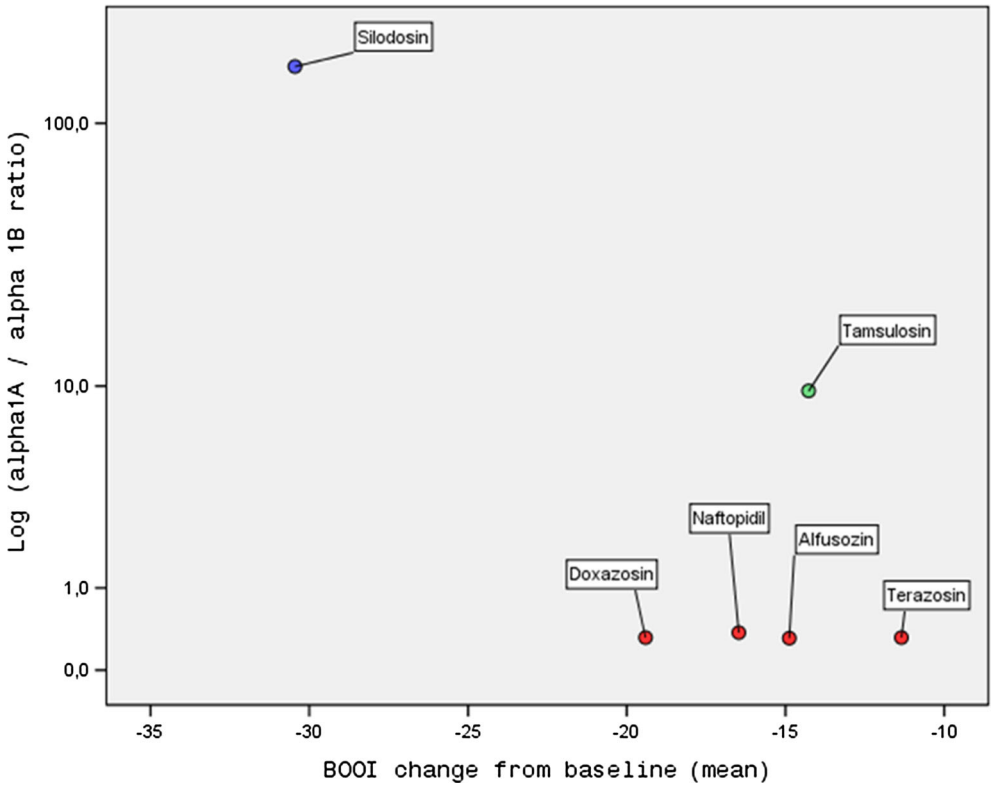


Fig. 2 Subgrouping of ABs based on BOOI change from baseline (*x-axis*) and α 1A/α 1B ratio (log-transformed) (*y-axis*). *Circles* represent ABs and are *colored* by cluster: *red circles* cluster 1, *green circles* cluster 2, and *blue circles* cluster 3

the percentage of patients with obstruction at baseline [5]. Although this was evident in patients receiving ABs, we cannot exclude that this relationship could be generalizable and independent of the treatment modality. The BOOI is calculated from two invasive urodynamic measures: the $P_{det}Q_{max}$ and the Q_{max}. The present study shed light on the behavior of these two urodynamic measures with respect to BOOI change. We demonstrated, for the first time, the existence of a quadratic relationship between $P_{det}Q_{max}$ changes and BOOI changes as well as between Q_{max} changes and BOOI changes. According to this model, when the magnitude of BOOI reduction is small, as after ABs therapy, the Q_{max} improvement is clinically irrelevant and the BOOI variation is mainly influenced by a $P_{det}Q_{max}$ decrease. In contrast, when the magnitude of BOOI reduction is robust, as after surgery, the Q_{max} improvement is also clinically meaningful. This observation has relevant pathophysiological and clinical implications.

From a pathophysiological point of view, we can speculate that the reduction of detrusor pressures represents a priority with respect to urinary flow improvement and, when the relief of outflow resistances is small, the lower urinary tract mainly adapts by reducing detrusor pressures thus potentially preserving the integrity of the bladder itself and of the upper urinary tract. Higher degrees of obstruction relief allow both a reduction of detrusor pressures and an improvement of urinary flow. From a clinical point of view, the assessment of BPO improvement on the basis of free uroflowmetry may be misleading after therapy with ABs, as it does not allow the detection of small BPO improvements and therapy may be wrongly considered ineffective from a urodynamic point of view. Interestingly, our analysis demonstrated that the magnitude of BOOI improvement after therapy with ABs was considerably higher in patients receiving silodosin and was comparable to values reported after TUMT. ABs represent a heterogeneous class of drugs which differ

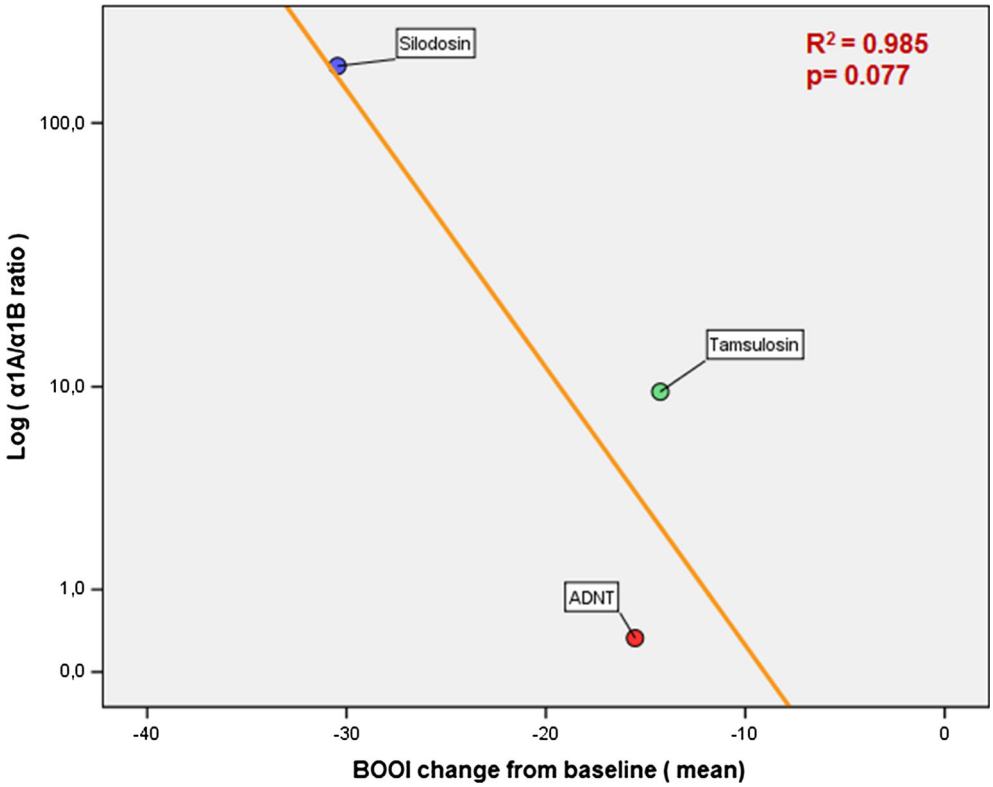


Fig. 3 Univariate linear regression analysis BOOI change from baseline relative to α1A/α1B ratio (log-transformed scale)

mainly in terms of receptor pharmacological selectivity. Silodosin is a highly selective AB approved in Japan in 2006 and more recently in the United States, Europe, and Korea [57–59]. Receptor binding studies show that silodosin has a very strong affinity for the α1A-AR, which represents the predominant α1 AR subtype in the human prostate and mediates human prostate contraction [60–64]. The α1B-AR is mainly expressed in the cardiovascular system where it mediates blood vessel contractions and is involved in the genesis of cardiovascular side effects in patents taking ABs. The affinity of silodosin for the α1A-AR is 162 times higher than that for the α1B-AR, and 55 times higher than that for the α1D-AR [55–58]. To date, clinical implications of receptor pharmacological selectivity have been mainly discussed in terms of side effects [57–59]. The relevance of such aspect in terms of urodynamic effectiveness has never been investigated, and there are no specific indications in favor of a single AB in specific clinical situations. We performed, for the first time, a cluster analysis in order to classify ABs, considering their receptor affinity ratio and their urodynamic outcome in terms of BOOI improvement. Based on the aforementioned features, results from the cluster analysis demonstrate the existence of three different subgroups of ABs, with silodosin being the only member of a subgroup characterized by significant higher BOOI improvement and α-1A/α-1B affinity ratio. The univariate analysis we performed demonstrated a positive correlation between BOOI reduction and α-1A/α-1B affinity ratio. This finding supports the existence of a relationship between α-1A-AR selectivity and urodynamic outcomes. However, further studies are needed to confirm this hypothesis.

This study has several limitations. Studies included are heterogeneous in terms of populations enrolled, baseline obstruction level, and urodynamic assessment methodology. Despite our efforts to be objective, there were several areas of subjectivity, including our selection of variables for clustering. Finally, the number of

objects included in the cluster analysis was low. Prospective randomized studies that directly compare ABs and ABs to surgical procedures in terms of urodynamic obstruction parameters improvement are needed in order to confirm findings from the present analysis.

CONCLUSIONS

In conclusion, ABs and surgery significantly improve BPO in patients with LUTS/BPE. A quadratic relationship is evident between BOOI changes and the variation of both $P_{det}Q_{max}$ and Q_{max}. When the reduction of BOOI is small, as after ABs therapy, the Q_{max} improvement is clinically irrelevant and the BOOI variation is mainly influenced by the $P_{det}Q_{max}$ decrease. In contrast, when the magnitude of BOOI reduction is robust, as after surgery, both $P_{det}Q_{max}$ and Q_{max} improvements are meaningful. The reduction of bladder pressure appears to be a biologic priority and represents a more desirable outcome with respect to urinary flow improvement, as it could potentially exert a favorable effect on the progression of the natural history of obstructive uropathy. When clustering ABs according to their receptor pharmacologic selectivity and urodynamic efficacy, three subgroups can be identified, with silodosin being the only member of a subgroup characterized by the highest levels of BOOI improvement and α-1A/α-1B affinity ratio. Although the analysis of published data suggests the existence of a positive relationship between α-1A/α-1B receptor affinity ratio and BPO improvement, this hypothesis needs confirmation.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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