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Medical Treatment of Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia

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Abstract

Context: Medical treatment is the primary option for most patients with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH; LUTS/BPH), but individual patients may have distinct treatment goals.
Objective: To describe the specific effects of available treatment options on symptom relief as well as on disease progression in relation to their potential side-effects.
Evidence acquisition: PubMed was screened for studies, meta-analyses, and reviews describing medical treatments of LUTS/BPH.
Evidence synthesis: The two main options for medical treatment are α_1-adrenoceptor antagonists (ARBs) and 5α-reductase inhibitors (ARIs). ARBs cause fast and persistent symptom relief but do not reduce prostate size or prevent progression as assessed (eg, by occurrence of urinary retention). All ARBs are similarly effective; alfuzosin and tamsulosin have the best tolerability. ARIs reduce prostate size and prevent disease progression, but symptom reduction occurs more slowly and is less pronounced than with ARBs. Dutasteride and finasteride appear to be similarly effective and tolerated. Due to differential modes of action, the combination of ARBs and ARIs has additive effects against combined end points of disease progression, but they also have additive side-effects. While several other treatment options are currently under investigation, none are sufficiently well documented to allow treatment recommendations.
Conclusions: We propose that ARBs and ARIs have distinct clinical effects and, hence, should be considered for distinct groups of LUTS/BPH patients based on specific treatment goals in a given patient.

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1. Introduction

Medical treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH; LUTS/BPH) is driven by two major factors. On the one hand, most patients primarily seek treatment to relieve their bothersome symptoms. In this regard, storage symptoms are considered to be more bothersome than voiding symptoms. On the other hand, LUTS/BPH on average is a chronically progressive condition, although it is difficult to predict its development for a given individual. Given that the average patient who is newly diagnosed with LUTS/BPH has a remaining life expectancy of 15–20 yr, any treatment approach needs to be sustainable for such a time frame. Therefore, the two main aims of any LUTS/BPH treatment are (1) a sustainable reduction of symptoms and (2) an inhibition of disease progression. While the relative importance of these two goals may differ among patients, any treatment should have as few side-effects as possible, particularly if comorbidities and associated comedications in many patients can affect the choice of optimal treatment. Against this background, we will review the three main options for medical treatment: α_1-adrenoceptor antagonists (ARBs), 5α-reductase inhibitors (ARIs), and their combination. Additional options, which are currently undergoing clinical evaluation, will be discussed briefly.

2. Methodologic considerations

This article is based on a PubMed search for studies, meta-analyses, and reviews describing medical treatments of LUTS/BPH. This evidence has been collected under conditions which have implications for the interpretation of the data. Therefore, it is useful to first look at some of the implications of the methods that have been used in the past.

2.1. *Are male lower urinary tract symptoms always due to benign prostatic hyperplasia?*

Animal studies and clinical data demonstrate that bladder outlet obstruction causes LUTS, and prostatic enlargement is a possible cause of obstruction; however, there is little evidence that the reverse is also true (ie, that male LUTS can always be explained by obstruction and/or prostate enlargement). This is illustrated by the finding that even men with small prostates may have severe symptoms, whereas even patients with very large prostates have only mild to moderate symptoms in some cases (Fig. 1). Moreover, storage symptoms in particular can persist even after successful deobstruction, and recent data show that treatment effects on obstruction only poorly correlate with those on LUTS [1]. Finally, treatment results in a large recent study in which classical inclusion criteria of earlier BPH and overactive bladder (OAB) trials were applied, differed considerably from those reported previously in a consistent manner when only BPH or only OAB criteria were used [2]. Nevertheless, most existing treatment studies have not vigorously excluded LUTS causes other than BPH, particularly a concomitant OAB. Thus, it is probably inappropriate to assume that male LUTS are always prostate related, but, to be in line with the patient populations which have largely been studied, we will adhere to the term LUTS/BPH for the purpose of this manuscript.

2.2. *How are lower urinary tract symptoms and disease progression being measured?*

LUTS are typically quantified by validated symptom scales such as the International Prostate Symptom Score (IPSS). Of note, the IPSS is a tool to quantify symptoms and not a tool to make the diagnosis of LUTS/BPH, a fact which is highlighted by the finding that women can also exhibit high IPSS values. Moreover, it should be noted that four of the seven IPSS items relate to voiding and postvoiding symptoms, whereas only three of the items relate to storage symptoms. This causes an inherent bias of the IPSS towards voiding symptoms and hence towards treatments reducing prostate size and/or bladder outlet obstruction. Additionally, the presence of a given symptom does not necessarily mean that it bothers the patient.

A frequently applied objective indicator of symptom severity in LUTS/BPH patients is free-flow

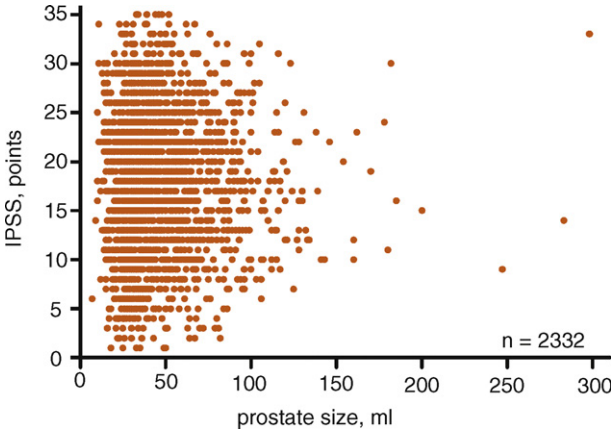

Fig. 1 – Correlation between prostate size and International Prostate Symptom Score (IPSS) is shown. Data are baseline findings from consecutive patients consulting Jean de la Rosette over the course of 10 yr.

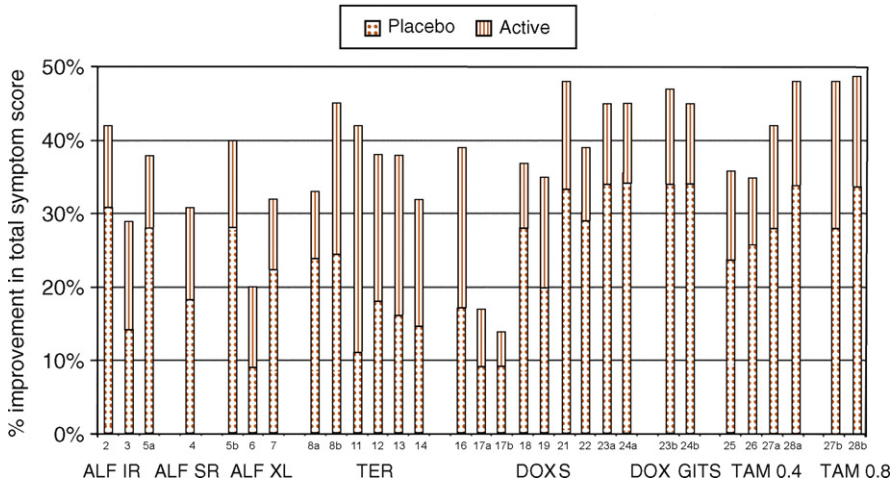

Fig. 2 – Improvements of International Prostate Symptom Score (IPSS) on treatment with various α1-adrenoceptor antagonists or with corresponding placebo are shown. Reproduced with permission from Elsevier [9]. ALF = alfuzosin; DOX = doxazosin; TAM = tamsulosin; TER = terazosin; IR = immediate release; SR = sustained release; XL = extended release; S = standard; GITS = gastrointestinal therapeutic system.

maximum flow rate (Q_{max}). However, in the absence of pressure-flow studies, Q_{max} is not a pure indicator of bladder outlet resistance but rather, at least in part, also reflects bladder contractility. Accordingly, neither Q_{max} baseline values nor their improvement on treatment correlate well with those of the IPSS or bladder outlet resistance [1].

Despite a lack of predictability in a given patient, LUTS/BPH is a progressive condition based on group averages. Progression can be assessed based on prostate size (or its surrogate parameter, prostate-specific antigen [PSA] level), occurrence of complications such as acute urinary retention (AUR), and need to change over to surgical treatment, as well as symptom progression; combined end points have also been applied [3]. The definition of progression has major implications on how effective specific treatments are considered. Prostate size can be reduced by ARIs but not by ARBs. While both ARIs and ARBs prevented AUR in short studies ($\leq$1 yr), in longer studies, which better reflect the remaining life expectancy of patients, only ARIs were effective [3]. In contrast, symptom progression was more effectively prevented by ARBs than by ARIs [3], unless a very large prostate was present at baseline [4]. Accordingly, both ARBs and ARIs were effective against combined end points, and that is where their combination may have specific benefits [3].

2.3. *Implications of study design*

The *classical* LUTS/BPH medical treatment studies have been based on a clinical diagnosis rather than on proof that symptoms were prostate related, and certain thresholds of IPSS and/or Q_{max} have been applied as enrolment criteria. These criteria look remarkably similar across studies, possibly reflecting the effect of regulatory requirements; nevertheless, improvements in IPSS in the placebo arm of controlled studies differed between 9% and 33% (Fig. 2). This makes indirect comparisons among studies difficult. While the major source of heterogeneity between studies is unclear, it should be noted that ARB studies have tended to include more symptomatic patients, whereas ARI studies have tended to include those with larger prostates and/or higher PSA levels.

The use of thresholds of IPSS and Q_{max} values as inclusion criteria has important implications for the interpretation of treatment results. Thus, if a patient at the time of randomisation needed to have an IPSS above a certain value and a Q_{max} below a certain value, a single-sided regression to the mean results (ie, for purely statistical reasons even without any treatment), and both values by average will ''improve,'' but that does not reflect any beneficial effect of treatment. Of note, more recent studies not requiring a certain Q_{max} as an inclusion criterion have reported much less (if any) Q_{max} improvement in the placebo arm than in earlier studies [5].

Another aspect of the study design is based on the fact that most controlled studies on medical treatment of LUTS/BPH have involved a single-blind, often placebo-controlled run-in period, and reported baseline parameters were only measured at the end of this run-in period. While few studies have specifically documented symptom alterations during this run-in period, those studies that did

document them have expectedly and consistently reported considerable ''improvements'' [6]. This has several implications: First, the ''real'' improvement of a patient during routine treatment, which lacks a run-in period, is likely to be the sum of those occurring during run-in and during active treatment in the randomised studies. This means that reported data from randomised studies systematically underestimate medical treatment results [6]. This also overemphasises the difference in efficacy among medical treatments and surgical treatments, which lack a run-in period. Second, the improvements during the single-blind run-in lead to an overestimation of the contribution of active drug to the overall treatment results. All of the above implications of study design need to be considered in the interpretation of the reported study outcomes.

3. Alpha-blockers

3.1. *Mechanism of action*

Historically it has been assumed that ARBs act by antagonising the effect of endogenously released noradrenaline on prostate smooth-muscle cells, thereby reducing prostate tone and hence bladder outflow obstruction. Contraction of the human prostate is mediated predominantly if not exclusively by α_{1A}-adrenoceptors [7]. ARBs, however, have only little effect on urodynamically determined outflow resistance [8], and treatment-associated improvement of LUTS correlated only poorly with those of obstruction [1]. Hence, α_1-adrenoceptors located outside the prostate (eg, in the urinary bladder and/or spinal cord and potentially including additional receptor subtypes) are being discussed as mediators of beneficial effects of ARBs. The α_1-adrenoceptors in blood vessels, in other nonprostatic smooth-muscle cells, and in the central nervous system are considered as mediators of side-effects associated with ARB treatment, and all three receptor subtypes may be involved. This concept has favoured the use of α_{1A}-selective ARBs, but it remains to be determined whether α_{1A}-selectivity is the only or even main reason for a good tolerability of tamsulosin.

3.2. *Available drugs*

Following the early and largely investigational use of phenoxybenzamine and prazosin in LUTS/BPH treatment, presently four drugs are mainly used: alfuzosin, doxazosin, tamsulosin, and terazosin.

Table 1 – Formulations and standard doses of clinically available drugs for lower urinary tract symptoms and benign prostatic hyperplasia

Drug	Dosage
α_1-adrenoceptor antagonists	
Alfuzosin	
Immediate release	3 × 2.5 mg
Sustained release	2 × 5 mg
Extended release	1 × 10 mg
Doxazosin	
Immediate release	1 × 4–8 mg
Gastro-intestinal therapeutic system	1 × 4–8 mg
Tamsulosin*	
Modified release	1 × 0.4 mg
Orally controlled absorption system	1 × 0.4 mg
Terazosin immediate release	1 × 5–10 mg
5α-reductase inhibitors	
Dutasteride	1 × 0.5 mg
Finasteride	1 × 5 mg

* In some Asian countries the registered tamsulosin dosage is 0.2 mg/d, although no published data demonstrate that the dose–response relationship differs between Asians and other ethnicities. In the Americas 0.8 mg/d is also registered, which may be associated with minor increases in efficacy at the cost of reduced tolerability.

Over time, alfuzosin has been clinically available in three formulations; doxazosin and tamsulosin have been clinically available in two formulations each; and terazosin has been clinically available in one formulation (Table 1). While different formulations of a given drug can differ in their pharmacokinetic behaviour and, perhaps, in their tolerability profile, the overall clinical impact of the different formulations is modest. Naftopidil and more recently silodosin are used in some countries, but only limited clinical data are available on these two drugs; therefore, they will not be discussed in detail in this article. The limited available evidence, however, does not suggest that they differ substantially from the other ARBs.

3.3. *Efficacy*

Indirect comparisons between the ARBs and more limited direct comparisons demonstrate that all of them have similar efficacy when applied in appropriate doses [9]. Thus, in controlled studies they typically reduce IPSS (after the run-in period) by about 35–40% and they increase Q_{max} by about 20–25%, but considerable improvements have also been seen in the corresponding placebo arms (Fig. 2) [9,10]. In real-life, open-label studies (lacking a run-in period), IPSS improvements of up to 50% and Q_{max} increases of up to 40% have been reported [11]. While improvements take a few weeks to fully develop,

statistically significant efficacy over placebo has already been demonstrated within hours to days. When efficacy is expressed as a percentage of improvement in IPSS, it appears to be similar in patients with mild, moderate, and severe symptoms [11]. ARB efficacy does not depend on prostate size [12] and is similar across age groups [11]. ARBs do not reduce prostate size and do not prevent AUR in multiyear studies [3]; accordingly, some patients require a change to a surgical treatment approach over time. While the efficacy of ARBs against symptoms appears to be maintained over at least 4 yr in controlled studies [3], the rate of changing to surgical treatment in real life may be considerably higher [13]; the reasons for this discrepancy are not well understood.

3.4. *Tolerability*

While alfuzosin, doxazosin, and terazosin are similar to each other chemically and with regard to a lack of α_1-adrenoceptor subtype selectivity. With regard to the side-effect profile, alfuzosin is more similar to tamsulosin than to doxazosin and terazosin. The mechanisms underlying such differential tolerability are not fully clear, but they may involve partitioning into lower urinary tract tissues by alfuzosin and tamsulosin. Moreover, factors such as subtype selectivity (tamsulosin) and smooth pharmacokinetic profiles of certain formulations may also contribute to the tolerability profile of specific drugs.

The most frequent side-effects of ARBs are asthenia, dizziness, and (orthostatic) hypotension. While a reduction of blood pressure may be beneficial in hypertensive patients, at least some of the observed asthenia and dizziness can be attributed to decreasing the blood pressure. Vasodilating effects are most prominent with doxazosin and terazosin, and much less common for alfuzosin and tamsulosin (odds ratios for vascular-related adverse events are 3.32, 3.71, 1.66, and 1.42, respectively, the latter not reaching statistical significance [10]). Patients with cardiovascular comorbidities and/or vasoactive comedications may be particularly susceptible to ARB-induced vasodilatation [14]. This includes not only antihypertensive drugs such as β-adrenoceptor antagonists, diuretics, Ca-channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists but also phosphodiesterase (PDE) inhibitors used in the treatment of erectile dysfunction [14].

Despite a long-standing and widespread use of ARBs, an adverse event related to ocular function termed *intraoperative floppy iris syndrome* (IFIS) has been discovered only recently in the context of cataract surgery [15]. While IFIS has been observed with all ARBs, most reports relate to the use of tamsulosin. Whether this reflects a greater risk with tamsulosin than with other ARBs, or rather its greater use, remains to be determined, particularly because the ratio between doses yielding ocular effects and those acting on the lower urinary tract, at least in experimental animals, are similar for all ARBs [16]. It appears prudent not to initiate ARB treatment prior to an already planned cataract surgery. Existing ARBs treatment should be stopped prior to eye surgery, but how long prior to surgery remains unclear. Of note, the occurrence of IFIS complicates cataract surgery and makes it technically more demanding for the ophthalmologist, but there are no reports that it puts the health of the patient at risk.

As LUTS/BPH and erectile dysfunction coexist frequently, medical BPH treatment should not further impair sexual function. A systematic review has concluded that ARBs do not adversely affect libido; if anything, they have a small beneficial effect on erectile function, but in some cases they can cause abnormal ejaculation [17]. While this has long been assumed to reflect retrograde ejaculation, more recent data demonstrate that it rather is due to a (relative) anejaculation. Young age is an apparent risk factor for ARB-associated abnormal ejaculation. While abnormal ejaculation has been observed more frequently with tamsulosin than with other ARBs, such difference did not reach statistical significance in studies directly comparing it with alfuzosin, and it is not associated with reductions in overall sexual function [17]. The apparently greater risk for abnormal ejaculation with tamsulosin is intriguing because, on the one hand, an even more α_{1A}-selective drug, silodosin, carries an even greater risk [18]; on the other hand, all ARBs are dosed to effectively block α_{1A}-adrenoceptors. Hence, the mechanism underlying abnormal ejaculation remains to be elucidated.

3.5. *Practical considerations*

All ARBs are now available in formulations which are suitable for once-daily administration. To minimise adverse events, it is recommended that dose titration be used on initiation of treatment with doxazosin or terazosin, whereas this is not required for alfuzosin or tamsulosin. Based on rapid onset of action, ARBs, specifically those not requiring dose titration, can be considered for intermittent use in patients who do not require long-term

treatment due to the fluctuating intensity of their symptoms.

4. Two 5α-reductase inhibitors

Two ARIs are available for clinical use: dutasteride and finasteride (Table 1).

4.1. *Mechanism of action*

Androgen effects on the prostate, similar to those on hair follicle cells, are mediated by the testosterone metabolite dihydrotestosterone, which is formed by the enzyme 5α-reductase [19]. Two isoforms of this enzyme exist: Finasteride inhibits only one of these effects, whereas dutasteride inhibits both with similar potency. The clinical role of dual inhibition remains unclear. ARIs cause a reduction of prostate size by about 20%, and they reduce circulating PSA levels by about 50% [20].

4.2. *Efficacy*

ARIs reduce the IPSS and increase Q_{max} in LUTS/BPH patients [20]. Symptom reduction by ARIs depends on prostate size and may not exceed that of placebo in patients with a gland of <40 ml [21]. Indirect comparison between individual studies and one direct comparative study (unpublished data) indicate that dutasteride and finasteride are equally effective in the treatment of LUTS/BPH. Most direct comparative studies with ARBs have demonstrated that ARIs reduce symptoms not only more slowly but also less effectively [3]. The exception is a recent 2-yr study in patients with very large prostates where dutasteride reduced symptoms as much or even more than tamsulosin [4]. In contrast, ARIs (but not ARBs) reduce disease progression as defined by AUR or progression to surgery [3,22]. Prevention of disease progression by ARIs is already detectable with prostate sizes considerably <40 ml [23].

4.3. *Tolerability*

The most relevant adverse effects of ARIs are related to sexual function. They include reduced libido, erectile dysfunction, and, less frequently, abnormal ejaculation [20].

4.4. *Practical considerations*

Due to the slow onset of action, ARIs are not suitable for intermittent treatment. Their rational use is only warranted if a multiyear treatment is intended. Their effect on the circulating PSA level needs to be considered in the use of this parameter for prostate cancer screening. Interestingly, ARIs can reduce blood loss during transurethral prostate surgery, possibly due to their effects on prostatic vascularisation [24]. Moreover, ARIs appear to reduce the risk of developing prostate cancer [25].

5. Combination treatment

Based on their differential mechanism of action, several studies have investigated possible benefits and risks of combining ARBs and ARIs. Initial studies of 6–12 mo duration have not demonstrated benefits with regard to symptom improvement for the ARB/ARI combination as compared with ARB monotherapy [26]. A 4-yr study, however, has demonstrated additive effects of both drug types on a combined end point of disease progression, reflecting that ARIs prevent the development of urinary retention, whereas ARBs prevent symptom progression [3]. This clinical benefit came at the expense of additive adverse events. Given the greater side-effects and treatment costs of combination treatment, it remains to be determined for which patients it indeed is beneficial. It appears plausible to assume that patients at a high risk of progression may specifically benefit from combination treatment. Alternatively, patients at a high risk of progression may retain a large absolute risk of progression, even in the presence of a considerable reduction of relative risk. Hence, such high-risk patients may benefit even more from surgical treatments.

6. Emerging novel treatments

Although ARBs and ARIs provide adequate symptom control and/or inhibition of disease progression for many patients with acceptable tolerability profiles, they do not sufficiently improve symptoms in some patients. While many drug classes are currently undergoing experimental or clinical evaluation for their potential usefulness in LUTS/BPH treatment, for the vast majority of them the available clinical data are too limited to allow any recommendation [27]. Among the possible candidates, intraprostatic botulinum toxin administration is of interest because it apparently shrinks the prostate to a major extent [27].

6.1. *Phosphodiesterase inhibitors*

Based on the expression of PDEs both in the prostate and the bladder, studies with sildenafil,

tadalafil, and vardenafil have explored the used of PDE inhibitors in LUTS/BPH treatment [5]. In the absence of direct comparative studies of adequate size, it appears that PDE inhibitors are as effective as ARBs in reducing IPSS but apparently lack effects on Q_{max}. While a once-daily administration of tadalafil has now been registered in some countries, its use for the treatment of LUTS/BPH has remained off-label. It may be attractive because it also addresses possibly coexisting erectile dysfunction, but in most countries, it is priced much higher than ARBs or ARIs.

6.2. *Muscarinic receptor antagonists*

In some men, storage symptoms in particular are insufficiently controlled by classical LUTS/BPH treatments, including surgical approaches. Because the storage symptoms attributed to BPH are basically the same as those of OAB and because muscarinic receptor antagonists are the standard treatment for OAB, several recent studies have evaluated the use of muscarinic receptor antagonists in LUTS/BPH patients. Most of these studies have been performed in addition to studies of ARB use, and they generally have yielded positive results. Moreover, there have been no major elevations of postvoiding residual urine, indicating a limited risk for urinary retention [28]. Whether these findings indeed demonstrate efficacy in LUTS/BPH or rather reflect that not all male LUTS are prostate related remains to be determined. In this regard, the most informative study has compared a muscarinic antagonist, an ARB, and their combination to placebo [2]. This study has used inclusion criteria which are a hybrid of those classically used in LUTS/BPH and in OAB studies. Accordingly, each of the two drugs in isolation did less well compared to placebo than may have been expected in their classical indication, but the combination of both showed remarkable efficacy. While muscarinic receptor antagonists may be the most promising novel treatment for LUTS/BPH in the near future, additional studies are needed to identify which patients indeed benefit from muscarinic antagonists alone and/or in combination with ARBs.

7. Conclusions

While several novel treatment options are currently under investigation, ARBs and ARIs are the only two drug classes that are approved for routine use in LUTS/BPH patients. While the main strength of ARBs is symptom reduction, the main strength of ARIs is prevention of disease progression on long-term use. There is little evidence for differences in treatment efficacy in either group, but the ARBs alfuzosin and tamsulosin have better tolerability. Based on these data, it appears plausible that the question of whether to use ARBs, ARIs, or their combination should mainly be driven by the specific treatment goals of a given patient.

Conflicts of interest

Within the past 5 yr Martin Michel has received research support, consultancy honoraria, and/or lecturer honoraria from the following companies in the LUTS/BPH field: Astellas, Bayer, Boehringer Ingelheim, Eli Lilly, and GlaxoSmithKline. Jean de la Rosette has received such support from Astellas and GSK.

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