Chapter 3: Results of the Treatment Outcomes Analyses

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Introduction

It is the hope that this clinical Guideline will provide a useful reference on the effective evidence-based management of male lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). The current Guideline reviews a number of important aspects in the management of LUTS presumed secondary to BPH (LUTS/BPH) in our male population as an update to the 2003 AUA Guideline on BPH. It speaks to diagnostic tests available to identify the underlying pathophysiology and help management of symptoms. Pharmacotherapy and watchful waiting as well as lifestyle issues are addressed, including complementary and alternative medicines (CAM). The current literature for standard surgical options, as well as that on minimally invasive procedures is similarly reviewed. Despite the rigorous methodology and detail used in these various areas, there are some areas where data could not be found (randomized controlled trials [RCTs]) for some topics. In some situations, the Panel, not surprisingly, was forced to recommend best practices based on expert opinion.

The expert Panel examined three overarching key questions for current and emerging pharmacotherapeutic, surgical, and alternative medicine therapies: (1) What are the comparative efficacy and effectiveness of currently available and emerging treatments for BPH? What are the predictors of beneficial effects from treatments? (2) What are the adverse events associated with each of the included treatments and how do the adverse events compare across treatments? (3) Are there subpopulations in which the efficacy, effectiveness and adverse event rates vary from those in general populations?

A qualitative analysis of the available evidence was performed on all interventions and outcomes. A narrative synthesis was presented along with in-text tables summarizing important study and population characteristics, efficacy and effectiveness outcomes and safety outcomes. Forest plots of study effect sizes were prepared when there were at least three to four points for an intervention. Studies were stratified by study design, comparator, follow-up interval and intensity of intervention. Meta-analyses (quantitative synthesis) of outcomes of RCTs were planned; however, data were either sparse (i.e., there were small numbers of studies in certain categories), or not sufficiently homogeneous for the pooled effect to be meaningful. The studies varied with respect to patient selection; randomization; blinding mechanism; run-in periods; patient demographics, comorbidities, prostate characteristics and symptoms; drug doses; other intervention characteristics; comparators; rigor of follow-up; follow-up intervals; trial duration; timing of the trial; suspected lack of applicability to current practice in the United Sates; and techniques of outcomes measurement. These data limitations affected the quality of the materials available for review, making formal meta-analysis impractical or futile. The resulting evidence tables for each treatment alternative evaluated are presented in Appendix A8.

Based on the evidence and Panel expertise guideline statements were developed by the Panel and are presented in Chapter 1. Statements that are new or have been updated from the 2003 Guideline are outlined in Table 3.1.

Table 3.1. New and updated guideline statements in the 2010 Guideline

Agent/Therapy	Guideline Statement
Alpha-adrenergic Blockers	***Option:*** **Alfuzosin, doxazosin, tamsulosin, terazosin are appropriate and effective treatment alternatives for patients with bothersome, moderate to severe LUTS secondary to BPH (AUA Symptom Index score ≥8). Although there are slight differences in the adverse events profiles of these agents, all four appear to have equal clinical effectiveness.*** [Based on review of the data and Panel consensus.] *Silodosin was approved by the FDA but there were no published articles in the peer- reviewed literature prior to the cut-off date for the literature search.
Intraoperative Floppy Iris Syndrome and Alpha blocker Use	***Recommendation:*** **Men with LUTS secondary to BPH for whom alpha blocker therapy is offered should be asked about planned cataract surgery. Men with planned cataract surgery should avoid the initiation of alpha blockers until their cataract surgery is completed.** [Based on review of the data and Panel consensus.] ***Recommendation:*** **In men with no planned cataract surgery, there are insufficient data to recommend withholding or discontinuing alpha blockers for bothersome LUTS secondary to BPH.** [Based on review of the data and Panel consensus.]
5-Alpha-reductase Inhibitors (5-ARIs) for Other Indications	<u>Hematuria</u> ***Option:*** **Finasteride is an appropriate and effective treatment alternative in men with refractory hematuria presumably due to prostatic bleeding (i.e., after exclusion of any other causes of hematuria). A similar level of evidence concerning dutasteride was not reviewed; it is the expert**

	opinion of the Panel that dutasteride likely functions in a similar fashion. [Based on review of the data and Panel consensus.] <u>Prevention of Bleeding During TURP</u> ***Option:*** **Overall, there is insufficient evidence to recommend using 5-ARIs preoperatively in the setting of a scheduled TURP to reduce intraoperative bleeding or reduce the need for blood transfusions.** [Based on review of the data and Panel consensus.]
Anticholinergic Agents	***Option:*** **Anticholinergic agents are appropriate and effective treatment alternatives for the management of LUTS secondary to BPH in men without an elevated post void residual and when LUTS are predominantly irritative.** [Based on Panel consensus.] ***Recommendation:*** **Prior to initiation of anticholinergic therapy, baseline post-void residual (PVR) urine should be assessed. Anticholinergics should be used with caution in patients with a PVR greater than 250 to 300 mL.** [Based on Panel consensus.]
Complementary and Alternative Medicines (CAM)	***Recommendation:*** **No dietary supplement, combination phytotherapeutic agent, or other nonconventional therapy is recommended for the management of LUTS secondary to BPH. This includes saw palmetto and Urtica dioica.** [Based on review of the data and Panel consensus.]

Minimally Invasive Therapies	***Standard:*** **Safety recommendations for the use of transurethral needle ablation (TUNA) of the prostate and transurethral microwave thermotherapy published by the U.S. Food and Drug Administration should be followed.** http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/default.htm [Based on review of the data.]
Transurethral Needle Ablation of the Prostate and Transurethral Microwave Thermotherapy	***Option:*** **TUNA and and Transurethral Microwave Thermotherapy (TUMT) of the prostate is an appropriate and effective treatment alternative for bothersome moderate or severe LUTS secondary to BPH.** [Based on review of the data and Panel consensus.]
Laser Therapies	***Option:*** **Transurethral laser enucleation (holmium laser resection of the prostate [HoLRP], holmium laser enucleation of the prostate [HoLEP]), transurethral side firing laser ablation (holmium laser ablation of the prostate [HoLAP] and photoselective vaporization [PVP]) are appropriate and effective treatment alternatives to transurethral resection of the prostate and open prostatectomy in men with moderate to severe LUTS and/or who are significantly bothered by these symptoms. The choice of approach should be based on the patient's presentation, anatomy, the surgeon's level of training and experience and discussion of the potential benefit and risks for complications. Generally, transurethral laser approaches have been associated with shorter catheterization time and length of stay with comparable improvements in LUTS. There is a decreased risk of the perioperative complication of transurethral resection syndrome. Information concerning certain outcomes, including retreatment and urethral strictures, is limited due to short follow-up. As**

	with all new devices, comparison of outcomes between studies should be considered cautiously given the rapid evolution in technologies and power levels. Emerging evidence suggests a possible role of transurethral enucleation and laser vaporization as options for men with very large prostates (> 100 g). There are insufficient data on which to base comments on bleeding. [Based on review of the data and Panel consensus.]
Transurethral Resection of the Prostate (TURP)	***Option:*** **TURP is an appropriate and effective primary alternative for surgical therapy in men with moderate to severe LUTS and/or who are significantly bothered by these symptoms. The choice of a monopolar or bipolar approach should be based on the patient's presentation, anatomy, the surgeon's experience and discussion of the potential risks and likely benefits.** [Based on review of the data and Panel consensus.]
Laparoscopic and Robotic Prostatectomy	***Option:*** **Men with moderate to severe LUTS and/or who are significantly bothered by these symptoms can consider a laparoscopic or robotic prostatectomy. There are insufficient published data on which to base a treatment recommendation.** [Based on review of the data and Panel consensus.]

Types of treatment outcomes

Two types of treatment outcomes -- efficacy and adverse events -- were evaluated in the development of this Guideline. Because efficacy outcomes were measured on a scale that could change with treatment and time course, while adverse events were measured as occurrences, restrictions were imposed on the data requirements and the analytic methods used for each type of outcome.

Efficacy and Effectiveness Outcomes

Efficacy outcome measures evaluate the efficacy of the treatment in relieving the symptoms or sequelae of BPH. In the past, the direct outcomes (e.g., those that patients can directly perceive) of BPH therapies have been measured in a qualitative fashion (e.g., as improved, unchanged, or worsened) and/or by global subjective assessment either by physicians or patients. More recently, quantitative measurement tools have been developed and validated. Symptom scores and quality of life (QoL) questionnaires are examples of instruments that provide an objective assessment of subjective phenomena and allow a numerical estimate of the severity of LUTS, the bother induced, interference with daily activities and impact on disease-specific QoL.

Symptom Scores

A variety of symptom scores utilized to evaluate BPH therapies are discussed below and are presented in Appendices A5 and A6. The current international standard, the American Urological Association Symptom Index/International Prostate Symptom Score (AUA-SI/I-PSS), is in widespread use.

Validated Symptom Scores

The AUA commissioned the development of a quantitative symptom severity and frequency score. The resulting instrument is a seven-question questionnaire with a response scheme from 0 to 5 for each question for a total score ranging from zero to 35 in the order of increasing symptom severity and frequency. Symptoms of both irritative and obstructive LUTS are addressed. This AUA-SI has been culturally and linguistically validated, has been translated into many languages and is identical to the first seven symptom questions of the I-PSS which is used worldwide.

The Danish Prostatic Symptom Score is another validated symptom scoring instrument that incorporates the concept of bother due to symptoms in addition to simple enumeration of symptom severity and frequency.[1]

Modified Symptom Scores

Modified symptom scores are slight modifications of recognized, but not necessarily validated, scoring systems. An example of a modified scoring system that has been utilized extensively in trials of the 5-ARI, finasteride, is the Quasi-AUA-SI. Only studies that employed complete symptom scores were included; those that used partial scales (e.g., bothersomeness or irritability scales) were excluded.

Studies using the AUA-SI or I-PSS with scoring based on ranges other than zero to 35 were rescaled for consistency.

Quality of Life Scoring Instruments

Quality of life scoring instruments can be classified under two broad categories: (1) generic instruments, such as the SF-36, that do not focus on the impact of a particular disease state or a set of symptoms and (2) disease-specific QoL instruments, which measure the impact of specific diseases or sets of symptoms on the health of a given individual. Of all generic and disease-specific QoL scoring instruments, the BPH Impact Index (BPH II) and the Disease Specific QoL Question have been validated and were used herein.

The BPH II was developed and validated by the AUA Measurement Committee (1995) with the objective of determining the degrees to which urinary problems affect various domains of health and impact the perception of health in a given individual. Three questions are scored on a scale from zero to three and one question on a scale from zero to four, for a total score ranging from zero to 13 in order of increasing severity.[2] The BPH II has been used in studies of medical as well as many invasive therapies, thus providing comparative data.

A single global question complements the seven individual symptom severity and frequency questions of the AUA-SI by adding a disease specific QoL (called the Disease Specific QoL Question) dimension. Clearly, a single question cannot possibly capture the global impact of LUTS on the quality of an individual's life; however, it has been accepted as a valuable beginning for a patient/physician conversation regarding this issue. The question simply asks, "If you were to spend the rest of your life with your urinary symptoms the way they are right now, how would you feel about this?" The answer scheme ranges from "delighted" to "terrible," on a score from zero to six, in the order of increasing severity.

Peak Urinary Flow Rate

The urinary flow rate is the strength or intensity of the urinary stream over time determined by measurement of the voided volume and the voiding or micturition time. Units are expressed in mL/sec. Dividing the voided volume by the voiding or micturition time yields the average urinary flow rate (e.g., 200 mL [voided volume] divided by 20 seconds [voiding time] yields an average urinary flow rate of 10 mL/sec). The most commonly reported measure is the peak or maximal urinary flow rate (Qmax). This parameter, however, is nonspecific in that Qmax decreases with advancing age in both sexes. In addition, a lower-than-expected urinary flow rate can be caused by bladder muscle weakness, subvesical or bladder outlet obstruction (BOO), or urethral stricture.

In the interpretation of the Qmax, a minimum voided volume is usually required for the flow rate recording to be valid. A flow rate of less than 10 mL/sec is more suggestive of an obstructed state, while a flow rate above 15 mL/sec is more suggestive of a nonobstructed state. Flow rates between 10

and 15 mL/sec are considered equivocal. The interpretation of this measurement is based on the correlation between free flow rates and invasive pressure-flow studies which suggest that the probability of obstruction is very low if the maximum flow rate is over 15 mL/sec, while the probability is relatively high if the maximum flow rate is under 10 mL/sec.

Unfortunately, Qmax correlates poorly with subjective symptoms such as severity and frequency of bother, QoL, residual urine or prostate size. Peak urinary flow is a weak, patient-oriented outcome in that the patient only marginally experiences flow rate differences (primarily based on urination time). Although Qmax is not particularly useful from a diagnostic point of view, it is recommended as an optional test prior to treatment discussion because the result may predict the natural history as well as the response to certain therapeutic interventions. The Panel elected to include this outcome in the analysis because repeated urinary flow rate recordings are useful for patient follow-up and in comparing treatment outcomes among trials using the same or different treatments.

Efficacy Outcomes Not Analyzed

Although initially considered for review, several efficacy and effectiveness outcomes were excluded from the final analysis as part of the 2010 BPH Guideline. These comprised the following urodynamic parameters: invasive pressure flow studies, percent (%) of residual volume voided, bladder capacity at first desire/strong desire to void, detrusor pressure at cystometric capacity, bladder compliance, detrusor opening pressure and the amplitude of overactive detrusor contractions. There were several reasons for their elimination, including concerns about test-retest reproducibility, predictability of long-term outcomes, controversy about the proper interpretations of measurement, lack of Panel consensus, applicability to general LUTS/BPH patients and a small number of articles for review.

Several papers reported on prostate volume as measured by digital rectal exam (DRE). Such outcomes were rejected because estimating prostate size by DRE is notoriously unreliable. Correlation coefficients between DRE and transrectal ultrasound (TRUS) measurements vary widely from 0.4 to 0.9 and unfortunately greater experience in performing this measurement does not necessarily lead to greater accuracy, although training with a dedicated model may improve precision.[3, 4] In general, the volume of smaller prostates is overestimated and of larger glands is underestimated with the degree of underestimation increasing with increasing actual size.

Symptom scores using only portions of validated questionnaires were excluded because of concerns about applicability, validation and interpretation of results. Similarly, symptom diaries with unvalidated scoring systems were also excluded. Biologic measures of dihydrotestosterone (DHT), estradiol and blood pressure were excluded because of concerns about clinical utility and applicability, laboratory assay variability, predictability of long-term outcomes and a small number of articles for review.

Safety Outcomes

The adverse events outcomes include side effects and complications of treatment and disease progression (e.g., development of urinary retention). Adverse events have been grouped together since there were no consistent reporting standards or naming standards for such events.

Watchful Waiting

The expectant management of LUTS/BPH is defined as "watchful waiting or active surveillance". Many men with BPH and LUTS do not require treatment because their symptoms are not significantly interfering with their QoL. Moreover, progression of symptoms or deterioration of QoL occurs only in a portion of men and treatment intervention is still effective, even when delayed. Watchful waiting studies, like the Veterans Affairs Cooperative Trial (VA CO-OP)[5], demonstrate slight symptom improvement in up to one third of men. However, the magnitude of the symptom improvement is small. Even placebo, arguably more effective than watchful waiting, produces no more than a one to two point mean improvement in symptom score in men followed for four years.[6]

Acute urinary retention (AUR) and invasive treatment occur in a certain subset of men followed conservatively. These complications are more frequent in men with larger prostates and higher serum prostate-specific antigen (PSA) levels than in other men. For example, men with a PSA of 3.3 ng/mL or greater have approximately a 5% annual risk of AUR or surgery compared to less than 2% annual risk for men with a PSA less than 1.3 ng/mL. Even in the highest risk groups, not all men develop AUR or require surgery.[6, 7] Therefore, serum PSA and prostate size can be used as parameters to advise men on their overall risk but not as the sole basis for treatment recommendations.[8]

Study Outcomes

In addition to the above citations that were published prior to the 2003 Guideline, a focused literature search was conducted to identify those studies with long term follow-up reporting outcomes in a group of men who received the approach of watchful waiting with no active therapy. Through this process, we identified four studies published in peer-reviewed journals that met the above criteria. Detailed evidence tables reviewing these studies are provided in Appendix A8. The Panel review of these data supports the following.

The placebo arm of the Medical Therapy of Prostate Symptoms (MTOPS) Trial was analyzed to determine the rate and clinical predictors of BPH progression.[9] A total of 737 men were randomized to placebo and the average length of follow-up was 4.5 years. Clinical progression of BPH [defined as an increase in the AUA symptom score of four or more points, AUR, urinary incontinence, renal insufficiency, or recurrent UTI (urinary tract infection)] occurred at the rate of 4.5 events per 100 person-years, which equals a cumulative incidence of 17% over the course of the study. Progression of the symptom score, as defined *a priori* as a sustained increase of four points on the I-PSS was the most

common event (3.6 per 100 person-years). BPH-related invasive treatment was delivered to 40 men (5.4%), with a rate of 1.3 events per 100 person-years.

In the MTOPS placebo group, a total prostate volume of more than 31 mL correlated with increased rates of clinical progression ($p<0.0001$), worsening of symptoms ($p=0.001$), urinary retention ($p=0.034$) and need for invasive surgical treatment ($p=0.0005$), compared with smaller prostates. Similarly, men with baseline PSA of greater than 1.6 mg/dL had significantly increased rates of clinical progression and other adverse outcomes ($p<0.05$). Qmax increased by 1.4 mL per second on average during MTOPS in the placebo group, however, men with a baseline Qmax of less than 10.6 mL per second had a significantly greater risk of clinical progression ($p=0.011$), worsening symptoms ($p=0.0005$), and surgical treatment ($p=0.033$) than subjects with a higher Qmax. Postvoid residual volume of more than 39 mL also predicted adverse outcomes. Age >62 years predicted clinical progression ($P=0.0002$) and worsening symptoms ($P=0.0003$), compared with younger men.

In an observational study, Djavan and colleagues (2004) examined 397 men with mild symptoms of BOO (I-PSS<8) over four years of follow-up.[10] Clinical progression as defined by an increase in I-PSS to $\geq$8 occurred at the following rates: six-months (6%); 12 months (13%); 24 months (24%); 36 months (28%); and 48 months (31%). Urinary retention occurring in 4.9% and 0.6% required transurethral resection of the prostate (TURP). Predictors for progression included higher baseline PSA ($p=0.001$), higher transition zone volume ($p=0.001$), and a greater obstructive symptom score ($p=0.04$). It is important to note that the differences in the definition of "progression" in such studies so as not to overestimate the risk of clinical progression.

Sarma and colleagues (2004) surveyed 369 African-American men in a prostate cancer and BPH study, recontacting them four years later to examine the progression of LUTS.[11] Only men with complete baseline AUA-SI data and no BPH-related treatment during the four-year follow-up were included in the final survey, which examined 149 men. In this select group, I-PSS did not change significantly during the four-year follow-up. Of men who initially had mild-to-no symptoms at baseline (AUA-SI $\leq$ 7), 26.4% reported moderate to severe symptoms at follow-up and this progression of symptoms occurred across age decade and increased with age to the seventh decade. Of men who initially had moderate-to-severe symptoms, at least 50% continued to report moderate-to-severe symptoms. In a multivariate model, older age predicted progression ($p=0.01$) and younger age predicted regression ($P<0.0001$).

In another longitudinal cohort study of men with mild LUTS (mean I-PSS score 4.6 [SE 0.05]), 456 men completed a five-year follow-up survey (53% of those who completed the baseline survey).[12] Treatment was not required by 72.8% of men, while 26% started pharmacotherapy and 1.5% had a TURP. No predictors of symptom progression were identified. Age ($p=0.0008$) and symptom bother ($p=0.007$) predicted the need for therapy.

Summary

Watchful waiting is an appropriate strategy for many men with LUTS/BPH. It is the recommended management for men who do not have bothersome symptoms and have not developed complications of BOO from BPH. Age, baseline symptom score, serum PSA and prostate size are helpful to predict the risk of AUR and need for surgery in men managed by watchful waiting. However, neither prostate size nor serum PSA should be used as the sole determinant of the need for active therapy. The overall benefit and risks of therapy must also be considered.

Medical Therapies

Alpha-adrenergic Antagonists (Alpha-blockers)

Alpha-adrenergic antagonists, also known as alpha-blockers, are a widely used class of medications for the treatment of LUTS secondary to BPH, a disease symptom complex attributed, with various levels of evidence, to arise from two major components: static and dynamic, with an increase in prostatic smooth muscle tone believed to be largely responsible for the latter. Noradrenergic sympathetic nerves have been demonstrated to effect the contraction of prostatic smooth muscle.[13] The prostate gland contains high levels of both α_1- and α_2-adrenergic receptors[14-17]; 98% of α_1-adrenoreceptors are associated with the stromal elements of the prostate, and are thus thought to have the greatest influence on prostatic smooth muscle tone.[15] Activation of these receptors and the subsequent increase in prostatic smooth muscle tone with urethral constriction and impaired flow of urine is thought to be a major contributor to the pathophysiology of LUTS secondary to BPH. In addition, there is variable evidence that adrenergic receptors further mediate LUTS secondary to BPH via their activation within the central nervous system (CNS) and bladder.

Alpha-blockers are not unique to the prostate. The two basic subtypes of alpha-receptors (α_1 and α_2) are distributed ubiquitously throughout the human body. In general, α_2-receptors are typically located presynaptically and down-regulate norepinephrine release via a negative feedback mechanism. α_1-receptors are the postsynaptic receptors that affect a response to neurotransmitter release. Several subtypes of the α_1-receptors have been identified and classified into three groups: α_{1A}, α^{1B} and α_{1D}.[16, 18, 19] Both α_{1A}- and α_{1B}-receptors have been identified within the prostate. The α_{1A}-receptors are the predominant adrenoreceptors expressed by stromal smooth muscle cells.[15] In contrast, the α_{1B} receptors are predominantly located in the smooth muscle of arteries and veins, including the microvasculature contained within the prostate gland.[19] Within the genitourinary system, α_{1D}-receptors are mainly located in the bladder body and dome.[20] α_{1D}-receptors are also located in the spinal cord where they are presumed to play a role in the sympathetic modulation of parasympathetic activity.[21]

Knowledge of α_1-receptor subtype location and action has been instrumental to targeting of BPH therapy to useful locations. Given their location, α_{1A}-receptors are optimal targets for therapy. Blockade of the α_{1A}-receptors has been shown to reduce prostatic tone and improve the dynamic

aspects of voiding. Blockade of α_{1B} receptors leads to venous and arterial dilation as smooth muscle cells in the vessel walls relax. In some patients this can cause dizziness and hypotension due to decreased total peripheral resistance, potentially serious side effects. Stimulation of α_{1D}-receptors can lead to detrusor instability and blockade of these receptors has been shown in animal models to reduce irritative voiding symptoms.

In an effort to maximally reduce LUTS and to minimize side effects, alpha-blocker development focused on binding to the α_1-receptors and with reduced activity at α_2-receptors (unlike phenoxybenzamine, a nonselective α_1/α_2-receptor blocker). These second generation agents included terazosin, doxazosin and alfuzosin. More recently available third generation agents (e.g. tamsulosin) are thought to be more selective antagonists for prostatic α_{1A}-receptors.[22, 23] These drugs target the smooth muscle cells contained within the prostate gland and exert lesser effects on the other alpha-blocker subtypes that regulate blood pressure**. Despite the convenient classification system mentioned above, it is critical that clinicians treating LUTS/BPH realize that the *in vitro* specificity of receptor antagonism and adrenergic generation does not necessary imply an advantage for the improvement of LUTS or the minimization of side effects.**

For the purposes of this Guideline the specific agents included are **alfuzosin, doxazosin, tamsulosin and terazosin** as they theoretically act in the location that will have the greatest benefit for symptoms with the fewest side effects, remain a mainstay of LUTS/BPH therapy, and thus will be reviewed individually below. For reference, detailed evidence tables are provided in Appendix A8.

Alfuzosin

Alfuzosin, a second-generation α_1-adrenoreceptor antagonist, is indicated for the management of moderate to severe BPH symptoms. Alfuzosin is approved for the treatment of bothersome urinary symptoms attributed to BPH as well as acute urinary retention. This medication is available in several countries other than the United States as immediate-release (two to three daily doses) and long-acting formulations (once daily dose).

Randomized Controlled Trials (RCTs)

We identified five unique RCTs that fulfilled the prespecified inclusion criteria[24-28] plus a meta-analysis of three RCTs,[29] two of which were included in the five RCTs, along with an additional unpublished data set. Patient inclusion and exclusion criteria were similar across studies. In particular, 'significant other urologic disease' was an exclusion criterion in all trials. Significant comorbidities, such as heart failure,[28] unstable angina,[25, 28] poorly controlled diabetes mellitus,[28] significant renal or hepatic disease,[25, 28] postural hypotension[25, 27, 29] and significant cardiac diseases contraindicating the use of alpha-blockers[30] were generally explicitly excluded. Studies varied greatly in population size, from 81[30] to 955.[29] Study follow-up periods were either three months,[24, 27-29] six months[25] or two years[26]. Most RCTs had a placebo run-in period of two to four weeks. Study participants were usually randomized at the end of the run-in period, however, one trial randomized beforehand and 18 subjects did not receive

the study drug.[28] In trials where the run-in period preceded randomization, it was unclear how many subjects were withdrawn during the run-in period.[24, 26, 27] The study settings were largely Western Europe and North America.

The mean patient ages in years in these trials ranged in the mid 60's. Some data were provided on comorbid conditions. Hypertension was common across study groups, ranging from 27% (treatment arm) to 41% (placebo arm).[25] Other co-morbidities were occasionally reported, including coronary heart disease (6% to 10%)[25], cardiovascular disease (46%)[27], and mild-to-moderate renal insufficiency (63%)[27]. I-PSS was reported at baseline in all studies, and ranged from 16.8 to 21.7 across treatment groups. Qmax ranged from 5.1 to 9.3 mL/s in the four studies reporting these data. Most of the trials examined the long-acting formulation of alfuzosin (10 mg once daily). One trial examined the short-acting formulation with up-titration from 2.5 mg to 5 mg twice daily,[28] and another trial compared 10 mg once daily to 2.5 mg three times daily.[27] Five of the randomized studies of alfuzosin were placebo-controlled; in the sixth the comparator was doxazosin.

Single-group Cohort Studies

Six observational studies of alfuzosin (in 12 publications) were identified.[30-41] These studies were included in the safety and adverse events analyses only. All were single-group cohort studies of men with LUTS suggestive of BPH. One study was an open-label extension of an (included) RCT.[38] Patient exclusion criteria were fairly uniform across studies and included severe medical comorbidities, history of postural hypotension, other urological disorders, and BPH surgery anticipated within three to 12 months of study initiation. Two studies excluded potential participants who had demonstrated lack of efficacy to prior alpha-blocker therapy: the ALF-ONE Study and a study reported by Saad and colleagues (2005).[32, 35]

Recruitment techniques were not described; in all studies it was unclear how participants were selected. Sample size varied greatly, from 33 participants in an open-label extension study[30] to the large ALF-ONE study[32, 40] and a study by Lukacs and colleagues (2000)[36, 41]. All cohort studies but one were ≥12 months in duration, generally longer than the RCTs.[35]

The mean age in years was generally in the mid 60's. Hypertension was common among study participants for whom data were reported 23%,[31] 35%[35] and 31.5%.[36] Patients with severe comorbidities were generally excluded with two studies that presented comorbidity rates reporting low rates of diabetes mellitus (5% in ALF-ONE)[31] and ischemic heart disease (5% in ALF-ONE[31] and 12.2% in a second study[35]). In a third study, comorbidities were reported in 60% of participants, however, details as to their nature were not reported.[36] There was some variation in baseline I-PSS, with four cohorts reporting scores between 15.5 and 19.6 and one reporting a score of 21.6 (SE 0.4).[37]

Alfuzosin doses and formulations varied across studies: alfuzosin 10 mg daily was administered in three studies,[33, 35, 38] alfuzosin SR 5 mg twice daily in one study[31] and the short-acting formulation (2.5 mg three times daily) in two studies.[36, 37]These cohort studies were conducted in Western Europe or

Canada, with ALF-ONE also including centers in Africa and the Middle East. None of these studies were conducted in the United States.

Efficacy and Effectiveness Outcomes

Morbidity

The incidence of surgical treatment during the follow-up period was similar between groups with six-months[25] and two-year[26] follow-up. The incidence of AUR was similar between the alfuzosin and placebo groups at two-years follow-up (p=0.82).[25, 26] McNeill and colleagues (2005) noted high rates of urinary retention during 3-month follow-up (64% with alfuzosin and 97% with doxazosin, p-value not reported).[25] This study included subjects with AUR at baseline who then had a successful trial without a catheter with alfuzosin (phase 1 of the study).

Symptoms and Quality of Life

Total I-PSS improved significantly (p<0.05) compared with placebo in all five RCTs. Data were insufficient to perform a meta-analysis; only two studies presented comparable doses and follow-up periods (three-month data for 10 mg daily).[24, 27] A third study with three-month data was a meta-analysis containing data from two included studies.[24, 27, 29] Roerhborn and colleagues (2006) published two-year data as cumulative incidence of I-PSS worsening in graphical form.[26] We attempted to obtain three- and six-month data from the study sponsor who has possession of the primary data for this trial, but received no response. The filling and voiding subscores of the I-PSS decreased significantly (p<0.05) in both studies reporting these outcomes.[24, 27]

In the active comparator trials, I-PSS improved more with doxazosin (mean dose, 6.1 mg daily; mean change, -9.2) than with alfuzosin 2.5 mg twice to three times daily (mean change, 7.5; between-group p<0.05).[28]

QoL score also improved in all five studies (p<0.05). Again, data were insufficient to perform a meta-analysis; only two studies presented comparable doses and follow-up periods.[24, 27] QoL was not reported in the active comparator trial of doxazosin vs. alfuzosin.[28]

Pressure, Flow, Volume Outcomes

Qmax also improved significantly with alfuzosin 10 mg daily compared with placebo in three trials with follow-up between three and 12 months[24, 26, 27], as well as in the meta-analysis at three months.[29] Improvements were approximately 1 to 2 mL per second. Significant improvement did not occur, however, with alfuzosin 15 mg daily at three months follow-up.[24] Postvoid residual volumes, prostate volume, and detrusor pressure at maximum flow were not reported as outcomes in these studies. In the active comparator trial of doxazosin vs. alfuzosin, Qmax improved in both treatment groups (approximately 3 mL per second), with no significant difference between groups (p>0.05).[28] In this same comparator trial post-void residual volume increased at 14-weeks follow-up with alfuzosin

(mean change, 9.6 mL; p>0.05) and decreased with doxazosin (mean change, -29.2 mL; between-group p<0.05). These differences do not appear clinically meaningful.

Prostate-specific Antigen Levels

Follow-up PSA decreased slightly with alfuzosin compared with placebo at two-year follow-up (p=0.07) in the only study reporting this outcome.[26]

Predicators of Efficacy, Effectiveness, and Harms

Few studies provided data on the predicators of either intended benefits or harms. No study examined the relationship between race/ethnicity and benefits or harms. One trial noted that lower I-PSS at baseline predicted worsening of symptoms over two-year follow-up, and that a higher I-PSS at baseline predicted BPH-related surgery.[26]

Several studies examined the relationship between patient age and outcomes. One trial found that age was not a predictor for the outcomes of I-PSS, AUR, or BPH-related surgery with alfuzosin treatment.[26] The incidence of adverse events related to vasodilation with alfuzosin 15 mg daily were increased in subjects 65 years of age and older, compared with younger subjects.[24] There were no significant differences in adverse events rates related to vasodilation between older and younger patients with 10 mg daily, however. Another trial examining the lower dosage found similar results.[27] Roehrborn and colleagues (2006) noted that alfuzosin was well tolerated in patients over 65 years of age and in persons taking antihypertensive medications.[26]

Safety Outcomes

Withdrawals and Adverse Events

Randomized Controlled Trials. Overall withdrawal rates were variable in the five placebo-controlled trials, ranging from 3% (six-month study)[25] to 33.9% (two-year follow-up)[26], with rates generally similar between treatment groups. Withdrawal rates were 19% with doses of alfuzosin 2.5 mg two or three times daily, compared with 12% with doxasosin 1 to 8 mg daily at 14 weeks follow-up.[28]

Mortality rates were reported in only two of the five placebo-controlled trials of alfuzosin[25, 28] with one sudden cardiac death in the alfuzosin group in a three-month study[28] and no deaths in a second, six-month trial.[25] Rates of treatment-emergent adverse events were generally similar between treatment and placebo groups. Rates varied significantly among studies, however, from 8.4% and 13.1% (treatment and placebo, respectively)[25], to more than 50% in a study with two years of follow-up.[26]

Rates of specific adverse events were low and similar between treatment and placebo groups. Dizziness was the most commonly reported adverse event, ranging from 2% to 9% with alfuzosin and somewhat lower rates with placebo. Sexual function was reported in four studies with no significant difference between treatment groups (alfuzosin, doxazosin and placebo). In the active controlled trials,

alfuzosin and doxasosin had similar rates of adverse events, including dizziness and erectile dysfunction (ED).

Single-group Cohort Studies. Withdrawals rates varied across studies and were generally higher with longer follow-up: up to 36% in the ALF-ONE cohort with three-year follow-up.[34] Withdrawals due to adverse events were generally low, ranging from 3.9%[38] to 8.6%.[34] Incidence rates for treatment-emergent adverse events varied greatly across studies, and were also generally higher with longer follow-up. The highest rate was reported in three-year follow-up of 689 subjects in ALF-ONE[34], where 71.4% reported at least one treatment-emergent adverse event. A high rate of one or more treatment emergent adverse event was also reported in a 12-month study (43%).[38] In contrast, 7% of participants reported a treatment-emergent event in another 12-month study where "the appearance of adverse medical events was carefully monitored and recorded throughout the trial."[37] Lukacs and colleagues (2000) noted that 61% of adverse events occurred in the first three months of treatment.[36]

Doxazosin

Doxazosin is also a second-generation α_1-adrenoreceptor antagonist, indicated for the management of moderate to severe BPH symptoms. As a long-acting agent, it is also dosed once-daily. Doxazosin not only elicits a dose-dependent response but its side-effect profile has also been shown to be dose dependent. In order to reduce the frequency of side effects (i.e., postural hypotension and syncope), doxazosin is typically initiated at a dose of 1 mg once daily. The dose may be increased to 8 mg/day, depending on response and tolerability.

Randomized Controlled Trials (RCTs)

The nine RCTs evaluating doxazosin that were identified involved various comparators, follow-up intervals, doses, and formulations, so that synthesis across all trials was not meaningful. For reader ease, the data is presented by comparator, dose,[42] formulation,[43, 44] whether placebo-controlled[44-47] or active–treatment controlled.[47-49] An additional study examined success of discontinuing doxazosin while taking finasteride, so-called "withdrawal therapy".[50] There were no cohort studies with a comparison group identified, but there were five single-group cohort studies reporting doxazosin adverse events.[51-55] The sample size of these five studies varied from 102 to 3,694.

The MTOPS study was included in the 2003 Guideline even though it was published after the cut-off date (June 1999) for study inclusion for that report.[46] This important study is included in the 2010 AUA BPH Guideline in a more abbreviated fashion for that reason. In this blinded study, 3,047 men were randomized to one of four treatments: doxazosin, finasteride, combination doxazosin and finasteride, and placebo. This trial was unique in that the primary outcome was clinical progression as defined by a composite endpoint (sustained four point rise in AUA-SI, acute retention, renal insufficiency, and recurrent UTI or urinary incontinence) examined over 4.5 years.

Similar to the MTOPS study, the Prospective European Doxazosin and Combination Therapy (PREDICT) trial was a blinded study of four treatments: doxazosin, finasteride, combination doxazosin

and finasteride, and placebo.[47] Of note, PREDICT differed from MTOPS in that it was only 52 weeks in duration and evaluated only the standard outcomes, I-PSS and Qmax, rather than assessing the impact on clinical progression.

As mentioned above, one RCT examined the clinical outcome of 272 men with enlarged prostates (>40 g) who were withdrawn from doxazosin therapy after initially receiving combination therapy with finasteride.[56]

Single-group Cohort Studies

The five single-group cohort studies that included 102 to 3,694 participants reported adverse events with doxazosin use.[51-55] One large observational study of men receiving 4 mg to 8 mg of doxazosin in a gastrointestinal therapeutic system (GITS) formulation[54] was a longitudinal extension of an earlier double-blind trial examining 178 hypertensive and 272 normotensive patients[51]. One study examined the effect of doxazosin 4 mg and tolterodine 2 mg in 144 consecutive men with BOO.[55]

Efficacy and Effectiveness Outcomes

Morbidity

A dose-ranging study comparing doxazosin 4 and 8 mg daily over three months (*n*= 82) noted adverse events rates were similar between treatment groups, although dizziness and nasal stuffiness were more common with the 8 mg dose; no statistical analysis was reported.[42] In the MTOPS study, the most common side effects reported in the doxazosin arm were dizziness, postural hypotension, and asthenia. Men receiving combination therapy experienced the same level of side effects noted in each of the monotherapy arms.

Symptoms and Quality of Life

AUA Symptom Index/International Prostate Symptom Score (Total). The doxazosin dose-ranging study comparing 4 mg and 8 mg daily doses over three months (*n*=82) noted improved AUA-SI in both treatment groups with a significant difference between groups (p=0.03).[42] Similar findings was noted when with the Boyarsky score (p=0.009, 4 vs. 8 mg doses). In a trial comparing doxazosin GITS with the standard formulation doxazosin and placebo, the total I-PSS improved in all three groups (p<.0.001) at 13-weeks of follow-up.[44] Both active treatments were more effective than placebo (p<0.001), but there was no difference between the active groups.

As mentioned above, MTOPS reported on the clinical progression of a composite endpoint.[46] The most common event triggering a progression event was a four point change in AUA-SI and the rate of this event was reduced in all three active-treatment groups. There was no significant difference between either finasteride or doxazosin monotherapies and the combination doxazosin and finasteride. In the shorter duration PREDICT study, I-PSS improved significantly with doxazosin monotherapy and the

combination, while the I-PSS decrease with finasteride therapy was not significantly different than with placebo.[47]

International Index of Erectile Function (IIEF). In a trial comparing the effects of doxazosin GITS and standard formulations on sexual function in sexually active men, investigators noted that the GITS consistently improved sexual function regardless of baseline function using the International Index of Erectile Function (IIEF) to measure intercourse and sexual satisfaction domains ($p<0.05$).[43] The difference between the GITS and standard formulation was significant for the erectile function domain ($p<0.005$). **The clinician is cautioned about considering alpha-blockers as a useful therapy for the treatment of ED as this was not adequately addressed in this limited study.**

BPH Impact Index. Several active-treatment controlled trials were identified that used the BPH II, including a comparison of the doxazosin GITS with tamsulosin in a blinded study.[48] The BPH II improved significantly in both treatment groups at 12 weeks ($p<0.05$) with no differences noted between the groups.

Other Custom Measures. As mentioned above, the MTOPS assessed the clinical progression of a composite endpoint.[46] Throughout the trial, the overall rate of clinical progression per 100 person years was 4.5 in the placebo group, 2.7 with doxazosin ($p<0.0001$ vs. placebo), 2.9 with finasteride ($p=0.002$ vs. placebo), and 1.5 in the combination group ($p<0.001$ vs. placebo). The risk of overall progression increased with increasing baseline PSA (a proxy for prostate volume) in the placebo and doxazosin groups ($p<0.006$), but not in the finasteride or combination groups. The numbers needed-to-treat analysis indicated that to prevent one case of progression 8.4 individuals would need to be treated with combination therapy, 13.7 with doxazosin and 15.0 with finasteride.

As mentioned previously, the "withdrawal therapy" trial was an RCT that examined success rates after discontinuing doxazosin.[56] Initially 272 men with prostate volume of at least 40 g were treated with finasteride 5 mg and doxazosin 2 mg, titrated up to 4 or 8 mg daily. Men with a favorable response (n=240) after one month were randomized to receive: 5 mg finasteride plus 2 mg doxazosin (n=100), 5 mg finasteride plus 4 mg doxazosin (n=80), and 5 mg finasteride plus 8 mg doxazosin (n=60) daily. Within each group, men were then randomized (but not in a blinded fashion) to discontinue doxazosin at three-month intervals. Among men discontinuing doxazosin at three months, successful discontinuation (defined as the patient declining to restart doxazosin) occurred in 20% of men receiving 2 mg doxazosin, 15% of men receiving 4 mg, and 13% of men receiving 8 mg. Success rates improved over time, with little difference among doxazosin dose groups. In men discontinuing doxazosin at 12 months, success was achieved by 84% of the 2 mg group, 85% in the 4 mg group, and 87% in the 8 mg group. The authors concluded that in men with moderately large prostates receiving combination therapy, the alpha blocker can be successfully discontinued after nine to 12 months in most men, regardless of dose. The lack of blinding is obviously a limitation of the study, as is the small number of subjects in each treatment group (there was no power calculation, but power was very likely insufficient to detect clinically important treatment effects). **The general applicability of withdrawal therapy noted here and**

elsewhere has not been determined, thus the clinician is warned to consider this approach as experimental.

Pressure, Flow, Volume Outcomes

Maximum Flow Rate. In the doxazosin dose-ranging study, the investigators noted improved Qmax in both 4 mg and 8 mg treatment groups with no difference between doses.[42] In the trial comparing doxazosin GITS with the standard formulation doxazosin, and placebo, Qmax improved with both formulations compared with placebo ($p<0.001$) but there were no differences between active treatments ($p=0.257$).[44]

In the PREDICT study, Qmax improved significantly with only doxazosin mono-therapies and the combination, while finasteride outcomes were no different than placebo.[57] The shorter duration of treatment may be a large factor in the modest effect noted with 5-alpha-reductase inhibition.

Prostate Volume (Measured by TRUS or Magnetic Resonance Imaging [MRI]). In a companion publication to MTOPS, investigators noted that in men with prostate volumes <25 mL, combination therapy was no better than doxazosin monotherapy in improving the risk of progression, AUA-SI and Qmax.[58] Among men with glands >25 mL, combination therapy led to greater clinical benefit than either monotherapy.

Acute Urinary Retention. As mentioned above, MTOPS assessed the clinical progression of a composite endpoint including AUR.[46] The rate of AUR was reduced with finasteride and combination therapy. Doxazosin delayed, but did not prevent AUR ($p=0.23$). Findings were similar for the rates of crossover to invasive therapy for BPH which were reduced by finasteride and combination therapy but not doxazosin. In the PREDICT study, AUR and need for surgery were infrequent and highest in the placebo group with no events in the combination arm.[57] It appears logical that the larger cohort and longer duration noted in MTOPS supports a time-limited impact of doxazosin on the hard outcomes of AUR and crossover to surgery. This effect noted with doxazosin is thought by the Panel to be a class effect.

<u>Safety Outcomes</u>

Withdrawals and Adverse Events

Single-Group Cohort Studies. In the doxazosin single-cohort studies, dizziness and symptomatic hypotension were the most commonly reported adverse events. Rates for these side effects varied across studies from 14.7% (dizziness)[51] to <1% (postural hypotension).[52, 54] Other adverse events were infrequently reported.

The large study by Hernandez and colleagues (2005) was an observational surveillance study of men on 4 mg to 8 mg of doxazosin GITS for six months. In total, 107 patients (2.9%) withdrew from the study due to adverse events.[54] The rate of postural hypotension was 1.1% and syncope 0.05% (an additional two men experienced syncope not attributed to the drug). Four men reported ED; three of

these cases were considered unrelated to the study drug. Importantly, this publication does not indicate how the researchers decided whether an adverse event was attributed to the study drug or not.

In a longitudinal extension of earlier double-blind trials, Fawzy and colleagues (1999) examined 178 hypertensive and 272 normotensive patients.[51] The dose of doxazosin could be titrated in hypertensive patients up to a dose of doxazosin 16 mg daily, whereas normotensive patients were titrated only up to 8 mg daily. The incidence of drug-related adverse events in normotensive men was approximately half the rate seen in hypertensive patients (6.6% vs. 12.4% per year). In hypertensive men achieving 48-month follow-up, the rate of drug-related adverse events was 14.3% per year. However, the incidence of severe adverse events was similar between the hypertensive and normotensive patients (7.1% vs. 6.6% per year, respectively). Drug-related adverse events were less common in older than younger hypertensive patients, although the discontinuation rate was slightly higher in the older subgroup (10.3% vs. 6.8% per year, p-value not reported).

In a study examining sexual effects of doxazosin after three months of treatment, overall IIEF scores improved at one month ($p=0.0177$), and improvements were maintained at the final follow-up of three months.[53] Among patients with lower IIEF scores at baseline (≤ 16), patients demonstrated a significant improvement in scores at three-month follow-up ($p<0.01$); statistically significant improvement was not seen among men with higher IIEF scores.

Lee and colleagues (2004) administered doxazosin 4 mg daily with added tolterodine 2 mg daily if needed, to 144 consecutive men with BOO, and compared outcomes between men with and without overactive bladder.[55] The most common adverse events reported with doxazosin were dizziness (2%), postural hypotension (1.3%), and abnormal ejaculation (1.3%). Dry mouth (27%), the most commonly reported adverse event in patients receiving tolteridine, led to treatment discontinuation in two of 16 patients with this complaint. Acute urinary retention developed in 3.3% of men on combined tolteridine and doxazosin and resolved with overnight catheterization.

Tamsulosin

Tamsulosin is a third-generation alpha-blocker with greater specificity for the α_{1A}-adrenoreceptor in relation to the α_{1B}-adrenoreceptor with a putative advantage in reduced need for titration (i.e., 0.4 mg, 0.8 mg) and less hypotensive side effects. Clinical studies have also demonstrated that tamsulosin can be co-administered with antihypertensive medications such as nifedipine, enalapril and atenolol without any increased risk of hypotensive or syncopal episodes.

Randomized Controlled Trials (RCTs)

Eight RCTs examined tamsulosin, including two placebo-controlled trials,[59, 60] two direct drug comparisons,[61, 62] three direct drug trials with a placebo comparison group[63-65] and a trial examining the effects of withdrawing tamsulosin when dutasteride therapy was continued ("withdrawal therapy").[66] In addition, a meta-analysis of three previously published RCTs comparing tamsulosin to placebo and to alfuzosin with respect to sexual side effects were identified.[67] The Combination of Adovart and

Tamsulosin (CombAT) trial, an RCT comparing tamsulosin, dutasteride, and the combination, is discussed in the section on dutasteride.

Sample sizes ranged from 205 to 2,152 with study duration ranging from 12 weeks to one year. Placebo run-in periods ranging from seven to 28 days were included in the design of five of the studies. The mean total I-PSS score at baseline ranged from approximately 16 to 20 and mean age from 60 to 65 years. Qmax was more heterogeneous across studies: mean values ranged from 8.7 to 13.4 mL per second. Several studies specifically excluded men with significant comorbidities.[61, 62]

Intervention dosing and drug formulation varied across studies. The most common dose was tamsulosin 0.4 mg daily.[59, 62-64, 67] One study compared the oral controlled absorption system (OCAS) at 0.4 mg and 0.8 mg daily to the standard modified release formulation (0.4 mg daily).[59] Several studies used lower doses of 0.2 mg twice daily[60] or 0.2 mg once daily.[61] In the Symptom Management After Reducing Therapy (SMART-1) study, Barkin and colleagues (2003) randomized 327 men with symptomatic BPH to 0.5 mg dutasteride plus 0.4 mg tamsulosin for 36 weeks, or to 0.5 mg dutasteride plus 0.4 mg tamsulosin for 24 weeks followed by dutasteride plus a tamsulosin-matched placebo for 12 weeks.[66]

Because of the considerable heterogeneity across comparators, study populations, and drug doses and formulations, the data were synthesized in a qualitative manner since the Panel did not believe that a meta-analysis would be meaningful.

Single-group Cohort Studies

Six single-group cohort studies of adverse events with tamsulosin as the primary intervention were identified. In addition, two single-group cohort studies were included with cataract surgery as the primary intervention, assessing the outcome of intraoperative floppy iris syndrome (IFIS).[68, 69] Follow-up ranged between 12 weeks[70] and 5 years[71].

Efficacy and Effectiveness Outcomes

Symptoms and Quality of Life

AUA Symptom Index/International Prostate Symptom Score (Total). Total I-PSS decreased compared with placebo in the three studies reporting this outcome ($P<0.05$), all with 12-week follow-up.[59, 63, 64] When compared with finasteride 5 mg daily, tamsulosin 0.2 mg daily[61] or 0.4 mg daily[62] did not differ in I-PSS or Qmax at 24- and 26-week follow-up. One trial randomized men to alfuzosin, tamsulosin, or placebo, but did not report changes or tests of significance for the comparison of the two active drugs.[64] Similarly, Kaplan and colleagues (2006) did not compare tamsulosin to tolterodine.[63]

In the Symptom Management After Reducing Therapy (SMART-1) RCT, Barkin and colleagues (2003) examined combination therapy with dutasteride 0.5 mg daily and tamsulosin 0.4 mg daily for 24 weeks followed by either continuation of both drugs or continuation of dutasteride with tamsulosin-placebo for 12 weeks.[66] Of men with baseline I-PSS less than 20, 84% switched to dutasteride

monotherapy at 24 weeks without deterioration in their symptoms by week 30. In men with severe BPH symptoms at baseline, 42.5% reported a worsening of symptoms after tamsulosin withdrawal at week 24, compared with 14% who reported symptom deterioration among those who continued dual therapy. **The general applicability of withdrawal therapy noted here and elsewhere has not been determined thus the clinician is warned to consider this strategy as experimental.**

QoL from I-PSS. As reported above, one study using the oral controlled absorption system (OCAS) reported that the QoL score improved more with tamsulosin OCAS 0.4 mg and modified-release 0.4 mg daily than with placebo.[59] Another study also reported a more favorable change in QoL for tamsulosin ($P<0.05$).[61]

Other custom measures. In one study the primary outcome was the Symptom Problem Index (SPI), a validated symptom questionnaire related to the I-PSS, but scored differently.[62] The SPI improved in both treatment groups (finasteride 5 mg or tamsulosin 0.4 mg once daily), but improved sooner with tamsulosin, with significant differences between groups ($p<0.05$) in favor of tamsulosin through week 18. Between weeks 26 and 52, however, there were no significant differences between the groups. Sexual function, as measured with a questionnaire that was not reported as validated, was not significantly different between the two drugs.[62]

Pressure, Flow, Volume Outcomes

Maximum Flow Rate. As reported above, in one study using the oral controlled absorption system (OCAS), Qmax improved significantly in one trial reporting that outcome.[59]

Predictors of Efficacy and Effectiveness

Included trials did not generally examine the predictors of efficacy or adverse events. A *post hoc* analysis of a trial comparing tamsulosin and finasteride demonstrated that the greater improvements in Qmax with tamsulosin compared with finasteride at weeks one, six and 18, was significant for patients with prostate volume less than 50 mL, but was not significant for larger glands.[62] There was no significant differential effect after 18 weeks between the two drugs with large or small glands.

Safety Outcomes

Withdrawals and Adverse Events

Randomized Controlled Trials (RCTs). Rates of total withdrawals from studies were variable; for the 12-week trials rates ranged from 5%[59] to 29%.[61] In the latter study, both tamsulosin and finasteride groups lost approximately the same percentage of subjects, the majority due to failure to return for follow-up. In addition, in this trial, there were more treatment-emergent adverse events with finasteride (2.5%) than with tamsulosin (3.9%). Rates of treatment emergent adverse events varied markedly across these trials. The highest rate was reported by Kawabe and colleagues (2006)where the rate was 82%

with tamsulosin and 72% with placebo.[60] This finding contrasts markedly with another trial where rates for tamsulosin were approximately 4%.[61]

Dizziness was commonly reported, with higher rates in the tamsulosin group compared with placebo in one trial,[63] similar rates in a second trial,[59] while a third trial reported higher rates in the placebo group.[72] Syncope and postural hypotension were uncommon (< 1% to 2%). Hofner and colleagues (1999) examined sexual function with tamsulosin and alfuzosin in a meta-analysis of two placebo-controlled trials of tamsulosin and a head-to-head trial of tamsulosin compared with alfuzosin.[67] Tamsulosin produced a higher rate of abnormal ejaculation than placebo ($p=0.045$) but rates of ED and decreased libido were not significantly different ($p>0.05$). Tamsulosin was comparable to alfuzosin with respect to adverse sexual effects.

Single-group Cohort Studies. In a study with five-year follow-up, Palacio and colleagues (2004) reported a total of 114 nonserious adverse reactions during the first year; only 3.6% of men had an adverse reaction, all within the first year.[71] Adverse reactions were not defined and it was unclear if any withdrawals were due to adverse events. Batista and colleagues (2002) examined more than 2,700 patients in a single-group cohort study, and included all patients with LUTS between 45 and 75 years of age who visited a group of urologists' offices.[73] Study participants therefore had a variety of comorbid conditions: hypertension 18.4%, diabetes mellitus 12.1%, and cardiovascular disease (unspecified) 10.5%.

In a much smaller cohort, 88% of subjects had a positive medical history, including 35% with cardiovascular disease.[70] Using prescription monitoring data, Mann and colleagues(2000) reported adverse events for men issued a tamsulosin prescription.[74] The response rate for the questionnaire was 57.4%, and 92% of returned forms had event data. After six months of treatment, 68.6% of men were still taking tamsulosin. Patients reported dizziness, malaise, and headache most commonly. General practitioners also reported adverse events; the most common events were dizziness, nausea, and palpitations.

Terazosin

Terazosin is an α_1-selective antagonist with a relatively long half-life that allows for once-daily dosing. As noted in the 2003 Guideline, terazosin is an effective medical treatment for reducing LUTS and the impairment of QoL due to urinary symptoms created by BPH. It has been shown that the response to terazosin is dose dependent. Not surprising, the side effect profile has also been shown to be dose dependent. In order to minimize the frequency of side effects (i.e., postural hypotension and syncope) terazosin is typically initiated at a dose of 1 mg once daily. Depending on response to therapy and tolerability, the dosage may be increased to 10 mg/day.

Randomized Controlled Trials (RCTs)

Two RCTs examined terazosin.[75, 76] A secondary analysis of the VA CO-OP trial[77] (included in the 2003 Guideline) by Johnson and colleagues (2003) assessed changes in nocturia with medical treatment.[75]

Single-group Cohort Studies

A two-group cohort study compared 60 patients with symptomatic BPH receiving either terazosin titrated up to 5 mg daily, or finasteride 5 mg daily.[78] Rates of adverse events were low, and dizziness occurred more frequently with terazosin (13%) than with finasteride (3%). Supine hypotension occurred in one patient on terazosin.

Efficacy and Effectiveness Outcomes

Morbidity

One RCT was a retrospective analysis of the Hytrin Community Assessment trial (HYCAT).[76] The incidence of blood pressure-related adverse events with terazosin was similar between men on no antihypertensive treatment (13.5%) and men on antihypertensive treatment (14.3%). The rates of blood pressure-related adverse events in the placebo groups were 9.0% in men not on antihypertensive therapy and 5.9% in men using such therapy.

Safety Outcomes

Symptoms and Quality of Life

Another RCT, the VA CO-OP trial, compared terazosin 10 mg daily, finasteride 5 mg daily, combination therapy of both drugs, and placebo. Of the original 1,229 men randomized, 1,078 completed one- year of treatment. Of those, all but 38 reported one or more episodes of nocturia, so that 1,040 men were included in this secondary analysis. After one-year of treatment, the mean number of episodes of nocturia was 1.8 with terazosin, 2.1 with finasteride, 2.1 with placebo, and 2.0 with combination therapy compared with baseline values of 2.5, 2.5, 2.4, and 2.4, respectively. Terazosin significantly reduced nocturia episodes compared with finasteride (p=0.0001), combination therapy (p=0.03) and placebo (p=0.0001). Combination therapy also reduced nocturia episodes compared with finasteride (p=0.04) and placebo (p=0.03).[75]

Intraoperative Floppy Iris Syndrome

Intraoperative floppy iris syndrome (IFIS) is a condition first described by Chang and Campbell (2005) as a triad of progressive intraoperative mioses despite preoperative dilation, billowing of a flaccid iris, and iris prolapse toward the incision sites during phacoemusification for cataracts.[79] Operative complications in some cases included posterior capsule rupture with vitreous loss and postoperative intraocular pressure spikes, though visual acuity outcomes appeared to be preserved. The original

report linked this condition with preoperative use of the alpha-blocker tamsulosin. A possible mechanism linking alpha blockers with IFIS is inhibition of the iris dilator smooth muscle.[79, 80]

To better understand the implications of IFIS for the use of alpha blocker therapy for men with LUTS attributed to BPH, two focused literature searches were conducted covering the period 1/1/1999 – 2/5/2009, using search terms as follows:

("Iris Diseases "[MeSH] OR "intraoperative floppy-iris syndrome"[TIAB] OR IFIS[TIAB] OR "Floppy Iris"[TIAB]) AND (BPH[TIAB] OR "Benign prostatic hyperplasia"[TIAB] OR "Prostatic Hyperplasia"[MeSH]) AND 1999/01/01[PDAT] : 2009/02/05[PDAT] AND English[Lang] NOT (Case Reports[PT] OR Editorial[PT] OR News[PT] OR Comment[PT] OR Letter[PT] OR "Historical Article"[PT] OR Biography[PT])("Iris Diseases"[Mesh] OR "intraoperative floppy-iris syndrome"[TIAB] OR IFIS[TIAB] OR "Floppy Iris"[TIAB]) AND ("tamsulosin"[TIAB] OR "Adrenergic alpha-Antagonists"[MeSH] OR "doxazosin"[TIAB] OR "prazosin"[TIAB] OR "tamsulosin"[TIAB] OR "alfuzosin"[TIAB] OR "terazosin"[TIAB] OR "trimazosin"[TIAB] OR "phenoxybenzamine"[TIAB]) AND ("1999/01/01"[PDAT] : "2009/02/05"[PDAT]) AND English[lang] NOT (Case Reports[PT] OR Editorial[PT] OR News[PT] OR Comment[PT] OR Letter[PT] OR "Historical Article"[PT] OR Biography[PT]) NOT (BPH[TIAB] OR "Benign prostatic hyperplasia"[TIAB] OR "Prostatic Hyperplasia"[MeSH])

The two searches yielded a total of 32 unique articles. In addition, reference lists of the retrieved papers were reviewed for original reports describing the risk of IFIS in association with alpha blockers.

Through this process, we identified 11 studies published in 10 reports providing information on the risk of IFIS with the use of various alpha blockers, and the implications of this condition for men prescribed alpha blockers for LUTS (Appendix A8). A review of these data supports the following conclusions:

The risk of IFIS is substantial among men taking tamsulosin, ranging from about 43% to 90% in 10 retrospective and prospective studies (sometimes the denominator for these risks is patients, and sometimes eyes).[68, 69, 79, 81-88]

The risk of IFIS appears lower with older, generic alpha blockers such as terazosin and doxazosin, with IFIS occurring in 0/11 patients (0%), 3/49 patients (6.1%), 1/51 eyes (2.0%), and 1/4 eyes (25%) in the four studies reporting on the risk of IFIS with these agents.[69, 79, 84, 88] There is insufficient exposure data to estimate the risk of IFIS with alfuzosin.

It is unclear whether dose or duration of alpha-blocker treatment influences the risk of IFIS. It is unclear whether stopping alpha-blocker treatment any period of time before surgery mitigates the risk of IFIS. If experienced ophthalmologists are aware of preoperative alpha-blocker use, pre- and intra-operative precautions can be taken to reduce the risk of IFIS complications and attain excellent visual

outcomes,[80, 85] though it remains unclear if the residual risk and outcomes are any worse than among patients without IFIS.

It is important to note that after the IFIS literature search and review was completed, a study was published in the Journal of the American Medical Association examining the association of recent tamsulosin use with serious postoperative complications (e.g., retinal detachment, lost lens or lens fragment, or endophthalmitis) requiring reintervention within 14 days of cataract surgery.[89] The study found that for every 255 men receiving tamsulosin in the immediate preoperative period, one of these complications would result. The study had insufficient power to determine whether discontinuation of tamsulosin reduced the risk of these complications, and no separate estimate of the risk was provided for other alpha blockers, including alfuzosin.[89] Therefore, the Panel believed that these new findings were supportive of their original conclusions.

Summary

Alpha-blockers produce significant symptom improvement compared to placebo that the average patient will appreciate as a moderate improvement from baseline. The minor differences in efficacy noted between the different alpha blockers are not statistically (when tested) or clinically significant.

The 2003 Guideline suggested that some patients treated with tamsulosin require the 0.8 mg dose to achieve the results obtained with doxazosin and terazosin titrated to response. This presents a cost-effectiveness problem for tamsulosin (which is not yet available generically) because the 0.8 mg daily dose requires two tablets and thus, twice the expense of the lower dose, while the terazosin and doxazosin recommended dosages are available as one unit generic products and priced accordingly. As this problem was not noted in the 2003 Guideline, it was the opinion of the Panel to include this comment in current guideline results.

Similarly, while in previous studies of one-year duration or less, combination therapy proved equal to alpha-blocker therapy, but superior to 5-ARI therapy, MTOPS demonstrated that in the long-term, among men with larger prostates, combination therapy is superior to either alpha blocker or 5-ARI therapy in preventing progression and improving symptoms. It was the opinion of the Panel that there is insufficient information to gauge the utility of alpha-blocker withdrawal therapy among men initially treated with combination therapy. Although not an unreasonable strategy, clinicians need to recognize that the optimal duration of combination therapy prior to discontinuation of the alpha-blocker remains in doubt.

Data from the long-term MTOPS trial suggests a time limited impact of alpha-blockers on the hard outcomes of AUR and crossover to surgery. That is, while AUR and surgery rates were lower with doxazosin compared to placebo in the early years of follow-up, by five years, rates of these outcomes were similar in both groups. The time-limited effect noted for doxazosin in MTOPS on these outcomes was judged by the Panel to be a class effect.

Qmax also improved significantly with alpha-blockers when compared with placebo. Improvements were approximately 1 mL to 2 mL per second from baseline.

Rates for specific adverse events were low and similar between treatment and placebo groups. Dizziness was the most common adverse event, with rates reported between 2% and 14% with alpha blockers and somewhat lower rates with placebo.

Sexual function was reported sporadically in the studies reviewed with no significant difference between treatment groups. Some studies report improved sexual function when using alpha blockers. **The clinician is cautioned about considering alpha-blockers as a useful therapy for the treatment of ED as this outcome was not globally addressed in these limited studies.** Tamsulosin produced a higher rate of abnormal ejaculation than placebo, but rates of ED and decreased libido were not significantly different.

In general, although doxazosin and terazosin require dose titration and blood pressure monitoring, they are inexpensive, can be taken once daily, appear equally effective to tamsulosin and alfuzosin, and have generally similar side effect profiles. Moreover, these older agents do not appear to increase the risk of the IFIS, and doxazosin has demonstrated efficacy relative to placebo over four years of follow-up. The Panel wished to remind clinicians that these agents remain excellent choices for the management of bothersome LUTS attributed to BPH.

In the expert opinion of the Panel, the caveat remains that alpha blocker monotherapy is not considered optimal therapy for hypertension. LUTS/BPH and hypertension should be managed separately.

5-Alpha-reductase Inhibitors (5-ARIs)

As the indication for treatment with 5-ARIs and combination therapy hinges on prostate volumes and PSA thresholds, the treating physician may discuss the relationship between PSA and prostate size with the patient. This conversion is enabled by the enzyme 5-AR, of which there are two isoenzymes known as types I and type II. Both testosterone and DHT bind to the androgen receptor, although dihydroxytestosterone (DHT) does so with greater affinity and is thus considered to be the more potent androgenic steroid hormone. The T/DHT-androgen receptor complex within the nucleus of the cells of the prostate initiates transcription and translation, thus promoting cellular growth and ultimately contributing to the condition of BPH with an imbalance between growth and apoptosis or cellular death in favor of growth, and subsequent cellular mass or volume increase.[90, 91]

While there are several medical and surgical ways to reduce the influence of androgenic steroids on the growth of the prostate (e.g., medical or surgical castration), the only hormonal therapies with an acceptable benefit–to-risk ratio are the 5-ARIs. These molecules act via the reduction of DHT in the prostate which leads to a reduction in the overall androgenic growth stimulus in the prostate, an increase in apoptosis and atrophy and ultimately a shrinkage of the organ ranging from 15-25% measured at six months. The atrophy is most pronounced in the glandular epithelial component of the prostate, which is the source of the production and release of serum PSA. It is for this reason that the

organ shrinkage is associated with a reduction in serum PSA by approximately 50% (and a concomitant decrease in serum free PSA by 50%, which means that the ratio of free/total PSA remains constant).[92, 93] For reference, detailed evidence tables reviewing the studies evaluated by the Panel per the below are provided in Appendix A8.

Finasteride

Randomized Controlled Trials (RCTs)

In the 2003 Guideline finasteride was found to be an appropriate BPH treatment option based on a thorough review of a large body of evidence consisting of randomized, placebo-controlled studies of one year, two years, and four years duration. The majority of studies with finasteride were published before the 2003 Guideline and since then the molecule has lost patent protection. Only a small number of subsets or post hoc analyses and open-label extension studies have been reported since the 2003 Guideline was published. We identified one placebo-controlled trial, the Proscar Long-Term Efficacy and Safety Study (PLESS).[94-96] The primary publication by McConnell and colleagues was published in 1998, thus was included in the prior report.[95] The PLESS trial randomized 3,040 subjects to either finasteride 5 mg daily or to placebo, and finasteride improved symptoms and reduced the risk of development of AUR and the need for BPH-related surgery.

A second open label extension study was identified, which reported six-year follow-up data from a one-year placebo-controlled RCT comparing finasteride 1 mg or 5 mg daily to placebo.[96] Data on 725 of the original 1,657 men randomized were available for five or six year follow-up of finasteride 5 mg daily (depending on whether they had received active treatment or placebo during the RCT in the first year).

Efficacy and Effectiveness Outcomes

Symptoms, Bother and Quality of Life

Previous analyses of randomized, placebo-controlled trials had shown an improvement in standardized symptom scores (I-PSS or Quasi I-PSS) superior to placebo. Numerically improvements of three to four points had been reported and were maintained for six to 10 years of follow up.[97, 98] The magnitude of improvement was similar when patients were stratified by prostate volume or serum PSA. However, the natural history is more accelerated in men with larger glands and higher serum PSA values, and thus, the difference between finasteride and placebo – the attributable effect – becomes more accentuated in those patients over time.[99-102]

Findings regarding bother, interference and QoL scores were similar to those regarding the I-PSS or quasi I-PSS score. Bruskewitz and colleagues (1999) examined bother as measured with questionnaire items similar to those in the AUA symptom problem index in the PLESS Study, and found that mean reductions in overall bother were significantly greater with finasteride than placebo from four-month through four-year follow-up ($p<0.001$).[103] Mean interference domain score and daily activity questions were also improved more with finasteride than placebo ($p<0.05$). In addition, no significant difference

was found between treatment groups with respect to ED, satisfaction with sexual activity, and sexual interest. On examination in the PLESS of age cohorts of men 65 years of age or more, and men less than 65 years, finasteride significantly improved a modified AUA-SI, and reduced prostate volume and the risk for AUR and/or BPH-related surgery at four-year follow-up in both age cohorts.[104] Rates of adverse events did not appear to relate to age, and there was no significant difference in cardiovascular events between finasteride and placebo treatment in either age cohort.

Urodynamic parameter and Prostate Volume Measures

Previous analyses of randomized, placebo-controlled trials had shown a sustained improvement in peak flow rates superior to placebo. Previous analyses of randomized, placebo-controlled trials had shown a reduction in prostate volume by about 15-25% which is achieved at 6 months and sustained over time. This decrease in prostate volume is independent of baseline volume and baseline serum PSA values

Safety Outcomes

Previous analyses of randomized, placebo-controlled trials had shown that in the first six to 12 months of treatment, patients on finasteride experience ED, libido disturbances and ejaculatory problems at about twice the rate as the placebo control patients. Thereafter the rates are similar suggesting that age-related deterioration in sexual and ejaculatory function is responsible rather than direct drug effects. In PLESS sexual adverse events were reported more frequently with finasteride (15%) than placebo (7%) during the first year of the study ($p<0.001$), however, during years two through four no between-group difference was noted in the incidence of new sexual adverse events (7% in both groups).[105] Study discontinuation due to sexual adverse events occurred in 4% of finasteride patients and 2% with placebo.

A two-year open-label extension study of PLESS reported no difference in serious adverse events between the finasteride and placebo groups.[106] The most common drug-related sexual adverse events were erectile dysfunction (2% in the group on finasteride during the RCT and the open label extension, and 4% in the group switched to finasteride from placebo). The incidence of prostate cancer was 3% with both continuous finasteride and men switched from placebo to finasteride. The most common drug-related adverse effects were sexual, including ejaculation disorders (3.1% year ibe, 0.4% year six), decreased libido (3.8% year one, 0.7% year six), and erectile dysfunction (4.8% year one, 0.4% year six). One clinical center participating in this open-label extension study published data on their 43 study participants at up to 10 years of follow-up.[107] These authors noted that 7.0% of men discontinued therapy due to sexual side effects; they did not report specific adverse events.

In another open-label extension study, Vaughan and colleagues (2002) reported outcomes at seven to eight years of follow-up from two phase two, double-blind, three- to six-month clinical trials of finasteride compared with placebo.[108] The most common drug-related adverse events were erectile

dysfunction (year one of the open label extension study, 6.4%; year five, 1.2%) ejaculation disorder (5.8% year one; 3.7% year five), and decreased libido (11% year one; 1.5% year five).

Dutasteride

Randomized Controlled Trials (RCTs)

Dutasteride is the second 5-ARI approved by the U.S. Food and Drug Administration (FDA) for the use in men with LUTS and BPH.[109] Pharmacologically it differs substantially from finasteride in that it inhibits both isoenzymes of the 5-alpha reductase (vs. only type II), has a longer half-life (five weeks vs.. six to eight hours), and thus leads to a more profound reduction in both serum and intraprostatic DHT levels. Direct comparison trials have not been published, and when indirectly comparing efficacy parameters one has to remember that in all clinical trials with dutasteride patients had to have a baseline prostate volume of > 30 mL by TRUS and a serum PSA of > 1.5 ng/mL, thus enriching the population for potential responders to 5-ARI treatment.

The clinical database for dutasteride consists mainly of the phase-three randomized, placebo-controlled trial of two year duration [110] with an open label extension trial,[111] a study aiming to test the effect of a placebo-controlled withdrawal of an alpha-blocker from a combination therapy arm (SMART 1),[112] and a four-year study comparing dutasteride vs. tamsulosin vs. combination (CombAT) for which only the two year interim data are published [113].

Efficacy and Effectiveness Outcomes

Symptoms, Bother and Quality of Life

Roehrborn and colleagues (2002) randomized 4,325 men with BPH and moderate to severe symptoms to dutasteride 0.5 mg daily or to placebo and followed them for 24 months.[114] These data are pooled from three identical phase-three clinical trials, encompassing 400 sites in the United States and 19 other countries. AUA-SI improved significantly in both treatment groups ($p<0.001$), with significantly greater improvement with dutasteride (-4.5) compared with placebo (-2.3) ($p<0.001$).

In the CombAT Trial, I-PSS improved in all three treatment groups (combination -6.2, dutasteride -4.9, tamsulosin -4.3) and combination therapy was superior to both monotherapies at nine months through 24 months($p<0.001$).[113] Quality of life, BPH II, patient perception of study medication were assessed in the CombAT Trial, and combination therapy was found to be superior to both monotherapies, with dutasteride being superior to tamsulosin in these measures at 24 months.[115]

Urodynamic Parameter and Prostate Volume Measures

In the phase-three trials, Qmax increased by +0.6 ml/sec under placebo and +2.2 ml/sec under dutasteride (between-group $p<0.001$). In CombAT the increase in Qmax was greatest with combination (+2.4), and greater with dutasteride (+1.9) than with tamsulosin (+0.9) ($p<0.0001$) at 24 months.
In the phase three trials total prostate and transition zone volumes were reduced by a mean of -25.7% and -20.4%, respectively, in the dutasteride arm ($P <0.001$). In CombAT at month 24 the adjusted

mean% change in total prostate volume from baseline was −26.9% in the combination group, −28.0% in the dutasteride group and 0.0% in the tamsulosin group (combination vs. tamsulosin p <0.001 and combination vs. dutasteride p not significant). At month 24, the adjusted mean% change in transition zone volume from baseline was −23.4 in the combination group, −22.8% in the dutasteride group and 8.8 in the tamsulosin group (combination vs. tamsulosin, p <0.001; and combination vs. dutasteride, p-value was not significant).

Safety Outcomes

Progression Events

In the phase three trials, the relative risk of AUR with dutasteride vs. placebo was 0.43 (95% CI, 0.29 to 0.62) and the relative risk for BPH-related surgery was also significantly decreased [relative risk 0.52 (95% CI, 0.37 to 0.74)]. No progression data are available from the CombAT trial interim two-year analysis.

Adverse Events

In the phase three trial, withdrawal rates were similar between groups (30% with dutasteride and 33% with placebo).[114] Withdrawal rates due to adverse events (approximately 9%), and incidence of all treatment-emergent adverse events (approximately 75%) were similar between groups. ED, decreased libido, gynecomastia, and ejaculation disorders were more common with dutasteride than placebo (p<0.001).

In CombAT, any adverse event was reported at a rate of 63% to 65% in all three treatment groups.[113] Any drug-related adverse event occurred at a higher rate in the combination group (24%) than with dutasteride (18%) or tamsulosin (16%) (combination therapy vs. dutasteride or tamsulosin, p<0.001).

Combination Therapy

Randomized Controlled Trials (RCTs)

In the 1990s, two studies of 12 months duration were conducted testing the hypothesis that combination medical therapy may be superior to monotherapy.[116, 117] The VA CO-OP used placebo vs. terazosin vs. finasteride vs. combination, and the European PREDICT trial used doxazosin instead of terazosin. Both studies concluded that combination therapy was **not** superior to alpha-blocker monotherapy. They were criticized on account of the relatively short duration of only one year and the fact that patients were enrolled regardless of prostate size and serum PSA leading to a study population of at or below average sized prostates and serum PSA values. A meta-analysis had shown that finasteride was superior to placebo only in men with enlarged prostates and/or higher serum PSA values [101, 118].

The National Institues of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK) also conducted in the 1990s a combination therapy study the primary outcome parameter being a composite progression endpoint.[119, 120] The MTOPS study enrolled over 3,000 men with at or below average sized prostates (similar to the VA COOP) and randomized them to placebo vs. doxazosin 4 mg or 8 mg daily vs. finasteride 5 mg daily vs. combination of doxazosin and finasteride. Men were treated and followed for up to 5.5 years. The risk of overall clinical progression--defined as an increase above base line of at least four points in the AUA-SI, AUR, urinary incontinence, renal insufficiency, or recurrent UTI was significantly reduced by doxazosin (39% risk reduction, $p<0.001$) and finasteride (34% risk reduction, $p=0.002$), as compared with placebo. The reduction in risk associated with combination therapy (66% for the comparison with placebo, $p<0.001$) was significantly greater than that associated with doxazosin ($p<0.001$) or finasteride ($p<0.001$) alone. The risks of AUR and the need for invasive therapy were significantly reduced by combination therapy ($p<0.001$) and finasteride ($p<0.001$) but not by doxazosin. Doxazosin ($p<0.001$), finasteride ($p=0.001$), and combination therapy ($p<0.001$) each resulted in significant improvement in symptom scores, with combination therapy being superior to both doxazosin ($p=0.006$) and finasteride ($p<0.001$) alone. Although not a primary outcome, symptom and flow rate improvement were superior in the combination therapy arm compared to both monotherapies.

The second major combination therapy study conducted was the CombAT trial in which 4,844 men were randomized to receive tamsulosin 0.4 mg vs. dutasteride 0.5 mg vs. combination therapy with both over four years; at present only the two year data are available and published.[113] In contrast to prior studies, but in keeping with the study protocol of only enrolling patients with prostatic enlargement in LUTS/BPH trials with dutasteride, men had to have a prostate volume > 30 mL by TRUS and a serum PSA of >1.5 ng/mL. Combination therapy resulted in significantly greater improvements in symptoms vs. dutasteride from month three and tamsulosin from month nine, and in BPH-related health status from months three and 12, respectively. A significantly greater improvement from baseline in Qmax for combination therapy vs. dutasteride and tamsulosin monotherapies from month six was also noted. There was a significant increase in drug related adverse events with combination therapy vs. monotherapies. The four-year data from CombAT are expected in 2009 and the primary endpoints will be progression to urinary retention and need for prostate surgery as well as symptom progression, similar to the MTOPS study.

When comparing results from MTOPS and CombAT differences must always be considered as they affect many aspects including the outcomes of the trials (Chapter 1, Table 1.3).

<u>Efficacy and Effectiveness Outcomes</u>

Symptoms, Bother and Quality of Life

MTOPS. The four-year mean reduction in symptom score was 4.9 in the placebo group, 6.6 in the doxazosin group, 5.6 in the finasteride group, and 7.4 in the combinationtherapy group (all active therapies superior to placebo).

CombAT. At month 24, mean decreases in I-PSS from baseline were 6.2 for combination therapy vs. 4.9 and 4.3 for dutasteride and tamsulosin, respectively. The decrease for combination therapy was significantly greater vs. that of either monotherapy (each comparison p<0.001). Superior improvements for combination therapy were also reported regarding storage and voiding subscores as well as BPH II, QoL scores and other humanistic questionnaires.

Urodynamic Parameter and Prostate Volume Measures

MTOPS. Maximal urinary flow rate improved over time in all active-treatment groups as compared with placebo (p<0.001 for each pairwise comparison). At four years, the mean improvement was 4.0 mL per second in the doxazosin group, 3.2 mL per second in the finasteride group, and 5.1 mL per second in the combination-therapy group.

CombAT. At month 24 increases in Qmax from baseline were 2.4 mL/sec for combination therapy vs. 1.9 and 0.9 mL per second for dutasteride and tamsulosin, respectively. At month 24 the adjusted mean percent change in total prostate volume from baseline was −26.9% in the combination group, −28.0% in the dutasteride group and 0.0% in the tamsulosin group (combination vs. tamsulosin, p<0.001 and combination vs. dutasteride, p-value not significant).

Safety Outcomes

Progression Events

MTOPS. Progression was defined as a twice verified worsening of the I-PSS by four points or greater *or* renal insufficiency *or* urinary retention *or* incontinence *or* recurrent UTI *or* renal insufficiency, the last occurring never, and the first being the most common accounting for 78% of all progression events. Over the duration of the study, the rate of overall clinical progression among men in the placebo group was 4.5 per 100 person-years. As compared with placebo, doxazosin reduced the risk of progression by 39%, to 2.7 per 100 person-years (p<0.001), and finasteride by 34%, to 2.9 per 100 person-years (p=0.002). The reduction in risk associated with doxazosin did not differ significantly from that associated with finasteride. As compared with placebo, combination therapy reduced the risk of overall clinical progression by 66%, to 1.5 per 100 person-years (p<0.001), a significantly greater reduction than was induced by either drug alone (p<0.001 for each pairwise comparison of combination therapy with monotherapy, with one degree of freedom).

CombAT. Not reported at the two-year interim analyses.

Adverse Events

MTOPS. The most common adverse events that occurred more frequently in the doxazosin group than in the placebo group were dizziness, postural hypotension, and asthenia. The most common adverse events that occurred more frequently in the finasteride group than in the placebo group were erectile dysfunction, decreased libido, or abnormal ejaculation. The individual adverse effects in the combination-therapy group were similar to those for each drug alone, with the exception of abnormal ejaculation, peripheral edema, and dyspnea, all of which occurred more frequently in patients taking both drugs.

CombAT. Drug related adverse events that were numerically more common in the combination group than in either monotherapy group were erectile dysfunction [7.4 vs. 6.0 (dutasteride) vs. 3.8 (tamsulosin)], retrograde ejaculation [4.2 vs. 0.6 (dutasteride) vs. 1.1 (tamsulosin)], altered (decreased) libido [3.4 vs. 2.8 (dutasteride) vs. 1.7 (tamsulosin)], ejaculation failure, semen volume decreased, loss of libido and nipple pain.

Anticholinergic Agents

Anticholinergic agents interrupt the interaction between acetylcholine and cholinergic (muscarinic) receptors (M1, M2, M3, M4, and M5). In the human bladder, the subtypes M2 and M3 are most predominant. While there are mostly M2 receptors in the bladder, the M3 receptors are primarily responsible for bladder contraction.[121] Blockade of this interaction results in a reduction in smooth muscle tone and theoretically an amelioration of diseases associated with excess contraction of these muscles. These drugs have typically been used to treat overactive bladder symptoms (OAB) in men and women. Recognizing that symptoms of OAB and LUTS secondary to BPH overlap, it is certainly possible that LUTS in many men who suffer from this condition may in fact be due to bladder dysfunction. For this reason, the use of anticholinergic agents is reasonable to consider in men with LUTS notwithstanding the concern about the development of AUR in those with potential BOO. For reference, detailed evidence tables reviewing the studies evaluated by the Panel are provided in Appendix A8.

Tolterodine

Tolterodine is a competitive muscarinic receptor antagonist. It acts on the M1, M2, M3, M4, and M5 muscarinic receptors and is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Generic tolterodine is available in 1 mg and 2 mg doses for twice daily use, and long-acting (LA) or extended-release (ER) tolterodine formulations are available in 2 mg and 4 mg doses for once-daily use.

Randomized Controlled Trials (RCTs)

There were only a small number of published studies on the use of anticholinergic agents either as monotherapy or in combination with other medical therapy for the treatment of BPH-related LUTS that met the inclusion criteria for this analysis. Three RCTs were identified; however they do not

sufficiently demonstrate the efficacy or effectiveness of tolterodine.[63, 122, 123] Although RCTs, these studied have limited patient enrollment and predominately report secondary, qualitative outcomes for assessment of BPH treatment response as compared to quantitative outcomes such as the I-PSS, uroflow, and serum PSA which makes analysis and comparison of these data difficult.

RCTs investigating treatments utilizing anticholinergic agents other than tolterodine for the treatment of LUTS secondary to BPH do not exist. Future studies investigating the effects of the newer agents on men with LUTS may be beneficial.

Single-group Cohort Studies

Two single-group cohort studies were identified. The first was a large prospective study that involved 1,080 men and evaluated men with LUTS/BPH for whom tolterodine 4 mg daily was prescribed for the treatment of frequency, urgency, or urgency incontinence and Qmax of at least 15 mL per second.[124] The cohort included men without BOO and men on alpha blocker therapy who had not improved after six weeks of treatment. Overall, 42% of men had tolterodine added to unsuccessful alpha antagonist treatment. Median I-PSS scores decreased from 17 to 10. Mean post-void residual did not increase although two patients did develop AUR requiring catheterization.

A second cohort study examined 43 consecutive men with BPH and LUTS in whom a mean of 5.7 months of alpha blocker treatment had failed due to lack of efficacy or adverse events.[125] Mean 24-hour micturition frequency decreased from 9.8 to 6.3 voids and nocturia decreased from 4.1 to 2.9 episodes nightly. Significant changes in the AUA-SI (-6.1), Qmax (1.9 mL per second), and post-void residual (-22 mL) were also observed.

Efficacy and Effectiveness Outcomes

Morbidity

The available data shows that the use of tolterodine as monotherapy or in combination with an alpha antagonist does not appear to increase the risk of urinary retention as compared to placebo. Mortality associated with the use of tolterodine was not reported.

Symptoms and Quality of Life

The three RCTs all have limited patient enrollment and predominately report secondary, qualitative outcomes for assessment of BPH treatment response. Only one study reported the use of the total AUA/I-PSS and found that combination therapy with tamsulosin and tolterodine significantly improved total I-PSS as compared with placebo.[63] There was no significant difference in total I-PSS changes from baseline between tamsulosin and tolterodine monotherapies.

In the largest of the three trials, combination therapy with tolterodine 4 mg daily and tamsulosin 0.4 mg demonstrated similar efficacy in QoL (*Urolife BPH Quality of Life 9 Questionnaire*) as monotherapy with tamsulosin primarily suggesting an alpha antagonist effect. Monotherapy with

tolterodine was not significantly different than treatment with placebo in total QoL outcomes.[63] Athanasopoulos et al found that QoL improved only in the combination group of tolterodine and tamsulosin as compared to tamsulosin alone.[123]

Pressure, Flow, Volume Outcomes

Abrams et al (2006) compared tolterodine to placebo and demonstrated no significant differences in maximum flow rates between the two groups however a statistically significant reduction in detrusor pressure at maximum flow in the tolterodine group was found.[122] Interestingly, post-void residual increased in both groups. In the study by Athanasopoulos et al when comparing tamsulosin alone vs. the combination with tolterodine, maximum flow rate improved in both groups, and QoL improved in the combination group, however, neither group experienced a significant reduction in post-void residual.[123]

Prostate-Specific Antigen Levels

There are no studies on the relationship between PSA, prostate size, and the effect of tolterodine for treatment of BPH/LUTS.

Predictors of Efficacy, Effectiveness and Harms

The included trials did not evaluate predictors of efficacy, effectiveness, or harms with the use of tolterodine.

Safety Outcomes

Withdrawals and Adverse Events

Randomized Controlled Trials. Three RCTs reported similar adverse event and withdrawal rates. In the study by Abrams et al (2006) in which men were randomized to either tolterodine 2 mg twice daily or placebo, the total number of adverse events was similar between the tolterodine (58%) and placebo (51%) groups.[122] The rates of withdrawal due to adverse events were also similar between tolterodine (6%) and placebo (7%). Dry mouth was much more common with tolterodine (24%) compared with placebo (1%). Other specific adverse events including urinary retention were reported at similar rates between the tolterodine and placebo groups.

In a smaller unblinded trial, 50 men were randomized between monotherapy with tamsulosin 0.4 mg and combination therapy with tamsulosin and tolterodine 2 mg twice daily.[123] The overall withdrawal rate due to adverse events was 8% with 4% of men withdrawing due to an adverse event in the monotherapy group and 12% in the combination group. Dry mouth was the cause for withdrawal in 8% of men in the combination group. No events of urinary retention were reported.

In a large double blinded, placebo controlled study by Kaplan and colleagues (2006), 879 men were randomized to either daily tamsulosin 0.4 mg, daily tolterodine ER 4 mg,daily combination therapy

with both medications and placebo.[63] The overall withdrawal rate due to an adverse event was 14% in this study. Dry mouth was the most commonly reported adverse event, occurring in 21% of men using combination therapy and in 7% of men in each of the monotherapy groups. The rates of AUR were low (<0.5%) in all treatment groups.

ED and ejaculation disorders were not reported with the use of tolterodine alone. Ejaculatory disorders were reported with tolterodine in combination with tamsulosin in 3.0- 4.3% of men.[63, 122, 123] Significant morbidity and mortality as a result of tolterodine use was not reported in any of the available RCTs.

Single-group Cohort Studies. Two single-group cohort studies using tolterodine ER 4 mg daily were reviewed. In the largest study in which 1,080 men were enrolled, the total withdrawal rate was 14.3% where 1.6% withdrew due to specifically to an adverse event and 3.2% withdrew due to a lack of efficacy.[124] In the second single group cohort study of 43 consecutive men four (9%) withdrew due to dry mouth.[125]

Summary

Anticholinergic agents are not approved by the FDA for the treatment for LUTS secondary to BPH. There are data however to suggest that the use of anticholinergics may be beneficial in the amelioration of LUTS in some men. Tolterodine has been the only anticholinergic agent significantly studied in men with LUTS to date. One study exists suggesting that the combination of tamsulosin and tolterodine (an anticholinergic agent) significantly improved total I-PSS compared to placebo and monotherapy with either agent.

Complementary and Alternative Medicines (CAM)

Most CAM therapies used for BPH are dietary supplements. These products are usually extracts of plants (phytotherapy) used alone or in combination. They are available over-the-counter in the United States[126] and as a result, most patients who use dietary supplements self-medicate with these products and often do not inform their physicians about their use.[127] The Dietary Supplement Health and Education Act, passed by the United Stages Congress in 1994, specifically exempted manufacturers of dietary supplements from prospective oversight by the FDA and requires manufacturers to demonstrate safety and efficacy prior to marketing.[128] Consumers and physicians, therefore, often have limited data of uncertain quality on which to make judgments about the wisdom of using or recommending a dietary supplement for the treatment of a medical condition. Furthermore, the quality and purity of these over-the-counter supplements are not rigorously monitored, adding further uncertainty about the value and safety of these products.[129-131]

Among the dietary supplements, the most commonly used, and the product for which the greatest evidence exists, is an extract of the berry of the saw palmetto plant (*Serenoa repens, Sabal serrulata*). Other products commonly marketed for BPH therapy include extracts of the African plum

tree (*Pygeum africanum*), stinging nettle (*Urtica dioica*), pumpkin seed (*Curcubita pepo*), South African star grass (*Hypoxis rooperi*) and rye pollen (*Secale cereale*).[132] Despite many years of research and a large number of publications, the quality, size, and length of most studies are suboptimal, making it impossible to offer firm recommendations and clear clinical guidance. Most studies have been small and very short in duration (often three months or less), and have used products of uncertain quality and purity and inadequate analytic strategies and outcome assessments for both efficacy and safety. Better studies have begun to appear in the literature recently, and these are included in below but the overall quality of the literature in this area remains poor. Apart from these few dietary supplements, saw palmetto and *Urtica dioica*, no other CAM modality has a sufficient evidence base to merit discussion about recommendations. For reference, detailed evidence tables reviewing the studies evaluated by the Panel are provided in Appendix A8.

Single-extract Products

Saw Palmetto

The saw palmetto plant is a dwarf palm tree that grows predominantly in the southeastern United States. Extracts of the saw palmetto berry have been used for centuries for treatment of LUTS and have become extremely popular in recent years for BPH therapy in Europe and the United States.

In vitro evidence suggests that saw palmetto extracts might have pharmacologic properties that would be expected to relieve BPH-related symptoms. Several lines of evidence of variable quality have proposed that saw palmetto has 5-ARI activity, anti-inflammatory effects, and anti-proliferative properties.[133]

A prior Cochrane meta-analysis (dated January 2002) found 21 randomized trials of saw palmetto and concluded that the evidence supported a modest beneficial effect of saw palmetto on both symptoms and flow rates and found few adverse effects associated with its use.[134] A recent update of this systematic review (dated April 2009), incorporating more recent trials, concluded that, "*Serenoa repens* was not more effective than placebo for treatment of urinary symptoms consistent with BPH."[135]

Since the prior publication of the 2003 Guideline, three new placebo-controlled trials compared saw palmetto with placebo.[136-138] These trials employed sample sizes of 85 to 225 participants with follow-up times lasting three to 12 months. All trials used a dose of 320 mg per day of the extract in single or divided doses.

In addition to the placebo-controlled trials, two trials compared saw palmetto 320 mg/day with tamsulosin 0.4 mg/day.[139, 140] Five other trials examined combinations of dietary supplements, in which one of the constituents was saw palmetto (see below).

Efficacy and Effectiveness Outcomes

Symptoms and Quality of Life

AUA-SI. Among the three most recently reported placebo-controlled trials, two found no significant between-group differences in AUA-SI scores at study closeout.[136, 138] The largest of these found a between-group difference of only 0.04 points with a 95% CI (-0.93 to 1.01 points) that excluded a clinically meaningful difference in AUA-SI scores between the saw palmetto and placebo groups.[136] The smaller study reported a 1.7-point between-group difference with a confidence interval of -0.5 to 4.0,[138] an interval that does not exclude a difference of at least three points, which is often considered a clinically meaningful change in AUA-SI scores.[141]

One trial found a modest benefit of saw palmetto compared to placebo (a between-group improvement in AUA-SI scores of 2.2 points; $p = 0.04$), though no parallel changes in any objective measurement of urinary function was found and 22% of participants had baseline Qmax values greater than 15 mL per second.[137]

One of the two trials that compared saw palmetto with tamsulosin in 704 men reported a decline in AUA-SI scores of 4.4 points in both treatment groups;[139] the other also reported no significant difference in the change in symptom scores among 40 randomized men.[140] Despite an apparent improvement in symptoms among the participants in each treatment group, within-group comparisons are of little value for assessment of specific pharmacologic efficacy of any supplement, as this response may be due to regression to the mean and a strong placebo effect.

BPH Impact Index. The BPH II is a four-item self-administered questionnaire designed to assess the impact of a patient's BPH symptoms on his general activities and perceptions of health. Bent et al (2006), found a nonsignificant difference in between-group changes in BPHII scores [-0.24 points (favoring saw palmetto) with a 95% CI: -0.60 to 0.13].[136] The BPHII was not assessed in either of the other two placebo-controlled studies nor in the studies comparing saw palmetto with an alpha blocker.[139, 140]

International Prostate Symptom Score Quality of Life Item. Most studies measured changes in the single QoL question from the I-PSS. In the two placebo-controlled studies reporting this outcome, there were no significant differences between groups in changes in the QoL question,[137, 138] despite the fact that one study found a significant difference in AUA-SI scores.[137] The largest placebo-controlled study did not report this outcome separately.[136]

In the two comparisons of saw palmetto with the alpha blocker tamsulosin, there was no significant difference in changes in LUTS-related QoL between the treatment arms.[139, 140]

Sexual Functioning. The O'Leary Sexual Functioning Questionnaire was measured in two of the placebo-controlled studies.[136, 137] In both studies, only small changes in any treatment group were observed over the follow-up periods and there were no statistically significant or clinically meaningful differences in changes between groups. The results were similar in the one trial with tamsulosin-treated controls that reported sexual-functioning outcomes; this study also reported that saw palmetto-allocated participants had fewer ejaculatory disturbances compared to those assigned to the alpha-blocker.[139]

Other Outcomes. The largest placebo-controlled study found no significant differences between groups in either the mental or physical subscales of the SF-36 scores.[136]

Pressure, Flow, Volume Outcomes

Peak Urinary Flow. Peak urinary flow was reported in all placebo-controlled trials. None of the trials reported a significant difference in Qmax between saw palmetto and placebo-treated participants, including the one trial that did find a difference in symptoms.[142, 137] The active-controlled studies comparing saw palmetto with tamsulosin also found no significant difference in urinary flow rates at closeout.[139, 140]

Postvoid Residual. Bent et al (2006) reported only small overall changes in PVR for both treatment groups in their study with small, nonsignificant differences between groups (-4.5 mL (favoring placebo), 95% CI: -24.4 to 15.4).[136] Neither of the other two placebo-controlled studies reported outcomes for PVR.[137, 138]

One of the tamsulosin-controlled studies reported similar reductions in PVR among treatment groups (declines of 23.6 to 28.1 mL, $p = 0.42$).[140] The other study did not report PVR results .[139]

Prostate Volume. One placebo-controlled trial reported changes in prostate size as measured by TRUS; in this study, the overall difference in prostate volume changes was -1.2 mL (favoring placebo; 95% CI: -3.9 to 1.5 mL). The change in the transition-zone volume was 1.3 mL (95% CI: -1.6 to 4.1 mL) (Bent 2006).[136]

In the two active-controlled trials, changes in prostate volume were $\leq$1.0 mL in all treatment groups with no significant between-group differences (p= 0.27[139] and p= 0.6[140]).

Safety Outcomes

Adverse Events

No significant differences in rates of adverse events were found between the two arms of all placebo-controlled trials, though only one study conducted thorough laboratory testing for potential toxicity.[136] The active-comparator trials (saw palmetto vs. tamsulosin) also found no significant difference in adverse events with the exception of a greater frequency of ejaculatory disturbances among participants randomized to the alpha blocker in one study.[139] Substantial evidence suggests that saw palmetto does not affect serum PSA levels.[136, 139, 143-145]

Urtica Dioica

In addition to saw palmetto, the only other single phytotherapeutic with recently published data is an extract of the stinging nettle plant (Urtica dioica). Prior studies of Urtica have been inconsistent; few trials of a pure Urtica extract exist.

Prior studies of Urtica dioica suggested that it may have moderate efficacy for treatment of BPH with few adverse effects. The recent single-extract study was a placebo-controlled RCT of Urtica (100 mg

daily) for six months in men with moderately severe symptoms of BPH.[146] Two studies of combination products containing Urtica dioica are discussed below.

Efficacy and Effectiveness Outcomes

Symptoms and Quality of Life

The single-extract study showed a substantially greater decline in the AUA-SI among the active-treatment group (-7.0 points) compared to the placebo-treated participants (-1.5 points, $p = 0.002$)[146], a difference that would generally be considered to be clinically meaningful. The BPH II, I-PSS QoL item, and sexual functioning were not assessed in this study.

Pressure, Flow, Volume Outcomes

Peak Urinary Flow. In this trial, the Qmax was substantially improved in the Urtica-treated group compared to the placebo group (+8.2 vs. +3.4 mL per second, $p< 0.05$).[146]

Postvoid Residual. Postvoid residual volume declined to a greater extent in the active treatment group compared to the placebo group (37 vs. 3 mL, $p<0.001$).[146]

Prostate Volume. Prostate volume, as measured by TRUS, decreased by 3.8 mL among the participants randomized to Urtica while the decrease was only 0.2 mL among those randomized to placebo; this difference in change scores was not statistically significant.[146]

Safety Outcomes

Adverse Events

No adverse events in either treatment group were reported in this trial and withdrawal rates were similar between the two arms.[146] PSA levels were essentially unchanged in the two groups over the course of the six-month study.

Combination Products

Phytotherapies for BPH are often sold as combination products, containing a blend of extracts proposed to be helpful for LUTS. Most of these products contain saw palmetto in addition to a variety of other dietary supplements. Among the more recently published randomized trials, six studies have reported comparative effects of five different herbal blends: two trials of a combination of saw palmetto and Urtica dioica (one placebo-controlled[147], the other using a tamsulosin comparator[148]), three placebo-controlled trials of a product containing saw palmetto[149-151] and one trial of an Ayurvedic herbal blend of phytotherapies that did not contain saw palmetto.[152]

Sample sizes for these trials ranged from 40 to 257 and follow-up times varied from three months to 15 months. All trials used the AUA-SI as the primary outcome measure; secondary outcomes and completeness of adverse-event assessments varied among the trials.

Efficacy and Effectiveness Outcomes

Symptoms and Quality of Life

AUA-SI. The two largest trials of saw palmetto-containing herbal combinations showed significant improvements in the active-treatment arms compared to the placebo arms;[147, 150] the two smaller trials found no significant differences but may have been hindered by insufficient statistical power[149, 151] (the first of these was a mechanistic study and was not intended to be fully powered for symptom outcomes). The tamsulosin-comparator trial with the saw palmetto-containing product found no differences between the treatment arms,[148] while the trial of the combination product without saw palmetto reported a significantly greater improvement in AUA-SI among the participants allocated to the herbal-treatment group.[152]

BPH Impact Index. The effect of study treatments on BPHII were not reported in any of these studies.

I-PSS QoL Question. The only trial of this set to report on changes in the QoL item from the I-PSS reported that the effect of the saw palmetto-Urtica blend was noninferior to the effect of tamsulosin.[148]

Sexual Functioning. The same study reported no effect of either the saw palmetto-Urtica blend or the alpha-blocker on indices of sexual or erectile functioning over the course of the trial.[148]

Other Outcomes. No other clinically relevant outcomes were reported in these trials. Marks et al (2000) reported that participants treated with a saw palmetto blend had a greater reduction in% epithelium and an increase in the percent of atrophic glands in biopsy specimens.[149]

Pressure, Flow and Volume Outcomes

Peak Urinary Flow. Peak urine flow outcomes were not reported for either of the active-comparator trials. Among the four placebo-controlled trials of saw palmetto-containing compounds, three found no significant difference between treatment groups while one reported a small but significant difference between groups.[151]

Post-void Residual. Three studies found no significant differences in changes in PVR between the active-treatment and placebo groups over the study period.[149, 150, 152]

Prostate Volume. Prostate volume was measured in two placebo-controlled studies of saw palmetto-containing combination products. In both of these trials, there was little change in overall prostate size and no significant differences between groups in observed changes in the prostate volume.[149, 151]

Safety Outcomes

Reported adverse events and withdrawal rates were generally low among all arms of all reported studies.

Minimally Invasive Therapies

Transurethral Radiofrequency Needle Ablation

Transurethral radiofrequency needle ablation (TUNA) of the prostate for treatment of the manifestations of BPH employs a cystoscope-like device. The lumen of the prostatic urethra is directly visualized with an endoscope and two needles are inserted from the prostatic lumen laterally into the prostatic adenoma. A double needled is inserted on both the right and left sides (some have likened the appearance to the antennae of a butterfly). Each needle simultaneously emits radiofrequency energy sufficient to heat the prostate to a temperature exceeding that necessary to cause prostatic tissue necrosis in an oval-shaped lesion around the needle tips. Four areas of necrosis result from each round of treatment, which lasts several minutes. Depending on prostatic size and length, multiple dual insertions at different levels along the length of the prostate may be utilized. The concept is to heat the transition zone of the prostate while sparing the urethral mucosa; preserving the mucosa reduce pain and improve patient tolerance. Over time the necrotic tissue will be absorbed, reducing prostatic volume. Considerable literature has been generated evaluating the prostate morphology before and after TUNA using TRUS, MRI, PSA and endoscopy to evaluate this volume reduction issue. The conclusion now is that the reduction in prostatic volume is less than initially anticipated. BPH histologic architecture is likely replaced, in part, with scar, leaving a modest at best volume reduction.

Efforts have turned to identifying possible alternative mechanisms of action for TUNA. Concepts such as prostatic muscle dysfunction, alpha adrenergic nerve dysfunction and other concepts were proposed; however, no clear conclusion has been reached. Attempts to identify favorable candidates for TUNA, both in terms of short-term response and in durability of improvement, have also been found to be difficult and inconsistent. Currently the only device available in the United States is the TUNA device marketed by Medtronic.

Randomized Prospective Trials

Four randomized, prospective trials comparing TUNA to TURP have been published. Roehrborn et al (1999) summarized outcomes of I-PSS, QoL, detrusor pressure and maximum urinary flow at six months and Hill et al (2004) provided five-year follow-up including I-PSS, QoL, max flow and post-void residual (PVR) in the same group of 121 patients.[7, 153] Hindley et al (2001) compared TUNA to TURP in 50 patients at 24 months, reporting on AUA-SI, QoL, maximum urinary flow and detrusor pressure.[154] No significant short-term complications, including need for transfusion, were reported in either arm of these three reports, nor was bleeding reported a fourth randomized trial.[155] Operative time for TUNA was 44 minutes compared to 55 minutes for TURP in this last report.[155]

Roehrborn et al (1999) found that AUA-SI decreased from 20 to 10.8 points in the TUNA group and the TURP patients had a score of 8.1 at six months.[7] By five years Hill et al (2004) reported that I-PSS (not AUA SI as originally reported by Roehrborn et al (1999) in the same patients) was now 11.7 and 7.8

for TUNA and TURP, respectively.[153] Hindley et al (2001) reported decreases in I-PSS at 24 months from 25 points to nine for TUNA and three for TURP.[154] **The Panel concludes that, based on these reports, the symptom improvement is significant and sustained for both treatments, with somewhat greater improvement in the symptom score for TURP.**

A similar trend can be seen for QoL in the Roehrborn et al (1999), with significant improvements at six months in both arms, but with TURP QoL the improvement was better than with TUNA.[7] The improvement for both arms was sustained at five years but there was a slight deterioration in both arms.[153] The Hindley et al (2001) recorded similar QoL changes.[154]

Maximum flow improvement in the Roehrborn report went from 8.8 mL per second at baseline to 13.5 and 20.8 mL per second for TUNA and TURP, respectively.[7] Hill et al (2004) found little change in flow for either TUNA or TURP over six month result when examining five year data from the same trial.[153] On the other hand, Hindley et al (2001) found much less improvement in flow for TUNA; the maximum flow improved from 8.5 to 9.8 mL per second for TUNA and from 9 to 18.4 mL per second for TURP.[154] Hill et al (2004) reported retreatment with TURP in 9/65 (14%) of TUNA treated-patients whereas one (2%) of TURP patients received TUIP retreatment.[153] One patient in the Hindley et al (2001) TUNA-treated group went on to subsequent TURP.[154] Hill et al (2004) reported no retrograde ejaculation for the TUNA group but a 41% incidence for the TURP arm.[153] ED developed in 3.1% of TUNA-treated patients and 21.4% of TURP-treated patients. This ED rate for TURP is significantly higher than generally reported for TURP.

In summary, these four randomized trials established that statistically significant improvements occur for symptoms, QoL, and urinary flow, with the exception of the Hindley et al (2001) study which reported a small improvement in maximum flow rates for TUNA. Short-term complications, including the need for transfusion, are uncommon or nonexistent. Erectile dysfunction and retrograde ejaculation are more common with TURP than TUNA, and generally very few sexual side effects are seen with TUNA. Retreatment rates are considerably higher for TUNA than TURP.

Single-Group Cohort Studies

Nine single-group cohort studies involving TUNA were identified in the literature. Four are larger group studies;[156-159] the others included fewer than 50 patients. These cohort studies are often retrospective and occasionally stated to include consecutive patients. These studies confirm that symptom scores, QoL and Qmax improve in a fashion very similar to that reported in the randomized trials and will not be detailed again here. Likewise these cohorts confirm that retrograde ejaculation is very rare to nonexistent. But these studies, which range in follow-up from two years to as long as 10 years, provide additional information on perioperative bleeding, patient selection, and need for retreatment. These issues are summarized.[157, 160, 161]

Generally these studies focused on patients who had failed medical therapy for BPH, with one exception in which previously untreated patients were recruited.[159] The prostates in these studies were

moderately enlarged, ranging from 38 to 57 mL.[161, 162] Rosario et al (2007) performed TUNA on six anticoagulated patients and encountered no significant bleeding, establishing that TUNA has a role in the actively anticoagulated patient.[158] These studies do not provide enough data on comorbidities to draw a conclusion about performing TUNA on patients with significant comorbidities. Significant procedure-related bleeding, which was not encountered in the randomized trails, did occur in two of 30 patients and required catheter balloon traction to control bleeding.[162] Another report encountered one case of bleeding (in one of 70 patients) requiring bladder irrigation.[158] Thus, bleeding is unusual but a risk nonetheless.

In the cohort studies, rates of urinary retention and the need for catheterization varied greatly but were common. Rosario et al (2007) noted that only one of their first nine patients voided after the procedure so they adopted routine postprocedure catheterization for all patients for seven days.[158] Specific practice variations and attitudes such as this make it difficult to discern the rate of retention and duration of retention. In another series, the failure to void rate by day one after TUNA was 32% with subsequent catheterization duration averaging 6.3 days.[163] High rates of retention were reported in other series as well.[162, 164]

Retreatment was common in studies with longer follow-up. Fujimoto and colleagues (2003) reported that 13 of 41 patients had either TURP or pharmacotherapy with 24 months of TUNA.[160] In a study with a median follow up of 112 months, 83% of 70 patients had deterioration of symptoms over time and of these, 50% had invasive therapy and 20% had drug treatment for BPH.[158] Zlotta et al (2003) reported retreatment rates of 23% by five years with more than half of retreated patients opting for invasive treatment.[159]

Attempts have been made to identify preoperative parameters that might predict success or failure. In a group of 41 patients, prostate volume and prostate transition zone volume decreased significantly at three months and the difference was not significant at 12 months; when patients were evaluated for differences in baseline prostate volume and transition zone, no differences were found between responders and those patients who fared less well.[160] In another study of 24 patients, 10 had obstructed voiding patterns. They were more likely at baseline to be over the age of 70, have a higher detrusor pressure, a greater residual volume and a worse QoL score.[165]

Summary

The Panel concludes based on the available literature that there remains a degree of uncertainty regarding TUNA because of a paucity of higher quality studies. There are only three prospective randomized trials (one trial is reported at two time points) and all reports taken together lack sufficient detail on the comorbidity of subjects. Most are cohort trials and the reporting of results varies considerably. Since the 2003 Guideline, little new information has been published. For reference, detailed evidence tables reviewing the studies evaluated by the Panel are provided in Appendix A8.

TUNA is safe with low perioperative complications including bleeding. TUNA has a low to nonexistent rate of sexual dysfunction and is attractive for that alone. Improvements in symptoms, QoL and urinary flow rates are significant but do not generally match the result of TURP and the bulk of the literature suggests a high retreatment rate when patients are observed over many years.

Transurethral Microwave Thermotherapy

Transurethral microwave thermotherapy (TUMT) has evolved through several iterations over the past 15 years. These have included variations in the route of administration (transrectal vs. transurethral), energy levels (low vs. high), and concomitant urethral cooling. The early 1980's and 1990's saw the advent of the first TUMT machines, beginning with the Primus (Tecnomatix Medical, Brussels, Belgium) prostate machine and the Prostathermer (Biodan Medical Systems Ltd., Rehovot, Israel), originally developed to treat prostate cancer. These systems were responsible for the term "hyperthermia" that evolved to describe their mechanism of action. Hyperthermia techniques failed, however, since early devices were unable to generate temperatures sufficient to ablate prostatic tissue and to adequately target the transition zone transrectally. Newer TUMT devices would seek greater temperatures (i.e., "thermotherapy,") as well as a transurethral approach to target the transition zone. EDAP-Technomed (Lyon, France) developed a TUMT device in the early 1990's that could achieve interstitial temperatures of 50°C to 80°C. These use of these higher temperatures led to the development of cooling systems to offset the higher energy effects on the urethra, bladder neck and adjacent tissues. The early cooling systems initially used in second generation TUMT devices were not highly efficient and often deeper lesions than intended were created in the prostatic peripheral and central zones. The development of thermotherapy devices also led to the new goal of TUMT paralleling the tissue ablation seen with TURP. Manufacturers have therefore continued developing higher energy systems with more complex and efficient cooling systems, leading to more effective third generation systems. These modifications have allowed higher microwave energy delivery while decreasing urethral morbidity. Ultimately, heat to the transition zone with preservation of the urethra mucosa would lead to delayed coagulation necrosis with comcomitant decreases in pain during the procedure and the ability to perform the procedure in an office setting.

<u>FDA-Approved Transurethral Microwave Thermotherapy Devices</u>

TMx-2000™ (TherMatrx®, American Medical Systems)

The TMx-2000™ system represents the lowest power (23W) TUMT device available, which operates at 915MHz and lacks a cooling mechanism. The catheter offers variable radiating helical coil lengths: 2.5 cm for prostatic urethral lengths of three to four cm, 3.5 cm for four to five cm length prostates and 4.5 cm for five to 5.7 cm length prostates. The TMx-2000 is contraindicated in patients who have received previous pelvic radiation and is FDA-approved only for symptomatic relief, not for improvement in urodynamic parameters or obstruction.

Prostatron® (Urologix, Inc.)

The original Prostatron device utilized a monopole antenna that exhibited significant backheating. The updated version of this antenna now employs an active urethral cooling system to compensate for backheating. It operates at a frequency of 1296 MHz, significantly higher than other TUMT systems and is capable of generating up to 80W of power.

Targis® (Urologix, Inc.)

A second generation microwave device, the Targis® system uses a dipole antenna with frequencies in the range of 902 to 928 MHz. The catheter balloon in the Targis system is inflated with water and positioned 0.4 cm away from the end of the antenna. Targis is unique in that it uses coolant water at 8°C during therapy to protect the urethra and bladder neck. Contraindications to Targis include a prostatic urethral length less than three cm and middle lobe enlargement. A third generation update to the Targis design employs an expandable urethral balloon along with changes in the device catheter to more effectively cool the urethral surface during treatment, allowing greater safe energy delivery to the prostate (Cooled ThermoCath®, CTC, Urologix, Inc.). The treatment time has been decreased to 28.5 minutes.

CoreTherm™® (Prostalund, Inc.)

CoreTherm® represents the only TUMT device to use an interstitial probe with three sensors to monitor intraprostatic temperature, thereby providing a mechanism to control and adjust the volume of tissue ablation.[166] It operates at a frequency of 915 MHz with three different length catheters: white (for prostates greater than 55 mm in length), blue (for prostates 30 to 55 mm), and yellow (for prostates less than 30 mm) and can deliver up to 100W of power. The heat distribution of the system reflects the backheating component, where an exposed inner conductor is positioned at the tip of a coaxial cable.

Prolieve™ (Boston Scientific Corporation)

The Prolieve™ system uses a frequency of 915 MHz with a monopolar antenna. It contains an expandable urethral balloon that inflates with circulated water maintained at 34°C. Despite the expected loss of energy that would be anticipated from heat dissipation with this large volume of cooling water, the system is capable of running at 50W to achieve interstitial temperatures of 41°C to 46°C.

Study Outcomes

Initial studies evaluating the efficacy of TUMT utilized low-energy protocols, mostly with the Prostatron device. Dahlstrand et al (1995) compared 32 patients treated with TURP vs. 37 patients treated with low energy TUMT.[167] Improvements were seen in Madsen-Iversen symptom score, PVR, and free flow rate, up to 24 months posttreatment, although improvements in the last category were

more pronounced with TURP. High energy (HE) TUMT was then developed to increase tissue destruction and theoretically yield greater improvements in voiding ability. These newer devices included Prostatron® 2.5 and Targis®, as well as the Urowave (Dornier Medical Systems, Inc., Wessling, Germany). Others now include Prolieve™ (Boston Scientific Corporation), TMx-2000™ (American Medical Systems) and CoreTherm® (Prostalund, Inc.). Generally, data from one manufacturer's device cannot be applied to other manufacturers' devices since each has unique power delivery characteristics, resulting in differing levels of tissue destruction.

TMx-2000™

The TMx-2000™ system was studied in a multi-institutional, randomized trial including 119 patients in 2002.[168] At three months after study initiation, patients were allowed to cross over from sham to active treatment. Statistically significant declines in AUA-SI (22.4 to 10.6) were seen at 12 months, although recatheterization was required in 16.8% of patients. Maximum Qmax increased from 8.9 to 13.5 mL per second. No major adverse events were noted. A 2003 update to this experience confirmed improvements in AUA-SI, although urodynamics data was not provided.[168]

Prostatron

D'Ancona et al (1998) compared the 2.5 year outcome of HE-TUMT using the Prostatron® 2.5 (31 patients) to TURP (21 patients).[169] After two years, Madsen-Iverson scores improved in 56% and 74% of patients after TUMT and TURP treatments, respectively. By urodynamic measurements, however, one-third of patients remained obstructed two years after treatment with TUMT. At 2.5 years follow-up, 19% of patients treated with TUMT required retreatment.

Francisca et al (1999) randomized 122 patients to treatment with Prostatron® 2.5 TUMT (66 patients) or TURP (56 patients).[170] While TURP demonstrated greater efficacy in improving Qmax, PVR, I-PSS, and prostate volume, TUMT demonstrated a significantly lower rate of sexual side effects, e.g. retrograde ejaculation (32% vs. 63% in TURP) at one year. Floratos et al (2001) updated the Francisca et al (1999) experience with 144 patients randomized to either HE-TUMT (78 patients) or TURP (66 patients) with a median follow-up of 33 months.[170, 171] In the TUMT-treated group, I-PSS decreased from 20 to 12 at three years, while Qmax increased from 9.2 to 11.9 mL per second. In the TURP group, at three years, I-PSS decreased from 20 to three, while Qmax increased from 7.8 to 24.7 mL per second. The cumulative risk of retreatment between the two groups was not statistically significant.

Ohigashi et al (2007) described the durability of TUMT effects after treatment with the Prostatron® 2.0; 102 patients were treated and the risk of necessity for retreatment calculated.[172] Kaplan-Meier analyses demonstrated that 67% of patients required additional treatment within five years after TUMT, with a median period of 37 months. Qmax greater than 6.5 mL per second, a urethral length less than 40 mm, and age >64 years were all significant predictors of durable results. Laguna et al studied 388 patients treated with Prostatron 2.5 or 3.5.[173] An improvement of 50% or more was

observed in I-PSS, QoL score, and Qmax in 57%, 62%, and 44% of patients, respectively. Absolute mean changes at one year were -9.7, -2.0, and 5.2 mL per second, respectively.

The broadest Prostatron experience has been published by Vesely et al (2005) with an 11 year follow-up of 452 patients treated with either Prostasoft 2.0 (323 patients) or Prostasoft 3.5 (129 patients).[174] With version 2.0, 67% of patients were satisfied with the results of treatment; 18% of patients experienced complications, 25% had transient UTI, 16% had urinary retention and 32% of patients required retreatment. I-PSS decreased from 15.9 and 2.9 and QoL scores decreased from 12.0 and 2.1. With Prostasoft 3.5, 82% of patients were satisfied; 17% experienced complications, 25% had UTIs, 26% had urinary retention, and 7% required retreatment. I-PSS decreased from 19.8 and 3.8 to 11.2 and 1.5, respectively.

Targis

Djavan et al (2001) compared 51 patients treated with Targis TUMT vs. 52 treated with alpha blockers.[175] While mean I-PSS, Qmax, and QoL scores improved for both groups, the TUMT group demonstrated a greater magnitude of improvement. Between-group differences were 35%, 22%, and 43% greater, respectively, for the TUMT group with a sevenfold lower actuarial treatment failure rate. These effects were maintained for at least 18 months.[175] In a prospective trial where 200 patients were treated with Targis TUMT, Thalmann et al demonstrated that median Qmax increased from six to 13 mL per second at 24 months.[176] Median PVR decreased from 170 mL to 27 mL, while I-PSS decreased from 23 to three. Two years after treatment, 59 patients agreed to undergo repeat urodynamic evaluation; median detrusor pressure at Qmax decreased from 86 to 58 cm H_2O. Osman et al (2003) compared the one-year subjective vs. urodynamic changes in 40 TUMT patients.[177] While AUA-SI decreased from 20.5 to nine, Qmax increased from 9.2 to 15 and the Schafer nomogram number decreased from four to two. Qmax paralleled improvement with the obstructive component of the AUA-SI for the first three months; afterwards, improvements in irritative symptoms accounted for the bulk of AUA-SI improvement.

Miller et al (2003) studied the durability of Targis® TUMT over three centers in 150 patients for five years.[178] AUA-SI improved 11.5 (53%) and 10.6 (47%) points at one and five years, while Qmax improved by 3.4 (48%) and 2.4 (37%); 31 patients required retreatment. Of note, five-year follow-up existed for only 59 of the original 150 patients. Berger et al (2003) studied Targis® TUMT in 78 high risk patients with AUR with a mean follow-up of 34 months; 87.1% of patients were able to void afterwards, although 7.3% experienced repeat retention within two years.[179] Mean Qmax improved to 11.1 mL per second while mean PVR decreased to 46 mL. The largest prospective Targis® trial involved 345 patients treated over nine institutions. In this study, Kaplan et al (2004) demonstrated that 65% of patients showed at least a 50% reduction in symptom scores the first year, with a mean I-PSS improvement of 11.1 points. In the 85 patients available for five-year follow-up, absolute I-PSS improvement was maintained at 8.4 points. Flow rates improved from 7.5 to 10.5 mL per second at three years.

Cooled ThermoCath

This microwave catheter technique is based on minor modifications of the initial Targis balloon device. It features different antenna structure and larger beds for cooling urethral membrane. Huidobro et al conducted the first multicenter trial with the cooled thermoCath (CTC) system vs. Targis®.[180] Forty patients were followed for 12 months after TUMT. Thirty-six demonstrated decreased prostate volume (8% with CTC vs. 21% with Targis 60), QoL (44% vs. 58%), AUA symptom score (41% vs. 60%), and increased Qmax (28% vs. 55%).

CoreTherm

Gravas et al (2007) reviewed the single-institution, 41 patient experience with ProstaLund Feedback Treatment (PLFT).[181] With PLFT, treatment is usually stopped when 55°C is measured in any part of the treatment zone. PLFT is thought to compensate for the interindividual and intraindividual differences in prostatic blood flow, in contrast to standard TUMT devices. I-PSS decreased from 21.9 to 7.1, while Qmax increased from 8.4 to 17.8 mL per second at 12 months. The mean change in prostate volume was 19 mL over the same time period. No serious adverse effects were seen, although ejaculatory ability was mildly diminished (78% to 51.4%). de la Rosette et al (2003) studied 180 patients pooled from three prospective clinical trials and followed for 12 months.[182] Improvements in prostate volume reduction (52 to 34 mL), Qmax (7.7 to 16.1 mL per second), and I-PSS (20.9 to 6.4) were seen. Prostate volume reduction correlated with changes in Qmax and voiding pressure. Schelin (2006) evaluated 24 patients with BPH and chronic urinary retention also treated with PLFT; 19 (80%) of the patients were treated successfully with removal of the indwelling catheter.[183] Five failures occurred in patients with enlarged median lobes or large protruding lobes into the bladder. No serious complications occurred. David et al (2004) reviewed the outpatient experience of PLFT in 102 patients with a mean follow-up of 5.6 months in a retrospective, multicenter trial.[184] Mean postoperative catheter duration was 13 days. Mean AUA symptom score decreased from 18 to 11 at three months. Qmax increased from 7.8 to 14 mL per second.

Schelin et al (2006) studied the efficacy of PLFT in 54 patients with chronic urinary retention against 52 TURP patients in a prospective, multicenter trial.[183] Both groups were catheter-free at six month follow-up. Mean catheterization time was 34 days for TUMT vs.verus five days for TURP. I-PSS at six months was significantly less for TURP (4.4) vs. TUMT (7.3). Qmax at six months was not statistically different between the two groups.

Wagrell et al (2004) reported a prospective, randomized, multicenter trial that studied 154 patients treated with either HE-TUMT via PLFT (103 patients) vs.verus TURP (51 patients) with a median follow-up of 36 months.[185] No statistically significant differences were found in Qmax or QoL between the two groups, although I-PSS was different at 36 months (8.2 for TUMT vs. 5.0 for TURP). TUMT had a lower rate of serious adverse events (2%) compared to TURP (17%). The most frequent side effects of TUMT were impotence (8%), PSA increase (5%), and hematuria (4%).

Mattiasson et al (2007) updated the Wagrell et al (2004) experience with an expanded five-year follow-up of TUMT (103 patients) vs. TURP (51 patients); 96 patients (62 TUMT, 34 TURP) were available for follow-up at 60 months.[185, 186] Ten percent of TUMT patients required additional BPH treatment, while 4.3% of TURP patients required retreatment. I-PSS decreased from 21.0 to 7.4 for TUMT and from 20.5 to 6.0 for TURP; QoL decreased from 4.3 to 1.1 and from 4.2 to 1.1 in the same groups. Qmax increased from 6.7 to 11.4 mL per second for TUMT and from 7.9 to 13.3 mL per second for TURP. PVR decreased from 106 to 70 mL for TUMT and from 94 to 51 mL for TURP. No statistically significant differences were found between the two groups' end results. Eighty complications were seen in the TUMT group, while 39 were seen in the TURP group.

Prolieve™

Bock et al (2004) reviewed the one-year clinical experience with the Prolieve™ system in a multicenter, randomized trial; 94 patients treated with Prolieve™ TUMT were compared to therapy with finasteride alone in 31 patients.[187] Fewer than 20% of patients required catheterization after TUMT. AUA-SI improvement was significantly greater in the TUMT group (49.3%) than in the finasteride group (19.1%) at six months. The magnitude of improvement was similar among patients with prostates greater and less than 50 g.

Summary

TUNA, as well as TUMT, has been utilized consistently over recent years with about 20,000 radiofrequency cases and around 80,000 microwave thermotherapy cases annually in the United States. A systematic review of TUMT data reveals a heterogeneous mix of studies of various sizes and TUMT protocols, often using different outcome measures with varying durations of follow-up. This leads to conflicting results, as may be seen in studies of shorter vs. longer follow-up. For reference, detailed evidence tables reviewing the studies evaluated by the Panel are provided in Appendix A8.

Older, low-energy TUMT devices similarly possess comparatively less clinical efficacy than newer, higher energy counterparts but also carry a lower risk of side effects. The durability of TUMT treatment appears to have improved with the advent of higher energy, later generation devices. One should also note however that the concept of durability with TUMT may be misleading, as the data suffer from a selection bias. Most studies analyze only those patients who remain in the study at the time of analysis; these patients would tend to represent the best "responders." In many studies, less than half of the initial group of men treated is analyzed at the end of the study period. Intent-to-treat analyses where therapeutic failures are considered are required to give a better idea of the true effectiveness and durability of TUMT. It is also important to note that the quality of the TURP comparator group in many of the series is influenced by surgeon skill and patient selection, and will therefore materially impact influence head-to-head comparisons between the therapies. The rate of utilization did not reach initial expectations, and has held more or less steady in recent years. Outpatient

capability, lack of sexual side effects and avoidance of actual surgery are attractive to patient and clinician alike. But perhaps the one issue that has held back greater utilization is not short term efficacy but the perception that these approaches lack sufficient durability of effect to assume a greater role in the management of LUTS.

Surgical Therapies

Surgery, by definition, is the most invasive option for the management of LUTS and BOO. The mechanism of action for surgical interventions is based on the classic BOO model wherein the enlarging or obstructing prostate tissue increases the urethral resistance to flow, thus requiring ever higher intravesical pressures to void. The physiologic obstruction then results in subjective symptoms that lead men to seek medical care. Surgical treatment of BOO is defined as the mechanical debulking of tissue within the prostatic fossa. Urodynamically, the underlying BOO and the surgical results can be demonstrated using multichannel measures of intravesical pressure and simultaneous flow. A classic picture of obstruction would appear urodynamically as an elevated intravesical pressure relative to a low urinary flow rate. Direct intraurethral pressure measures have also been applied as a measure of BOO though it has not gained widespread acceptance due in part to concerns over reliability.

As a management option, surgery is typically performed in the operating room setting, requires anesthesia and is associated with the greatest risks for morbidity and higher costs. Traditionally, the gold standards have been an open prostatectomy (retropubic, suprapubic) for very large prostates or those with large bladder calculi and a monopolar TURP. For small prostates (<30 g), the option for a transurethral incision of the prostate (TUIP) has been found to be associated with fewer complications but comparable efficacy.

In the 21st century, surgical management of BPH continues to evolve towards less invasive, endoscopic procedures that are viable alternatives to open prostatectomy. In addition to open prostatectomy and TURP, newer surgical options include bipolar or saline TURP, transurethral holmium laser enucleation of the prostate (HoLEP), potassium-titanyl-phosphate photovaporization of the prostate (PVP) laser ablation of the prostate, holmium laser ablation of the prostate (HoLAP), and transurethral electrovaporization of the prostate (TUEVP). The clinical data supporting the use of these surgical procedures including several comparative trials are herein reviewed. Systematically, current evidence describing the background literature and outcomes for each procedure have been considered. For reference, detailed evidence tables reviewing the studies evaluated by the Panel are provided in Appendix A8.

Open Prostatectomy

Randomized Controlled trials (RCTs)

Two surgical approaches to open prostatectomy for BPH are in common use: the Millin modified retropubic prostatectomy and the classical transvesical prostatectomy.[188] No new RCTs examining effectiveness were identified in the current review of the literature.

Cohort Studies with a Comparison Group

One retrospective study was identified that compared rates of repeat prostatectomy between open prostatectomy and standard TURP using a population-based cohort in Western Australia.[189] Hospital data and death records were gathered on all 19,598 men undergoing prostate surgery for BPH between 1980 and 1995. In a second study, open prostatectomy (*n*=69) was compared with TURP (*n*=16) in 85 Kenyan men.[190]

Single-group Cohort Studies

The 12 single-group cohort studies examining open prostatectomy that were identified in this review generally included subjects with larger glands or patients needing surgery for bladder or other pelvic or inguinal conditions. Otherwise, inclusion and exclusion criteria were similar to those of other surgical interventions, including significant LUTS and no prior history of prostate surgery or suspicion of prostate cancer. Approximately half of the studies were retrospective series and a number of the studies examined only intra- and peri-operative outcomes and complications without examination of efficacy and effectiveness outcomes. Follow-up intervals ranged from the immediate postoperative period up to 11 years.[191] The various techniques of open prostatectomy included transvesical[192-197] and retropubic.[198] In some studies various techniques were used with the data and not stratified by approach. [191, 199] Bernie et al compared the three techniques, namely transversica, retropubic, and perineal. [200] Other reports did not indicate the specific surgical approach.[201]

Efficacy and Effectiveness Outcomes

Symptoms and Quality of Life

I-PSS or AUA-SI and QoL scores improved in all studies reporting this outcome, with follow-up between three months and more than three years. IIEF[194] and the Madsen-Iversen score[196] improved significantly at six and 12 months, respectively. Postvoid residual and Qmax also improved significantly in all studies examining this outcome at mean follow-up up to three years. In the only study of sexual function after surgery, a significant increase in sexual desire and overall satisfaction was observed.[194]

Safety Outcomes

Withdrawals and Treatment Failures

Few prospective studies reported attrition and few retrospective studies reported the completeness of data collection at the end of the follow-up interval. Reoperation for treatment failure was rarely reported. Follow-up of 56 men at up to 11 years (mean 36 months) after open prostatectomy identified only one patient who needed additional therapy for BPH (continued drug treatment).[191] In another study, the reoperation rate was 3.9% at mean follow-up of 42 months, but no details were provided as to the treatment rendered. [197]

Perioperative and Short-Term Outcomes

Intraoperative blood loss more than 1000 mL was reported in several studies using the retropubic approach.[191, 200, 202] Serretta and colleagues (2002) reported "severe bleeding" in 11.6% of subjects, with 8.2% of subjects requiring blood transfusions, while others reported even higher rates of intra- or peri-operative transfusions: 16%and 19%.[192, 199, 202] However, several studies did report lower transfusion rates (<10%).[193, 195, 197] Hospital stay for open prostatectomy ranged between five to seven days in many studies;[191, 193, 195-197, 199, 200] however, the mean length of stay was approximately 11 days in other studies of transvesical prostatectomy.[192, 202] Bernie and Schmidt compared hospital stays among surgical approaches and reported five and six days for retropubic and suprapubic approaches, respectively.[200] Mean catheter duration was between five and seven days.

Longer-term Complications

Mortality was infrequently reported in these studies and perioperative death rates were low (≤1%) and generally related to cardiovascular disease.[193, 195, 202] In the large (*n*=1,800) series by Serretta and colleagues, one perioperative death was reported.[199] The discovery of incidental prostate cancer in resected specimens was reported at rates of 2%,[193] 3.1%,[201] 6.5%,[192] 11%[195] and 17%.[202] Incontinence was reported at rates between 0.5% and 8%, with several studies reporting much lower rates of permanent incontinence.[196, 199] Bladder neck contracture was reported at 3% to 6%[191, 196, 197, 202] and in one of six subjects undergoing perineal open prostatectomy in a single series.[200]

Laparoscopic Prostatectomy

Cohort Studies with a Comparison Group

A single cohort study (*n*=60) compared consecutive patients undergoing laparoscopic prostatectomy with a consecutive retrospective cohort of open prostatectomy.[203]

Single-group Cohort Studies

Sotelo and colleagues (2005) in the U.S. and Venezuela reported a series (*n*=17) of laparoscopic retropubic simple prostatectomies.[198] Subjects had glands at least 60 g (mean 93 g).

When laparoscopic and open approaches were compared, the mean operative time was greater in the laparoscopic group (115 vs. 54 minutes, $p<0.01$)[203] while blood loss, catheter duration, and hospital stay were greater with the open procedure. There was no difference in the rate or severity of complications. Sotelo reported a mean operative time of 156 minutes (range 85 to 380) and a mean blood loss of 516 mL (range 100 to 2500 mL).[198] Five patients required transfusion and complications occurred in three patients. AUA-SI and Qmax improved significantly at follow-up between three months and two years.

Laser Therapies

Holmium Laser Ablation of the Prostate (HoLAP)

Single-group Cohort Studies

One publication updated previously published data reviewed in the 2003 Guideline, thereby fulfilling inclusion criteria for this revision.[204] Gilling and colleagues (1996) published seven year follow-up on a serious of 79 men undergoing HoLAP. [205, 206] At seven-years follow-up, only 34 men in the original cohort were available.

Holmium Laser Enucleation of the Prostate (HoLEP)

Randomized Controlled Trials (RCTs)

Procedures involving the holmium laser were examined in eight RCTs, with various comparators: one small (*n*=40) trial that compared HoLEP to plasmakinetic enucleation of the prostate and followed patients for 12 months,[207] standard monopolar TURP,[208-211] holmium laser bladder neck incision,[212] and open prostatectomy.[213, 214] Inclusion criteria were similar across studies: men presenting with LUTS of severity suggesting that surgical treatment was indicated. Follow-up intervals ranged from six months[213] to five years.[215] Sample size ranged between 40[207, 212] and 200 subjects.[209] Few studies provided any details on how subjects were selected. Mean age in the studies ranged between approximately 65 and 71 years, mean I-PSS ranged between 19 and 26, and QoL score between four and five. Large prostate glands were examined in several studies: >100 g,[213, 215] 40 to 200 g[211] and 70 to 220 g.[214] The percentage of subjects in urinary retention at baseline was generally not reported; in two studies such subjects were excluded from study participation.[210, 211]

Cohort Studies with a Comparison Group

One small study (*n*=20) compared a cohort of patients who received HoLEP with a cohort of patients who had open prostatectomy.[216] Four studies examined HoLEP compared with TURP.[208-211]

Single-group Cohort Studies

There were 15 publications of single-group cohort studies examining HoLEP. Several of these publications reported overlapping populations.[209, 217-223] Few details were provided on participant

recruitment and many of the studies were retrospective examinations of surgical series including only patients where complete data were available.[224-226 218] Follow-up was generally less than one year, although several included longer follow-up.[217, 218, 220, 227] Mean age was between 65 and 74 years. I-PSS ranged 19 to 23, although one study had a somewhat lower baseline mean value of approximately 14.[224] Mean baseline Qmax ranged between 4.5 and 9.0 mL per second. A significant percentage of subjects were in urinary retention at baseline in several studies, although this information was infrequently reported at baseline. [217, 221, 222, 224] The majority of studies examined the holmium:YAG (Versapulse) end-firing laser produced by Lumenis, Inc. used with the Lumenis tissue morcellator.[217-224, 226-228] Wattage used was between 65W and 100W.

Holmium Laser Resection of the Prostate (HoLRP)

Randomized Controlled Trials

The effectiveness and safety of holmium-YAG laser (HoL-YAG) was compared to TURP in one RCT with two-year follow-up.[229, 230]

Single-group Cohort Studies

Two single-group cohort studies were identified which examined HoLRP.[231, 232] Chilton and colleagues reported a retrospective series of 259 men undergoing HoLRP.[231] Yamanishi and colleagues described a small, prospective series (*n*=32) of HoLRP.[232]

Potassium-Titanyl-Phosphate Photovaporization of the Prostate (PVP)

Randomized Controlled Trials (RCTs)

The effectiveness of the PVP laser was reported one RCT (PVP laser vs. TURP: early results of a randomized trial).[233]

Cohort Studies with a Comparison Group

A cohort study compared PVP using the GreenLight™ laser with standard TURP.[234]

Single-group Cohort Studies

We identified 18 publications of single-group cohort studies examining the potassium-titanyl-phosphate (PVP) laser.[235-252] Inclusion criteria for treatment with the PVP laser in cohort studies was typical of BPH surgical series (i.e., men with LUTS suggestive of BPH). Sample size varied greatly, ranging from 10[238] to 208[249]. Follow-up interval ranged from six weeks[236] to three years,[246] with only two studies providing data for longer than 12 months.[246, 249] Mean age of study participants ranged between 64 and 79 years, and the mean age was 75 years or greater in several studies.[237, 243, 251] Baseline mean I-PSS ranged broadly, from 16[241] to approximately 30 in a study of high-risk men with larger prostates.[237] Qmax also varied across studies, with mean values between 5.5 mL per second[237] and 13 mL per

second.[239] Men in urinary retention were excluded in some studies,[234, 238, 242, 252] while in others a significant pecentage had chronic urinary retention.[237, 243, 244, 251]

Thulium: YAG Laser

Single-group Cohort Studies

Bach and colleagues (2007) reported a cohort of 54 consecutive patients treated with the RevoLix™ laser for LUTS due to BPH.[253] Mean prostate size was 30.3 mL and mean resection time was 52 minutes.

Efficacy and Effectiveness Outcomes

Similar to the analysis of the surgical therapies in the 2003 analysis, the symptom score and peak-flow data were available for most laser treatments and QoL scores were available for most treatments. The BPH II scores were not recorded for any surgical trials. When laser therapies were evaluated in RCTs, TURP was the most common comparison group and often referred to as the historical gold standard. Other comparison groups included open prostatectomy, bipolar TURP and laser therapy with and without 5-ARIs.

Symptoms and Quality of Life

AUA Symptom Index. All studies evaluating AUA-SI symptom improvement following laser therapy of the prostate reported improved AUA-SI scores three weeks[254] to six years[255] after therapy. The AUA-SI improvements were not significantly different from the comparison groups in those studies with a randomized controlled design or those with a cohort group. Data from RCTs are limited to holmium laser therapies. The difference in AUA symptom scores when compared open prostatectomy (at three months and five years),[256, 257] and TURP (at 12 and 24 months) did not reach statistical significance in three trials[258-260] but there was a greater improvement with HoLEP than TURP in one trial with 12 month follow up.[261] Further, the improvement in AUA-SI following HoLEP do not appear to be significantly different in men with larger prostates. When HoLEP was compared with holmium laser bladder neck incision (HoBNI), there was no significant difference between treatment groups for AUA symptom score at three-, six- and 12-month follow-up.[262]

A single-group cohort study of holmium ablation of the prostate reported improvements in AUA-SI score three months postoperatively that were sustained at seven years, although no statistics were provided.[258] Holmium laser resection of the prostate also resulted in improved AUA-SI scores and these improvements were sustained at 24 months but were not significantly different from a cohort TURP group.[263] Single-cohort studies utilizing PVP laser therapy reported that I-PSS or AUA-SI improved consistently in all studies, with follow-up intervals ranging from six weeks[264] to five years.[265] Monoski and colleagues (2006) examined the relationship between preoperative urodynamic parameters and outcomes in 40 patients in urinary retention.[266] Postoperatively, subjects with detrusor overactivity had more voiding symptoms than those without detrusor overactivity. Men without impaired detrusor

contractility at baseline had a better I-PSS, flow rates, and post-void residual volumes at up to six months of follow-up compared with men with impaired detrusor contractility. Single-cohort studies involving PVP laser reported that men with no evidence of bladder instability and lower PSA values (representing smaller prostates with an average volume of 48.3 mL) prior to therapy were noted to have greater improvement in their AUA-SI scores compared to men with greater pretreatment PSA values (representing a mean prostate volume of 83 mL).[267] The concurrent use of 5-ARIs did not appear to impact the AUA symptom score at one year in men who have been treated with the PVP laser.

The I-PSS associated with HoLEP decreased 13 to 18 points at one month, and the reduction in symptom score (11.7 point decrease from baseline) was maintained at the five-year follow-up. The reductions in scores for the PVP laser were slightly less at one month (range 4 to 16 point decrease), although by three months the decrease in AUA-SI score was comparable to HoLEP (range 9 to 20.9 point decrease) and at five years was lower than HoLEP (19.4 point decrease in symptom score form baseline). The outcomes associated with the thulium laser were reported for 54 patients in a single cohort study and improvement in the AUA-SI score at 12 months;[253] however, there was insufficient information to assess statistical validity of this improvement.

Summary

All laser therapies produce major improvements in the AUA-SI scores. While there are no direct comparisons between the various laser technologies, the improvements in symptom scores appear to be comparable to other surgical therapies and durable to five years.

International Prostate Symptom Score Quality of Life Question

A greater percentage of studies included QoL scores compared to the analysis conducted for the 2003 AUA Guideline; however, the only RCTs that pursued QoL data involved holmium laser enucleation/ablation of the prostate compared to TURP or bipolar TURP, and these studies support that the QoL improved in all treatment groups with no significant differences at one- and two-[258-260] and six-years[255] follow-up and greater improvement in HoLEP compared to TURP at one-year in one study.[261]

In general, HoLEP QoL scores appeared to improve 3.5 points at one month following therapy. Data from a single investigator suggest that the QoL assessment in the interval between one year and six years follow-up is still improved but variable, as reported scores ranged between -2.6 compared to baseline at one-year, -3.4 at three years, and -2.2 points below baseline at six years. Single group cohort studies using holmium ablation of the prostate report that the improvements in QoL scores noted at three months postoperatively were sustained at seven years although no statistics were provided.[258] When HoLEP was compared with HoBNI, there was no significant difference between treatment groups for QoL at the three-, six- and 12-month follow-up.[262]

Quality of life data associated with outcomes from PVP laser therapy also improved in all studies and the variability over time appeared to be less than with HoLEP.[265, 268] The improvement in the initial QoL scores at one month was less than HoLEP (range -2.2 points to -2.7 points) but improvements at

three months appeared equivalent (range -2.8 to -4 points); by one year QoL scores were consistently better (range -3.9 to -4.1 points) and were maintained in the longest reported study at two years (single study -3.9 points).

The QoL score improved in all single-cohort group studies of the PVP laser. In the single cohort study that included 54 patients improvement was found in the QoL score at one-year however, due to limited data, conclusions about this modality cannot be drawn.[253]

Summary

Although data are limited, the QoL score improved post-laser therapy when evaluated at one- and two-year follow-up regardless of the procedure type (except for thulium, for which conclusion could not be drawn).

Pressure, Flow, Volume Outcomes

Peak Urinary Flow Rate. The only RCTs of laser therapy that reported Qmax involved HoLEP; Qmax improved in both treatment groups in the three of four studies reporting this outcome. In general, there were no significant differences between groups at one-year.[258, 259, 261] Further, Qmax was improved but not significantly different from open prostatectomy[256, 257] and bipolar TURP[269] between three months and five years of follow-up. Long-term randomized studies that compared HoLEP to bipolar TURP reported improved Qmax at up to five-years of follow-up.[270] All other studies involving laser therapy reported improved maximum flow rate.

Maximum urinary flow rates improved in all studies reporting this parameter after HoLEP. The improvements in maximum flow rate at three months (range from 9.8 to 23.2 mL per second) appeared to be maintained at two years in a single study reporting average maximum flow rate of 12 mL per second)[271] and was reported to decrease slightly at six years in another single study that reported an average maximum flow rate 9.9 mL per second.[255] When a holmium laser was used to ablate the prostate, a single-group cohort study reported that the improvements in QoL scores noted at three months postoperatively were sustained at seven years although no statistics were provided.[272]

When HoLEP was compared with HoBNI, there were no significant differences between treatment groups for Qmax at the three-, six- and 12-month follow-up.[262] Single-group cohort studies involving HoLAP and TURP indicate that the Qmax improved in both groups with improvements sustained at up to 24 months follow-up and was similar in both groups.[263] Maximum flow rates following PVP laser therapy also increased in all studies reporting this parameter with a range at one month of 7.5 to 11.8 mL per second; and a range of 7.7 to 19.5 mL per second 3 months posttherapy.[265, 273, 274] The maximum urine flow rates at two years (range 18.8 to 21.1 mL per second) and five years (a single study reporting 14.4 mL per second) after therapy appeared to improve significantly, but the five-year data are limited to a single study center.[265] The outcomes associated with the thulium laser were reported for 54 patients in a single-cohort study and suggested a significant improvement in the Qmax at 12 months.[253]

Outcomes of RCTs, where available, yielded no statistically significant differences among laser therapies beyond the initial six months. All surgical therapies provided similar outcomes over time with regard to peak flow.

Urinary Postvoid Residuals. In one RCT, HoLEP and TURP achieved similar improvements in the post-void residuals at six months after therapy;[258] however, at 12 months, further improvements in the post-void residuals favored the HoLEP-treated patients.[275] When HoLEP was compared in RCTs to open prostatectomy at three months and five years, both therapies showed improvement in the post-void urinary residuals and there was no significant difference between these therapies.[256, 257] Similar findings were reported in an RCT comparing bipolar TURP and HoLEP, and the improvements in the post-void residuals were not significantly different between arms at 12 months[269] or 72 months.[270] A single-cohort study reported that the improvement in post-void residual was not related to the size of the prostate gland.

PVP laser therapy also produced a significant improvement in post-void residuals; there was no significant difference at one year if the patient was treated with concurrent 5-ARIs.[276] The single-cohort studies of PVP reported that the improvements in the post-void residual were durable at two years[267, 273] and five years[265] following treatment. The studies involving thulium laser therapy did not report the outcomes for the post-void urinary residuals.

Summary

Laser therapies, with the exception of thulium lasers, appear to offer similar improvements in the post-void residuals compared to other surgical therapies such as TURP and open prostatectomy. Further, the improvements in the post-void residuals following holmium laser therapy and PVP are durable; however, there is insufficient evidence to evaluate the durability for the thulium laser.

Prostate Volume. Changes following laser therapy may impact the outer diameter of the prostate as well as the inner lumen of the urethra. Thus total prostate volume measured after ablative therapies may not accurately reflect the amount of prostate tissue removed or the changes in the prostate. Studies concerning holmium lasers do not address changes in prostate volume following therapy but do refer to weight of resected tissue. Four studies examined HoLEP compared with TURP.[258-261] Weight of resected tissue was significantly greater with HoLEP compared with TURP in two studies,[258, 259] with no significant difference in a third study.[261] PVP lasers are reported in single-cohort studies to be associated with a decrease in prostate volume when assessed at three months and 12 months following therapy.[265, 274, 277-280] There is no information concerning the impact of the thulium laser on prostate volume or the impact of any laser therapy on the transition zone volume.

Detrusor Pressure at Maximum Flow. The literature does not contain information concerning the impact of the various laser therapies on the detrusor pressures at maximum flow.

Prostate-specific Antigen. PSA values have been indentified as a useful marker for risk of progression of LUTS leading to surgical therapy. The implications of changes in the PSA value following

laser therapy are unknown. PSA was unchanged in six studies reporting PSA values after laser therapy.[265, 274, 277-280] One study reported that PSA values decreased following PVP laser therapy, and cautioned that if the PSA increased the patient should be treated with an appropriate antibiotic and the PSA repeated upon completion of the antibiotics; if the PSA did not decrease, a prostate needle biopsy should be completed to rule out prostate malignancy. The authors reported that patients whose PSA failed to decrease had a 50% risk of a diagnosis of prostate cancer.

Safety Outcomes

Total Withdrawals or Loss to Follow-up

Reported withdrawal rates from RCTs of holmium lasers compared to TURP were similar for both groups. Randomized controlled studies of the holmium laser compared to open prostatectomy found a total withdrawal rate of 38.3% at five years. In single cohort studies utilizing the PVP laser, the withdrawal rate was very high in the long-term, but the reasons for withdrawal were not reported.

Perioperative Mortality

There are limited data concerning the mortality rates associated with laser therapy in articles published since the 2003 AUA guideline. Mortality was reported in two studies comparing HoLEP with bipolar TURP, with rates ≤1%.[255, 281] Mortality rates were infrequently reported in the PVP series and typically mortality was unrelated to prostate surgery.[264-268, 273, 274, 277-280, 282-289] There is great difficulty estimating the mortality rate for all surgical therapies that treat the obstruction causing LUTS. The concerns for mortality rates associated with laser therapies are referred to the section addressing mortality for all surgical therapies.

Short-term Adverse Events

Intraoperative Complications. Intraoperative, immediate, postoperative, and short-term complications involve a broad spectrum of events and reporting rates may be based on subjective thresholds. Some technologies have complications unique to that treatment modality, such as morcellation injuries associated with HoLEP. Randomized studies that compared HoLEP to bipolar TURP reported complications due to morcellation, including incomplete tissue morcellation due to blade malfunction (1.9%)[290] and bladder mucosal injury (1.9%[291] and 2.8%[292]). Capsular perforation was reported in HoLEP studies at rates of 0.3%,[270] 0.6%,[293] 1.5%[291] and 1.9%[290] while the incidence in HoLRP was one out of 281 study participants.[263, 294]

Operative time. The ability to directly compare laser therapies with respect to the operative time is constrained by the fact that each laser modality seems to select from patient populations with different baseline characteristics and seldom selects the same comparison therapy as a control. When HoLEP was compared with HoBNI, the operating time was significantly shorter with HoBNI (mean seven minutes) than HoLEP ($P<0.001$).[262] RCTs comparing HoLEP to open prostatectomy indicate similar

weight of prostate tissue resected but a longer operative time for holmium enucleation.[256, 295] This is in contrast to a cohort comparison study that reported operative times were similar despite greater tissue resection with holmium enucleation. A single-group cohort study of HoLEP indicated that operative time was related to prostate gland size, which would seem logical. When compared to bipolar TURP, RCTs report a wide range of operative times for HoLEP compared to bipolar TURP. One study reported that operative times and, importantly, the weight of resected tissue was similar for both HoLEP and bipolar TURP.[269] However, other studies reported enucleation times of 86 minutes in a large series, which was improved from 112 minutes in their initial series of 118 cases.[255] The longest mean operative time was reported in a series by Kuo et al (2003) (133.6 minutes), where mean resected weight was 68 g and morcellation time ranged between 12 and 19 minutes.[291, 293]

An RCT of laser ablation of the prostate indicated that this modality required a significantly shorter operative time compared to TURP (P< 0.001), but HoLEP also resected significantly less prostate tissue weight.[296, 297] A single-cohort study reported that the average weight of prostate tissue resected was 11 g and the procedure required an average operative time of 47 minutes.[294] All of the reported studies involving PVP laser ablation of the prostate are single-cohort studies, and the reported operative ranged from 38 to 137 minutes;[264-268, 273, 274, 277-280, 282-289] however, because of the ablative nature of the PVP laser it is not possible to accurately report a weight of resected tissue, which limits comparison. The sole study for the thulium laser is a single-cohort study reporting an operative time of 52 minutes in men with a mean pretreatment prostate volume of 32 mL.

Hematuria. Data from RCTs indicated that HoLEP was associated with less hematuria compared to open prostatectomy[256, 295], while comparison studies with a single cohort would support that there is no statistically significant difference with HoLEP. When HoLEP was compared to a cohort group, the report indicated that the extent of blood loss is related to the size of the prostate gland.[261] Studies concerning HoLEP did not report the blood loss associated with the procedure. Only one study involving PVP laser attempted to quantify the blood loss associated with PVP laser ablation, which was estimated to be 56 mL.[268] A second single cohort study reported "uncontrolled bleeding in 11.3% of patients.[280]

Transfusion. Data concerning transfusion risk associated with laser therapies for LUTS due to BPH are limited. There is a single RCT involving HoLRP indicating a lower risk of transfusion when compared to TURP. Data from the single cohort studies utilizing HoLEP report a transfusion rate of less than 1% while studies of PVP laser ablation and thulium laser ablation indicated that no patient required a transfusion. The single-group cohort studies utilizing HoLEP reported two of 281 patients who required perioperative transfusion, both of whom had an underlying bleeding disorder or were on anticoagulants.[263, 294] PVP laser studies consistently reported a decrease in hemoglobin, but statistical significance was rarely reported. No study reported administration of blood transfusions or any case of TUR syndrome or significant electrolyte imbalance in the perioperative period.[264-268, 273, 274, 277-280, 282-289] In a small single-cohort study of the outcomes associated with the thulium laser, no patient required

transfusion; however the Panel felt that the small study population of 54 patients was not sufficient to reliably estimate the risk for blood transfusion.[253]

Transurethral Resection Syndrome. The ramifications of TUR syndrome dictated the historical concerns for the incidence of this complication. While there are no RCTs involving laser therapies that discuss TUR syndrome, single-cohort studies utilizing PVP and thulium laser reported that no patients developed TUR syndrome. The use of lower procedure irrigation pressures, better optics used in today's cystoscopes and normal saline irrigation appear to have significantly decreased the risk of TUR syndrome.

Infections/Urinary Tract Infections (UTIs). The category of infections or UTIs includes a wide variety of infectious diseases, such as wound infections, epididymitis, orchitis, and bacterial UTI reported at any time after an intervention. The published data in the interval from the 2003 analysis of the literature does not provide sufficient information to assess a change in risk. There was a single-cohort study concerning thulium laser ablation that reported an 11% UTI rate following treatment.[72] This rate is higher than expected from other transurethral technologies available today and the reason for the difference is not clear. Meta-analyses of RCTs showed rates of infection/UTI in patients treated with transurethral laser coagulation, TUIP, or transurethral vaporization of the prostate (TUVP) were not statistically significantly different from those for TURP-treated patients; single RCTs also found similar results for either TUVP or open prostatectomy compared to TURP. Results from systematic reviews revealed rates ranging from 5% for TUIP to 9% for transurethral laser coagulation and TUVP one small single-arm study reported a 1% rate in patients treated with holmium laser resection/enucleation. No RCTs reported UTI rates for holmium laser resection/enucleation.

Irritative Voiding Symptoms. Minimally invasive and surgical procedures induce irritative voiding symptoms immediately after and for some time subsequent to the procedure. Periprocedure and postprocedure adverse events associated with voiding symptoms include frequency, urgency, and urge incontinence and are categorized as postprocedure irritative adverse events. Such events are reported more often following heat-based therapies than following tissue-ablative surgical procedures. Because they impact QoL, irritative events are important and warrant documentation. Unfortunately, all patients will have some symptoms during the healing process immediately following the procedure. Because there is no standard for reporting this outcome, some studies reported these early symptoms while others did not. Further, because it is not possible to stratify these complaints according to severity, it is not possible to compare the degree of bother of these symptoms across therapies.

RCTs involving HoLEP found a significantly greater rate of irritative voiding in the HoLEP patients (59%) compared to TURP patients (30%),[259] while single-cohort HoLEP studies indicated that only 7% to 11% of patients experience irritative voiding symptoms in the postoperative period.[259, 298] Single-cohort studies utilizing the PVP laser indicated that 6%[285] to 52%[268] of patients reported a mild transient dysuria, while 9.4% of patients experienced a prolonged period of irritative voiding and 2.9% patients required medical therapy to help control the irritative symptoms.

Acute Urinary Retention. The category of AUR reflects the number of patients requiring repeat catheterization after a protocol-defined postprocedure period of catheterization. Unfortunately, some studies report "protocol-required" or "investigator option" episodes of postprocedure catheterization while others report only catheterization performed for inability to urinate. Further, new technologies are resulting in earlier removal of catheters with much shorter hospital stays. The earlier attempts to remove the catheter are likely to increase the reported rates of repeat catheterization compared to historical rates associated with other technologies and longer hospital stays. Such differences in reporting are reflected in the wide confidence intervals (CI) for frequency estimates. The only literature concerning rates of repeat catheterization available for this analysis involves the PVP laser where single-cohort studies indicate repeat catheterization rates of <5% in several studies,[265, 268, 278, 283, 288] while other studies indicate repeat catheterization rates between 10% and 15%.[267, 274, 279, 284, 285] Single-cohort studies utilizing the PVP laser report that the urinary catheters were generally removed between 18 and 36 hours postoperatively.[264-268, 273, 274, 277-280, 282-289] In fact, several series noted patients were not catheterized postoperatively, at the surgeon's discretion.[264, 267, 278, 283, 286] The mean catheter time associated with the thulium laser was 1.7 days.[253]

Hospital Stay. Randomized controlled studies comparing HoLEP to open prostatectomy[256, 295] and to TURP[258, 261] all found that hospital stays were significantly shorter for patients treated with HoLEP ($p<0.01$), yet HoLEP and bipolar TURP were associated with an equivalent number of days in the hospital.[259] Studies comparing HoLEP to open prostatectomy showed that the number of days in the hospital were significantly shorter for HoLEP;[257] one single-cohort study reported that length of hospital stay was independent of prostate size.[261] Randomized controlled studies also showed a shorter length of stay for patients treated with holmium resection of the prostate.[263, 294] When HoLEP was compared with HoBNI the hospital stay and catheter duration were short (<24 hours) in both groups.[262]

Studies concerning PVP ablation are limited to single-cohort studies and the range of hospital stay was short in some series,[265, 280, 282] while more than three days in other series.[274, 279, 283, 288, 299] This wide range is believed to be a reflection of the change in technology over the review period as the laser energy increased in increments from 40W to 100W over time. In addition, various protocols in select institutions facilitated early discharge from the hospital. The average hospital stay reported in the study utilizing the thulium laser was 3.5 days.[253]

Long-term Adverse Events

Urinary Incontinence. The category urinary incontinence represents a heterogeneous group of adverse events, including total and partial urinary incontinence, temporary or persistent incontinence, and stress or urge incontinence. The update of the literature in the interval since the 2003 AUA Guideline provides limited additional information concerning incontinence. Randomized controlled studies involving HoLEP compared to TURP present mixed information with the incontinence rate reported as similar on in one study,[261] while a second study reported an increased incontinence rate in

the HoLEP population.[258] The Panel recognized that this rate was higher than expected but felt the general urologist's experience with HoLEP was less than other technologies and the report warranted observation. When HoLEP was compared with HoBNI, incontinence was reported in 44% of HoLEP patients and none after HoBNI.[262] In a small trial that compared HoLEP to the bipolar TURP that followed patients for 12 months, the incontinence rates were almost identical.[188] Unfortunately, there was no information concerning PVP ablation or thulium laser therapy.

Secondary Procedures. The issues surrounding secondary procedures were well presented in the 2003 AUA guideline and reiterated here.[8] Secondary procedures, defined as interventions rendered by the treating physician for the same underlying condition as the first intervention, are challenging to classify. Examples of such procedures include initiation of medical therapy following a minimally invasive or surgical treatment, minimally invasive treatment following surgical intervention, or surgical intervention following a minimally invasive treatment. Enumerating secondary procedures from published reports is difficult. First, the threshold for initiating a secondary procedure varies by patient, physician, and the patient-physician interaction. In the absence of clearly defined thresholds for the success or failure of an initial intervention, secondary procedures are initiated on the basis of subjective perceptions on the part of either patients or treating physicians, which may not be reproducible or comparable between investigators, trials, or interventions. In many cases, patients involved in treatment trials feel a sense of responsibility toward the physician; given this commitment, patients may abstain from having a secondary procedure even through they may feel inadequately treated. Conversely, patients involved in treatment trials are more closely scrutinized in terms of their subjective and objective improvements; therefore, failures may be recognized more readily and patients may be referred more quickly for additional treatment. Moreover, the duration of trials and follow-up periods both affect rates at which secondary procedures are performed. Thus, although patients receiving long-term follow-up are at greater risk for treatment failure than those followed for short periods, it is virtually impossible to construct Kaplan-Meier curves or perform survival analyses for secondary procedure rates. In short, while it is quite clear that secondary procedures and treatment failures cause major health expenditures for the treatment of patients with BPH, it is also clear that the current literature does not allow a meaningful comparison of secondary procedures across therapies. As a result, the estimates for secondary procedure rates should be viewed with caution.

Reoperation rates following various laser therapies are inconsistently reported, often due to the limited length of follow-up or the small numbers of patients in these studies. Randomized controlled studies comparing HoLEP with open prostatectomy reported similar reoperation rates of 10% compared to 8.3% for open prostatectomy.[257] Other RCTs compared HoLEP to bipolar TURP and found that the reoperation rates (0.3% at three years;[270] and 4.2% at five years[255]) were less with HoLEP compared to bipolar TURP. Single-cohort studies involving HoLEP reported a reoperation rate of 0.3% after Three years and 4.2% after five years which would appear to be similar to the results from the RCTs.[277, 279]

When HoLEP was compared with HoBNI the need for a second surgical procedure over the one year follow-up occurred in four of 20 HoBNI patients and in none after HoLEP.[262]

Single-cohort studies concerning PVP lasers found a reoperation rate of 0% in a number of studies[265, 273, 277, 279] and less than 5% in other studies.[267, 274, 278, 284] In one cohort with three-year follow-up, the retreatment rate was 4.3%, but the entire series had not yet completed the three-year evaluation at the time of publication, so additional cases may present.[267] A five-year cohort study reported no retreatments.[265]

Bladder Neck Contracture/Urethral Stricture. RCTs utilizing HoLEP indicated that the rate of bladder neck contracture was similar to the rate following open prostatectomy[256, 257] and bipolar TURP,[269] while single-cohort studies indicated that the rate of bladder neck contracture was between 1.3 and four%.[270, 281, 291, 300] The rate of bladder neck contracture following PVP laser ablation of the prostate was reported at 0% and 1%[277, 279] to 2%[265, 267, 274, 278, 280] in single-cohort studies. Urethral stricture was reported in between 0%[277] and 7.6%[274] of study participants. Urethral strictures following HoLEP were reported at rates of 0%,[291] 1.3%,[270] to 5.6%. [254]

Sexual Dysfunction. Surgical interventions have the capacity to induce sexual dysfunction in the form of ED or in the form of retrograde or absent ejaculation. These adverse events were classified as either ED or ejaculatory dysfunction. Randomized controlled studies indicate that both HoLEP and TURP increase the risk of ED and that the risk following therapy is not significantly different with either treatment.[258, 261] When HoLEP was compared with HoBNI, decreased erectile function occurred at similar rates in both groups and retrograde ejaculation was very common postoperatively (80% for HoBNI and 100% for HoLEP).[262]

Postoperative sexual function was infrequently reported after PVP therapy and studies reporting ED reported no new cases postoperatively.[265, 268, 273, 277, 286] Paick and colleagues (2007) examined sexual function at 6 months postoperatively and found that all IIEF domains improved.[289]

Ejaculatory disorders were common after HoLEP and their rate of occurrence was not significantly different from TURP.[258, 261] Single-cohort studies of HoLRP also reported similar high rates of ejaculatory disorders following treatment.[276, 294]

Transurethral Incision of the Prostate

Randomized Controlled Trials (RCTs)

A single RCT compared TUIP to TURP in 100 subjects with prostate weights not exceeding 30 g with a two-year follow-up.[301]

In this RCT, both groups improved significantly in nocturnal voiding frequency, I-PSS, QoL, and Qmax but there were no statistically significant differences in these outcomes between groups, except for QoL, for which the percentage change was greater with TURP.[301]

Transurethral Vaporization of the Prostate

Randomized Controlled Trials (RCTs)

We identified 10 RCTs comparing TUVP with standard TURP using a variety of electro-vaporization devices.[302-312] Inclusion and exclusion criteria were generally similar across studies, excluding subjects with prior pelvic surgery, prostate cancer, and neurologic disorders. Recruitment occurred from accessible populations awaiting surgery for BPH but details were rarely provided on how subjects were selected. The mean age of study participants was similar across studies, ranging between approximately 65 and 70 years. The mean baseline I-PSS was generally between 20 and 25; however, in two studies some of the study groups had lower mean scores.[305, 312] The QoL score was between four and five in studies reporting those baseline data. There was significant variation in Qmax at baseline, ranging from two to 20 mL per second in individual treatment groups. There was also much variation in preoperative prostate gland size: one study examined small glands (mean prostate volume of treatment groups ranged from 24 to 34 mL),[305] while another examined larger glands (mean of treatment groups, 54 mL and 63 mL).[308] TUVP was performed with a variety of vaporization devices and the comparator in these studies was standard TURP. Several studies reported on "vaporization" techniques using the bipolar vaporization device (Gyrus Medical)[313-315] and these studies are examined in the section on TURP in this report.

Efficacy and Effectiveness Outcomes

AUA-SI was measured in all 10 trials comparing TURP to TUVP.[302-312] These trials consistently demonstrated improvements in I-PSS after both TURP and TUVP, generally with no statistically significant difference between treatment groups. The only study that demonstrated a significant difference reported that I-PSS improved more with a thick loop TUVP than with the standard thin loop TURP at one-year of follow-up.[302] Several studies examined I-PSS and QoL at longer follow-up periods and found no difference between treatments. Qmax improved in both treatment groups; however the between-group error was inconsistent across studies. In studies where post-void residual was compared between treatments, no significant differences were found, with improvements noted with both treatments.[302, 304, 306, 308-311]

Safety Outcomes

Withdrawals and Treatment Failure

Withdrawal rates were only reported in three of the 10 trials, with high rates of attrition when follow-up was two years or more. Mortality rates were low, largely due to cardiovascular disease, and never attributed to the surgical intervention. Reoperation rates were higher with TUVP than with TURP. At 12-months follow-up, reoperation for AUR rates were 8% with TUVP and 4% with TURP.[303] At the five-year follow-up, 13% of both the TURP and TUVP treatment arms required reoperation.[309]

Perioperative and Short-term Adverse Events

The weight of resected tissue was similar between groups in studies reporting this outcome.[302, 305, 308, 310, 312] Operative time was similar in TURP and TUVP in six studies,[302-305, 311] significantly longer with TURP in two studies[308, 310], and significantly longer with TUVP than TURP in another study.[309] Operative blood loss was significantly greater with TURP than TUVP in the three studies examining this outcome.[303, 304, 308] Blood transfusions were given in the perioperative period more frequently with TURP than TUVP.[304, 306]

Duration of catheterization was significantly greater with TURP than TUVP in several studies,[304, 309, 312] although two studies noted no difference[306, 308]. Duration of hospital stay was consistently longer with TURP than with TUVP,[306, 308-310, 312] with a statistically significant difference in two studies.[309, 310] Recatheterization rates were generally low and similar between TUVP and TURP groups. One study, however, reported higher rates of postoperative urinary retention: 23% with TUVP and 8% with TURP.[309]

Longer-term Adverse Events

Urethral stricture and bladder neck stenosis were uncommon and occurred with both treatments. ED at follow-up was reported at rates identical to baseline in both groups in three studies.[302, 304, 306, 311]

Transurethral Resection of the Prostate

Randomized Controlled Trials (RCTs)

A total of 11 RCTs compared standard monopolar TURP to various bipolar TURP techniques.[313-323] One additional RCT compared preoperative treatment with dutasteride to placebo, both followed by standard TURP.[324] Subjects all had LUTS suggestive of BPH; in most studies few other inclusion criteria were reported. Total sample size ranged between 40[323] and 240 subjects[317] and follow-up intervals varied between three weeks[319] and 21 months.[323] The mean age of subjects in these RCTs was in the 60's, with baseline I-PSS between 20 and 24, QoL score between two and four, and Qmax between 5.1 and 10.9 mL per second. The two main bipolar techniques used were the Gyrus Plasmakinetic System (Gyrus, Birmingham, UK),[313-317, 319, 320] and the AMCI Elite system (ACMI Corp).[322] One study referred to transurethral resection in saline (TURIS) system using bipolar electrodes at 270W for cutting and 75W for coagulation, with no other specification.[321]

Cohort Studies with a Comparison Group

We identified two cohort studies with comparison groups.[325, 326] Lee and colleagues (2005) compared TURP to TURP plus TUIP over a mean follow-up of 38 months with 1135 patients available for the retrospective analysis.[325] A second study compared the Gyrus Plasmakinetic system with monopolar TURP.[326]

Single-group Cohort Studies

Nineteen single-group cohort studies were identified which examined TURP efficacy, effectiveness, or adverse events.[327-345] Inclusion criteria were similar across cohort studies and were similar to those reported above for RCTs of TURP. Methods for recruiting subjects or identifying the study cohort were not generally reported. Sample size varied greatly (ranging from 21 to 1,014 participants), and seven studies had a sample size greater than 200 participants.[327, 335, 336, 339, 342-344] Duration of follow-up ranged between one day[330] and 13 years,[344] with most studies ranging between three and 12 months. One study reported a combined cohort of TURP (65%) and open prostatectomy (35%).[338]

The mean age of included subjects was generally in the late 60's and early 70's, thus somewhat older than the mean age in RCTs of TURP. Standard monopolar TURP procedures were examined in most of these studies, with no additional details provided. Three studies examined the Gyrus Plasmakinetic (bipolar) system[328, 334, 335] and another a coagulating intermittent cutting device.[327]

Efficacy and Effectiveness Outcomes

Total I-PSS and QoL improved significantly in all studies reporting these outcomes. Erectile function did not change significantly as assessed with the IIEF six months post-TURP.[342]

Postvoid residual decreased significantly in all studies and Qmax increased in all studies in the range of 6 to 10 mL per second. Prostate volume decreased by approximately 20 g in two studies.[334, 342]

Predictors of Efficacy and Effectiveness Outcomes

Several studies examined the relationship between various demographic and clinical characteristics and efficacy or effectiveness outcomes.[337, 340, 343-345] Machino and colleagues (2002) categorized 62 patients into those with equivocal obstruction and those with obstructive symptoms, as defined by the Abrams-Griffins nomograph.[337] The authors concluded that neither urodynamic obstruction nor detrusor instability alone predicted outcomes of TURP; however, outcomes were significantly worse in patients who were not obstructed but had detrusor instability. Age was predictive of postoperative Qmax and overall complication rates.[340] Seki and colleagues (2006) found that a higher degree of BOO (Schafer obstruction grade) predicted improvements in I-PSS and QoL and that baseline detrusor overactivity negatively predicted these outcomes.[343] In a retrospective cohort study of 217 patients who underwent TURP with a long-term mean follow-up (13 years, SD 4.1) symptomatic failure and decreased flow rate were associated with detrusor underactivity rather than obstruction.[344] Preoperative obstruction grade (Schafer) correlated with improvements in obstruction grade, symptom index, and QoL.[345] Patients with a stable bladder postoperatively (either stable or unstable preoperatively) showed significantly better improvement in I-PSS and QoL than patients in whom an unstable bladder persisted or developed postoperatively.

Safety Outcomes

Withdrawals and Adverse Events

Treatment Failure. Treatment failure rates were infrequently reported; in one study, 13.3% were operated on for urinary retention post-TURP.[327]

Perioperative and Short-term Adverse Events. Intracapsular perforation was reported in 5% of 522 subjects in the only study reporting this outcome.[342] TUR syndrome was reported at rates of 1.1%[327] and two% of subjects.[342] Transfusions occurred in 2% to 9% of patients, with the highest rate occurring in a study with prostates estimated between 70 g and 150 g preoperatively.[340] Clot retention was infrequent in the only study reporting this outcome (2.3%).[335] Mean catheter time was 1.3 days in one study[335] and longer in another study of larger prostates.[340]

Longer-term Complications. Urethral stricture was reported in 1.8% of men with glands less than 70 g and 3.5% of those with larger glands (70-150 g) in one study[340] and 10%[335] in a second study. Bladder neck stenosis was reported in approximately 1.5%.[345,335] Mortality rates were infrequently reported in prospective cohort studies.

Monopolar TURP vs. Various Bipolar TURP. Operating or resection time varied across studies and was similar between the Gyrus Plasmakinetic system and standard TURP in four studies,[346-349] but significantly less with the Plasmakinetic system compared with standard TURP in other studies.[350-352] TUR syndrome was reported at rates of 0%,[346, 349, 351-353] 0.8%,[354] 1.7%[350] and 3.9%[347] with standard TURP and 0% with the comparison bipolar technique in all studies.

Hemorrhage requiring transfusion was reported more frequently with standard TURP (5.3%,[350] 2.0%[347] and 5.4%[351]) compared with the Plasmakinetic system (0.8%, 0% and 0%, repectively). Perioperative transfusion was reported more frequently with the TURIS system than with standard TURP (3.4% vs. 0.8%). Intraoperative complications were rarely reported; capsule perforation occurred in 5.7% of subjects with TURP and 1.7% with PK-TURP.[350] Hospital stay was significantly shorter ($P<0.05$) with the PK-TURP than with standard TURP.[348, 350, 351] Duration of catheterization was also shorter with the Plasmakinetic system than with standard TURP.[346-348, 350-352] Duration of catheterization was not significantly different between the AMCI Elite system and TURP.[353]

Use of preoperative 5-alpha-reductase inhibitors. Four randomized, placebo-controlled, well executed studies,[355, 356 357, 358] two non-controlled[359, 360] and one randomized study with poorly defined methods of measuring the blood loss[361] explored the ability of 5-ARIs prior to TURP to reduce blood loss associated with TURP. Only one of the randomized and the two nonrandomized studies showed a reduction in blood loss or transfusion requirements. Other studies found no significant differences between the treatment group and placebo for blood loss during surgery, excessive or severe bleeding, or clot retention.[362]

Summary

Surgical therapies remain a principal option in management of men with moderate to severe LUTS and/or those who are significantly bothered by these symptoms. The updated literature review revealed remarkable evolution in the technology and broadening evidence for various forms of transurethral lasers and bipolar TURP. Open prostatectomy, TUIP and monopolar TURP remain as gold standards by which newer transurethral approaches are compared.

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