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Systematic Review in Patients with Benign Prostatic Hyperplasia for The Role of Prostatic Arterial Embolization

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Abstract
This study aimed at reviewing the role of Prostatic Arterial Embolization (PAE) as a new treatment producer for patients with Benign Prostatic Hyperplasia (BPH). The study reviewed the recent researches of Prostatic Arterial Embolization (PAE) as a new treatment technique and concluded that the initial reported results of PAE seem promising, mainly during the first 12 months after treatment. However, no comparison was made to medical therapy or surgical therapies. Overlapping patient data and reporting bias could not be excluded. None of the included studies performed a power analysis. Also, a relatively small number of patients are treated with a short follow-up period. Therefore, more studies are needed with more patients and longer periods of follow-up, compared with standard medical and surgical therapies, to assess whether PAE is an effective and safe alternative treatment for BPH.

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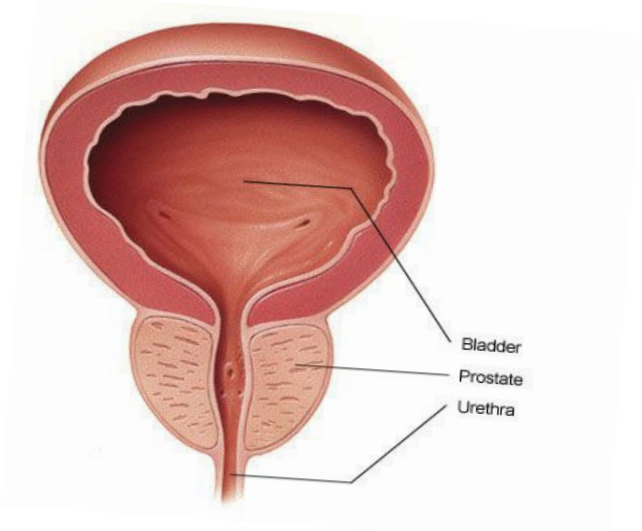
This research was prepared by joint efforts by researchers, each with a specific task, DR. YAZEED HAMOUD M ALBALAWI, DR. TARIQ SAEED M DALMAKH and DR. ABDULLAH HABIB M KIMAWI as main authors, and Dr. MOHAMMED OWAID O. ALSHAMMARI and DR. MARYAM ALI M HABIBI as co-authors.

1.1 Introduction

Benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy, is a histologic diagnosis characterized by proliferation of the cellular elements of the prostate. Chronic bladder outlet obstruction (BOO) secondary to BPH may lead to urinary retention, renal insufficiency, recurrent urinary tract infections, gross hematuria, and bladder calculi. The image below illustrates normal prostate anatomy.

The problems of BPH may be reviewed in the context of histology or clinical symptomatology. The prostate gland is composed of glandular and stromal tissue, and hyperplasia of the per urethral tissue defines this process. Histologically, autopsy studies have revealed that BPH essentially never occurs before age 30 years and then progressively increases until it reaches almost 90% for men in their 80s. These numbers have been found consistently across the globe (Paolone, 2010).



Figurer (1): Normal prostate anatomy. The prostate is located at the apex of the bladder and surrounds the proximal urethra

Benign prostatic hyperplasia (BPH) is a progressive condition characterized by prostate enlargement

accompanied by lower urinary tract symptoms (LUTS) (Roehrborn, Siami & Barkin, 2009).

Benign prostatic hyperplasia arises in the periurethral and transition zones of the prostatic gland and represents an inescapable phenomenon for the ageing male population (Untergasser, Madersbacher & Berger, 2005).

Although BPH is uncommon before age 40, roughly 50% of men develop BPH-related symptoms at 50 yrs. of age. The incidence of BPH increases by 10% per decade and reaches 80% at approximately 80 yrs. of age (Irani, Brown, van der Meulen & Emberton, 2003).

An estimated 75% of men >50 yrs. of age have symptoms arising from BPH, and 20–30% of men reaching 80 yrs. of age require surgical intervention for the management of BPH (Parsons & Kashefi, 2008).

Despite the high impact of BPH on public health, however, the pathogenesis of BPH is still largely unresolved. Indeed, although multiple theories have been proposed, the aetiology of BPH still remains uncertain in some aspects. Several mechanisms seem to be involved in the development and progression of BPH. Although ageing represents the central mechanism implicated, recent novel findings also highlighted the key role of hormonal alterations, metabolic syndrome, and inflammation, see figure 2 (Liu, Huang & Li, 2007).

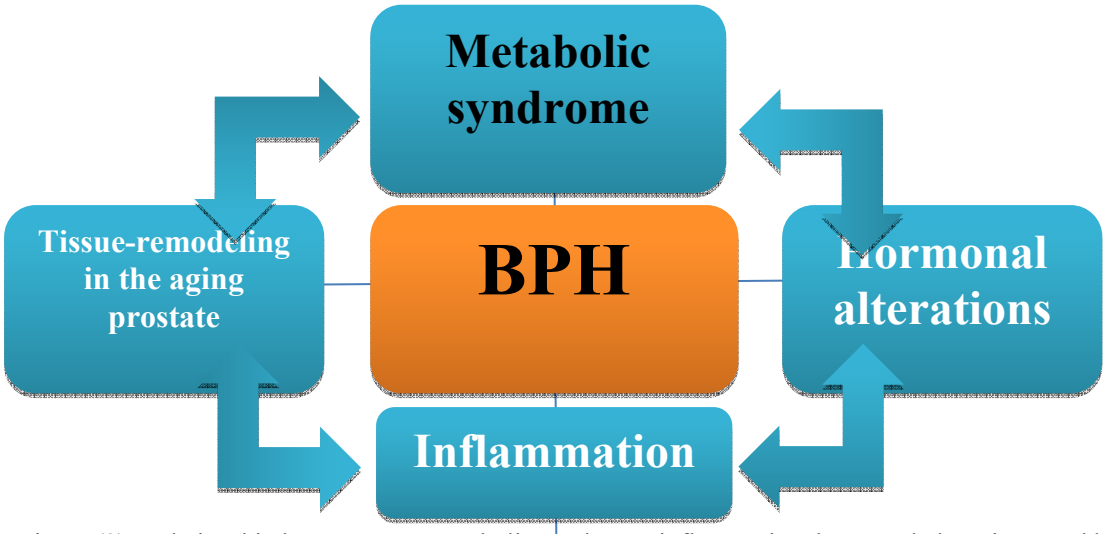


Figure (2): Relationship between age, metabolic syndrome, inflammation, hormonal alterations, and benign prostatic hyperplasia (BPH)

Prostatic arterial embolization (PAE) gained special attention in the past years as a potential minimally invasive technique for patients with moderate-to-severe LUTS due to BPH. Previous animal studies have shown that PAE can induce prostatic volume reduction and is safe, with no procedure-related sexual dysfunction (Jeon, Won & Lee, 2009).

In this research, the authors systematically summarized all evidence on PAE in humans to assess the quantitative clinical outcomes [prostate volume (PV), prostate-specific antigen (PSA), peak urinary flow (Qmax), post void residual (PVR)], qualitative clinical outcomes [International Prostate Symptom Score (IPSS), QOL, and International Index of Erectile Function (IIEF)], and complications related to the procedure.

1.2 Literature review

During the 2009 annual meeting of the European Association of Urology in Stockholm, Sweden, a satellite symposium was held on BPH and its treatment. This paper is based on one of the presentations at the symposium. A structured, comprehensive literature review was performed. Separate searches were done within the MEDLINE database and The Cochrane Library Central Search.

1.2.1 Tissue re-modelling in the ageing prostate

Ageing is the most significant risk factor for the development of BPH and the occurrence of LUTS (Kok, Schouten, Bohnen, Groeneveld, Thomas & Bosch, 2009).

Several studies have demonstrated a relationship between age and markers of BPH progression. For instance, in the population-based Olmsted County study, moderate to severe urinary symptoms were recorded in 13% of men 40–49 yr of age versus 28% in subjects >70 years (Chute, Panser & Girman, 1993).

Recently, Loeb et al performed pelvic magnetic resonance imaging in 278 men without prostate cancer, and prostate volume measurements were assessed over time. The authors reported a median rate of prostatic volume change of 0.6 ml per year of age, corresponding to a median growth rate of 2.5% per year (Loeb, Kettermann, Carter, Ferrucci, Metter & Walsh, 2009).

In ageing males, a significant tissue-remodeling process takes place within the prostate, especially in the

transition zone (TZ). Interference in the delicate balance of interacting growth factor signaling pathways occurs, and stromal– epithelial interactions generate an increase in prostate volume. Specifically, the most significant modifications take place in the basal cells, which change their intracellular metabolism and become enlarged and hypertrophic. The development of BPH is also accompanied by the occurrence of corpora amylacea and prostatic calculi. These elements typically contain phosphate salts of calcium, magnesium, potassium, calcium carbonate, or calcium oxalate (Geramoutsos, Gyftopoulos & Perimenis, 2009).

Subsequently, the altered secretions of luminal cells and the presence of corpora amylacea and prostatic calculi lead to further calcification, and clogged ducts become visible. All of this tissue remodeling leads to alterations of highly specialized cell types responsible for tissue homeostasis and function.

1.2.2 Hormonal alterations

Although androgens do not cause BPH, the development of BPH requires the presence of testicular androgens during prostate development, puberty, and ageing. Studies on intraprostatic sex-steroid hormone levels have shown that bioavailable prostatic testosterone levels decline with age (Roberts, Jacobson, Rhodes, Klee, Leiber & Jacobsen, 2004).

Luminal secretory cells require androgens, particularly the intracellular metabolite of testosterone, dihydrotestosterone (DHT), for terminal differentiation and secretory functions. DHT is predominantly generated by the prostatic 5-a reductase, which is present in fibroblasts of the stroma and in basal epithelial cells. In two interesting papers, Roberts et al reported higher DHT activity in BPH relative to normal prostate gland tissue resulting as a permissive, rather than a transformative, mediator in the development of BPH. Moreover, in studies based on the analysis of cadaver specimens, an increased accumulation of DHT was observed in BPH tissues (Geller, Albert, Lopez, Geller & Niwayama, 1976).

Conversely, other authors reported no differences in DHT pattern when fresh specimens of prostate tissue were used (Walsh, Hutchins & Ewing, 1983).

Recently, O'Malley et al succeeded in quantifying the expression of four different androgen-responsive genes—ELL associated factor 2 (EAF2, also known as U19), elongation factor, RNA polymerase II, 2 (ELL2), FK506 binding protein 5 (FKBP5), and phosphoserine aminotransferase 1 (PSAT1, also known as PSA)—in either BPH or normal tissue (O'Malley, Dhir, Nelson, Bost, Lin & Wang, 2009).

They demonstrated that all of the assayed genes displayed increased expression in BPH as compared with the adjacent normal glandular tissue. The authors concluded that androgen signalling is significantly elevated in hyperplastic tissue relative to the adjacent normal prostate. Understanding the mechanisms causing elevated androgen signalling may lead to a clarification of the role of DHT in the pathophysiology of BPH and potentially to the identification of novel approaches for its prevention and/ or treatment.

1.2.3 Metabolic syndrome

The association between metabolic syndrome and BPH has also been studied recently. Hammarsten et al were the first to demonstrate that noninsulin-dependent diabetes mellitus (NIDDM), hypertension, obesity, and low high-density lipoprotein cholesterol (HDL-C) levels constitute risk factors for the development of BPH [38,39]. In a Swedish study of 250 patients with BPH, the authors reported a median annual BPH growth rate of 1.04 ml/yr. Men with fast-growing BPH had a higher prevalence of NIDDM ($p = 0.02$) and hypertension ($p = 0.04$) (Hammarsten & Hogstedt, 1999).

Moreover, they had elevated fasting plasma insulin levels ($p = 0.02$) and lower HDL-C levels ($p = 0.02$) than men with slow-growing BPH. The annual BPH growth rate correlated positively with diastolic blood pressure ($p = 0.01$), body mass index (BMI) ($p < 0.001$), and fasting plasma insulin level ($p = 0.008$). Conversely, it was negatively correlated with HDL-C level ($p = 0.001$) [40]. The authors concluded that BPH is a component of metabolic syndrome and that patients with BPH may share the same metabolic abnormalities of a defective insulin-mediated glucose uptake and secondary hyperinsulinemia as patients with metabolic syndrome. These findings support the hypothesis of a causal relationship between high insulin levels and the development of BPH, and they give rise to a hypothesis of increased sympathetic nerve activity in men with BPH. In a recent paper, Ozden et al confirmed that patients affected by BPH and metabolic syndrome had significantly higher median body weight, BMI, serum glucose, serum triglyceride, and prostate-specific antigen (PSA) levels but lower serum HDL-C levels compared with BPH patients without metabolic syndrome. Median annual total prostate growth rate (1.0 ml/yr) and median annual TZ EUROPEAN UROLOGY SUPPLEMENTS 8 (2009) 865–871 867 growth rate (1.25 ml/yr) were significantly higher in the first group versus the second group (0.64 ml/yr and 0.93 ml/yr, respectively; $p < 0.05$) (Ozden, Ozdal, Urgancioglu, Koyuncu, Gokkaya & Memis, 2007).

1.2.4 Inflammation

In the last few years, the role of chronic inflammation in the pathogenesis of BPH has emerged (Table 1). BPH has indeed been frequently associated with chronic prostatitis. Chronic inflammation is believed to support the process of fibromuscular growth in BPH (Kramer, Steiner & Handisurya, 2002).

Kohnen et al reported inflammatory infiltrate prevalence in 98% of 162 analysed BPH specimens (Kohnen & Drach, 1979).

The Reduction by Dutasteride of Prostate Cancer Events trial also confirmed a significant correlation between BPH-associated inflammation and BPH symptoms (Nickel, Roehrborn, O'Leary, Bostwick, Somerville & Rittmaster, 2008).

The subgroup analysis of the Medical Therapy of Prostate Symptoms Study found a chronic inflammatory infiltrate in 43% of the men. Moreover, inflammation was associated with significantly larger prostates, higher PSA levels, and a greater risk of acute urinary retention. The prostate is normally populated by small numbers of T cells, B lymphocytes, macrophages, and mast cells. Interestingly, several studies showed that the prostatic tissue in BPH patients contains a disseminated infiltration of T and B lymphocytes and numerous colonies of macrophages. The immune response in the prostate is primarily T-cell mediated, with regulatory T cells (CD-4) in the stroma and cytotoxic T cells (CD-8) in the epithelium (Bostwick, de la Roza, Dundore, Corica & Iczkowski, 2003).

In this context, by using analyses of T-cell activation marker expression, Steiner et al demonstrated that such inflammation mediators remain chronically activated. Because local accumulation of activated lymphocytes can cause tissue destruction, high concentrations of cytokines, and consequently tissue rebuilding, might contribute to the pathogenesis of BPH.

1.3 Prostate artery embolization

Prostate artery embolization PAE (see figure 3) is a non-surgical way of treating an enlarged and troublesome prostate by blocking off the arteries that feed the gland and making it shrink. It is performed by an interventional radiologist, rather than a surgeon, and is an alternative to a TURP (trans urethral resection of prostate) operation. PAE was first performed in 2009.

The gold standard treatment for benign prostate hyperplasia (BPH) is transurethral resection of the prostate (TURP) or open prostatectomy (OP). Recently, there has been increased interest and research in less invasive alternative treatments with less morbidity including prostate artery embolization (PAE). Several studies have shown PAE to be an effective alternative to TURP to treat lower urinary tract symptoms (LUTS) associated with BPH with decreased morbidity. Specifically, PAE has been advantageous in selected patient populations such as those with prostates too large for TURP or unsuitable surgical candidates, showing a promising potential for the future care of patients with BPH. Further studies are being done to demonstrate the clinical applications and advantages of this therapy in reduction of LUTS (Noor & Fischman, 2016).

Prostate artery embolization (PAE), a minimally invasive treatment, is known to offer symptom relief to men with benign prostatic hyperplasia (BPH), or an enlarged prostate gland. A Portuguese study of 1,000 men presented at the 2017 Society of Interventional Radiology (SIR) annual meeting shows that PAE maintains its effectiveness for at least three years following treatment. The study is the largest of its kind to evaluate the long-term effectiveness of the procedure (Pisco, Bilhim, Pinheiro, Fernandes, Pereira, Costa & Oliveira, 2017).

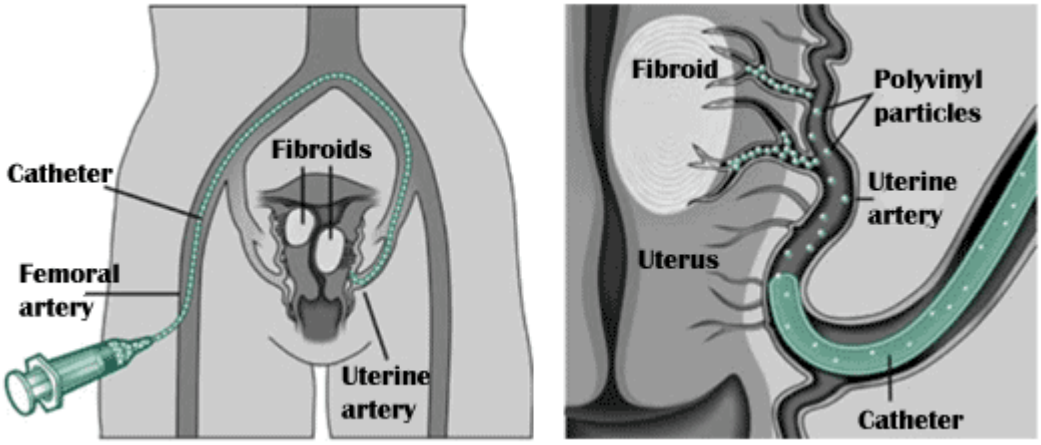


Figure (3): Prostate artery embolization PAE

Results are very promising (see figure 4) with greater than 90 percent of patients seeing extreme improvement. Approximately 7 percent of patients see moderate improvement and 1 to 2 percent may see no improvement.

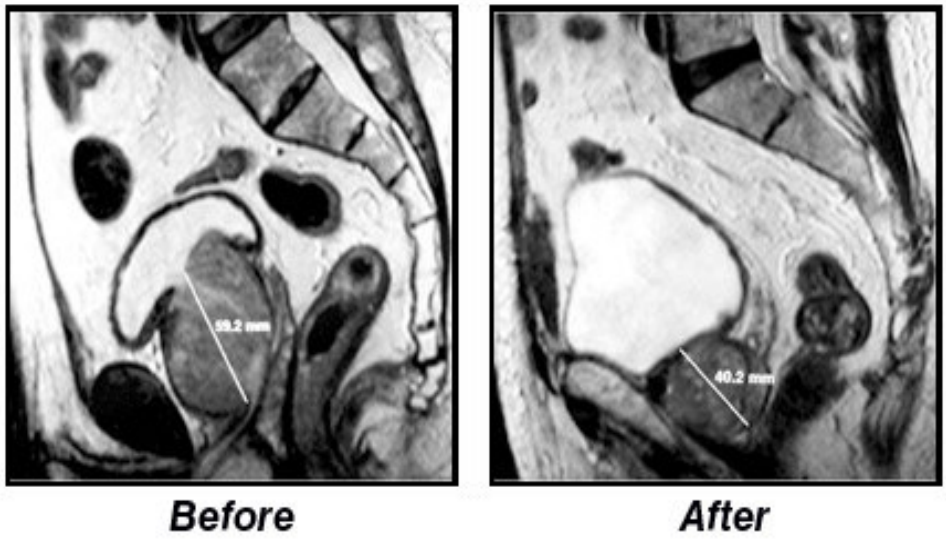


Figure (4): Before and after Prostate artery embolization PAE treatment

1.4 Embolization Procedure Description

In the studies of Bilhim, Pisco, Campos & Pinheiro (2013) and Bagla, Martin & van Breda (2014), the authors explicitly stated that the embolization procedure was performed by an interventional radiologist. However, we presume that interventional radiologists also performed the procedure in the other studies. The embolization procedure was performed using 90–180 or 180–300 µm non-spherical polyvinyl alcohol (PVA) particles, 300–500 µm microspheres, or 100–400 µm spherical embolic agents. Mean total procedure time varied from 70.4 to 96.3 min (mean of the means 80.1 min), and the mean fluoroscopy time varied from 18 to 85.9 min (mean of the means 36.5 min). Most studies had the intention to perform the embolization bilaterally; however, in some cases only unilateral embolization was performed due to atherosclerosis. One cohort study compared bilateral versus unilateral embolization. In total, 564 patients underwent a bilateral embolization, 91 a unilateral embolization, and for 22 patients it was unclear if one or both sides were treated (Antunes, Carnevale, da Motta & Leal Filho, 2013).

1.5 Patient Evaluation

In another study by Wang, Guo, Duan, Yuan, Zhang, Li & Kang (2016) conducted between April 2010 to December 2013 at a single institution, a total of 115 consecutive patients (mean [range] age 71.5 [56–85] years) diagnosed with severe LUTS attributable to BPH that was refractory to medical treatment underwent PAE. Of the 115 patients, 64 patients (55.7%) were in group A with a prostate volume >80 mL (mean [range], 129 [82–168] mL); and the remaining 51 patients (44.3%) were in group B with a prostate volume of 50– 80 mL (mean 64 mL). The baseline data of the two groups are shown in table 1.

Table (1): Baseline characteristics of the study population (N = 115)

Characteristic	Group A (n = 64)	Group B (n = 51)	P
Age, years	72.5 ± 9.5	66.0 ± 8.5	0.04
IPSS	26.0 ± 5.0	23.5 ±6.5	0.08
QoL score	5.5 ±1.0	4.5 ±1.5	0.1
Prostate volume, mL	129.0 ± 25.0	64.0 ± 13.0	0.01
Qmax, mL/s	7.50 ± 2.50	8.50 ± 1.5	0.5
PVR, mL	145.0 ± 30.0	120.0 ± 20.0	0.2
PSA, ng/mL	4.20 ± 1.5	3.90 ± 1.0	0.6
IIEF-5 score	10.0 ± 4.5	18.0 ± 6.0	0.03

The mean IPSS, quality of life (QoL), peak urinary flow rate (Qmax), post-void residual urine volume (PVR) and PSA level were not significantly different between groups, while the mean age, prostate volume and International Index of Erectile Function short form (IIEF-5) score were significantly different between groups ($P < 0.05$).

Eight patients (7.0%) had urinary retention before PAE (seven patients in group A and one patient in group B), with placement of an indwelling catheter for a mean (range) duration of 147 (22–260) days. Inclusion criteria included patient age >50 years with a diagnosis of severe LUTS (IPSS > 18 points, QoL score > 3, Qmax < 12 mL/s) attributable to BPH refractory to medical treatment for at least 6 months (a-1-adrenergic receptor antagonists or/and 5-a-reductase inhibitors) and a prostate volume >50 mL measured by MRI. Patient selection

was carried out in a multidisciplinary manner in conjunction with urologists and interventional radiologists. Eighteen patients underwent TRUS-guided prostate biopsy because they had a PSA level >4.0 ng/mL, with negative results for malignancy. Exclusion criteria included malignancy, large bladder diverticula (>5 cm), large bladder stones (>2 cm), chronic renal failure, active UTI, neurogenic bladder and detrusor failure, urethral stricture and unregulated coagulation parameters.

All patients were evaluated by clinical observation. Efficacy variables of IPSS, QoL, IIEF-5, Qmax, PVR and prostate volume were assessed before PAE and at 1, 3 and 6 months after the procedure, and every 6 months thereafter. PSA level was assessed before PAE and at 24 h, 1 week, 1, 3 and 6 months after the procedure, and every 6 months thereafter. Prostate volume was measured using MRI. The MRI protocol for all examinations was the same, including axial and sagittal T2-weighted and non-contrast-enhanced and contrast enhanced T1-weighted pulse sequences, and a 1.5-T magnet was used with a phased-array 12-channel body coil (GE Healthcare, Milwaukee, WI, USA). All magnetic resonance images were assessed independently by two radiologists who were unaware of the outcomes of PAE, and disparate measurements were resolved by consensus. Prostate volume was determined using the standard ellipsoid formula: length 9 width 9 height 9 0.52.

1.6 Conclusion

In conclusion, the authors state that the initial reported results of PAE seem promising, mainly during the first 12 months after treatment. However, no comparison was made to medical therapy or surgical therapies. Overlapping patient data and reporting bias could not be excluded. None of the included studies performed a power analysis. Also, a relatively small number of patients are treated with a short follow-up period. Therefore, more studies are needed with more patients and longer periods of follow-up, compared with standard medical and surgical therapies, to assess whether PAE is an effective and safe alternative treatment for BPH.

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