Development of Research Agenda in Prostate Artery Embolization: Summary of Society of Interventional Radiology Consensus Panel

Clifford Davis, MD, Jafar Golzarian, MD, FSIR, Sarah White, MD, MS, FSIR, Aaron Fischman, MD, FSIR, Ardeshir Rastinehad, DO, Ari Isaacson, MD, Francisco C. Carnevale, MD, PhD, FSIR, Harris Foster, Jr, MD, Laura Findeiss, MD, FSIR, Marc Sapoval, MD, PhD, Michael Borofsky, MD, Raj Ayyagari, MD, Riad Salem, MD, MBA, FSIR, Shivank Bhatia, MD, and Theresa Caridi, MD, FSIR

ABSTRACT

Purpose: To summarize the Society of Interventional Radiology Foundation's Research Consensus Panel development of a research agenda on prostate artery embolization (PAE).

Materials and Methods: PAE for the treatment of lower urinary tract symptoms has been shown to be safe and effective in decreasing symptoms and prostate size. Lack of randomized controlled trials (RCTs) on PAE in the United States has prevented inclusion in American Urologic Association guideline recommendations for treatment of lower urinary tract symptoms resulting from benign prostatic hyperplasia. Recognizing the need for well-designed trials, the SIR Foundation funded a Research Consensus Panel to prioritize a research agenda. The panel included interventional radiologists, urologists, SIR Foundation leadership, and industry representatives. The goal of the meeting was to discuss weaknesses with current data and study design for development of US trials to report long-term outcomes data.

Results: Final consensus on a research design could not be made because the group was split on 3 research designs: (*i*) RCT of PAE versus sham with crossover of the sham group. (*ii*) RCT of PAE versus simple prostatectomy. (*iii*) RCT of PAE versus holmium laser enucleation of the prostate/thulium laser enucleation of the prostate. The panel recommended a nonindustry-funded registry to obtain real-world data.

Conclusions: Level 1 data are required to be included in the American Urologic Association guidelines for treatment of benign prostatic hyperplasia. Because of concerns with all 3 study designs, the panel did not reach a consensus. Further meetings are planned with the panel to select among these research designs.

From the College of Medicine and Radiology (C.D.), University of South Florida, Tampa, Florida; Department of Radiology (J.G.), University of Minnesota, Minneapolis, Minnesota; Department of Radiology (S.W.), Medical College of Wisconsin, Milwaukee, Wisconsin; Department of Radiology and Surgery (A.F.), Icahn School of Medicine at Mount Sinai, New York New York; Department of Urology and Radiology (A.R.), Icahn School of Medicine at Mount Sinai, New York, New York; Department of Vascular and Interventional Radiology (A.I.), University of North Carolina School of Medicine, Chapel Hill, North Carolina; Interventional Radiology (F.C.C.), University of Sao Paulo, Sao Paulo, Brazil; Department of Urology (H.F.), Yale School of Medicine, New Haven, Connecticut; Department of Radiology and Imaging Services (L.F.), Emory University School of Medicine, Atlanta, Georgia; Vascular and Oncological Interventional Radiology (M.S.), Hôpital Européen Georges-Pompidou, Paris, France; Department of Urology (M.B.), University of Minnesota, Minneapolis, Minnesota; Department of Radiology and Biomedical Imaging (R.A.), Yale School of Medicine, New Haven, Connecticut; Department of Radiology (R.S.), Northwestern University, Chicago, Illinois; Department of Radiology (S.B.), University of Miami, Miami, Florida; and Department of Radiology (T.C.), MedStar Georgetown University, Washington, DC. Received September 19, 2019; final version accepted September 20, 2019. **Address correspondence to** C.D., Interventional Radiology, Room J342, Tampa General Hospital, One Tampa Circle, Tampa, FL 33606; E-mail: cliffrdavis@yahoo.com; Twitter handle: @DrCliffDavis

C.D. receives personal fees from Boston Scientific (Marlborough, Massachusetts), and Merit Medical (South Jordan, Utah). S.W. receives research support from Guerbet (Villepinte, France), Siemens (Munich, Germany), and Instylla (Boston, Massachusetts), and personal fees from Guerbet, Cook Medical (Bloomington, Indiana), and BTG (London, United Kingdom). A.F. received personal fees from Terumo (Shibuya, Japan), Boston Scientific, and Embolx (Sunnyvale, California). A.I. receives grants from Terumo and personal fees from Terumo, Boston Scientific, CrannMed (Galway, Ireland), and Guerbet. L.F. is president of the Society of Interventional Radiology (Fairfax, Virginia). M.S. received personal fees from Merit Medical and BTG, and grant funds from the French Ministry of Health. M.B. is a paid consultant for Boston Scientific and Auris Health (Redwood City, California). R.A. receives personal fees from Embolx and Merit Medical. R.S. receives personal fees from BTG. S.B. receives research grants from SIR, and personal fees from Merit Medical, Terumo, Embolx, Mentice (Gothenburg, Sweden), and Siemens. T.C. receives personal fees from Boston Scientific, Embolx, and Terumo. None of the other authors have identified a conflict of interest.

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ABBREVIATIONS

AB = alpha blocker, AUA = American Urologic Association, BPH = benign prostatic hyperplasia, 5-ARI = 5-alpha reductase inhibitor, FDA = US Food and Drug Administration, HoLep = holmium laser enucleation of the prostate, IPSS = International Prostate Symptom Score, LUTS = lower urinary tract symptoms, MIST = minimally invasive surgical therapies, PAE = prostate artery embolization, RCP = research consensus panel, RCT = randomized controlled trial, SP = simple prostatectomy, ThuLep = thulium laser enucleation of the prostate, TURP = transurethral resection of the prostate

BACKGROUND

Benign prostatic hyperplasia (BPH) affects more than 70% of men older than 70 years of age (1). Symptoms of BPH can overlap with other disease processes and are termed lower urinary tract symptoms (LUTS). LUTS are tracked by a subjective but validated survey termed the International Prostate Symptom Score (IPSS) (2). The constellation of symptoms that lead to poor quality of life can progress without therapy to cause bladder dysfunction, chronic renal insufficiency, urinary tract infections, bladder stones, and acute urinary retention. Medical therapy primarily consists of alpha-blockers (AB) and 5-alpha reductase inhibitors, which significantly reduce the risks of urinary retention and progression of symptoms; however, approximately 30% of patients quit medical therapy for various reasons (3). In addition, 80% of patients with moderate to severe LUTS progress over 5 years despite medical therapy, and 39% require surgical therapy (4).

Surgical therapy for BPH is recommended once symptoms have progressed to moderate to severe on the IPSS scale or if the patient is having medical complications related to BPH (5). Selection of the surgical procedure is based on patient comorbidities, local availability, and prostate size. Current American Urologic Association (AUA) guidelines recommend evaluation of prostate size before surgical therapy to select the most appropriate procedure with lowest risks for a given patient. There are numerous surgical procedures to treat BPH that are divided into 3 categories: minimally invasive surgical therapies (MIST); transurethral resection/ablation procedures; and open/laparoscopic/robotic simple prostatectomy. Although the list of available procedures is long, the available options in patients with prostate size >80 g are limited. The AUA does not specifically state which procedure should be used for prostates >80 g, but the current MIST therapies are approved for prostates up to 80 g only. The AUA guidelines previously noted increased complication rates and urinary catheter times in transurethral resection of the prostate (TURP) for prostates >70 g. The AUA guidelines state that "large" prostates should be considered for open simple prostatectomy (SP), and if expertise exists laser enucleation (thulium laser enucleation of the prostate [ThuLep]/holmium laser enucleation of the prostate [HoLep]) or robotic/laparoscopic simple prostatectomy as acceptable alternatives. All of these therapies offer definitive therapies for BPH in prostates >80 g but require spinal or general anesthesia, urinary catheters from 1 to 3 days, inpatient admission, risk of urethral/bladder neck strictures/hemorrhage, frequent retrograde ejaculation, and small risks of permanent incontinence (6).

Prostate artery embolization (PAE) is unique as a treatment for BPH because is performed independently of prostate size. In fact, 2 small comparative studies suggest prostates >80 g have a greater improvement in symptoms compared with prostates 50–80 g (7,8). PAE is also unique in that the procedure can be performed with no sedation in patients with high anesthesia risks. If necessary, PAE can be performed with concomitant antiplatelet or anticoagulation therapy. Although PAE does require an angiography suite, it is an outpatient procedure that can be performed without a urinary catheter. These unique attributes allow PAE to cross the line between traditional transurethral, MIST, and open surgeries because it can be performed on an outpatient basis in the setting of massive prostate enlargement and/or with high-risk patients. In addition, results of the initial prospective randomized trials for PAE suggest there is significantly less risk of retrograde ejaculation, which occurs in 20%–70% of patients following transurethral therapies.

Clinically, PAE has been performed in Brazil and Portugal for more than 10 years and in other European countries (France, UK, Italy) for 7 years. Merit Medical's Embospheres was given US Food and Drug Administration (FDA) approval for PAE in June 2017 and Boston Scientific's Embozene received 510k approval for PAE in 2018. The UK Registry of Prostate Embolisation registry cleared PAE for clinical use in the National Health Service for BPH treatment in 2018 (9). The FDA approval has increased the clinical use of PAE in the United States, although long-term randomized controlled data comparing PAE to traditional surgeries are still lacking.

To date, there have been no published randomized controlled trials in the United States comparing PAE with MIST or traditional surgical procedures. As summarized in the recent Society of Interventional Radiology (SIR) Position Statement on Prostate Artery Embolization (10), there have been 3 small randomized controlled trials in Europe and Asia comparing PAE with TURP. All 3 concluded that PAE was similar in effectiveness in lowering the IPSS rating compared (11–13) with TURP; however, the total number of patients was small and only 1 study evaluated patients up to 2 years.

A single matched pair analysis was performed in Italy of PAE versus open SP in 160 patients with prostate size >80 g

with 12-month follow-up data (14). In that study, PAE was found to be inferior to SP in reduction of symptoms (IPSS reduction of 13.6 versus 20 points at 12 months); however, the PAE group had an 8.75% complication rate with no serious complications versus 31.25% in the SP group with 3.75% major complications.

The previously mentioned Registry of Prostate Embolisation registry-based observational study performed in the United Kingdom evaluated outcomes of 305 patients who received TURP (N = 89) versus PAE (216) (9). Patients in the PAE group were younger with larger prostates (mean, 66 years old and 101 g vs 70 years old and 65.6 g). As in other comparisons, PAE offered significantly fewer complications and shorter hospital stays. Improvement in IPSS, quality of life, and flow was more significant in the TURP group, but the clinical strength of the data has been questioned given the differences in the treatment groups because complication rates with TURP are known to increase with prostate size >80 g.

Despite the position statement on PAE developed by SIR and several international societies based on these and other similarly supportive studies, the AUA has not embraced PAE. Every few years, the AUA publishes guidelines for treatment of BPH. The last full update was in 2011, which included recommendations on medical and surgical therapy (15). In 2018, the AUA published the guideline Surgical Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia, which was then updated in 2019 (5). These guidelines are developed by a team of expert urologists who review MEDLINE, Cochrane Library, and Agency for Healthcare Research and Quality databases. Results are ranked based on strength of supporting evidence. Based on the data available in early 2019, the 2019 AUA Surgical Management guidelines stated that "PAE is not recommended for the treatment of LUTS attributed to BPH outside the context of a clinical trial. (Expert Opinion)." Given the lack of current randomized trials in the United States, the lack of long-term PAE outcomes data, and the recent release of the AUA guidelines, the SIR Foundation chose to sponsor the PAE Research Consensus Panel (RCP) to discuss possible PAE research protocol designs.

MATERIALS AND METHODS

An institutional review board was not required because this project did not involve human subjects. On April 15, 2019, the SIR Foundation assembled an RCP for the development of a research agenda for PAE. The panel included 9 interventional radiologists who perform PAE research, urologists familiar with PAE including 1 on the AUA review committee, SIR Foundation leadership, and representatives from industry. The goal of the meeting was to discuss weaknesses/shortcomings with current data on PAE and study design for development of US trials to report long-term outcomes data.

Meeting Agenda

Before the meeting, each physician member was assigned a topic to cover during the morning presentations. Research topics and goals were collected from each member before the meeting, which overlapped significantly among several attendees. The top 3 research priorities collected before the meeting were as follows.

1. Development of a randomized controlled trial comparing PAE to surgical therapy (TURP/SP/HoLep) with long-term outcome data
2. Safety/effect of PAE on low-grade (Gleason 6) prostate cancer
3. Development of a nonindustry-sponsored registry to evaluate real-world outcomes

The meeting began with introductions of the RCP physician members and SIR Foundation leadership. Overview or the meeting agenda and goals were discussed before presentations. The first 4 hours were devoted to topical presentations by the physician members, each 15–20 minutes in length, relating to BPH therapies. Approximately 50% of the presentations were devoted to surgical and medical therapies for BPH and 50% were focused on PAE. The first portion of the meeting was deemed necessary to both educate the interventional radiology physicians on newer trends in medical/surgical data as well as inform the urologists on current data in PAE.

Following the presentations, each member was again asked to rank their 3 top research goals, which was rapidly combined using ranking software and presented to the group. The last 3 hours of the meeting were devoted to a roundtable discussion on optimal study design for a future PAE trial. During the roundtable discussion, the group repeated the ranking of research goals to determine if there had been a shift in the opinions as the discussion progressed.

Outcome and Discussion

Presentations devoted to medical and surgical therapies of BPH mirrored current AUA guidelines and reviewed data on complications and long-term outcomes of several surgical techniques.

Radiation Considerations. Urologists on the panel expressed concern over the radiation doses to the patients during PAE. Although dose area product was reported in 2 PAE trials (11,13), it was not converted to region/organ-specific effective dose and the associated risks of those doses were not discussed.

Medical Therapy. The urologist participants reviewed randomized controlled trials (RCTs) on medical therapy, which are briefly summarized here: alpha blockers lower IPSS scores and quality-of-life measures but do not alter rates of surgical therapy or episodes of acute urinary retention (16). 5-alpha reductase inhibitor (5-ARI) therapy

results in significant decreases in prostate size, progression rate, and rates of surgical therapy compared with placebo over 4.5 years. In each RCT study of 5-ARI, the placebo group had a drop of 1–4 points on the IPSS survey despite progression in prostate size and decreased flow. Combination therapy with AB and 5-ARI was noted to decrease progression of symptoms more than placebo and 5-ARI alone (17).

Surgical Therapy. Surgical therapy should be offered to patients once symptoms have progressed into the moderate to severe range on the IPSS scale if medical therapy has failed or a patient cannot tolerate medical therapy. Treatment is also recommended if a complication of BPH related to bladder outlet obstruction puts the patient at risk for a more serious event (recurrent urinary tract infection, bladder stones, or hematuria) (5).

Evaluation of flow rates with uroflowmetry and evaluation of postvoid residual is suggested by the AUA guidelines as the minimum test to diagnose bladder outlet obstruction. To choose the most appropriate surgical procedure, the AUA now suggests measuring prostate size by transrectal ultrasound if the prostate size has not been recorded in prior testing (computed tomography/magnetic resonance imaging) (5). Cystoscopy, urodynamics, multiparametric prostate magnetic resonance imaging, and computed tomography urography remain tools to rule out other disease processes if suspected by a treating physician.

TURP remains the gold standard to which other procedures are compared in most surgical trials. The AUA guidelines on procedural selection and complications are based on several RCTs comparing surgical techniques to TURP. Long-term RCT data exist for TURP versus prostatectomy (simple open, laparoscopic, robotic) (18–22), transurethral vaporization (23,24), photoselective vaporization of the prostate (25–28), and laser enucleation (HoLEP/ThuLEP) (29–45). MIST therapies have less compelling data, although AUA recommendations were nonetheless still based on RCTs with more than 12 months of outcome data (46–52). The participating urologist member of the AUA BPH guideline committee noted that the AUA recommendations were based solely on RCTs that met the guideline panel's minimum requirements, explaining why PAE was not considered in the guidelines. The Abt et al (13) trial on PAE was published soon after the updated AUA recommendations but included only 12-week outcomes data; other available RCTs available were not performed in the United States and remaining single-arm prospective or retrospective evaluations were not considered.

After explanation of the criteria required for data from a PAE study to meet the threshold for integration into AUA guideline committee recommendations, the panel moved on to a discussion of possible PAE study designs. Initial proposals included case control, RCT, and blinded-sham studies. Consensus on study design by the group was difficult but focused on the following agreed-on statements.

1. A PAE study would have to include ≥24-month follow-up to be equivalent to current data on other surgical therapies for LUTS resulting from BPH.
2. A prospective single-arm PAE trial would not be adequate to prove efficacy because it would not include a control arm or be randomized.
3. The importance of a placebo/control arm was explained by review of several RCTs demonstrating a decrease in the IPSS of 3–4 points in placebo/sham arms.
4. Registries, although helpful to obtain real-world outcomes, are not controlled well enough to prove efficacy.
5. Case control studies could be feasible to compare PAE versus other surgical options but are not considered level 1 data for guideline recommendations.

Significant time during the roundtable discussion was devoted to the optimal treatment against which PAE should be measured in an RCT. There was difficulty coming to a consensus because of concerns about the reliance on urologist enrollment of patients into an RCT, which might be subject to specialty and patient selection biases. Merit Medical had previously developed an FDA-approved investigational device exemption RCT (BEST) comparing PAE with TURP, but had difficulty enrolling patients, and dropout was significant in the TURP group. This was attributed to patients' reluctance to undergo surgery instead of PAE and have follow-up invasive tests after a TURP, which was available to patients outside of a trial. After 3 years of inadequate enrollment and early dropout, the BEST study was closed.

Based on this experience, if an RCT was performed, the following consensus statements were agreed on.

1. Comparison of PAE to medical therapy was not recommended because medical therapy is first-line therapy to avoid surgery. The ongoing RCT Partem in France is comparing PAE with combination AB and 5-ARI therapy and will complete enrollment in 6 months; results should be available in 2021.
2. Comparison should include a therapy that is primarily used in patients with prostate size >80 g because these patients have fewer treatment options and PAE outcomes are likely better in this subset.
3. SP (open, laparoscopic, robotic) would be an acceptable procedure to compare with PAE. The urologists noted that at most major medical centers the use of SP has significantly decreased because of the range of other medical and surgical therapies. Patient resistance to enrollment should be cautiously evaluated before putting together efforts in this direction.
4. HoLEP/ThuLEP are considered less invasive alternatives to SP in prostates >80 g. However, less than 5% of all prostate surgeries are HoLEP/ThuLEP and only a handful of centers perform the procedure in the United States, most of which do not have PAE experience.
5. Comparison to HoLEP would likely demonstrate inferiority of PAE in patients with prostate size >80 g, but a research design focused on safety, overall costs, and

patient satisfaction would be appropriate to demonstrate the value of PAE as an alternative.
6. A trial comparing PAE versus a sham procedure would be feasible and easier to control with a single operator, but would be difficult to enroll because patients are seeking therapy and do not desire sham procedures. Ethics of running a sham trial were discussed. There is a current sham study in process of review by the team of Pisco and Bilhim, which provide evidence in this study design.
7. RCTs are extremely costly. Funding of PAE versus surgical trial would likely require National Institutes of Health grants.

The group of interventional radiologists performing PAE felt that comparing PAE with other surgical therapies (TURP, water vapor ablation, photoselective vaporization of the prostate, UroLift) in smaller prostates was not optimal given the consensus that larger prostates have better outcomes with PAE. Currently, surgical procedures considered optimal for treatment of prostates >80 g include HoLEP/ThuLEP, SP, and robotic and laparoscopic SP. All of these procedures require spinal or general anesthesia and urinary catheters, with small risks of hemorrhage and incontinence. However, based on available study data regarding these therapies, improvements in IPSS and maximum flow volume per second would likely be meaningfully better than PAE. There were significant concerns among the group regarding an RCT comparing these procedures with PAE because many believed there would be specialty selection bias and difficulty enrolling patients because many patients would be enrolled by a urologist. Additionally, HoLEP/ThuLEP and SP combined were noted to compose fewer than 8% of all procedural treatments for BPH on the last National Surgical Quality Initiative Project report from 2015. Regardless of the study design, evaluation of radiation effective dose and associated risks should be discussed in future trials.

The meeting was ended because of time constraints despite an active conversation regarding study design for several hours. Final consensus on a research design could not be made because the group was split on 3 major research designs:

1. RCT Trial of PAE versus sham with crossover of the sham group,
2. RCT Trial of PAE versus prostatectomy (open/robotic/laparoscopic), and
3. RCT Trial of PAE versus HoLEP/ThuLEP.

The entire group was able to reach a consensus on the need for a nonindustry-sponsored registry for PAE treatment to better evaluate the real-life outcomes of PAE patients. There are many questions about optimal technique, comparative efficacy, adverse events, and ideal means for outcomes measurement that remain. With a large sample size, a PAE registry may help answer some of these questions and will likely assist in the future design of PAE research protocols.

In conclusion, there is still debate about the optimal research design protocol for a trial to further validate PAE. The recently published Abt trial is designed to obtain long-term follow-up but, at this point, no other RCTs of PAE versus surgical therapy have been developed in the United States. In France, the Partem trial comparing medical treatment to PAE will help to clarify the landscape as well. The acceptance of PAE as an alternative to other BPH therapies by the AUA will require an RCT. The interventional radiologists on the consensus panel hope to meet again in the near future to develop a design based on this progress. A nonindustry-sponsored registry is recommended to assist in future research design and evaluation of real-life outcomes; the panel therefore recommends that SIR place high priority on devoting resources to the development of that registry.

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