Prostate artery embolisation for benign prostatic hyperplasia

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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List of abbreviations

AMSTAR ..... Assessing the Methodological Quality of Systematic Reviews
BPH ..... Benign Prostatic Hyperplasia
CRD ..... Centre for Reviews and Dissemination
DARE ..... Database of Abstracts of Reviews of Effects
DRE ..... Digital Rectal Examination
EAU ..... European Association of Urology
EUnetHTA ... European network for Health Technology Assessment
FDA ..... Food and Drug Administration
GRADE ..... Grading of Recommendations Assessment, Development and Evaluation
HRQoL ..... Health-Related Quality of Life
HTA ..... Health Technology Assessment
IIEF ..... International Index of Erectile Function
IPSS ..... International Prostate Symptom Score
LUTS ..... Lower Urinary Tract Symptoms
NHS-EED .... NHS Economic Evaluation Database
PAE ..... Prostate Artery Embolisation
PSA ..... Prostate Specific Antigen
PVA ..... Polyvinyl Alcohol
Qmax ..... Peak Urinary Flow
RCT ..... Randomised Controlled Trial
TUIP ..... Transurethral Incision of the Prostate
TUMT ..... Transurethral microwave therapy
TUNA ..... Transurethral Needle Ablation
TURP ..... Transurethral Resection of the Prostate
UTI ..... Urinary Tract Infection

Summary

Introduction

Health Problem

The scope of this assessment includes benign prostatic hyperplasia (BPH) causing moderate-to-severe lower urinary tract symptoms (LUTS). Benign enlargement of the prostate gland, bladder outlet obstruction, and LUTS are independent factors, in any combination referred to as LUTS suggestive of BPH. The symptoms of BPH are classified as voiding (e.g. hesitancy, intermittency, dysuria), storage (e.g. frequency, nocturia, urgency) or post-micturition symptoms (e.g. incomplete voiding, dribbling). Approximately 2.5 per cent of men with untreated symptomatic BPH will develop acute urinary retention, and another six per cent will require invasive therapy within five years.

benign prostatic hyperplasia (BPH) causes moderate-to-severe lower urinary tract symptoms (LUTS): problems with urination

The severity of LUTS is measured using the International Prostate Symptom Scores (IPSS) questionnaire, whereby a score of 1-7 indicates mild symptoms, 8-10 moderate, and 20-35 severe. The global prevalence of histological BPH is estimated to be 42 per cent of men aged between 51 and 60, and 82 per cent of men aged between 71 and 80. However, not all of these men will be symptomatic or require treatment. A representative survey of Austrian men estimated the prevalence of moderate-to-severe LUTS to be 9.1 per cent of men between the ages of 15 and 89, noting that BPH is not the only cause of LUTS.

severity of LUTS: measured with IPSS

prevalence: 42% men 51-60 y 82% men 71-80 y not all symptomatic

Description of Technology

Prostate artery embolisation (PAE) is a minimally invasive alternative to surgical resection, which aims to shrink the prostate gland rather than remove it. In PAE, an interventional radiologist inserts a catheter into the femoral artery at the top of the leg, and guides the catheter to the prostate arteries. A solution of microscopic particles is injected through the catheter, which mechanically block the prostate arteries and partially reduce the blood supply. The reduction in blood supply induces ischaemic necrosis, causing the gland to soften and shrink in size over time.

prostate artery embolisation (PAE): minimally invasive therapy microscopic particles injected to block the prostate arteries

There are at least four different types of embolisation agents that can be used in PAE, which vary in size and material, but all of which operate under the same biomechanical principles.

four different types of embolisation agents

Methods

In patients with BPH and moderate-to-severe LUTS, is PAE safer concerning adverse events, and as effective concerning changes in IPSS, International Index of Erectile Function (IIEF) score, and quality of life scores, compared to surgical resection?

research question: efficacy and safety of PAE

The research question was investigated through a systematic review of the current literature on PAE. Four databases (Medline, Embase, Cochrane Library, CRD-Database) were searched; two authors independently conducted the study selection, data extraction, and quality appraisal.

systematic search in 4 databases, 2 authors: study selection, extraction, quality appraisal

Results

available evidence: efficacy (n = 304 pts): comparative studies with TURP or open prostatectomy: 2 RCTs, 1 matched-pairs study

Effectiveness outcomes were addressed by randomised controlled trials (RCTs) and non-randomised studies comparing PAE to transurethral resection of the prostate (TURP) or open prostatectomy. For safety outcomes, further five studies (e.g. single arm trials with at least 150 participants) were included.

Two RCTs comparing PAE to TURP (n = 144), and one matched-pairs study comparing PAE to open prostatectomy (n = 160), were identified for effectiveness outcomes. In addition to these studies, one additional RCT comparing PAE particle sizes, two non-randomised studies comparing different populations treated with PAE, and two single-arm studies of PAE were included for safety outcomes. The additional studies included a total of 1,168 patients.

safety (n = 304 + 1,168 pts): observational studies and RCTs comparing different agents or patient groups

All studies with one exception included patients with more severe symptoms (IPSS ≥ 8). The mean age of all included patients ranged between 63 to 73 years (for effectiveness analysis) and 63 to 83 years (for safety analysis).

pts characteristics

Clinical effectiveness

PAE vs TURP low strength of evidence: conflicting evidence in improvements in IPSS and HRQoL at 12 months no long-term data beyond 24 months

The overall strength of evidence for the effectiveness of PAE compared to TURP was low. The included RCTs demonstrated conflicting evidence in relation to improvements in IPSS and HRQoL at 12 months. The larger trial (n = 114) reported no significant differences in IPSS and HRQoL at 12 or 24 months between PAE and TURP, whereas the smaller trial (n = 30) favoured TURP for both outcomes at 12 months. Disease progression was a rare outcome, and as such meaningful comparisons between PAE and TURP cannot be drawn for this outcome. There was no long-term data beyond 24 months.

PAE vs OP low strength of evidence: significant better improvement in IPSS and IIEF at 12 months with OP

The overall strength of evidence for the effectiveness of PAE compared to open prostatectomy was low. The matched-pairs trial reported open prostatectomy was associated with a significantly greater improvement in mean IPSS (-19.04 vs. -13.58, $P < 0.01$) at 12 months compared to PAE. Disease progression was a rare outcome, and as such meaningful comparisons between PAE and open prostatectomy could not be formed for this outcome. There was no long-term data beyond 12 months.

Safety

PAE vs TURP vs OP moderate to low strength of evidence

The overall strength of evidence for the safety of PAE compared to TURP and open prostatectomy was low or moderate. There were no reported cases of perioperative mortality in any of the included studies. One RCT reported PAE to be associated with significantly more adverse events compared to TURP, while the matched-pairs trial found significantly fewer adverse events for PAE compared to open prostatectomy.

no perioperative mortality SAE: rare

AE conflicting evidence on minor AE urethral burning, acute urinary retention, blood in the urine etc.

The overall strength of evidence for the safety of PAE from non-randomised and single-arm studies was low or very low. Serious adverse events were rare, and included one case of bladder wall ischemia, and eight technical or clinical failures across the entire safety population (n = 1,472). The most commonly reported adverse events associated with PAE were minor, including urethral burning (range 10.2% to 100.0%), acute urinary retention (range 8.6% to 30.8%), blood in the urine (range 0.0% to 13.3%), blood in the semen (range 1.25% to 11.2%), and urinary tract infections (range 1.25% to 4.8%).

Upcoming evidence

There are five ongoing RCTs of PAE compared to TURP in patients with moderate-to-severe LUTS, which are currently scheduled for completion before February 2021. In addition, there is one ongoing RCT of PAE compared to medical therapy, scheduled for completion in February 2021, and one RCT of PAE compared to sham procedure, scheduled for completion in September 2017. In addition to the ongoing RCTs, there is one substantive non-randomised registry trial comparing PAE, TURP and open prostatectomy, which aims to enrol 300 patients, and is scheduled for completion in September 2017. Most of the ongoing trials are limited to 12-month follow-up, and as such will not fill the current evidence gap for the long-term safety and efficacy of PAE.

5 ongoing RCTs:
PAE vs. TURP: 2021

1 ongoing RCT:
PAE vs. medical therapy

Registry: PAE, TURP, OP

Discussion and Conclusion

The available RCTs reported conflicting results for the main effectiveness outcomes, and adverse events rates were reported variably across the included studies. A consistent system for recording or rating the severity of adverse events was not present; however, severe adverse events were rare. The study populations were broadly generalizable in relation to symptoms, history, and demographics. Medium- to long-term follow-up data of safety and effectiveness outcomes beyond 12-24 months are limited. It is currently unknown if placing embolisation particles in the prostate arteries may lead to long-term adverse events. Different embolisation agents were used in the included studies, including particles with a range of shapes, materials, and sizes. One RCT that compared outcomes of different sized particles found no significant difference in effectiveness or safety. It is unknown whether particle material or size have an impact on long-term outcomes.

conflicting results
no consistent system of reporting (S)AE
study populaton generalizable

follow-up data:
12-24 months

different embolisation agents (size, shape, material)

The current evidence is not sufficient to prove that PAE [in adult patients with moderate to severe LUTS] is as effective, but more safe than the comparator(s) TURP and open prostatectomy. New study results will potentially influence the effect estimate considerably. The re-evaluation is recommended in 2021.

current evidence is not sufficient to prove effectiveness
re-evaluation in 2021

Zusammenfassung

Einführung

Indikation und therapeutisches Ziel

gutartige Prostatahyperplasie (BPH):

Bei der benignen Prostatahyperplasie (BPH) handelt es sich um eine gutartige Vergrößerung der männlichen Vorsteherdrüse (Prostata). Die BPH verursacht eine Verengung der Harnröhre und damit mäßige-bis-schwere Symptomatiken der unteren Harnwege (*lower urinary tract symptoms*, LUTS), was mit Problemen beim Wasserlassen einhergeht. Die Symptome von LUTS sind verzögertes Einsetzen der Blasenentleerung trotz starken Harndrangs, das Bedürfnis zu pressen, um die Blase zu entleeren (Pressmiktion), das Gefühl, die Blase werde nicht ganz leer (Restharnempfinden), ein schwacher Harnstrahl, nachtröpfelnder Urin, lange Dauer der Blasenentleerung und schon kurze Zeit nach dem Urinieren einsetzender erneuter Harndrang. Etwa 2,5 Prozent der Männer mit unbehandelten symptomatischen BPH entwickeln akute Harnretention (Harnverhaltung oder Ischurie), und weitere 6 Prozent benötigen eine Therapie innerhalb von fünf Jahren.

Vergrößerung der Prostata verursacht mäßige bis schwere Symptome des unteren Harntraktes (LUTS)

Harndrang, Blasenentleerungsstörungen etc.

LUTS Schweregrad: gemessen mit IPSS

Der Schweregrad von LUTS wird mit dem Patientenfragebogen des *International Prostate Symptom Scores* (IPSS) gemessen, wobei eine Punktzahl von 1-7 milde, 8-19 mäßige und 20-35 schwere Symptome, anzeigt.

Prävalenz: 42 % Männer 51-60 J, 82 % 71-80 J nicht alle symptomatisch österr. Umfrage zu LUTS: 9,1 % aller Männer jeglichen Alters

Die weltweite Prävalenz der BPH wird auf 42 Prozent der Männer im Alter zwischen 51 und 60 und bereits 82 Prozent der Männer im Alter zwischen 71 und 80 geschätzt. Allerdings werden nicht alle diese Männer symptomatisch und/oder bedürfen eine Behandlung. Eine repräsentative Umfrage unter österreichischen Männern schätzte die Prävalenz von mäßiger bis schwerer LUTS auf 9,1 Prozent der Männer im Alter zwischen 15 und 89; allerdings ist festzuhalten, dass BPH nicht die einzige Ursache für LUTS ist.

Standarddiagnostik:

Da Störungen beim Wasserlassen bei älteren Männern relativ häufig sind und aufgrund der Symptomvielfalt der BPH, wird nur auf der Basis einer Stufendiagnostik eine Therapieempfehlung ausgesprochen.

Stufen-/ Differentialdiagnostik

1. Anamnese einschließlich einer genauen Medikamentenanamnese
2. IPSS (International Prostate Symptom Score) oder vergleichbare Symptomscores
3. Körperliche Untersuchung mit digito-rektaler Untersuchung (DRU)
4. Laboruntersuchungen: Serum-Kreatinin, Prostataspezifisches Antigen (PSA) (bei einem Lebensalter von über 50 Jahren), wenn sich daraus therapeutische Konsequenzen ergeben (dies allerdings derzeit fakultativ), Urinstatus und Urinsediment
5. Uroflowmetrie
6. Restharnbestimmung
7. Uro-Sonographie (Nieren, Blase, Prostata [vorzugsweise Transurethraler Ultraschall (TRUS)])

Vielzahl von Therapieoptionen

Für die Behandlung der BPH steht eine Vielzahl von Therapieoptionen zur Verfügung. Alle haben die Linderung der LUTS Symptome als Therapieziel. Das Spektrum reicht von anfänglichem Beobachten, ob sich die Beschwerden von selbst bessern, über Medikamente bis hin zu zahlreichen Operationsverfahren, bei denen die Prostata teilweise entfernt wird. Die Prostatakapsel bleibt immer bestehen. *Transurethrale Resektion der Prostata (TURP)* gilt aber als die Standardmethode zur Behandlung des BPH.

TURP gilt als Standardmethode

2015 wurde TURP 5.983 mal und die offene Prostatektomie 150 mal in österreichischen Spitälen abgerechnet.

LKF-Abrechnung 2015

Beschreibung der Technologie

Die Prostata-Arterie-Embolisation (PAE) ist eine minimal-invasive Alternative zur chirurgischen Resektion. Die PAE zielt darauf ab, die Prostata zu schrumpfen, anstatt sie zu entfernen. Bei der PAE wird von einem interventionellen Radiologen über eine Leistenarterie ein dünner Katheter in die Arterie der Prostata eingeführt: mittels einer injizierten Lösung von mikroskopischen Partikeln (Durchmesser 80-500 μm) werden die kleinen Äste dieser Arterie dauerhaft verschlossen, indem die Partikel die Blutversorgerung der Prostata mechanisch blockieren, was ein Schrumpfen der Prostatazellen zur Folge hat: Die Verringerung der Blutversorgung führt zu einer ischämischen Nekrose, wodurch die Drüsen im Laufe der Zeit erweichen und schrumpfen.

Prostata-Arterie-Embolisation (PAE): minimal-invasive Methode

mittels mikroskopischer Partikel wird die Blutversorgung der Prostata reduziert, diese schrumpft in Folge

Vier verschiedene Arten von Embolisationspartikeln, die bei er PAE verwendet werden können, verfügen über eine Europäische Marktzulasssung (CE-Mark), keine jedoch eine US-amerikanische (FDA-)Zulassung. Die Partikeln unterscheiden sich in Größe, Form und Material, arbeiten aber alle mit den gleichen biomechanischen Prinzipien.

vier unterschiedliche Embolisations-Partikel verfügbar: CE Mark keine FDA Zulassung

Tabelle: Characteristika von Embolisationspartikeln zur Behandlung der BPH

Produkt Charakteristika	Embozene™ Microspheres	Bead Block®	Embosphere® Microspheres	PVA Foam Embolisation Particles
Hersteller	Boston Scientific Corporation*	Biocompatibles UK Ltd	Merit Medical Systems Inc	Cook Medical
Material	HydroGel core with Polyzene-F coating	Polyvinyl alcohol hydrogel	Trisacryl with gelatin	Polyvinyl alcohol
Form	Spherical particles	Spherical particles	Spherical particles	Non-spherical particles
Durchmesser (µm)	100- 400	100–300, 300-500	100–300, 300-500	90–180, 180–300
CE Mark	Ja, November 2005, erneuert Oktober 2015	Ja, November 2003, erneuert Dezember 2014	Ja, März 2013	Ja, Mai 2013
FDA Zulassung	Nein	Nein	Nein	Nein

* *Formerly manufactured by CeloNova Biosciences, Inc.*

BPH = benign prostatic hyperplasia; FDA = Food and Drug Administration; PVA = polyvinyl alcohol; UK = United Kingdom.

Methoden

Im folgenden Bericht gingen wir der folgenden Frage nach: Ist PAE im Vergleich zur chirurgischen Resektion (TURP oder offene Prostatektome) bei Patienten mit BPH mit mäßigen bis schweren LUTS sicherer bezüglich unerwünschter Ereignisse und wirksamer in Bezug auf Veränderungen in *International Prostate Symptom Scores* (IPSS), *International Index of Erectile Function* (IIEF) Score und Lebensqualität Scores?

Fragestellung

Zur Beantwortung der Forschungsfragen, wurde eine systematische Literatursuche in vier Datenbanken durchgeführt (Medline via Ovid, Embase, Cochrane Library, CRD-Database). Ergänzend erfolgten eine Suche in Studienregistern und eine Studienanfrage bei den Herstellern. Die Daten der entscheidungsrelevanten Endpunkte wurden aus den einzelnen Studien zusammengefasst und nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet. Die Studienauswahl, Datenextraktion sowie die Bewertung der methodischen Qualität der Studien wurde von zwei Autorinnen unabhängig voneinander durchgeführt.

systematische Literatursuche in 4 Datenbanken; Anfrage bei den Herstellern; Datenextraktion und -bewertung durch 2 AutorInnen

Klinische Wirksamkeit und Sicherheit

Endpunkte Wirksamkeit: HRQoL, IPSS, IIEF

Die folgenden Endpunkte wurden für die Bewertung als entscheidend definiert, um eine Empfehlung zur Wirksamkeit von PAE abzuleiten: gesundheitsbezogene Lebensqualität Scores (HRQoL), IPSS, IIEF und Krankheitsprogression.

Endpunkte Sicherheit: Mortalität, AE, SAE

Die folgenden Endpunkte wurden für die Bewertung als entscheidend definiert, um eine Empfehlung zur Sicherheit von PAE abzuleiten: (Schwerwiegende) Unerwünschte Ereignisse und Prozedur-bedingte Mortalität.

Ergebnisse

Verfügbare Evidenz

Wirksamkeit: nur vergleichende Studien

Sicherheit: auch Beobachtungsstudien > 150 Pts.

Insgesamt konnten drei vergleichende Studien identifiziert werden, die zur Beurteilung der Wirksamkeit herangezogen wurden: Sie verglichen die PAE mit der transurethralen Resektion der Prostata (TURP) oder mit der offenen Prostatektomie. Für die Beurteilung der Sicherheit wurden auch Beobachtungstudien (einarmige-Studien mit mindestens 150 Teilnehmern) und vergleichende Studien (mit unterschiedlichen Partikeln und Patientenpopulationen) herangezogen.

Wirksameit: 2 RCTs (n = 144) 1 matched-pairs Studie (n = 160) Sicherheit: zusätzlich: 2-einamige Studien + 3 weitere vergleichende Studien (n = 1.168)

Es konnten zwei RCTs, die PAE mit TURP (n = 144) verglichen, und eine Matched-Pairs-Studie, in der PAE mit der Prostatektomie (n = 160) verglichen wurde, eingeschlossen werden. Zusätzlich zu diesen Studien wurde ein RCT, der PAE-Partikelgrößen verglich, zwei nicht-randomisierte Studien, die verschiedene Patientenpopulationen verglichen und zwei einarmige Studien für die Sicherheitsergebnisse herangezogen werden. Die zusätzlichen Studien umfassten insgesamt 1.168 Patienten.

Patientencharakteristika Schweregrad: IPSS ≥ 18 Alter: 63-73/83 J

In allen eingeschlossenen Studien (mit nur einer Ausnahme) wurden Patienten mit schweren Symptomen (IPSS ≥ 18) behandelt. Das Durchschnittsalter aller Patienten lag zwischen 63 und 73 Jahren (in den Studien zur Wirksamkeitsbeurteilung) und zwischen 63 und 83 Jahren (in den Studien zur Sicherheitsbeurteilung).

Klinische Wirksamkeit

PAE vs TURP: niedrige Stärke der Evidenz

widersprüchliche Ergebnisse in 2 RCTs

Die Stärke der Evidenz für die Wirksamkeit von PAE im Vergleich zu TURP war niedrig. Die eingeschlossenen RCTs machten widersprüchliche Aussagen in Bezug auf Verbesserungen bei IPSS und HRQoL nach 12 Monaten. Die größere Studie (n = 114) berichtete keine signifikanten Unterschiede zwischen PAE und TURP nach 12 oder 24 Monaten, während die kleinere Studie (n = 30) TURP nach 12 Monaten in Bezug auf IPSS, HRQoL und IIEF begünstigte. Die Progression der Krankheit ist ein seltenes Ereignis und es kann deshalb kein Ergebnis aus den zwei Studien abgeleitet werden. Daten zu langfristigen (> 24 Monate) Ergebnissen liegen keine vor.

PAE vs OP: niedrige Stärke der Evidenz signifikant bessere Ergebnisse in IPSS und IIEF zugunsten von OP

Die Stärke der Evidenz für die Wirksamkeit von PAE im Vergleich zur offenen Prostatektomie war ebenfalls niedrig. Die Matched-Pairs Studie berichtet für die offene Prostatektomie eine signifikant größere Verbesserung im IPSS (-19,04 vs. -13,58, $P < 0,01$) nach 12 Monaten im Vergleich zur PAE. Auch in dieser Studie gilt, dass die Progression der Erkrankung ein seltenes Ereignis ist und keine Schlussfolgerungen abgeleitet werden können.

Sicherheit

PAE vs TURP und OP: moderate/niedrige Stärke der Evidenz

Die Stärke der Evidenz für die Sicherheit von PAE im Vergleich zu TURP und offener Prostatektomie war moderat. Ein RCT fand bei PAE signifikant mehr unerwünschte Ereignisse als bei TURP, während die Matched-Pair-Studie (niedrige Evidenz) deutlich weniger unerwünschte Ereignisse für PAE im Vergleich zu offener Prostatektomie berichtete. Es gab keine berichteten Fälle von peri-operativer Mortalität in den eingeschlossenen Studien. Schwerwiegende Nebenwirkungen waren selten und beinhalteten einen Fall von Blasenwand-Ischämie und acht technische oder klinische Komplikationen über die gesamte Sicherheitspopulation (n = 1.472).

sehr wenige SAE (n = 8) bei 1.472 Pts

hauptsächlich geringfügige AE

Die in allen Studien am häufigsten berichteten Nebenwirkungen, die mit PAE assoziiert waren, waren geringfügig, einschließlich Brennen/Schmerzen beim Urinieren (10,2 % bis 100,0 %), akute Harnverhaltung (8,6 % bis 30,8 %), Blut im Urin (0,0 % bis 13,3 %), Blut im Samen (1,25 % bis 11,2 %) und Harnwegsinfektionen (1,25 % bis 4,8 %).

Laufende Studien

5 RCTs zu PAE vs. TURP
1 RCT PAE vs. medizinische Therapie
1 RCT PAE vs. Placebo
1 Registerstudie

nur 12 Monats FU

Derzeit laufen fünf RCTs zu PAE im Vergleich zu TURP bei Patienten mit mäßigen bis schweren LUTS, deren Ende für Februar 2021 geplant ist. Darüber hinaus gibt es eine laufenden RCT zu PAE im Vergleich mit medizinischer Therapie (ebenfalls mit Ende 2021) und ein RCT zu PAE im Vergleich mit Placebo (September 2017). Zusätzlich zu den geplanten RCTs läuft eine Register-Studie (n = 300) zum Vergleich PAE, TURP und offene Prostatektomie (September 2017). Die meisten der laufenden Studien sind auf 12-Monats-Follow-up begrenzt, und füllen damit nicht die aktuelle Evidenzlücke zur langfristigen Sicherheit und Wirksamkeit von PAE.

Diskussion und Empfehlung

geringe Stärke der Evidenz und widersprüchliche Ergebnisse für Wirksamkeits- und Sicherheitsendpunkte

wenige SAE
„realistische" Patienten

Die Stärke der Evidenz zur Abschätzung der Sicherheit und Wirksamkeit der PAE ist niedrig. Die verfügbaren RCTs berichteten über widersprüchliche Ergebnisse für die wichtigsten Wirksamkeitsendpunkte und die unerwünschten Ereignisse wurden in den eingeschlossenen Studien sehr unterschiedlich erhoben und berichtet. Ein einheitliches System zur Dokumentation oder Bewertung der Schwere von unerwünschten Ereignissen war nicht vorhanden. Allerdings waren schwere unerwünschte Ereignisse selten. Die Studienpopulationen waren in Bezug auf Symptome, Erkrankung und Demographie weitgehend verallgemeinerbar.

Mittel- bis langfristige Follow-up-Daten zu Sicherheits- und Wirksamkeitsendpunkten > 12-24 Monate liegen nicht vor. Es ist derzeit unbekannt, ob das Injizieren von Embolisationspartikeln in die Prostata-Arterie zu langfristigen Nebenwirkungen führen kann oder gar eine Kontraindikation für eine chirurgische Folgeintervention darstellt.

verschiedene Medizinprodukte zur Embolisation: keine Evidenz zu Unterschieden

In den eingeschlossenen Studien kamen verschiedene Medizinprodukte zur Embolisation zur Anwendung, die sich in Form, Material und Größe unterscheiden. Ein RCT verglich die Ergebnisse von Partikeln unterschiedlicher Größe und fand keinen signifikanten Unterschied in der Wirksamkeit und Sicherheit. Es ist unbekannt, ob Partikelmaterial, -form oder -größe einen Einfluss auf die langfristigen Ergebnisse haben.

vorliegende Evidenz reicht nicht aus

Die vorliegende Evidenz reicht nicht aus, um zu beweisen, dass PAE [bei erwachsenen Patienten mit mäßigen bis schweren LUTS] gleich wirksam, aber sicherer ist als der/die Komparator/en TURP und/oder offene Prostatektomie.

Re-Evaluation 2021

Neue Studienergebnisse aus den laufenden RCTs werden die Beurteilung erheblich beeinflussen. Eine neuerliche Evaluierung wird im Jahr 2021 vorgeschlagen, sofern Ergebnisse aus RCTs vorliegen.

1 Scope

1.1 PICO question

PIKO-Frage

Is prostate artery embolisation (PAE) in comparison to surgical resection in patients with benign prostatic hyperplasia (BPH) with moderate-to-severe lower urinary tract symptoms (LUTS) safer concerning adverse events, and as effective concerning changes in International Prostate Symptom Scores (IPSS), International Index of Erectile Function (IIEF) score, and quality of life scores?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion criteria

Population	Second line treatment of benign prostatic hyperplasia (BPH) with moderate-to-severe lower urinary tract symptoms (LUTS). Moderate-to-severe LUTS are defined by an International Prostate Symptom Score (IPSS) score of 8 to 35 [1]. International classification of diseases (ICD)-10-CM code: N40.1 Benign prostatic hyperplasia with lower urinary tract symptoms. Contraindications/exclusions: prostate cancer, bladder cancer, neurogenic bladder. MeSH Terms: Prostatic Hyperplasia [C12.294.565.500], Lower Urinary Tract Symptoms [C23.888.942.343]
Intervention	Prostate artery embolisation (PAE), delivered percutaneously by an interventional radiologist. There are several embolisation agents currently available in Europe for PAE, including: • Embosphere® trisacryl microspheres (Merit Medical Systems Inc, USA) • Embozene™ polymer microspheres (Boston Scientific, USA) • Bead Block® polyvinyl alcohol hydrogel (Biocompatibles UK Ltd, UK) • PVA Foam Embolisation Particles (Cook Medical, USA) MeSH Term: Embolisation, Therapeutic [E02.520.360, E02.926.500]
Control	Surgical resection of the prostate by any method, including but not limited to trans-urethral resection of the prostate (TURP), and open prostatectomy [2]. MeSH Term: Prostatectomy [E04.950.774.860.625] **Rationale**: International guidelines on the recommended use of PAE are not currently available, due to the experimental nature of the intervention. Recently published clinical trials have investigated PAE as an alternative to surgical resection, as it is more invasive than medical therapy [3, 4]. Surgical resection is a second-line therapy for BPH following failure of, or intolerance to, medical therapy – or as a first-line therapy in cases of absolute indications for surgery [2].

Outcomes	
Effectivness	*Clinical endpoints include changes from pre- to post- treatment measurements:* • Decrease in Health-related quality of life (HRQoL) scores • Decrease in International Prostate Symptom Scores (IPSS) • Increase in International Index of Erectile Function (IIEF) scores • Disease progression or recurrence requiring re-intervention after 12 months *Surrogate outcomes include changes from pre- to post- treatment measurements of:* • Peak urinary flow (Qmax) • Post-voiding residual urine volume **Rationale**: BPH primarily affects quality of life (QoL) through LUTS. Therefore, the main outcomes of interest are direct meaures of QoL, including IPSS, IIEF and QoL questionnaire scores [5, 6]. Surrogate outcomes of QoL related to function are also relevant.
Safety	• Adverse events (including an increase in IPSS or HRQoL, and a decrease in IIEF) • Re-intervention rates within 12 months • Procedure-related mortality **Rationale**: PAE is claimed to be less invasive than surgical resection. Perioperative and long-term adverse events are the main safety outcomes associated with surgical resection and PAE, and are therefore the key safety outcomes for this assessment [7]. Procedure-related mortality is a rare but important outcome of TURP and open prostatectomy (0.32% and 0.51% respectively), and is therefore relevant to this assessment [8, 9].
Study design	
Effectivness	Systematic reviews of randomised and non-randomised controlled trials (with an AMSTAR quality score of > 5). In the absence of systematic reviews, the following will be included: • Randomised controlled trials • Prospective non-randomised controlled trials Excluded: conference abstracts, narrative reviews, letter to the editor, author response, case reports, case series.
Safety	Systematic reviews of randomised and non-randomised controlled trials, and prospective case series with > 150 participants (with an AMSTAR quality score of > 5). In the absence of high quality systematic reviews, the following will be included: • Randomised controlled trials • Prospective non-randomised controlled trials • Prospective/retrospective single-arm studies with >150 participants Excluded: conference abstracts, narrative reviews, letter to the editor, author response, case reports, retrospective and prospective single-arm studies with ≤ 149 participants.

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What are prostate artery embolisation and surgical resection?
B0002	What is the claimed benefit of prostate artery embolisation in relation to surgical resection?
B0003	What is the phase of development and implementation of prostate artery embolisation and surgical resection?
B0004	Who administers prostate artery embolisation and the surgical resection and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use prostate artery embolisation and surgical resection?
B0009	What supplies are needed to use prostate artery embolisation and surgical resection?
A0020	What is the marketing authorisation status of prostate artery embolisation?
A0021	What is the reimbursement status of prostate artery embolisation?

Health problem and Current Use	
Element ID	**Research question**
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for benign prostatic hyperplasia?
A0004	What is the natural course of benign prostatic hyperplasia?
A0005	What are the symptoms and the burden of disease for the patients with benign prostatic hyperplasia?
A0006	What are the consequences of benign prostatic hyperplasia for society?
A0024	How is benign prostatic hyperplasia currently diagnosed according to published guidelines and in practice?
A0025	How is benign prostatic hyperplasia currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is prostate artery embolisation utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of prostate artery embolisation on mortality?
D0005	How does prostate artery embolisation affect symptoms and findings (severity, frequency) of benign prostatic hyperplasia?
D0006	How does prostate artery embolisation affect progression (or recurrence) of benign prostatic hyperplasia?
D0011	What is the effect of prostate artery embolisation on patients' body functions?
D0016	How does the use of prostate artery embolisation affect activities of daily living?
D0012	What is the effect of prostate artery embolisation on generic health-related quality of life?
D0013	What is the effect of prostate artery embolisation on disease-specific quality of life?
D0017	Was the use of prostate artery embolisation worthwhile?

Safety	
Element ID	**Research question**
C0008	How safe is prostate artery embolisation in comparison to surgical resection?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of prostate artery embolisation?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0007	Are prostate artery embolisation and surgical resection associated with user-dependent harms?

2.2 Sources

Description of the technology, health problem and current use

Quellen

- Background publications identified in hand search of databases
- Clinical practice guidelines identified by hand search of databases
- Documentation provided by the manufacturers

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 9th of December 2016 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

Kontaktaufnahme mit Herstellern

The systematic search was limited to articles published in English or German, no other search limits were applied. After deduplication, overall 375 citations were screened for inclusion. The specific search strategy employed for each database can be found in the Appendix.

insgesamt 376 Publikationen identifiziert

Manufacturers of two embolisation agents (Bead Block and Embozene) submitted 19 publications, from which no new citations were identified.

One additional article was found by hand searching reference lists of included studies, resulting in overall 376 hits.

2.4 Flow chart of study selection

Literaturauswahl

Overall 536 hits were identified. The references were screened by two independent researchers and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

In total, nine existing systematic reviews on PAE were identified, but were subsequently excluded due to limitations related to quality and selection criteria. Quality appraisal scores for the identified reviews are presented in Table A-5. Consequently, only primary studies were included in this review.

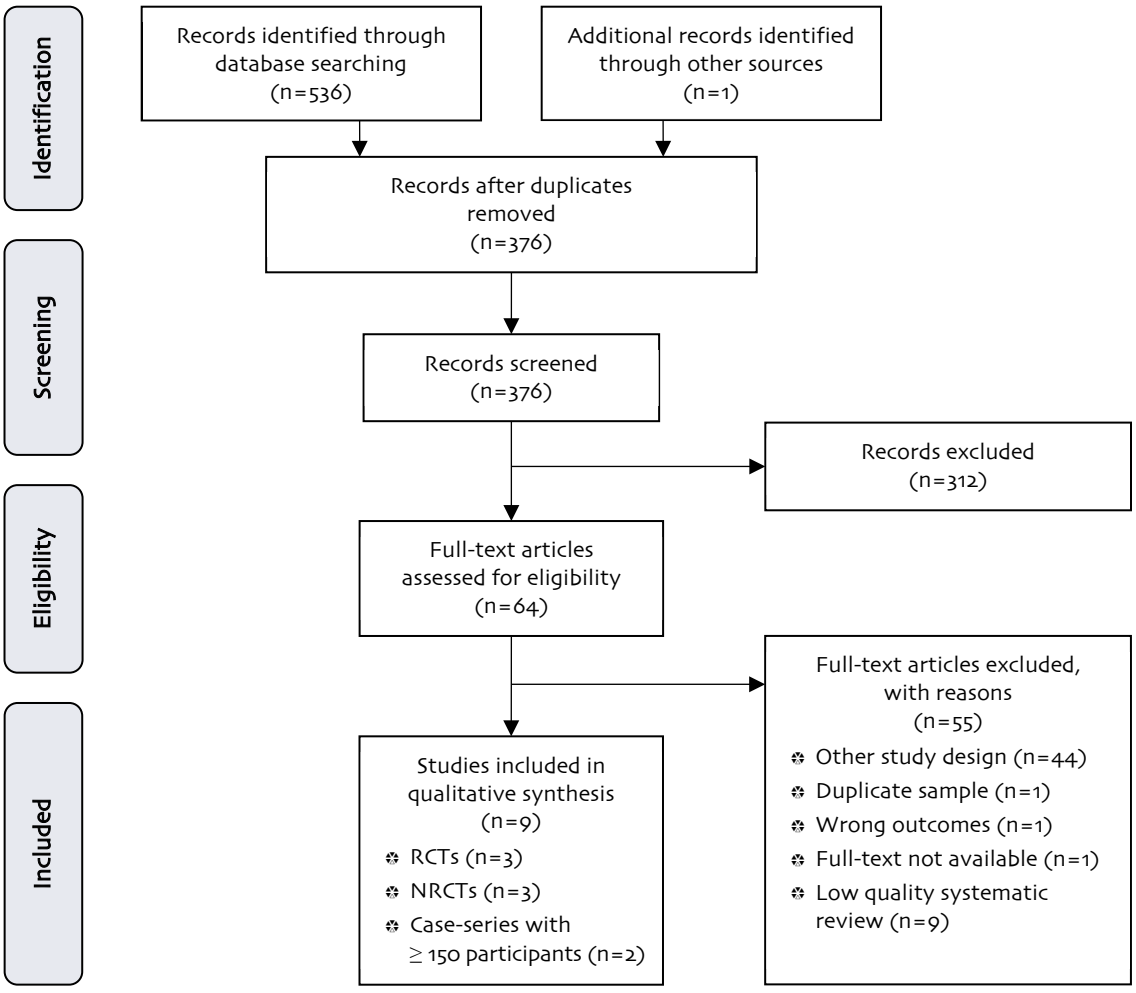


Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Datenextraktion

Data from the included studies was systematically extracted into data extraction tables based on study design and research question (See Appendix Tables A-1 to A-4). The extracted data were validated for accuracy by an independent researcher. Direct evidence of the effect of PAE on quality of life outcomes were identified in the search strategy. Therefore, no further analysis of the data was conducted.

Qualitätsbeurteilung

SR: AMSTAR
RCT: Cochrane Risk of Bias v1.0
nRCT: ROBINS-I

Two independent researchers conducted quality appraisal, with differences settled via consensus. Quality appraisal was conducted with different tools, depending on study design (see Appendix Tables A-5 to A-8). Systematic reviews were appraised using the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) quality appraisal tool [10]. Randomised studies were evaluated using the Cochrane Risk of Bias v1.0 tool, and non-randomised studies were evaluated using the ROBINS-I tool (formerly the ACROBAT-NRSI tool) [11], as advised by the EUnetHTA Joint Action 2 reports on internal validity of randomised [12] and non-randomised studies [11]. Single arm case series were evaluated using the Institute of Health Economics checklist [13].

2.6 Synthesis

Zusammenfassung der Evidenz:

GRADE

The research questions were answered in plain text format, with reference to GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence tables included in Table 7-1, and the data-extraction tables in the Appendices (See Appendix Tables A-1 to A-4) [14]. No quantitative analysis of outcomes was performed, due limited number of RCTs (N = 2) and the small number of patients included.

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What are prostate artery embolisation (PAE) and surgical resection?

PAE is a minimally invasive alternative to surgical resection, which aims to shrink the prostate gland rather than remove it. In PAE, an interventional radiologist inserts a catheter into the femoral artery at the top of the leg, and guides the catheter to the prostate arteries. A solution of microscopic particles is injected through the catheter, which mechanically block the prostate arteries and partially reduce the blood supply (see Figure 3-1). The reduction in blood supply induces ischaemic necrosis, causing the gland to soften and shrink in size over time [15].

PAE minimal-invasive Methode: Katheter wird zur Prostata-Arterie eingeführt

mikroskopische Partikel injiziert: Teilblockade der Blutzufuhr

ischämische Nekrose: Drüsen schrumpfen

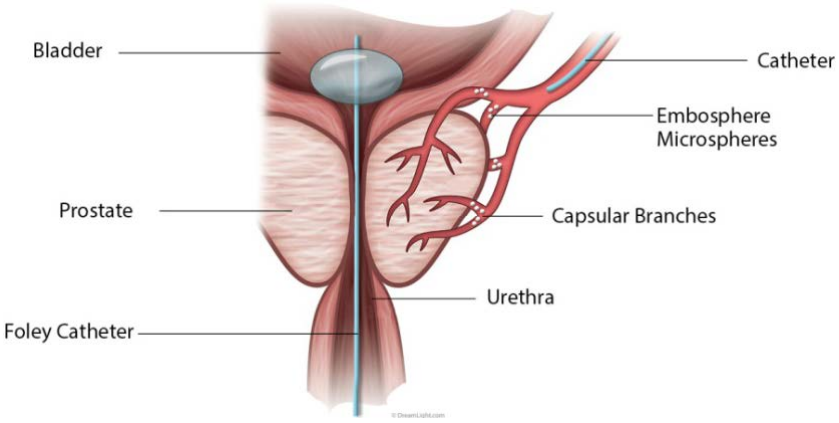


Figure 3-1: Diagram of PAE microspheres being inserted into the prostate arteries through a catheter. (Source: Merit Medical Systems, Inc. [16])

There are a number of embolisation agents currently available for PAE, ranging in shape (spherical and non-spherical), material (polyvinyl alcohol, trisacryl gelatin, or hydrogel with a proprietary coating), and diameter (80 µm to 500 µm) [3, 4, 17-22]. While the particle size and materials differ, they all operate under the same biomechanical principle of providing long-term occlusion of the prostate arteries. The characteristics of currently available embolisation agents are outlined in Table 3-1.

Embolisations-Partikel: unterschiedlich in Form, Größe und Material

aber gleiches biomechanisches Prinzip

Surgical treatments for LUTS suggestive of BPH involve the removal of adenomatous prostate tissue, for the relief of symptoms and obstruction. There are many methods for ablating adenomatous prostate tissue and de-obstruction of the prostatic urethra, the most common of which include open prostatectomy and TURP.

chirurgische Therapie von LUTS: am Gebräuchlichsten: TURP

Open prostatectomy involves the surgical removal of obstructive prostate tissue through an incision in the lower abdomen. Due to its high level of invasiveness, open prostatectomy is usually reserved for patients with very large prostates, or in concomitant diseases such as bladder diverticulitis, or in whom TURP or transurethral holmium or thulium laser enucleation is not possible [2, 5].

offene Prostatektomie: invasivste Methode

zahlreiche weitere Methoden

Table 3-1: Characteristics of embolisation agents used to treat benign prostatic hyperplasia

Device characteristics	Embozene™ Microspheres	Bead Block®	Embosphere® Microspheres	PVA Foam Embolisation Particles
Manufacturer	Boston Scientific Corporation*	Biocompatibles UK Ltd	Merit Medical Systems Inc	Cook Medical
Material	HydroGel core with Polyzene-F coating	Polyvinyl alcohol hydrogel	Trisacryl with gelatin	Polyvinyl alcohol
Shape	Spherical particles	Spherical particles	Spherical particles	Non-spherical particles
Diameter (µm) used to treat BPH	100- 400	100–300, 300-500	100–300, 300-500	90–180, 180–300
CE Mark	Yes, November 2005, renewed October 2015	Yes, November 2003, renewed December 2014	Yes, March 2013	Yes, May 2013
FDA Approval	No	No	No	No

** Formerly manufactured by CeloNova Biosciences, Inc.*

BPH = benign prostatic hyperplasia; FDA = Food and Drug Administration; PVA = polyvinyl alcohol; UK = United Kingdom.

TURP: Entfernung von adenomatösem Gewebe

In TURP, a resectoscope is inserted into the penile urethra and forwarded to the prostatic urethra, where the adenomatous tissue is removed piece by piece (See Figure 3-2). TURP is currently the most common method for prostate reduction to treat LUTS suggestive of BPH and obstruction, due to its lower level of invasiveness compared to open prostatectomy.

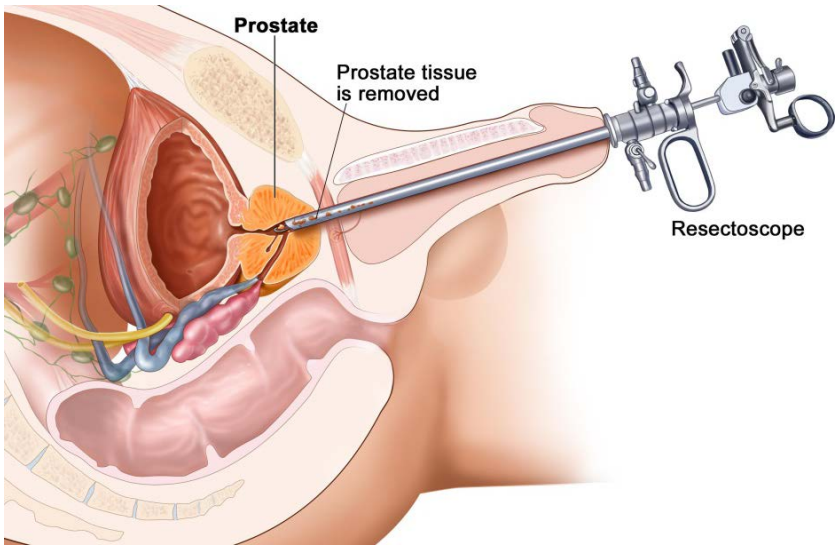


Figure 3-2: Trans Urethral Resection of the Prostate using a resectoscope (Source: National Cancer Institute [23])

B0002 – What is the claimed benefit of prostate artery embolisation in relation to surgical resection?

Prostate artery embolisation is thought to result in fewer complications and adverse events than surgical resection, while providing equivalent improvements in quality of life and symptom relief [24]. As PAE is less invasive than resection, it requires less recovery time in hospital, with patients often able to return home on the same day as the procedure [15].

PAE verspricht weniger Komplikationen und AE als bei chirurgischen Methoden

B0003 – What is the phase of development and implementation of prostate artery embolisation and surgical resection?

PAE was first established in the 1970s as a method for controlling prostate bleeding, either due to prostate carcinoma, or perioperative complications [25, 26]. It was first described as a potential therapy for treating bladder outlet obstruction due to BPH in the early 2000s [27], and was first trialled in human patients in 2010 [28]. In 2013, PAE was considered an experimental procedure by the National Institute of Clinical Excellence (NICE) in the United Kingdom, largely due to the lack of comparative studies with long-term follow-up [29]. PAE is currently not included in European or American urology guidelines for the treatment of BPH [2,5], but is currently disseminating in clinical practice around the world.

PAE seit 1970er

NICE 2013: experimentell

in urologischen Leitlinien derzeit nicht als Therapieoption erwähnt

Both TURP and open prostatectomy are well-established methods for the treatment of benign prostatic hyperplasia. Open prostatectomy is a surgical treatment for moderate-to-severe LUTS secondary to BPH, first described in 1894, and is the current standard of care for patients with prostates larger than 80mL [2, 30]. TURP is currently the most common procedure for treating BPH in patients with prostate volume of 30-80mL, due to its lower level of invasiveness compared to open prostatectomy [2].

TURP und offene Prostatektomie (OP) etablierte Methoden

TURP: Standard

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers prostate artery embolisation and surgical resection and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use prostate artery embolisation and surgical resection?

B0009 – What supplies are needed to use prostate artery embolisation and surgical resection?

Prostate artery embolisation is conducted by a highly skilled interventional radiologist in an outpatient setting. The procedure is technically demanding, and requires a high degree of expertise. Patients treated with PAE are typically treated as day-patients, and are able to return home within 4 hours after the procedure [20]. In the rare event of a serious adverse event, patients may be kept overnight. PAE involves the use of a microcatheter and wire, embolisation agents, local or epidural anaesthesia, and intraoperative fluoroscopy. The average procedure time reported in the literature ranges between 70 to 90 minutes [19, 20, 31], due to the challenging task of placing a catheter in the target arteries. As a result, prolonged fluoroscopy exposure may be required.

PAE: intervenioneller Radiologe

tagesklinisch

technisch anspruchsvoll: braucht Erfahrung

Surgical resection of the prostate is conducted by a urologist in an inpatient hospital setting. Due to the invasive nature of surgical resection, patients are required to be admitted to hospital for several days in order to aid recovery, and manage potential post-surgical adverse events [9]. Surgical equipment

chirurgische Resektion: Urologe

stationäre Aufnahme

varies depending on the type of procedure. TURP is conducted using a resectoscope, while open prostatectomy is conducted using standard surgical equipment. Resection is most commonly conducted under general or epidural anaesthesia.

Regulatory & reimbursement status

A0020 – What is the marketing authorisation status of the technology?

vier unterschiedliche Embolisations-Partikel mit CE Mark:

Four embolisation agents used for PAE have received marketing authorisation in the European Union:

Embozene™ Microspheres

1. Embozene™ Microspheres, manufactured by Boston Scientific (Marlborough, USA), received an EC Certificate in November 2005, which was renewed in October 2015 (CE 425968). The device was approved for use in patients with BPH. The manufacturer supplied the EC Certificate.

Bead Block®

2. Bead Block® polyvinyl alcohol hydrogel, manufactured by Biocompatibles UK Ltd (London, UK), received an EC Certificate (CE 79333) in November 2003, updated in December 2014. This device was approved for the treatment of BPH. The manufacturer supplied the EC Certificate.

Embosphere®

3. Embosphere® trisacryl microspheres, manufactured by Merit Medical Systems Inc. (South Jordan, USA), received an EC Certificate in March 2013 for the relief of symptoms related to BPH [32].

PVA Foam Embolisation Particles

4. PVA Foam Embolisation Particles, manufactured by Cook Medical (Bloomington, USA), received an EC Certificate in May 2013 for the treatment of BPH [33].

keine FDA Zulassung

None of the four embolisation agents used for PAE holds a FDA-approval (see Table 3-1).

A0021 – What is the reimbursement status of prostate artery embolisation?

bislang keine Refundierung in Österreich

Currently, PAE is not included in the Austrian hospital benefit catalogue, and therefore is not reimbursed by the Austrian health care system.

4 Health Problem and Current Use

Overview of the disease or health condition

A0002 – What is the disease or health condition in the scope of this assessment?

The scope of this assessment includes BPH causing moderate-to-severe LUTS. Benign prostatic hyperplasia is a non-cancerous growth of the prostate gland, leading to different degrees of enlargement in most cases. Benign enlargement of the prostate gland, bladder outlet obstruction, and LUTS are independent factors, in any combination referred to as "LUTS suggestive of BPH". The symptoms of BPH are classified as voiding, storage or post-micturition problems [34].

gutartige Prostatahyperplasie (BPH): Vergrößerung der Prostata verursacht mäßige bis schwere Symptome des unteren Harntraktes (LUTS)

Lower urinary tract symptoms suggestive of BPH can be classified as mild to severe based on the IPSS, a self-administered patient questionnaire on symptoms and quality of life. A score of 8 to 19 is considered moderate LUTS and a score of 20 to 35 is considered severe [1].

LUTS Schweregrad: gemessen mit IPSS

A0003 – What are the known risk factors for benign prostatic hyperplasia?

The strongest risk factors for BPH are age over 50 years, and obesity. Other, weaker risk factors include: race (black men are more likely than Caucasian men to have larger prostate volume and more moderate-to-severe LUTS; Asian men are less likely than Caucasian and black men to have BPH); higher free prostate specific antigen (PSA) levels; heart disease; family history of bladder cancer; prostatitis; use of beta-blockers and lack of physical exercise [35, 36].

Risikofaktoren: Alter >50 J, Übergewicht

A0004 What is the natural course of benign prostatic hyperplasia?

Approximately 20 to 30 per cent of patients with BPH experience disease progression (symptom progression of ≥ 3 points), but the speed and likelihood of progression varies greatly between individuals [2, 37, 38]. If left untreated, BPH can cause acute urinary tract infections, bladder calculi, bleeding from prostatic varicose veins, hydronephrosis and renal failure. Approximately 2.5 per cent of men with symptomatic BPH who are not treated will develop acute urinary retention, and another 6 per cent will require invasive therapy, over a 5-year time-frame [39, 40]. Older age, previous diagnosis of BPH or erectile dysfunction, and lower high-density lipoprotein cholesterol, testosterone and low socioeconomic status have been observed to predict progression of LUTS [34].

20-30 % der Männer Progression ≥ 3 Punkte

unbehandelt: mögliche Folgeerkrankungen

Effects of the disease or health condition on the individual and society

A0005 – What are the symptoms and the burden of disease or health condition for the patient?

There are three main categories of LUTS due to BPH, including storage, voiding and post-micturition symptoms. Enlargement of the prostate caused by BPH can be related to a range of LUTS including [34, 36]:

typische Symptome von LUTS:

- Urinary frequency; — Harndrang
- Urinary urgency; — Blasenentleerungsstörungen
- Nocturia (the need to get up frequently at night to urinate);

Postmiktionsträufeln

- Incomplete bladder emptying (the feeling of persistent residual urine regardless of the frequency of urination);
- The need to strain or push to initiate and maintain urination to fully evacuate the bladder;
- Decreased force of stream;
- Dribbling (the loss of small amounts of urine due to a poor urinary stream);
- Other problems such as pain in the perineum, painful urination and blood in the urine.

A0006 – What are the consequences of benign prostatic hyperplasia for society?

mäßige bis schwere LUTS:

häufiges Gesundheitsproblem unter Männern

3 in 4 Männern > 70J

hohe Krankheitslast, Kosten

Moderate-to-severe LUTS due to BPH is one of the most common medical conditions in men, affecting three in four men over the age of 70 [41]. BPH carries a large societal cost, in terms of direct medical treatments, as well as indirect losses in daily functioning caused by decreased quality of life [42].

It is difficult to estimate the overall cost of BPH to society, due to under-diagnosis and the absence of available data on disease prevalence and treatments. The majority of costs associated with BPH in Austria are related to outpatient care, but the total financial impact is unclear [43]. Estimates of the total economic burden due to BPH vary greatly in the literature. In the United Kingdom, BPH has been estimated to cost £180.8 million in 2008 [44], while studies from the United States range between $2.3 to $4 billion in 2006 [41]. The burden of BPH is likely to rise in future, as it is strongly associated with age [45].

Current clinical management of the disease or health condition

A0024 – How is benign prostatic hyperplasia currently diagnosed according to published guidelines and in practice?

initiales Assessment von LUTS:

Patientengeschichte Symptome und Schweregrad (IPSS) Risikofaktoren

The initial assessment of LUTS is conducted by reviewing the patient's history, including questions about risk factors, voiding problems (hesitancy, intermittency, weak stream, straining, incomplete emptying and post-void dribbling) and storage problems (urinary frequency, nocturia and urgency) [2, 6, 7]. Symptom score questionnaires, such as IPSS, are used during the initial assessment to quantify the severity of a patient's LUTS. If voiding symptoms are present, a frequency and volume voiding diary may be used to document and clarify symptoms, in order to exclude polyuria [7].

körperliche Untersuchung

Stufendiagnostik:

digito-rektale Untersuchung

Uro-Sonografie

Physical examination is also used to identify potential causes of LUTS, through bladder palpitation and inspection, and digital rectal examination (DRE) [2, 6]. The DRE is used to assess anal sphincter tone, estimate the size of the prostate and assess for prostate nodules or rectal masses. Transrectal ultrasound may be used to complement DRE, as it is able to provide a more accurate measure of prostate volume. Other imaging tests, such as urinary tract and renal ultrasound, are only recommended if the patient has one of the following [7]:

- Chronic retention;
- Recurrent urinary tract infection/haematuria;
- Renal insufficiency;
- Urolithiasis; or
- History of prior urinary tract surgery.

Urinanalyse

PSA

Initial evaluations also typically include a urinalysis (assessment of the urine for the presence of blood, leukocytes, bacteria, protein or glucose) and prostate specific antigen (PSA) testing. PSA testing should only be used in appropriate circumstances: not as a general screening tool, not in men > 75 years and not when life expectancy is less than 10 years [2, 6, 7]. Cystoscopy may be used in certain cases, and urodynamic studies may be used to demonstrate obstruction and to exclude neurogenic bladder disorders [2].

Diffentialdiagnostik

The combination of clinical history, physical examination, symptom score questionnaires, and testing aims to provide a differential diagnosis of LUTS due to BPH, and exclude other potential causes of symptoms, including: overactive bladder, prostatitis, prostate cancer, urinary tract infection (UTI), bladder cancer, neurogenic bladder and urethral stricture. If necessary, biopsy may be required to exclude prostate cancer and confirm the diagnosis of BPH.

A0025 – How is benign prostatic hyperplasia currently managed according to published guidelines and in practice?

Europäische Gesellschaft für Urologie: Leitlinie 2016 zu LUTS

The European Association of Urology (EAU) published a clinical practice guideline for patients with LUTS including benign prostatic obstruction in 2016 [2, 6]. In patients with moderate-to-severe LUTS, who are not indicated for surgery, symptoms are initially managed with lifestyle advice and medical therapy. The choice of pharmaceutical depends on the predominant symptoms and treatment preferences, and includes [2]:

diverse Medikamente

- α_1-blocker;
- muscarinic receptor antagonist;
- 5α-reductase inhibitor;
- phosphodiesterase type 5 inhibitors; or
- combination therapy.

medikamentöse Therapie: Re-Evaluation alle 6-12 Monate

Medical therapy and response should be reassessed every 6 to 12 months. Behavioural management programmes may also be used in addition to medical therapy, to decrease symptoms and improve quality of life [2].

chirurgisches Management von LUTS:

Surgical management of LUTS is indicated for patients with an absolute indication for surgery, that have not responded to medical therapy, or do not want medical therapy but request active treatment [2]. Absolute indications for surgery include intractable urinary retention and renal insufficiency caused by benign prostatic obstruction [46]. Relative indications for surgery include [2, 46]:

nur bei absoluter Indikation

relative Indikationen

- moderate-to-severe LUTS (i.e. IPSS score greater than 8);
- recurrent cystitis;
- overflow incontinence
- bladder stones or diverticula;
- failure or intolerance to medical therapy;
- recurrent urinary tract infection; and
- treatment-resistant macroscopic haematuria due to BPH.

Therapiewahl hängt auch von Größe der Prostatadrüse und Kardio-Risiko ab

In patients with a low cardiovascular risk, the choice of first-line surgical therapy depends on the size of the prostate gland (See Figure 4-1) [2]:

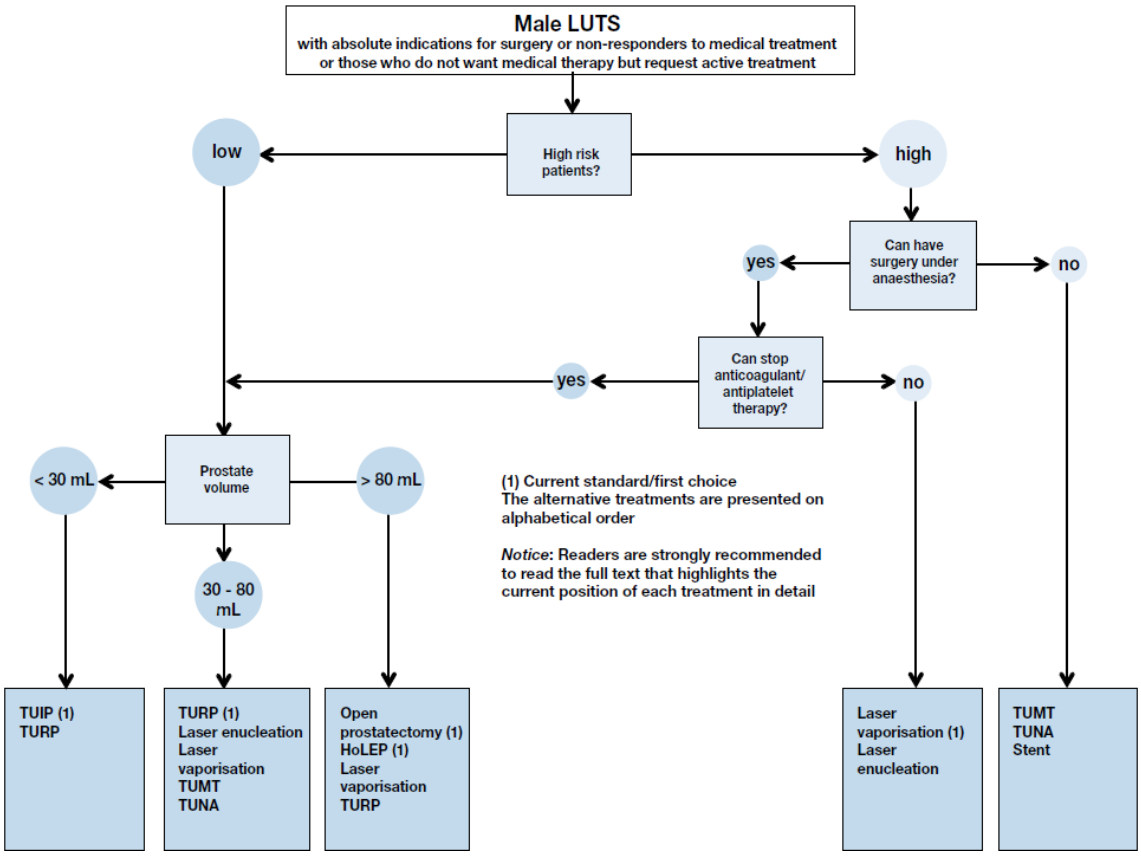
- < 30mL: transurethral incision of the prostate (TUIP)
- 30-80mL: transurethral resection of the prostate (TURP)
- > 80mL: open prostatectomy or holmium laser enucleation (HoLEP)

weitere mögliche Therapien

Alternative surgical treatments for low-risk patients include transurethral vaporisation of the prostate (TUVP), transurethral needle ablation (TUNA), laser enucleation, transurethral microwave therapy (TUMT), GreenLight laser vaporisation or plasmakinetic enucleation [2, 6].

bei hohem Kardio-Risiko

In patients with a high cardiovascular risk, who cannot undergo anaesthesia or stop anticoagulant therapy, the surgical options include laser vaporisation, laser enucleation, TUMT, TUNA and prostatic sent [2, 6].



TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate; TUMT = transurethral microwave therapy; TUNA = transurethral needle ablation; HoLEP = holmium laser enucleation.

Figure 4-1: Clinical management algorithm for the surgical treatment of moderate-to-severe LUTS (Source: EAU Guideline [2])

Target population

A0007 – What is the target population in this assessment?

Zielpopulation PAE: IPSS > 8 Punkte

The target population in this assessment includes patients with BPH causing moderate-to-severe LUTS. Moderate-to-severe LUTS are defined as an IPSS of 8 to 35 [47]. Patients with LUTS caused by bladder abnormalities (e.g. bladder cancer, neurogenic bladder), or prostate cancer, were excluded from this assessment.

A0023 – How many people belong to the target population?

Global estimates of BPH vary depending on how BPH is defined, and whether or not it is associated with moderate or severe LUTS [7]. The prevalence of histological BPH has been estimated to be 42 per cent of men aged between 51 and 60, and 82 per cent of men aged between 71 and 80 [48].

Prävalenz:
42 % Männer 51-60 J,
82 % 71-80 J

In 2009, a population-based cross-sectional survey of 1,926 Austrian men aged 15 to 89 years found that 64.6 per cent reported some degree of LUTS [45]. Moderate-to-severe LUTS was reported by 9.1 per cent of respondents, reflecting an IPSS score greater than eight, and quality of life described as 'dissatisfied' or worse. It is important to note that BPH is not the only condition that contributes to LUTS. Therefore, this is likely an overestimate of the size of the eligible population.

nicht alle symptomatisch
österr. Umfrage zu LUTS: 9,1 % aller Männer jeglichen Alters

A0011 – How much is prostate artery embolisation utilised?

The current and likely utilisation of PAE in Austria is difficult to estimate, due to the current stage of development of the intervention. The Diagnosis-Related Group codes (LKF JG020 TURP, JG030 open prostatectomy, JG040 laparoscopic prostatectomy) for the main comparators, TURP and prostatectomy, were claimed for 5,983 (TURP), 150 (open prostatectomy) and 22 (laparoscopic prostatectomy) procedures in 2015 respectively. While PAE will not replace TURP or open prostatectomy entirely, this is a reasonable estimate for the size of the population that may be eligible for PAE therapy in Austria.

2015:

TURP 5.983 x und offene Prostatektomie 150 x

in Österreich abgerechnet

5 Clinical effectiveness

5.1 Outcomes

für eine Empfehlung entscheidende Endpunkte

The following outcomes were defined as *crucial* to derive a recommendation:

- International Prostate Symptom Scores (IPSS)
- Health-related quality of life scores (HRQoL)
- International Index of Erectile Function (IIEF)
- Disease progression or recurrence

International Prostate Symptom Scores (IPSS)

The **International Prostate Symptom Score** is a 7-question survey instrument used to screen for, diagnose and measure the symptoms of BPH [1]. Patients are asked to score how frequently they had symptoms of incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia for the past month, on a scale from 0 (not at all) to 5 (always). Scores are then added to give an overall symptom score, whereby 1-7 indicates mild LUTS, 8-19 indicates moderate LUTS, and 20-35 indicates severe LUTS. In the included studies clinical success was often defined as an reduction in IPSS score of 3 to 7 points [21, 22], or a 25 per cent reduction from baseline IPSS [17, 18, 20]. A 3-point reduction in IPSS indicates a slight improvement in symptoms, and a 5-point reduction indicates a moderate improvement [39].

Health-related quality of life scores (HRQoL)

In addition to the symptom-specific questions, the IPSS questionnaire includes one question on **health-related quality of life** caused by the urinary symptoms of BPH. The question asks patients how they would feel if they had to spend the rest of their life with their current urinary symptoms. Answers are scored using a 6-point scale ranging from 0 (delighted) to 6 (terrible) [1]. A reduction in baseline QoL score of 1 point, or a score lower than 3 (mixed), was most commonly used as a marker for clinical success [17, 18, 20-22].

International Index of Erectile Function (IIEF)

International Index of Erectile Function, is derived from a self-reported questionnaire of male sexual function [49]. Unlike IPSS, IIEF is not specific to BPH; it is a generic score for measuring erectile dysfunction. There are two versions of the IIEF instrument, which include either 15 (IIEF) or 5 (IIEF-5) questions related to sexual function. The questionnaires ask patients to score questions about how they felt over the previous six months in relation to sexual intercourse. Scores for each question range from 1 to 5, and the sum of all scores provides the overall IIEF score. An IIEF score ranging from 1 to 7 indicates severe sexual dysfunction, 8 to 11 moderate, and 12 to 16 mild. Minimum clinically important differences in IIEF scores were not defined in the included studies.

Fortschreiten der Erkrankung

Disease progression or recurrence was evaluated by symptom recurrence or progression significant enough to require intervention more than 12 months after the procedure (e.g. an increase in IPSS $\geq$ 4 points) [50].

Surrogate outcomes for health-related quality of life were deemed important, but not crucial to derive a recommendation:

- Peak urinary flow (Qmax)
- Post-voiding residual urine volume

5.2 Included studies

Wirksamkeit: vergleichende Studien: 2 RCTs, 1 nRCT (matched-pairs comparison)

To evaluate the effectiveness of PAE, we included RCTs and non-randomised studies comparing PAE to either TURP or open prostatectomy. Two RCTs comparing PAE to TURP [3, 19], and one propensity score matched-pairs comparison of PAE compared to open prostatectomy were identified [4].

Study characteristics

Studienorte: China, Portugal, Italien
keine Sponsoren genannt
12-24 Monate Follow-up

The RCTs were conducted in China [19] and Portugal [3], and the matched-pairs trial was conducted in Italy (open prostatectomy group) and Russia (PAE group) [4]. None of the included studies reported a financial sponsor or relevant conflicts of interest. The length of follow-up ranged between 12 [3, 4] and 24 months [19]. Long term comparative data for clinical outcomes beyond 24 months is not currently available.

unterschiedliche Embolisationspartikel verwendet
aber alle: 300 to 500 µm

The RCTs that compared PAE to TURP used different embolisation particles. One RCT used spherical Embosphere Microspheres (Merit Medical Systems Inc., USA) [3], while the other used non-spherical PVA foam embolisation particles (Cook Medical, USA) [19]. Both particle types had the same average diameter (300 to 500µm).

Patient characteristics

2 RCTs:
144 Pts PAE vs. TURP
1 nRCT:
160 Pts PAE vs. OP

1RCT underpowered

In total, there were 144 patients included in the RCTs comparing PAE and TURP (72 vs. 72) [3, 19], and 160 patients in the matched-pairs trial comparing PAE to open prostatectomy (80 vs. 80) [4]. Of note, the RCT reported by Carnevale et al (2016) only included 15 patients in each treatment arm, and was unlikely to be sufficiently powered to detect clinically important differences in the critical outcomes [3]. In contrast, Gao et al (2014) estimated the sample size required to detect a 3-point difference in IPSS with 80% power and a type I error $\alpha < 0.5$ [19]. Russo et al (2015) reported their study was sufficiently powered, but did not provide a power calculation [4].

Alter: 63-73 J

The mean age of participants in each treatment arm was equivalent within each study, as well as across included studies (range 63.5 ± 8.7 to 68.4 ± 6.1).

Schweregrad:
2x IPSS ≥ 18, 1 IPSS > 8

The included trials reported similar inclusion and exclusion criteria, with the exception of symptom severity. One RCT included severe LUTS only (IPSS > 18) [3], whereas the other included moderate-severe LUTS (IPSS > 8) [19]. As a result, the mean baseline IPSS scores for patients treated with PAE (25.3 ± 3.6 vs. 22.8 ± 5.9) and TURP (27.6 ± 3.2 vs. 23.1 ± 5.8) were higher in Carnevale et al (2016) compared to Gao et al (2014).

Detailed patient and study characteristics of the included studies are presented in Table A-1 and Table A-2.

5.3 Results

Treatment effect on mortality of BPH

D0001 – What is the expected beneficial effect of prostate artery embolisation on mortality?

keine Ereignisse berichtet

Mortality is a very rare outcome of BPH [51]. None of the included studies reported any cases of overall or disease-specific mortality, in either the PAE or prostatectomy groups.

Treatment effect on morbidity of BPH

D0005 – How does prostate artery embolisation affect symptoms and findings (severity, frequency) of benign prostatic hyperplasia?

This research question was answered using the direct outcomes of IPSS.

PAE compared to TURP

PAE vs TURP

widersprüchliche Ergebnisse bei IPSS

kein Unterschied bei IIEF

In regards to urinary symptoms, both RCTs reported significant improvements in IPSS in both the PAE and TURP groups at 12 months [3, 19]; however, Gao et al (2014) reported no significant difference between PAE and TURP in relation to the change in mean IPSS score at 12 months (-13.8 vs. -14.1, $P > 0.05$) or 24 months (-15.6 vs. -16.3 $P > 0.05$) [19]. In contrast, Carnevale et al (2016) reported significantly greater improvements in the mean IPSS scores in the TURP group at 12 months (-12.5 vs. -21.5, $P < 0.001$) [3]. There was no significant difference in mean IIEF-5 score between PAE and TURP at 12 months (12.6 vs. 16.1, P > 0.05) [3].

PAE compared to open prostatectomy

PAE vs OP

signifikant bessere Ergebnisse in IPSS zugunsten von OP

In the matched-pairs trial, open prostatectomy was associated with a significantly greater improvement in mean IPSS (-13.58 vs. -19.04, $P < 0.01$) at 12 months compared to PAE [4].

D0006 – How does prostate artery embolisation affect progression (or recurrence) of benign prostatic hyperplasia?

keine Evidenz zu Fortschreiten der Krankheit

No evidence was found to answer this research question.

Function

D0011 – What is the effect of prostate artery embolisation on patients' body functions?

gemessen mit Surrogaten

Surrogate outcomes for obstruction, peak urinary flow (Qmax) and post-voiding residual volume, were used to evaluate this research question.

PAE compared to TURP

PAE vs TURP

widersprüchliche Ergebnisse

The RCTs reported conflicting results regarding functional outcomes. The larger RCT reported no significant difference in Qmax (+14.3 mL/s vs. +15.8 mL/s, P > 0.05) or post-voiding residual volume (-107.5 cm^3 vs. -100.2 cm^3, P > 0.05) at 12 months [19]. In contrast, the smaller RCT reported TURP to be associated with significantly greater improvements in Qmax (+3.1 mL/s vs. +17.4 mL/s, P < 0.0001) and mean post-voiding residual volume (-64.7 cm^3 vs. -70.0 cm^3, $P = 0.006$) at 12 months [3].

PAE compared to open prostatectomy

PAE vs OP signifikant bessere Ergebnisse zugunsten von OP

In the matched-pairs comparison, open prostatectomy was associated with significantly greater improvements in Qmax (+9.29 mL/s vs. +15.97 mL/s, P < 0.01) and mean post-voiding residual volume (-45.87 cm^3 vs. -58.8 cm^3, P < 0.01) at 12 months compared to PAE [4].

D0016 – How does the use of prostate artery embolisation affect activities of daily living?

keine Evidenz

Research question D0005 addressed the impact of PAE on sexual function and symptoms, in relation to improvements in IPSS. No other evidence was found to answer this research question.

Health-related quality of life

D0012 – What is the effect of prostate artery embolisation on generic health-related quality of life?

keine Evidenz

No evidence was found to answer this research question.

D0013 – What is the effect of prostate artery embolisation on disease-specific quality of life?

This research question was assessed using the disease-specific quality of life question included in the IPSS questionnaire.

PAE compared to TURP

PAE vs TURP

widersprüchliche Ergebnisse bei disease-specific QoL

Gao et al (2014) reported a significant improvement in disease-specific quality of life in both PAE and TURP groups at 12 and 24 months ($P = 0.001$) [19]. However, there was no significant difference between PAE and TURP in relation to the change in quality of life at 12 months (-2.9 vs -2.8, $P > 0.05$) or 24 months (-3.2 vs. -3.2, $P > 0.05$).

Carnevale et al (2016) reported a significant improvement in disease-specific quality of life in both groups at 12 months ($P < 0.05$) [3]; however, TURP was associated with a greater improvement compared to PAE at 12 months (-2.5 vs -3.7, $P = 0.004$).

PAE compared to open prostatectomy

PAE vs OP keine Evidenz

No evidence was found to answer this research question.

Patient satisfaction

D0017 – Were patients satisfied with the technology?

keine Evidenz

No evidence was found to answer this research question.

6 Safety

6.1 Outcomes

The following outcome was defined as *crucial* to derive a recommendation:

für eine Empfehlung entscheidende Endpunkte

- Adverse events (including minor adverse events, major adverse events, decrease in IIEF, and increase in IPSS and HRQoL)
- Re-intervention rates within 12 months
- Procedure-related mortality

In accordance with the EUnetHTA guidelines on Safety outcomes, adverse events are defined as "any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device" [52]. Adverse events, including total, major and minor adverse events, which may occur during the perioperative period or during long-term follow-up, are the most common safety issues associated with PAE and the comparator interventions. These outcomes are non-specific in order to be inclusive of all types of adverse events that may be related to PAE or surgical resection. The most frequently reported adverse events have been highlighted.

geringfügige und schwerwiegende Nebenwirkungen

Reintevention

Prozedur-bedingte Mortalität

Procedure-related mortality (typically measured at 30 days post-procedure) is a rare but potential outcome of TURP and open prostatectomy (0.32% and 0.51% respectively) [8, 9]. Therefore, this outcome is relevant to a comparison of the relative safety of PAE and surgical resection.

Prozedur-bedingte Mortalität relevant bei TURP und OP

6.2 Included Studies

To evaluate the safety of PAE, RCTs, non-randomised studies and prospective single-arm studies with at least 150 patients were selected for inclusion. In addition to the studies described in the Section 5 (Clinical Effectiveness), the following studies were identified:

Sicherheit: vergleichende Studien (wie oben + 3) und 2 Beobachtungsstudien >150 Pts

- One RCT comparing PAE with 100µm particles to 200µm particles [17];
- Two prospective non-randomised studies comparing PAE in different patient groups (age, prostate size) [21, 22];
- Two retrospective single-arm studies with more than 150 patients [18, 20].

1 RCT mit PAE verschiedene Partikelgrößen

2 nRCT: verschiedene Patientengruppen

2 single-arm Studien

Study characteristics

Three of the additional safety studies were conducted in Portugal [17, 18, 20] and two in China [21, 22]. The three studies from Portugal were from the same group of authors; however, only one study reported conflicts of interest – a key author received a consulting fees from Cook Medical (USA), the manufacturer of the embolisation agent [17, 18, 20]. The remaining studies did not report any significant conflicts of interest.

Zusätzliche Studienorte: China, Portugal

1 x CoI

6-78 Monate Follow-up

The reported follow-up periods ranged between 6 to 78 months, with most studies reporting a mean or median follow-up period of between 6 to 24 months [17, 18, 20-22]. The largest retrospective single-arm study (n = 630) reported a median follow-up period of 24 months, with the longest duration of observation of 78 months [20].

unterschiedliche Embolisationspartikel verwendet

Four studies investigated the PVA particles (Cook Medical, USA) [17, 20-22], two used Bead Block (Biocompatibles, USA) [18], and one used the Embozene Microspheres (Boston Scientific, USA) [20].

heterogene Berichterstattung der AE

Safety outcomes were recorded variably across studies, resulting in heterogeneous reporting of outcomes and adverse event severity. The grading system used to evaluate the severity of adverse events included the Clavien–Dindo classification system [4, 19, 22], the Society of Interventional Radiology reporting criteria [17, 18, 20, 21], or the National Cancer Institute Common Toxicity Criteria for Adverse Events [3].

Patient characteristics

304 Pts aus RCTs/nRCT (Wirksamkeit) + 1.168 Pts zu Sicherheitsendpunkten = 1.472 Pts

The additional studies included a total of 1,168 patients that underwent PAE [17, 18, 20-22]. The mean age of patients in the additional safety trials ranged between 63.4 to 82.5 years. All of the additional trials included patients with severe LUTS (IPSS ≥ 18) that was refractory to medical therapy for at least 6 months.

Alter 63 bis 83 J Schweregrad: IPSS ≥ 18 Doppelpublikation von Pts

There was overlap between the sample populations of Wang et al (2016) [21] and Wang et al (2016) [22], and also Bilhim et al (2013) [18], Bilhim et al (2016) [17] and Pisco et al (2016) [20]. These studies reported different analyses on patients recruited during overlapping enrolment periods.

Patients and study characteristics of the included studies are presented in Table A-1 to Table A-4.

6.3 Results

Patient safety

Cooo8 – How safe is prostate artery embolisation in comparison to surgical resection?

keine Evidenz zu perioperativer Mortalität

None of the included studies reported any cases of perioperative mortality in either the PAE or prostatectomy groups. Specific adverse event rates associated with PAE studies are presented in Table A-1 to Table A-4.

PAE compared to TURP

PAE vs TURP unterschiedliches Reporting der AE

Safety outcomes could not be pooled, due to variability in the measurement and reporting of complications between studies.

1 RCT: signifikant mehr Komplikationen mit PAE

mehr schwerwiegende AE: nicht signifikant

In the larger RCT, PAE was associated with significantly more overall complications compared to TURP (n = 30 of 57 [52.6%] vs. 17 of 57 [29.8%], $P = 0.03$) [19]. There were more major complications in the PAE group (technical and clinical failures) compared to the TURP group (transurethral resection syndrome, clinical failure, bladder neck stenosis), but this was not statistically significant (n = 8 of 57 [14.0%] vs. 4 of 57 [7.0%], $P = 0.28$). This study defined clinical failures as *"persisting severe symptoms (decrease in IPSS*

of ≤ 25%, IPSS ≥ 18, decrease of QoL score by ≤ 1, and QoL score of ≥ 4), and/or peak urinary flow increase of less than 2.5 mL and peak urinary flow of 7 mL/sec or lower after the procedure" [19].

PAE was associated with higher rates of minor complications (n = 22 of 57 [38.6%] vs. 13 of 57 [22.8%], $P = 0.1$), including post-embolisation syndrome (n = 6 of 54 [11.1%] vs 0 of 53 [0.0%], $P = 0.038$), and acute urinary retention (n = 14 of 54 [25.9%] vs 3 of 53 [5.7%], $P = 0.004$). There were no other significant differences between study groups. The most commonly reported complications associated with PAE were acute urinary retention (n = 14 of 54 [25.9%]), post-embolisation syndrome (n = 6 of 54 [11.1%]), and clinical failure (n = 5 of 53 [9.4%]). Both PAE and TURP were associated with a decrease in IIEF score, however this was not statistically significant (-1.7 vs. -3.6, P = NR) [3].

mehr leichte AE: signifikant

The smaller RCT reported specific perioperative complications for PAE and TURP, but did not conduct a comparison between groups [3]. Overall, 15 PAE patients experienced 22 complications, and 15 TURP patients experienced 23 complications. The authors noted no major complications in the PAE group, and one in the TURP group (intraoperative damage to venous sinus and rupture of prostatic capsule, treated successfully with Foley balloon catheter for 2 hours post-resection to control bleeding). The most commonly reported complications associated with PAE were local pain or moderate urethral burning for 3-4 days post-procedure (n = 15 of 15 [100%]), reduced ejaculate (n = 2 of 15 [13.3%]) and hematuria (n = 2 of 15 [13.3%]).

1 RCT

kein Unterschied

In total, 9.4 to 13.3 per cent of patients that underwent PAE and 0.0 to 3.8 per cent of patients that underwent TURP required re-intervention at or before 12 months [3,19].

mehr Reinterventionen mit PAE

PAE compared to open prostatectomy

In the matched-pairs comparison study, PAE was associated with significantly fewer minor adverse events (n = 7 of 80 [8.75%] vs. 25 of 80 [26.25%], $P < 0.05$), compared to open prostatectomy [4]. Similarly, PAE was associated with a small increase in IIEF-5 (i.e. a clinical improvement), while open prostatectomy resulted in a significant decrease (+0.68 vs. -4.22, $P < 0.01$) [4]. No patients in either treatment group required re-intervention [4].

PAE vs OP
nRCTs:
signifikant weniger AE mit PAE
keine Reintervention in beiden Gruppen

Safety of PAE from observational trials

Only one major complication, a case of bladder wall ischaemia treated with surgical intervention, was reported in the observational trials [20]. The remaining studies reported no serious adverse events. The most consistently reported minor adverse events were hematospermia (range 7.5% to 11.2%) [17, 18, 20-22], hematuria (range 7.5% to 11.7%) [17, 18, 20-22], and urinary tract infection (range: 2.5% to 4.8%) [17, 18, 20]. Specific adverse events are reported in further detail in response to question C0002 and C0005.

nur 1 SAE in großen Beobachtungsstudien
leichte AE:
Hämospermie 8-11 %
Hämaturie 8-12 %
Harnwegsinfekt: 3-5 %

C0002 – Are the harms related to dosage or frequency of applying prostate artery embolisation?

While not related explicitly to "dosage", one RCT compared the outcomes of patients treated with PAE using two different sizes of particles [17]. The study did not find any significant differences in complication rates between patients treated with 100µm or 200µm particles. The most commonly reported adverse events were irritative voiding (n = 12 of 40 [30.0%] vs. 16 of 40 [40.0%], $P > 0.99$), dysuria (n = 8 of 40 [20.0%] vs. 9 of 40 [22.5%], $P > 0.99$), and hematospermia (n = 3 of 40 [7.5%] vs. 2 of 40 [5.0%], $P > 0.99$).

100 µm oder 200 µm Partikel:
kein signifikanter Unterschied bei Komplikationen

The reported radiation dose associated with PAE ranged between 1130.5 ± 267.1 dGy/cm^2 [19] and 2401 dGy/cm^2 (range: 655-9202) [18].

C0004 – How does the frequency or severity of harms change over time or in different settings?

keine Evidenz

No evidence was found to answer this research question.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of prostate artery embolisation?

nRCT:

mehr Komplikationen bei Pts > 75 J

A non-randomised comparison of PAE in different age groups reported that patients aged 75 years or older experienced significantly more urethral burning (n = 10 of 52 [19.2%] vs. 12 of 105 [11.4%], $P = 0.027$), and acute urinary retention (n = 16 of 52 [30.8%] vs. 9 of 105 [8.6%], $P = 0.031$) compared to patients aged under 75 years [22]. There was no significant difference in IIEF score from baseline to 12 months in either group.

mehr Komplikationen bei Pts > 80 mL Prostatavolumen

A non-randomised comparison of PAE in patients with different sized prostates reported that patients with a prostate volume greater than 80mL reported significantly more urethral burning (n = 10 of 60 [16.7%] vs. 5 of 49 [10.2%], $P = 0.04$) and acute urinary retention (n = 17 of 60 [28.3%] vs. 5 of 49 [10.2%], $P = 0.02$) compared to patients with prostate volume between 50mL and 80mL [21].

There were no significant differences reported for other complications in either study.

C0007 – Are prostate artery embolisation and surgical resection associated with user-dependent harms?

keine Evidenz

No evidence was found to answer this research question.

7 Quality of evidence

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [14] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [14].

GRADE uses four categories to rank the strength of evidence:

hoch, moderat, niedrig, sehr niedrig

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in Table 7-1, Table 7-2 and Table 7-3.

Stärke der Evidenz: niedrig

Overall the strength of evidence for the effectiveness of PAE in comparison to TURP is low. The strength of evidence for the effectiveness of PAE in comparison open prostatectomy is moderate. The strength of evidence for the safety of PAE in comparison to TURP open prostatectomy is moderate.

Table 7-1: Evidence profile: effectiveness and safety of PAE compared to TURP

No. of studies/patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy – PAE vs. TURP							
Mean change in quality of life (QoL) score at 12 months*							
2/144 [19] [3]	RCT	-2.9 vs. -2.8, *P* > 0.05 [19] -2.5 vs. -3.7, *P* = 0.004 (favours TURP) [3]	-1 [A B]	-1	direct	-1 [C]	Low
Mean change in International Prostate Symptom Score (IPSS) at 12 months*							
2/144 [19] [3]	RCT	-13.8 vs. -14.1, *P* > 0.05 [19] -12.5 vs. -21.5, *P* < 0.001 (favours TURP) [3]	-1 [A B]	-1	direct	-1 [C]	Low
Symptom recurrence or progression requiring re-intervention after 12 months							
NR							
Safety – PAE vs. TURP							
Major complications (total)							
2/144 [19] [3]	RCT	8 (14%) vs. 4 (7%), *P* = 0.3 [19] 0 (0%) vs. 2 (13.3%), *P* = NR [3]	-1 [A B]	no important inconsistency	direct	-1 [C]	Moderate
Re-intervention within 12 months							
1/114 [19]	RCT	9.4% to 13.3% vs. 0.0% to 3.8% (*P* = NA)	no serious limitation	-1	direct	no	Moderate
Mean change in International Index of Erectile Function (IIEF) score at or before 12 months							
1/30 [3]	RCT	-1.7 vs. -3.6, *P* = NR (favours PAE)	-1 [B]	NA	direct	-1 [C]	Low
Minor complications (total)							
1/114 [19]	RCT	22 (38.6%) vs. 13 (22.8%), *P* = 0.1	-1 [A]	NA	direct	no	Moderate
Minor complications – hematospermia							
1/30 [3]	RCT	1 (6.7%) vs. 0 (0%), *P* = NR	-1 [B]	NA	direct	-1 [c]	Low
Minor complications – hematuria							
2/244 [19] [3]	RCT RCT	0 (0%) vs. 4 (7.5%), *P* = 0.12 [19] 2 (13.3%) vs. 1 (6.7%), *P* = NR [3]	-1 [A B]	no important inconsistency	direct	-1 [C]	Moderate
Minor complications – urinary tract infection							
1/114 [19]	RCT	1 (1.9%) vs. 2 (3.8%), *P* = 0.99	-1 [A]	NA	direct	no	Moderate

* *Reported P values were for the between group comparison at 12 months. Baseline scores were equivalent between groups.*

[A] *Overall risk of bias was scored "High" due to unclear allocation concealment, and unadjusted confounding due to additional treatments before or after the intervention.*

[B] *Overall risk of bias was scored "High" due to unclear randomisaton method, unclear allocation concealment, unclear patient and physician blinding, unclear selective reporting, and differences between groups at baseline in relation to Qmax, bladder contractility and prostate volume.*

[C] *Very small patient numbers in each treatment arm in [3]*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency

Indirectness: 0: direct, no uncertainty

Table 7-2: Evidence profile: efficacy and safety of PAE compared to open prostatectomy

No. of studies/patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy – PAE vs. Open Prostatectomy							
Mean change in quality of life (QoL) score at 12 months							
NR							
Mean change in International Prostate Symptom Score (IPSS) at 12 months							
1/160 [4]	nRCT	-13.58 vs. -19.04, *P* < 0.01 (favours TURP)	no serious limitation	NA	direct	-1 [A]	Low
Symptom recurrence or progression requiring re-intervention after 12 months							
NR							
Safety – PAE vs. Open Prostatectomy							
Major complications (total)							
1/160 [4]	nRCT	0 (0.0%) vs. 3 (3.75%), *P* = NR	no serious limitation	NA	direct	-1 [A]	Low
Re-intervention within 12 months							
1/160 [4]	nRCT	No patients in either arm required re-intervention	no serious limitation	NA	direct	-1 [A]	Low
Mean change in International Index of Erectile Function (IIEF) score at 12 months							
1/160 [4]	nRCT	+0.68 vs. -4.22, *P* < 0.01 (favours PAE)	no serious limitation	NA	direct	-1 [A]	Low
Minor complications (total)							
1/160 [4]	nRCT	7 (8.75%) vs. 21 (26.25%), *P* < 0.05 (favours PAE)	no serious limitation	NA	direct	-1 [A]	Low
Minor complications - hematospermia							
1/160 [4]	nRCT	1 (1.3%) vs. 0 (0.0%), *P* = NR	no serious limitation	NA	direct	-1 [A]	Low
Minor complications – hematuria							
1/160 [4]	nRCT	0 (0.0%) vs. 4 (5.0%), *P* = NR	no serious limitation	NA	direct	-1 [A]	Low
Minor complications – urinary tract infection							
1/160 [4]	nRCT	1 (1.3%) vs. 3 (3.8%), *P* = NR	no serious limitation	NA	direct	-1 [A]	Low

[A] *This study was conducted in two different countries (Italy and Russia), so while patients were matched with propensity scores, it is difficult to determine whether or not the clinical scenario in which patients were treated was comparable.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations
Inconsistency: NA: Not applicable (only one trial)
Indirectness: 0: direct, no uncertainty
Other modifying factors: -1: study design

Table 7-3: Evidence profile: safety of PAE from observational trials

No. of studies/patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Safety - PAE							
Major complications							
1/630 [20]	Prospective case series	Bladder wall ischemia: 1 (0.2%)	-1 [A]	NA	direct	no	Low
Minor complications – total							
NR							
Minor complications – hematospermia							
5/1168 [17,18,20-22]	Cohort studies and prospective case series	Range 7.5% to 11.2%	no serious limitation	No important inconsistency	-1 [B]	-1 [C]	Very low
Minor complications – hematuria							
5/1168 [17,18,20-22]	Cohort studies and Prospective case series	Range: 7.5% to 11.7%	no serious limitation	No important inconsistency	-1 [B]	-1 [C]	Very low
Minor complications - urinary tract infection							
3/856 [17,18,20]	Cohort studies and Prospective case series	Range: 2.5% to 4.8%	no serious limitation	No important inconsistency	-1 [B]	-1 [C]	Very low

[A] *Single arm case series design. No additional modifying factors were applied.*

[B] *The research questions targetted specific populations (i.e. varying prostate sizes, older vs. younger age) and particle sizes that may not reflect clinical practice.*

[C] *There was considerable sample overlap between two pairs of studies (Wang and Wang, Bilhim and Pisco).*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations
Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency
Indirectness: 0: direct, no uncertainty; -1: some uncertainty
Other modifying factors: -1: imprecise data

8 Discussion

Benign prostate enlargement is a significant contributor to the overall burden of disease in men over the age of 50. PAE is a novel method for treating the symptoms related to BPH, by reducing the blood supply to the prostate gland and causing it to shrink over time. Currently, at least four embolisation agents have received market approval in the European Union (i.e. CE mark) for the treatment of BPH; however, none of these devices have received approval by the United States FDA for this indication. In this review, we sought to identify the current evidence for the safety and effectiveness of PAE at treating the symptoms of BPH, compared to existing therapies – TURP and open prostatectomy.

BPH bedeutsame Krankheitslast bei Männern > 50 J

PAE neue Methode derzeit bereits 4 Embolisations-Partikel erhältlich CE-Mark, keine FDA Zulassung

Interpretation of findings

Study quality, validity and overall level of evidence

The overall level of evidence for the estimates of effectiveness of PAE was low.

Stärke der Evidenz zur Wirksamkeit: niedrig

The RCTs that investigated PAE compared to TURP had a high risk of bias due to small patient numbers, inadequate or unclear randomisation, lack of allocation concealment, and lack of blinding for both the patients and treating physicians [3, 19]. These RCTs reported conflicting results for the main effectiveness outcomes, which are not easily explained by differences in study design or inclusion criteria. One of the included RCTs was claimed to be adequately powered to detect clinically important differences in effectiveness outcome, but not rare outcomes such as major adverse events [19]. The other RCT was inadequately powered to detect differences in effectiveness or safety outcomes, with only 15 patients in each treatment arm [3], but reported significant differences between TURP and PAE nonetheless.

beide RTCs:

hohes Biasrisiko unklare Randomisierung und Gruppenzuweisung

1 kleiner RCT: underpowered

widersprüchliche Ergebnisse

The matched-pairs comparison of PAE and open prostatectomy was of low quality, limited mainly by a lack of blinding of clinicians and patients [4].

The remaining trials that were included for safety only, including one RCT, four non-randomised studies and two single-arm studies, had a high risk of bias. This was largely due to significant differences between groups at baseline, and missing follow-up data.

Stärke der Evidenz zur Sicherheit: niedrig bis sehr niedrig

Due to the inconsistent nature in which adverse events rates were reported across the included studies, it is difficult to provide strong recommendations for the likely adverse event rates associated with PAE. A consistent system for recording or rating the severity of adverse events was not present. As a result, it is currently unclear which adverse events are most likely to occur following treatment with PAE, and the rate at which they are likely to occur; however, severe adverse events were rare. Notably, there appears to be significant overlap between the study populations of Wang et al (2016) and Wang et al (2016) [21, 22], as well as Pisco et al (2016), Bilhim et al (2013) and Bilhim et al (2016) [17, 18, 20]. As a consequence of this overlap, there may be substantial duplication of data for the reported safety outcomes.

heterogene Bericherstattung der Komplikationen und Nebenwirkungen

unklare Datenlage

Doppelpublikation von Patienten

Long-term follow-up data of safety and effectiveness outcomes beyond 12-24 months were limited. It is currently unknown if the effects of PAE are sustained, or if placement of PAE particles may lead to long-term adverse events beyond 24 months.

langfristige Daten > 24 Monate liegen nicht vor

Factors that may influence the external validity

Mehrheit der Patienten in den Studien IPSS ≥ 18

The majority of included studies enrolled patients with an IPSS ≥ 18, while one RCT from China used a cut-off for IPSS ≥ 8 [19]. Current European guidelines for TURP and open prostatectomy state that comparator interventions are indicated for patients with moderate-to-severe LUTS, but it is unclear what thresholds are used to select patients for surgical treatments in Austrian clinical practice [2]. Although IPSS scores are used to triage patients for surgery, ultimately the decision to perform surgery is subjective, and is based on the patient's bother from symptoms. Other than this issue, patient selection and baseline demographic were reasonably consistent across the included studies, and reflect the intended population in clinical practice (i.e. contraindication or failure of medical therapy, symptoms not related to bladder or cancer, mean age 62.7 to 72.5 years).

Patientenselektion für Therapieoptionen ist regional unterschiedlich und subjektiv

Patientenkollektiv realistisch: bez. Alter und Schweregrad übertragbar

verschiedene Embolisations-Partikel: keine Evidenz zu Unterschieden bei Wirksamkeit/Sicherheit

Different embolisation agents were used in the included studies, including particles with a range of shapes, materials, and sizes. One RCT that compared outcomes of different sized particles found no significant difference in effectiveness or safety [17]. No direct evidence was identified to inform whether particle shape or material impact long-term outcomes.

Mehrheit der Patienten in den Studien aus China, Brazilien und Russland Umfeldbedingungen?

The comparators, TURP and open prostatectomy, were equivalent to existing therapies for PAE currently used in clinical practice. There was limited evidence from European populations; one trial was conducted in Italy, and two were conducted in Portugal. The remaining trials were conducted in China, Brazil and Russia. The issues affecting the applicability of the current evidence base for PAE to the Austrian context are presented in Table A-9.

Relevance of the outcomes assessed to the potential patient-relevant benefits

Outcome-Messung mit IPSS, IIEF und HRQoL valide

The effectiveness outcomes included in this review directly measured the impact of PAE on disease-related quality of life. The main effectiveness endpoints – IPSS, IIEF and HRQoL – were valid, and measured and reported in a consistent way. However, all three of these outcomes are measured with user questionnaires, which involve a level of subjectiveness; however, IPSS has been demonstrated to be a valid and reliable tool for measuring the severity and impact of LUTS on quality of life [1].

Evidence gaps and ongoing studies

mehrere Studien laufen derzeit

There is currently no long-term follow-up data for PAE relative to TURP or open prostatectomy beyond 24 months. It is also unclear if PAE is a contraindication for future surgery, due to the potential to dislodge the embolisation particles. Several ongoing studies, identified in Table A-10 to Table A-13, will provide additional data for the safety and effectiveness of PAE compared to TURP, medical therapy, and placebo; however, these comparative trials are planned to have up to 24 months follow-up, and as such will not fill this gap in the existing evidence. Only one, small (n = 50), single arm trial has a planned follow-up time greater than 24 months.

Langzeitoutcomes!

Limitation:

Studienauswahl > 150 Pts.

The inclusion criteria for this review excluded single-arm studies with less than 150 patients. It may be possible that case series studies with less than 150 patients, but with more than 24 months follow-up may exist to provide evidence for the long-term safety of PAE; however, such studies would be considered a very low level of evidence, and are likely to be underpowered to detect rare adverse events.

Conclusion

obwohl zahlreiche SR vorliegen, nur wenige vergleichende Primärstudien

Although many systematic reviews have investigated the safety and effectiveness of PAE for the treatment of BPH, there is limited primary data on its long-term clinical effectiveness and safety compared to existing therapies. The current evidence base comparing PAE to TURP includes two RCTs, with a total of 144 patients, which reported conflicting results. One additional trial of 160 patients compared PAE to open prostatectomy, which reported inferior effectiveness outcomes in the PAE group, but fewer complications.

Bedenken zur Langzeitsicherheit: Migration der Embolisations-Partikel

Concerns have been raised about the long-term safety of PAE, particularly in relation to the migration of embolisation particles, necrosis of surrounding tissues, and prolonged radiation exposure [53]. To date, these concerns have not been sufficiently addressed in the existing clinical trial data, due to the highly variable nature in which adverse events have been measured and reported. While the vast majority of adverse events associated with PAE are mild, the incidence of rare but severe complications is unclear.

PAE mag eine Therapielücke füllen

derzeit aber zuwenig Evidenz, um Vor-/ Nachteile abzuwägen

Prostate artery embolisation might reasonably fill a small gap in current clinical practice for patients with medically refractory BPH, moderate-to-severe LUTS, and who cannot or will not have surgery. In particular, men may choose to undergo PAE in order to minimise the potential negative impacts on sexual function associated with surgery. These patients have limited treatment alternatives; however, given the current status of the evidence for PAE, it is not recommended as an alternative to current therapies to treat BPH.

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence is not sufficient to prove, that prostate artery embolisation [in adult patients with moderate-to-severe LUTS] is as effective, but safer than the comparators TURP and open prostatectomy. New study results will potentially influence the effect estimate.

keine Evidenz, dass gleich wirksam wie TURP

The re-evaluation is recommended in 2021, after which time several ongoing clinical trials will be completed – noting that these trials will not provide additional long-term (i.e. >24 months) data on safety or effectiveness outcomes.

Re-valuation 2021

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Prostate artery embolisation: Results from randomised controlled trials of PAE compared to TURP

Author, year	Gao et al, 2014 [19]	Carnevale, 2016 [3]
Country	China	Brazil
Sponsor	Not stated	Not stated
Intervention	Unilateral or bilateral PAE with 355-500µm polyvinyl alcohol microspheres (Ivalon; Cook Medical, USA)	Unilateral PAE with 300-500µm tris-acryl gelatin microspheres (Embosphere; Merit Medical, USA)
Comparator	TURP under epidural anaesthesia	TURP under epidural anaesthesia
Study design	Prospective randomised controlled trial	Prospective randomised controlled trial
Number of patients (Int vs. Co)	57 vs. 57	15 vs. 15
Population	Patients with moderate-severe LUTS secondary to BPH	Patients with severe LUTS secondary to BPH
Inclusion criteria	IPSS >7; failed medical therapy with 2-week washout period; prostate volume 20-100mL; peak urinary flow <15mL/sec; written informed consent	Age >45 years; IPSS >19; symptoms refractory to medical therapy for at least 6 months; prostate volume between 30 and 90cm³ on magnetic resonance imaging; bladder obstruction confirmed by urodynamic examination
Exclusion criteria	Detrusor hyperactivity or hypocontractility at urodynamic study; urethral stricture; prostate cancer; diabetes mellitus; previous prostate, bladder neck and urethral surgery	Renal failure; bladder calculi or diverticula; suspected prostate cancer; urethral stenosis; neurogenic bladder disorders
Mean age of patients (yrs)	67.7 ± 8.7 vs. 66.4 ± 7.8, P = 0.4	63.5 ± 8.7 (range 46-75) vs. 66.4 ± 5.6 (range 55-78), P = 0.06
Follow-up	1, 3, 6, 12, and 24 months Mean 22.5 months	12 months (all patients)
Loss to follow-up, n (%)	6 months: 1 (1.8) vs. 2 (3.5) 12 months: 1 (1.8) vs. 1 (1.8)	NR
Outcomes		
Efficacy		
Mean QoL score (lower is better)	***Baseline:*** 4.8 vs. 4.6, *P* > 0.05 ***1 month:*** 3.7 vs. 2.8, *P* = 0.0001 ***3 months:*** 2.9 vs. 2.3, *P* = 0.0001 ***6 months:*** 2.2 vs. 2.3, *P* > 0.05 ***12 months:*** 1.9 vs. 1.8, *P* > 0.05 ***24 months:*** 1.6 vs. 1.4, *P* > 0.05	***Baseline:*** 4.7 ± 0.6 (4-6) vs. 4.6 ± 0.8 (4-6), *P* > 0.05 ***12 months:*** 2.2 ± 1.2 (range 1-4) vs. 0.9 ± 1.4 (range 0-4), *P* = 0.004
Mean IPSS (lower is better)	***Baseline:*** 24.7 vs. 24.3, *P* > 0.05 ***1 month:*** 19.2 vs. 13.7, *P* = 0.0001 ***3 months:*** 15.6 vs. 11, *P* = 0.0001 ***6 months:*** 12.8 vs. 11.3, *P* > 0.05 ***12 months:*** 10.9 vs. 10.2, *P* > 0.055 ***24 months:*** 8.7 vs. 8.4, *P* > 0.05	***Baseline:*** 25.3 ± 3.6 (19-30) vs. 27.6 ± 3.2 (20-34), *P* > 0.05 ***12 months:*** 12.8 ± 8.0 (range 2-27) vs. 6.1 ± 8.6 (range 0-27), *P* < 0.001
Mean IIEF score (higher is better)	NR	***Baseline:*** 14.3 ± 6.8 (0-21) vs. 12.5 ± 6.6 (0-21), *P* > 0.05 ***12 months:*** 12.6 ± 7.7 (range 0-21) vs. 16.1 ± 5.7 (range 5-12), *P* = NR

Author, year	Gao et al, 2014 [19]	Carnevale, 2016 [3]
Symptom recurrence requiring re-intervention, n (%)	5 (9.4%) vs. 2 (3.8%), *P* = 0.262	2 (13.3%) vs. 0 (0.0%), *P* = NR
Mean Qmax (mL/s) (higher is better)	***Baseline:*** 7.8 vs. 7.3, *P* > 0.05 ***1 month:*** 13.1 vs. 18.2, *P* = 0.0001 ***3 months:*** 17.3 vs. 21.4, *P* = 0.0001 ***6 months:*** 21.5 vs. 23.7, *P* > 0.05 ***12 months:*** 22.1 vs. 23.1, *P* > 0.05 ***24 months:*** 21.5 vs. 22.1, *P* > 0.05	***Baseline:*** 7.0 ± 3.6 (2.9-13.7) vs. 9.7 ± 3.8 (5.0-18.0), *P* = 0.05 ***12 months:*** 10.1 ± 6.5 (range 2-25) vs. 27.1 ± 8.7 (range 12-45), *P* < 0.0001
Mean post-voiding residual urine volume (mL) (lower is better)	***Baseline:*** 126.9 vs. 115.4, *P* > 0.005 ***1 month:*** 88.6 vs. 47.5, *P* = 0.0018 ***3 months:*** 56.8 vs. 33.2, *P* = 0.012 ***6 months:*** 39.2 vs. 30.9, *P* > 0.05 ***12 months:*** 27.3 vs. 22.3, *P* > 0.05 ***24 months:*** 19.4 vs. 15.2, *P* > 0.05	***Baseline:*** 127.0 ± 99.9 (20-230) vs. 78.3 ± 73.3 (0-200), *P* > 0.05 ***12 months:*** 62.3 ± 71.0 (0-250) vs. 8.3 ± 11.9 (0-30), *P* = 0.006
Safety		
Overall complications, n (%)	30 (52.6) vs. 17 (29.8), *P* = 0.03	NR
Perioperative complications, n (%)	***Intraoperative:*** Technical failure: 3 (5.3) vs 0 (0), *P* = 0.3 Blood transfusion: 0 (0) vs 2 (3.8), *P* = 0.4 Transurethral resection syndrome: 0 (0) vs 1 (1.9), *P* = 0.97 ***Early complications (<30 days):*** Postembolisation syndrome: 6 (11.1) vs 0 (0), *P* = 0.038 Severe pelvic pain: 1 (1.9) vs 0 (0), *P*>0.99 Acute urinary retention: 14 (25.9) vs 3 (5.7), *P* = 0.004 Hematuria: 0 (0) vs 4 (7.5), *P* = 0.12 Urinary tract infection: 1 (1.9) vs 2 (3.8), *P* = 0.99 Clot retention: 0 (0) vs 1 (1.9), *P* = 0.99 ***Late complications (30 days to 24 months):*** Clinical failure: 5 (9.4) vs 2 (3.9), *P* = 0.26 Urethral stricture: 0 (0) vs 1 (2.1), *P*>0.99 Bladder neck stenosis: 0 (0) vs 1 (2.1), *P* > 0.99	***Perioperative complications (PAE):*** Local pain at the prostate site, mild to moderate urethral burning during voiding and urinary frequency for 3-4 days post-procedure: 15 (100) Transient rectal bleeding: 1 (6.7) Hematospermia: 1 (6.7) Reduced ejaculate volume: 2 (13.3) Transient pubic bone ischaemia: 1 (6.7) Hematuria: 2 (13.3) ***Perioperative complications (TURP):*** Pollakuria, dysuria, hematuria for up to 2 weeks: 15 (100) Urinary incontinence: 4 (26.7) Intra-operative damage to left venous sinus and rupture of prostatic capsule: 1 (6.7) Hematuria requiring hospital readmission: 1 (6.7) Retrograde ejaculation: 15 (100)
Major adverse events, n (%)	8 (14) vs. 4 (7), *P* = 0.3	0 (0) vs. 2 (13.3), *P* = NR
Minor adverse events, n (%)	22 (38.6) vs. 13 (22.8), *P* = 0.1	See above
Radiation dose (dGy/cm²)	1130.5 ± 267.1 vs. 0 ± 0, *P* < 0.0001	NR
Procedure-related mortality, n (%)	0 (0)	0 (0)

Abbreviations: BPH = benign prostatic hyperplasia; dGy = decigray; cm = centimetre; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; mL = mililetre; ng = nanogram; NR = not reported; PAE = prostate artery embolisation; PSA = prostate specific antigen; PVA = polyvinyl alcohol; Qmax = Peak urinary flow; QoL = quality of life; TURP = transurethral prostate resection

Table A-2: Prostate artery embolisation: Results from observational studies; PAE vs open prostatectomy

Author, year	Russo, 2015 [4]
Country	Italy (OP)/Russia (PAE)
Sponsor	Not stated
Intervention	Bilateral PAE with tris-acryl microspheres (Embosphere; Merit Medical, USA)
Comparator	Open prostatectomy
Study design	Prospective 1:1 propensity score matched-pair comparison of patients treated at two centres
Number of pts	80 (PAE) vs 80 (OP)
Population	Patients with moderate-severe LUTS due to BPH
Inclusion criteria	Symptomatic LUTS; IPSS ≥ 12; PSA level < 4 or PSA level 4 to 10 ng/mL – negative on biopsy; prostate volume > 80 cm3; Qmax < 15 mL/s
Exclusion criteria	Neurogenic bladder dysfunction; sphincter decompensation; coagulation disorders and/or anticoagulant therapy; chronic kidney disease; previous surgical or medical treatment for LUTS; life expectancy < 2 years; bladder stones; catheter or acute retention episode in last 4 weeks
Age of patients (yrs)	67.0 ± 5.72 vs 68.38 ± 6.13, *P* = 0.19
Follow-up	1, 6 and 12 months (all patients not lost to follow-up)
Loss to follow-up, n (%)	From 287 eligible patients, 18 (6.27) were lost to follow-up, 82 (28.57) excluded by the matched-pair comparison
Outcomes	
Efficacy	
Mean QoL score (lower is better)	NR
Mean IPSS (lower is better)	***Baseline:*** 23.98 ± 5.93 vs. 23.35 ± 4.66, P = 0.53 ***1 month:*** 12.2 ± 3.95 vs. 6.02 ± 3.96, P < 0.01 ***6 months:*** 11.35 ± 3.09 vs. 4.93 ± 3.33, P < 0.01 ***12 months:*** 10.4 ± 4.66 vs. 4.31 ± 3.02, P < 0.01
Mean IIEF score (higher is better)	***Baseline:*** 14.45 ± 4.83 vs. 15.10 ± 6.12, P = 0.56 ***1 month:*** 15.25 ± 5.14 vs. 9.6 ±7.48, P < 0.01 ***6 months:*** 15.53 ± 5.13 vs. 10.69 ± 7.76, P < 0.01 ***12 months:*** 15.13 ± 5.07 vs. 10.88 ± 7.63, P < 0.01
Symptom recurrence requiring re-intervention	No paitents in either group required re-intervention
Mean Qmax (mL/s) (higher is better)	***Baseline:*** 7.26 ± 3.29 vs. 7.85 ± 1.76, P = 0.21 ***1 month:*** 14.95 ± 4.42 vs. 22.87 ± 5.03, P < 0.01 ***6 months:*** 16.23 ± 4.49 vs. 24.5 ± 5.34, P < 0.01 ***12 months:*** 16.89 ± 4.88 vs. 23.82 ± 5.92, P < 0.01
Mean post-void residual (cm^3) (lower is better)	***Baseline:*** 64.25 ± 33.10 vs. 64.95 ± 63.46, P = 0.95 ***1 month:*** 19.75 ± 8.55 vs. 13.78 ± 10.2, P < 0.01 ***6 months:*** 19.23 ± 10.13 vs. 4.31 ± 3.97, P < 0.01 ***12 months:*** 18.38 ± 9.6 vs. 6.15 ± 4.26, P < 0.01
Safety	
Overall complications, n (%)	7 (8.75) vs. 25 (31.25), *P* = NR
Perioperative complications, n	***Grade 1:*** Hematuria: 0 vs 4; Urgency: 0 vs. 2; Hematospermia: 1 vs 0; Other: 5 vs 5 ***Grade 2:*** UTI: 1 vs 3; Anemia: 0 vs. 5; Other: 0 vs 2 ***Grade 3:*** Urethral/bladder neck stricture: 0 vs. 2; Urgency: 0 vs 1
Major adverse events, n (%)	0 (0) vs. 3 (3.75), *P* = NR
Minor adverse events, n (%)	7 (8.75) vs. 21 (26.25), *P* < 0.05
Radiation dose (dGy/cm^2)	NR
Procedure-related mortality, n (%)	0 (0)

Abbreviations: BPH = benign prostatic hyperplasia; dGy = decigray; cm = centimetre; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; mL = mililetre; ng = nanogram; PAE = prostate artery embolisation; PSA = prostate specific antigen; PVA = polyvinyl alcohol; Qmax = Peak urinary flow; QoL = quality of life; TURP = transurethral prostate resection; UTI = urinary tract infection.

Table A-3: Prostate artery embolisation: Results from a randomised controlled trial comparing PAE particle sizes

Author, year	Bilhim, 2013 [17]
Country	Portugal
Sponsor	Not stated, two authors were paid consultants to Cook Medical
Intervention	PAE with 80-180µm (mean 100µm) nonspherical PVA particles (Product NR; Cook Medical, USA)
Comparator	PAE with 180-300µm (mean 200µm) nonspherical PVA particles
Study design	Prospective randomised controlled trial
Number of patients	40 (100µm PAE) vs. 40 (200µm PAE)
Population	Patients with moderate-severe LUTS secondary to BPH
Inclusion criteria	Age ≥ 40 years; symptomatic BPH refractory to medical therapy for ≥ 6 months or experiencing acute urinary retention; prostate volume ≥ 30cm³; IPSS > 18 points and/or QoL score related to LUTS > 3 points
Exclusion criteria	Age <40 years; prostate or bladder malignancy; prostate volume <30cm²; IPSS ≤ 18 points, QoL ≤ 3 points; bladder diverticula >5cm or stones >2cm; chronic renal failure; acute urinary tract infection; atherosclerotic changes on CT angiography
Age of patients (yrs)	Mean 64.4 ± 6.9 [100µm] vs Mean 63.4 ± 6.8 [200µm], *P* = 0.48
Follow-up	1 week, 3 months and 6 months Mean follow-up NR
Loss to follow-up, n (%)	***At 6 months (100µm vs. 200µm)*** 6 (15.0) vs. 12 (30.0)
Safety	
Overall complications, n (%)	NR
Perioperative complications, n (%)	***Pain (100µm vs. 200µm)*** During PAE: 3.20 ± 2.97 vs. 2.93 ± 3.28, *P* = 0.70 6-8 hours after PAE: 0.10 ± 0.50 vs. 0, *P* = 0.20 Week after PAE: 0.85 ± 1.65 vs. 0.87 ± 1.35, *P* = 0.96 ***Adverse events 1-week post-PAE (100µm vs. 200µm)*** Dysuria/urethral bleeding: 8 (20) vs. 9 (22.5), *P* > 0.99 Irritative voiding: 12 (30) vs. 16 (40), *P* = 0.48 Hematospermia: 3 (7.5) vs. 2 (5), *P* > 0.99 Hematuria: 3 (7.5) v.s 1 (2.5), *P* = 0.62 Rectal bleeidng: 0 (0) vs. 1 (2.5), *P* > 0.99 Urinary tract infection: 1 (2.5) vs. 1 (2.5), *P* > 0.99 Inguinal hematoma: 2 (5) vs. 1 (2.5), *P* > 0.99
Major adverse events, n (%)	0 (0) vs. 0 (0)
Minor adverse events, n (%)	See above (perioperative complications)
Radiation dose (dGy/cm²)	NR
Procedure-related mortality, n (%)	0 (0)

Abbreviations: BPH = benign prostatic hyperplasia; dGy = decigray; cm = centimetre; cm = centimetre; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; mL = mililetre; ng = nanogram; PAE = prostate artery embolisation; PSA = prostate specific antigen; PVA = polyvinyl alcohol; Qmax = Peak urinary flow; QoL = quality of life;TURP = transurethral prostate resection.

Table A-4: Prostate artery embolisation: Results from observational studies of PAE; different populations, different particle sizes, single-arm trials

Author, year	Wang, 2016 [22]	Wang, 2016 [21]	Pisco, 2016 [20]	Bilhim, 2016 [18]
Country	China	China	Portugal	Portugal
Sponsor	National Scientific Foundation Committee of China and the Chinese PLA Scientific Foundation of the Twelve-five programme	National Scientific Foundation Committee of China and the Chinese PLA Scientific Foundation of the Twelve-five programme	NR	NR
Intervention	Bilateral PAE with nsPVA (Product NR; Cook) in patients ≥ 75 years	Unilateral or bilateral PAE with nsPVA (Product NR; Cook) in patients with medium (50-80 mL) prostate volume	Unilateral or bilateral PAE with nsPVA (Product NR; Cook) in 418 pts; spherical PVA (Bead Block; Biocompatibles) in 167 pts; and in polyezene microspheres in 33 (Embozene; Boston Scientific) pts.	Unilateral or bilateral PAE with spherical PVA (Bead Block; Biocompatibles)
Comparator	Bilateral PAE with nsPVA (Product NR; Cook) in patients < 75 years	PAE with nsPVA (Product not stated; Cook) in patients with large (> 80 mL) prostate volume	Not applicable	Not applicable
Study design	Prospective cohort study	Prospective cohort study	Retrospective case series	Retrospective case series
Number of pts	52 (≥ 75 years) 105 (< 75 years)	64 (volume > 80 mL) 51 (volume 50-80 mL)	630	186
Population	Patients with moderate-severe LUTS due to BPH that were refractor to medical treatment	Patients with moderate-severe LUTS attributale to BPH and refractory to medical treatment.	Patients with moderate-severe LUTS secondary to BPH	Patients with moderate-severe LUTS secondary to BPH
Inclusion criteria	Age > 50 years; IPSS ≥ 18 and QoI ≥ 3; Qmax ≤ 12 mL/s or acute urinary retention; BPH refractory to medical treatments for at least 6 months; prostate volume > 40 mL on magnetic resonance imaging;	Age > 50 years; IPSS ≥ 18 and QoL score > 3; Qmax < 12 mL; refreactory to medical treatments for at least 6 months; prostate volume > 50 mL on magnetic resonance imaging	Age > 40 years; BPH with IPSS ≥ 18 and QoL ≥ 3; Qmax ≤ 12 mL/s or acute urinary retention; refractory to medical treatment for at least 6 months; prostate volume < 30 ml if there was infravesical obstruction	Age > 55 years; severe LUTS (IPSS ≥ 18); refractory to, or refusing, medical therapy; QoL score ≥ 3; Qmax of up to 12 mL/sec or acute urinary retention; prostate volume > 30 mL; sexual dysfunction or those willing to undergo tratement that might cause sexual dysfunction
Exclusion criteria	Pelvic malignancy; large bladder diverticula; large bladder stones; chronic renal failue; active UTI; neurogenic bladder and detrusor failure; urethral stricture; unregulated coagulation parameters; allergy to IV contrast	Pelvic malignancy; large bladder diverticula; large bladder stones; chronic renal failue; active UTI; neurogenic bladder and detrusor failure; urethral stricture; unregulated coagulation parameters	Malignancy, advanced atherosclerosis and tortuosity of arteries; secondary renal insufficiency; large bladder diverticula or stones; neurogenic bladder or detrusor failure; active UTI; unregulated and uncontrollable coagulation parameters	Malignancy; advanced atherosclerosis and tortuosity of prostate and/or iliac arteries; secondary renal insufficiency; bladder stones or large diverticula; neurogenic bladder; detrusor muscle failure; active UTI; unregulated coagulation parameters
Age of patients (yrs)	82.5 ± 7.5 (≥75 years) 67.5 ± 14.0 (< 75 years)	72.5 ± 9.5 (prostate volume> 80 mL) 66.0 ± 8.5 (prostate volume 50-80 mL)	65.1 ± 8.0 years	65.5 ± 7.79 years (sPVA arm)
Follow-up (months)	1, 3 and 6 months, then every 6 months Mean 20 months (12-46)	1, 3 and 6 months, then every 6 months Mean 17 months (12-33)	1, 3 and 6 months, then every 6 months for up to 3 years Median 24 months (12-78)	1, 6, 12, 18 and 24 months Median 6 months (range NR)

Author, year	Wang, 2016 [22]	Wang, 2016 [21]	Pisco, 2016 [20]	Bilhim, 2016 [18]
Loss to follow-up, n (%)	10 (6.4)	***12 months*** 5 (9.8) (prostate volume > 80 mL) 3 (4.7) (prostate volume 50-80 mL)	47 (7.5)	***6 months:*** 68 (36.6) ***12 months:*** 147 (79.0)
Outcomes				
Safety				
Overall complications, n (%)	NR	NR	NR	NR
Major adverse events, n (%)	0 (0)	0 (0)	Bladder wall ischemia: 1 (0.2) Persistent perineal pain: 1 (0.2)	0 (0)
Minor adverse events, n (%)	***Age ≥75 vs. <75 years*** Urethral burning: 10 (19.2) vs 12 (11.4), *P* = 0.027 Haematuria: 6 (11.5) vs 8 (7.6), *P* = 0.722 Haematospermia: 4 (7.7) vs 8 (7.6), *P* = 0.656 Rectal bleeding: 4 (7.7) vs 7 (6.7), *P* = 0.604 Acute urinary retention: 16 (30.8) vs 9 (8.6), *P* = 0.031 Inguinal hematoma: 3 (5.8) vs 3 (2.9), *P* = 0.060	***Prostate volume > 80 mL vs. 50-80 mL*** Urethral burning: 10 (16.7) vs 5 (10.2), *P* = 0.04 Haematuria: 7 (11.7) vs 4 (8.2), *P = 0.8* Haematospermia: 7 (11.2) vs 4 (8.2), *P = 0.8* Rectal bleeding: 6 (10.0) vs 4 (8.2), *P = 0.7* Acute urinary retention: 17 (28.3) vs 5 (10.2), *P* = 0.02	Dysuria: 152 (24.1) Frequency: 145 (23.0) Obstipation: 76 (13.3) Hematuria: 48 (8.0) Hematospermia: 46 (8.0) Rectal bleeding: 34 (5.9) Urinary tract infection: 27 (4.7) Acute urinary retention: 11 (1.9) Inguinal hematoma: 12 (1.9) Balanitis: 4 (0.7)	Urinary frequency of greater severity than baseline 95 (51.1) Dysuria 79 (42.5) Hematospermia 15 (8.1) Hematuria 14 (7.5) Rectal bleeding 10 (5.4) Groin hematoma 6 (3.2) UTI 1 (4.8) Skin lesions 9 (4.8) Transient decrease in erectile function 6 (3.2)
Radiation dose (dGy/cm²)	NR	NR	NR	Median 2401 (range: 655-9202)
Procedure-related mortality, n (%)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: BPH = benign prostatic hyperplasia; dGy = decigray; cm = centimetre; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; mL = mililetre; ng = nanogram; ns = non spherical; PAE = prostate artery embolisation; PSA = prostate specific antigen; PVA = polyvinyl alcohol; Qmax = Peak urinary flow; QoL = quality of life; s = spherical; TURP = transurethral prostate resection; UTI = urinary tract infection.

Risk of bias tables

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [12] and in the Guidelines of EUnetHTA [11].

Table A-5: Risk of bias – existing systematic reviews of PAE for BPH [10]

AMSTAR Item	Wang et al 2016 [54]	Feng et al 2016 [55]	Schreuder et al 2014 [56]	Shim et al 2016 [57]	Teoh et al 2016 [58]	Uflacker et al 2016 [59]
1. Was an 'a priori' design provided?	No	No	Yes	Yes	No	Yes
2. Was there duplicate study selection and data extraction?	Yes	Yes	Yes	No/Can't answer	No/Can't answer	Yes
3. Was a comprehensive literature search performed?	Yes	Yes	No/Can't answer	No/Can't answer	Yes	No/Can't answer
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Can't answer	No	No	No	No/Can't answer	No
5. Was a list of studies (included and excluded) provided?	No	No	No	No	No	No
6. Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes	No	Yes	Yes	Yes	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	No	Yes	No	Yes	Yes
9. Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Not applicable	No	Not applicable	Yes
10. Was the likelihood of publication bias assessed?	No	No	No	No	No	No
11. Was the conflict of interest included?	No	No	Yes	No	No	Yes

Table A-6: Risk of bias – study level (randomised studies) see [60]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely*	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
PAE vs TURP							
Gao et al, 2014 [19]	Yes	No[A]	No	No	Yes	No[B]	High[A,B]
Carnevale, 2016 [3]	Unclear[C]	Unclear[D]	Unclear	Unclear	Unclear	No[e]	High[C,D,E]
100µm PAE vs 200µm PAE							
Bilhim, 2013 [17]	Yes	Unclear[D]	Yes	No	Unclear	No[F,G]	High[D,F,G]

* *This risk was defined as unclear if author's didn't explicitly state that a protocol was published before/the study was not registered;*

[A] *Patients were aware of their allocation prior to the procedure (and hence so to were investigators), and were given the option to change allocation. Only patients that agreed to their allocation were included in the analysis*

[B] *Some patients had repeat procedures during the study period*

[C] *Randomisation method was not reported*

[D] *It was not reported if operators were blinded to the allocation sequence prior to inclusion*

[E] *Patients in the TURP and PAE groups had significantly different Qmax and bladder contractility index scores at baseline (and likely prostate volume, but differences were not reported adequately)*

[F] *Not all patients were included in the efficacy analysis*

[G] *Patients had additional treatments after PAE, but it was unclear if this was during the study period or after last follow-up*

Table A-7: Risk of bias – study level (non–randomised studies) see [61]

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias
PAE vs open prostatectomy								
Russo, 2015 [4]	Moderate	Low	Low	Low	Moderate	Moderate[A]	Moderate	Moderate
PAE (small vs. medium vs. large prostate size)								
Wang, 2016 [21]	Serious[B]	Low	Low	Moderate	Moderate	Moderate[C]	Moderate	Serious[D]
PAE (age <75 vs. > 75 years)								
Wang, 2016 [22]	Serious[E]	Moderate	Low	Moderate	Moderate	Moderate[F]	Moderate	Serious[G]

[A] *Investigators and patients were aware of the assigned intervention.*

[B] *Significant differences in patient demographics (age, IIEF-5 score, prostate volume) were not controlled for in the analysis.*

[C] *Investigators and patients were aware of the assigned intervention.*

[D] *One or more criteria scored as "serious", but none as critical.*

[E] *Groups were significantly different at baseline (heart disease, hypertension, COPD, urinary retention, antiplatelet use, Qmax, post-void residual volume, PSA, IIEF score), but this was largely by design (older versus younger patients). Most important confounding factors were measured.*

[F] *Investigators and patients were aware of the assigned intervention.*

[G] *One or more criteria scored as "serious", but none as critical.*

Table A-8: Risk of bias – study level (case series), see [13]

Study reference/ID	Pisco, 2016 [20]	Bilhim, 2016 [62]
Study objective		
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes
Study population		
2. Are the characteristics of the participants included in the study described?	Yes	Yes
3. Were the cases collected in more than one centre?	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Yes
5. Were participants recruited consecutively?	Yes	Unclear
6. Did participants enter the study at similar point in the disease?	Yes	Yes
Intervention and co-intervention		
7. Was the intervention clearly described in the study?	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	Yes	Yes
Outcome measures		
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes
Statistical Analysis		
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes
Results and Conclusions		
13. Was the length of follow-up reported?	Yes	Yes
14. Was the loss to follow-up reported?	N/A[A]	Unclear
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Yes	Yes
16. Are adverse events reported?	Yes	Yes
17. Are the conclusions of the study supported by results?	Yes	Yes
Competing interest and source of support		
18. Are both competing interest and source of support for the study reported?	Yes	Yes
Overall Risk of bias	Low	Low

[A] *Study was a retrospective cohort study, losses to follow-up were not relevant, only patients with complete data were included.*

Applicability table

Table A-9: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Most studies only included patients with severe LUTS (i.e. IPSS > 18), which is likely to have influenced the treatment effects relative to the target population (i.e. IPSS > 8). The remaining study populations did not differ in any significant way from the population intended for clinical practice. The mean age of participants was consistent across studies (median 65.75 years, range 62.7-72.5), and was reflective of the target population in clinical practice.
Intervention	The interventions ranged between particle size and shape. Particle size varied between a mean 100µm to 200µm in diameter. Particles were either spherical or non-spherical. Some procedures were bilateral, while others were unilateral. Most particles were made of PVA. Three studies did not report what material of particles were made from. It is unclear if variations in the type of embolisation agent are likely to have a meaningful impact on patient outcomes.
Comparators	The comparators in the RCTs (i.e. TURP), and the matched pairs comparison (i.e. open prostatectomy) represent the current standard of care for moderate-to-severe LUTS secondary to BPH.
Outcomes	Not all critical efficacy outcomes were reported by all studies. Gao et al (2014) did not report IIEF. Gao et al (2014) and Carnevale et al (2016) reported all outcomes at a minimum 12-month follow-up. Gao et al (2014) reported all outcomes at 24 months follow-up. Safety was reported variably, and was measured using different scales. As a result, we have a low level of confidence in the reported rates of minor adverse events, but a moderate degree of confidence that adverse events occur rarely in PAE.
Setting	The included randomised evidence of PAE compared to TURP was conducted in China and Brazil. The matched pairs trial of PAE compared to open prostatectomy was conducted in Italy and Russia. Single arm evidence for the safety of PAE was conducted in China, Portugal, and the United States of America. All studies were conducted in tertiary teaching hospitals. PAE was conducted exclusively in interventional radiology departments, while comparators were conducted in Urology departments.

List of ongoing clinical trials

Table A-10: List of ongoing randomised controlled trials of PAE compared to TURP

Identifier/Trial name	Patient population	Estimated enrolment	Intervention	Comparison	Primary Outcome	Estimated completion	Sponsors
NCT02054013 Prostatic Artery Embolisation vs. Conventional Transurethral Prostatectomy in the Treatment of Benign Prostatic Hyperplasia	Moderate-to-severe LUTS secondary to BPH, failed first line medical therapy	100	PAE	TURP	Changes in IPSS (time frame: 12 weeks, 24 months)	February 2021	Daniel Stephan Engeler, MD, Cantonal Hospital St Gallen
NCT01789840 Prostate Artery Embolisation With Embosphere Microspheres Compared to TURP for Benign Prostatic Hyperplasia	Moderate-to-severe LUTS secondary to BPH, failed or refused first-line medical therapy	186	PAE with Embosphere® Microspheres (Merit Medical, USA)	TURP	Change in IPSS (time frame:12 months)	May 2018	Merit Medical Systems, Inc.
NCT02566551 Prospective Controlled Randomized Study of PAE vs TURP for BPH Treatment	Moderate-to-severe LUTS secondary to BPH, failed or refused first-line medical therapy	100	PAE with gelatin microspheres	TURP	Change in IPSS (time frame:12 months)	April 2018	Group of Research in Minimally Invasive Techniques
NCT01963312 Clinical Trial to Evaluate the Efficacy and Safety of the Transarterial Supra-selective Embolisation of the Prostate to Treat the Urinary Symptoms	Moderate-to-severe LUTS secondary to BPH, failed first-line medical therapy	60	PAE with Bead Block (Biocompatibles UK Ltd)	TURP	Change in maximum urinary flow (time frame: 12 months)	December 2016	Fundacion Miguel Servet
DRKS00008079 Prospective randomised interventional single-center study to evaluate pre-operative transarterial embolisation of the prostate before prostatectomy	Moderate-to-severe LUTS secondary to BPH	100	PAE prior to TURP	TURP without prior PAE	Conversion of patients primarily planned for open prostatectomy to TURP or conservative management (time frame: not stated)	Not reported	Universität des Saarlandes

Table A-11: List of ongoing randomised controlled trials of PAE compared to medical therapy

Identifier/Trial name	Patient population	Estimated enrolment	Intervention	Comparison	Primary Outcome	Estimated completion	Sponsors
NCT02869971 Prostatic Artery Embolisation Versus Medical Treatment in Symptomatic Benign Prostatic Hyperplasia (PARTEM)	Moderate-to-severe LUTS secondary to BPH, failed first line medical therapy	90	PAE with Embosphere® Microspheres (Merit Medical, USA)	Drug therapy with Combodart® (GlaxoSmithKline, UK)	Change in IPSS score (time frame: 3, 9, 18, 24 months)	February 2021	Assistance Publique - Hopitaux de Paris Ministry of Health, France

Table A-12: List of ongoing randomised controlled trials of PAE compared to sham procedure

Identifier/Trial name	Patient population	Estimated enrolment	Intervention	Comparison	Primary Outcome	Estimated completion	Sponsors
NCT02074644 Clinical Trial of Prostatic Arterial Embolisation Versus a Sham Procedure to Treat Benign Prostatic Hyperplasia	Moderate-to-severe LUTS secondary to BPH, failed or refused first-line medical therapy	80	PAE with Bead Block (Biocompatibles UK Ltd)	Sham procedure (catheterisation with angiography but no embolisation)	Change in IPSS (time frame: 6 months)	September 2017	João Martins Pisco, MD PhD, Hospital St. Louis

Table A-13: List of ongoing observational trials of PAE

Identifier/Trial name	Patient population	Estimated enrolment	Intervention	Comparison	Primary Outcome	Estimated completion	Sponsors
NCT01924988 Prostate Embolisation for Benign Prostatic Hyperplasia	LUTS secondary to BPH	30	PAE with Embosphere® Microspheres (Merit Medical, USA)	None	Bladder or rectal ischemic injury (time frame: 1 week, 3, 6 and 12 months)	January 2019	James B. Spies, MD, Georgetown University Medical Center
NCT02849522 ROPE Registry Project to Determine the Safety and Efficacy of Prostate Artery Embolisation for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Enlargement	Moderate-to-severe LUTS secondary to BPH, failed first-line medical therapy	300	PAE	TURP or open prostatectomy	Change in IPSS (time frame: 12 months)	September 2017	Cedar, United Kingdom National Institute for Health and Care Excellence (NICE) British Society of Interventional Radiologists (BSIR) British Association of Urological Surgeons (BAUS)
NCT02434575 ROPE Registry Project to Determine the Safety and Efficacy of Prostate Artery Embolisation for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Enlargement	LUTS secondary to BPH	300	PAE	TURP or open prostectomy	Change in IPSS (time frame: 12 months)	December 2016	Cardiff and Vale University Health Board British Society of Interventional Radiologists British Association of Urological Surgeons National Instutite of Health and Care Excellence

Identifier/Trial name	Patient population	Estimated enrolment	Intervention	Comparison	Primary Outcome	Estimated completion	Sponsors
NCT02509975 Safety and Efficacy of OCL 503 in Prostate Artery Embolisation	Moderate-to-severe LUTS secondary to BPH, failed or refused first-line medical therapy	15	PAE with OCL 503 (IMBiotechnologies Ltd., Canada)	None	Adverse events (time frame: 12 months) Change in IPSS (time frame: 12 months)	March 2017	IMBiotechnologies Ltd.
NCT02822924 Prostate Artery Embolisation for Symptomatic Benign Prostatic Hyperplasia	LUTS secondary to BPH, failed or refused first-line medical therapy	40	PAE	None	Successful prostatic arterial catheterisation and embolisation (time frame: 1 hour post-procedure)	April 2018	Chinese University of Hong Kong
NCT02026908 Prostatic Artery Embolisation for Treatment of Benign Prostatic Hyperplasia	LUTS secondary to BPH, failed or refused first-line medical therapy	50	PAE	None	Adverse events (time frame: 5 years)	January 2020	Northwestern University
NCT02167919 Efficacy of Prostatic Artery Embolisation in Patients With Severe Benign Prostatic Hyperplasia	Moderate-to-severe LUTS secondary to BPH, failed first line medical therapy	15	PAE	None	Redction in prostate size (time frame: 1 year) Improvement of LUTS (time frame: 1 year)	May 2017	University of North Carolina
NCT02930889 Prostate Artery Embolisation for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia	Moderate-to-severe LUTS secondary to BPH, failed first line medical therapy	100	PAE	None	Adverse events (time frame: 3 months)	October 2021	University of Minnesota
NCT02206243 Embozene® Microspheres for Prostatic Arterial Embolisation in Patients With Symptomatic Benign Prostatic Hyperplasia (EmboProstate)	Severe LUTS secondary to BPH, failed or refused first line medical therapy	7	PAE with Embosphere® Microspheres (Merit Medical, USA)	None	Change in IPSS and peak flow rate (time frame: 3 and 6 months)	December 2016	Jena University Hospital Boston Scientific Corporation
NCT02679430 Analysis of Prostatic Arterial Embolisation for Benign Prostatic Hyperplasia Using Embosphere Microspheres	Moderate-to-severe LUTS secondary to BPH, failed first line medical therapy	16	PAE with Embosphere® Microspheres (Merit Medical, USA)	None	Change in IPSS (time frame: 12 months)	November 2017	Sergei Sobolevsky, MD, Maimonides Medical Center
NCT02396420 Prostate Artery Embolisation as a Treatment for Benign Prostatic Hyperplasia in Men With Prostates Larger Than 90 Grams	Moderate-to-severe LUTS secondary to BPH, failed or refused first-line medical therapy	60	PAE with Embosphere® Microspheres (Merit Medical, USA)	None	Change in IPSS (time frame: 12 months)	November 2022	South Florida Medical Imaging, PA

Identifier/Trial name	Patient population	Estimated enrolment	Intervention	Comparison	Primary Outcome	Estimated completion	Sponsors
NCT02676544 Prostate Embolisation for Massive Benign Prostatic Hypertrophy	Moderate-to-severe LUTS secondary to BPH	50	PAE with Embosphere® Microspheres (Merit Medical, USA)	None	Change in IPSS (time frame: 24 months)	July 2017	Rhode Island Hospital
NCT02167009 Benign Prostatic Hyperplasia and Prostate Size Greater Than 90 Grams	Moderate-to-severe LUTS secondary to BPH, failed or refused first-line medical therapy	30	PAE with Embosphere® Microspheres (Merit Medical, USA)	None	Change in IPSS (time frame: 12 months)	May 2019	Tampa General Hospital
NCT02689830 Prostate Embolisation for Acute Urinary Retention Study	Acute urinary retention secondary to BPH.	20	PAE with Bead Block (Biocompatibles UK Ltd)	None	Procedure success, indicated by lack of surgery or cateheter post-procedure (time frame: 6 months)	December 2017	ClinSearch Biocompatibles UK Ltd European Georges Pompidou Hospital
NCT02592473 Prostate Artery Embolisation for Treatment of Benign Prostatic Hyperplasia	LUTS secondary to BPH	50	PAE with Embozene Microspheres	None	Change in maximum urinary flow (time frame: 12, 24 months) Adverse events (time frame: 12, 24 months) Change in IPSS (time frame: 12, 24 months) Change in quality of life (time frame: 12, 24 months)	November 2017	University of Virginia Siemens Medical Solutions
DRKS00006308 Prospective, single-center, clinical trial phase - I- II study to evaluate the safety and clinical feasibility and efficacy of arterial Prostataembolisation in patients with moderate-to-severe symptomatic benign prostatic hyperplasia	Moderate-to-severe LUTS secondary to BPH, failed or refused first-line medical therapy	36	PAE	None	Post-operative complications (time frame: not stated)	Not reported	Universitätsklinikum Magdeburg

Literature search strategies

Search strategy for the Cochrane Library

Search Name: Prostate Artery Embolisation	
Database Cochrane library	
Search Date: 09/12/2016	
ID	Search
#1	MeSH descriptor: [Prostatic Hyperplasia] explode all trees
#2	Prostat* near Hypertroph* (Word variations have been searched)
#3	benign prostat* hyperplasia* (Word variations have been searched)
#4	BPH:ti,ab,kw (Word variations have been searched)
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Embolisation, Therapeutic] explode all trees
#7	prostat* artery embolisation* (Word variations have been searched)
#8	prostat* artery embolisation* (Word variations have been searched)
#9	MeSH descriptor: [Microspheres] explode all trees
#10	Embosphere* (Word variations have been searched)
#11	Embozene* (Word variations have been searched)
#12	Bead Block* (Word variations have been searched)
#13	Merit Medical (Word variations have been searched)
#14	Boston Scientific (Word variations have been searched)
#15	CeloNova (Word variations have been searched)
#16	"Biocompatibles" (Word variations have been searched)
#17	"PAE":ti,ab,kw (Word variations have been searched)
#18	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19	#5 and #18
Total: 26 Hits	

Search strategy for MEDLINE

Search Name: Prostate Artery Embolisation	
Database: Ovid MEDLINE(R) Epub Ahead of Print <December 08, 2016>, Ovid MEDLINE(R) <1946 to November Week 5 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 08, 2016>, Ovid MEDLINE(R) Daily Update <December 07, 2016>	
Search Date: 09/12/2016	
ID	Search
#1	exp Prostatic Hyperplasia/
#2	Prostat* Hypertroph*.mp.
#3	benign prostatic hyperplasia*.mp.
#4	BPH.mp.
#5	1 or 2 or 3 or 4
#6	exp Embolisation, Therapeutic/
#7	prostat* artery emboli#ation*.mp.
#8	exp Microspheres/
#9	Embosphere*.mp.

#10	Embozene*.mp.
#11	Bead Block*.mp.
#12	Merit Medical.mp.
#13	Boston Scientific.mp.
#14	CeloNova.mp.
#15	Biocompatibles.mp.
#16	PAE.mp.
#17	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
#18	5 and 17
Total: 190 Hits	

Search strategy for Embase

Search Name: Prostate Artery Embolisation	
Search Date: 09/12/2016	
ID	Search
#1	'prostate hypertrophy'/exp
#2	'benign prostat* hyperplasia*'
#3	bph:ti,ab
#4	'prostate hypertrophy'/exp OR 'benign prostat* hyperplasia*' OR bph:ti,ab
#5	'artificial embolism'/exp
#6	'prostat* artery emboli*ation*'
#7	'microsphere'/exp
#8	embosphere*:tn,dn
#9	embozene*:tn,dn
#10	'embolic particle'/exp
#11	'bead block*':tn,dn
#12	'merit medical':df,mn
#13	'boston scientific':df,mn
#14	celonova:df,mn
#15	biocompatibles:df,mn
#16	pae:ab,ti
#17	'artificial embolism'/exp OR 'prostat* artery emboli*ation*' OR 'microsphere'/exp OR embosphere*:tn,dn OR embozene*:tn,dn OR 'embolic particle'/exp OR 'bead block*':tn,dn OR 'merit medical':df,mn OR 'boston scientific':df,mn OR celonova:df,mn OR biocompatibles:df,mn OR pae:ab,ti
#18	'prostate hypertrophy'/exp OR 'benign prostat* hyperplasia*' OR bph:ti,ab AND ('artificial embolism'/exp OR 'prostat* artery emboli*ation*' OR 'microsphere'/exp OR embosphere*:tn,dn OR embozene*:tn,dn OR 'embolic particle'/exp OR 'bead block*':tn,dn OR 'merit medical':df,mn OR 'boston scientific':df,mn OR celonova:df,mn OR biocompatibles:df,mn OR pae:ab,ti)
Total: 319 Hits	

Search strategy for CRD (DARE, NHS-EED, HTA)

Search Name: Prostate Artery Embolisation	
Search Date: 09/12/2016	
ID	Search
#1	MeSH DESCRIPTOR Prostatic Hyperplasia EXPLODE ALL TREES
#2	(Prostat* NEAR Hypertroph*)
#3	(benign prostatic hyperplasia*)
#4	(BPH)
#5	#1 OR #2 OR #3 OR #4
#6	MeSH DESCRIPTOR Embolisation, Therapeutic EXPLODE ALL TREES
#7	(prostat* artery embolisation*)
#8	(prostat* artery embolisation*)
#9	MeSH DESCRIPTOR Microspheres EXPLODE ALL TREES
#10	(Embosphere*)
#11	(Embozene*)
#12	(Bead Block*)
#13	(Merit Medical)
#14	(Boston Scientific)
#15	(CeloNova)
#16	(Biocompatibles)
#17	(PAE)
#18	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	#5 AND #18
Total: 1 Hit	

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