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RETHINKING THE ARTIFICIAL URINARY SPHINCTER: FROM CURRENT KNOWLEDGE TO THE DEVELOPMENT OF A NEW SMART DEVICE

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Rethinking the artificial urinary sphincter: from current knowledge to the development of a new smart device

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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In loving memory of my father

In celebration of my mothers' unconditional love

'It's important to evolve and not sit in one space'

Virgil Abloh

POPULAR SCIENCE SUMMARY OF THE THESIS

Background

Urinary leakage touches millions of adult men and women across the globe and affects their social interactions, dignity, quality of life, as well as their family. The common causes are delivery, anatomic malformations, neurological illnesses, procedures in the pelvis and radiotherapy. Many patients must wear pads/diapers and are not always aware that surgery can help them get dry. The device of reference today is the AMS 800™ (Boston Scientific - Marlborough, Massachusetts, USA) artificial urinary sphincter (AUS), created in the 70's to treat severe urinary leakage in men after prostate surgery (post-prostatectomy urinary incontinence or PPUI). In women, this device is considered as a second alternative after other procedures, like mid-urethral slings (MUS), fail, which are the first recommended options in moderate to severe leakage. Although the device proved its efficiency, it has several issues, like the fact that it cannot adjust to the patient's physical activities, is not user-friendly, and is subject to high reoperation rates.

Aims

To address the weaknesses of the AMS 800 ™, a new electronic urinary sphincter was created in France in 2007. This thesis tells the journey of the development of a novel smart device for the treatment of severe urine leakage in both men and women whilst fulfilling three objectives: 1) to conduct a literature review of the current AMS™ for literature gaps identification, 2) to establish and analyze data from bench tests and clinical studies and 3) to conduct pre-clinical feasibility, performance and safety studies on human cadavers and animals prior to FIM trials. The 6 constituent papers will show the results of a rethinking process, from what we know today, through the lens of scientific literature (papers I-III), to the design of a new device (paper IV), taking it to pre-clinical studies in preparation for the clinical trials (papers V-VI), leading to CE marking.

Materials and Methods

In ***Paper I***, we reviewed international scientific papers over the past 30 years and investigated the short to long-term efficacy and complications of the AMS 800 ™ in adult women with severe urine incontinence. ***Paper II*** studies the 24-h pad weight test (PWT) as urine leakage measurement tool to assess how efficient the AMS 800 ™ is. This is important to standardize published results in scientific papers but can also help us define the primary objectives of the First in Man (FIM). We analyzed this test in 180 men who primarily underwent AMS 800 ™ surgery for severe urine leakage after prostate cancer treatment. Second, we looked at the relationship between 24-h PWT and quality of life. In ***paper III*** we compared the long-term urinary leakage results and safety profiles of two AMS 800 ™ surgical techniques, one using urethral access via the scrotum (transscrotal) and the other via the perineum (transperineal) in 183 men suffering from PPUI in a single center. We also compared the two techniques in terms of their impact on quality of life. ***Paper IV*** measured the exact *in vivo* volume the AMS 800™ occlusive cuff (OC) could accommodate after its pressurization, when implanted in 67 men treated for PPUI. After bench and *in-vivo* tests, we proceeded to *pre-clinical* studies, to determine if the latest prototype design was easily implanted, if the surgery was feasible and if the device was functional. We also wished to demonstrate its performance, safety, and biocompatibility. In the *performance study* we used urodynamic investigations to study the pressures generated by the device and compare them with the AMS 800™. Feasibility of implantation testing was conducted in 4 anatomical subjects and performance in another 4 as part of a pilot study **(*Paper V*)**. Further animal testing on 2 castrated rams was carried out, in accordance with current FDA and European regulations on novel devices in development, *in* ***Paper VI.***

Results

Paper I compiled 12 articles, which concluded that the level of evidence is very low. We need further well-designed studies with larger numbers of patients. We also underline the importance of post-market studies for patient safety. In ***Paper II*** we concluded that the 24-h PWT test was dependable, reproducible, objective and strongly correlated with quality of life. The study in ***Paper III*** showed no significant differences between the two techniques regarding long-term efficacy results, quality of life and device longevity. However, the transperineal technique had worse long-term safety results, probably because the devices were implanted for a longer period. The results in ***Paper IV*** demonstrated that the larger the cuff, the more volume the OC could take, which was maximum 1 cc. This information helped the engineers to complete the design of the final prototype, an important developmental stage. The cadaver study **(*Paper V)*** confirmed the device could easily be implanted. In the performance study, the new device showed it could use urodynamical randomly obtained urethral pressure profiles, with maximum urethral closure pressure (MUCP) ranges equivalent to those of the AMS 800™. Finally, in the ultimate step preceding the FIM study ***(Paper VI),*** we wished to ascertain the novel device's feasibility of implantation and histopathological safety in an animal pilot study using two wether models. The study showed the model was suitable, the device easily implanted and that no complications were reported. We could safely consider a larger Pivot study.

Conclusion

The development of a new artificial urinary sphincter is a long, pricey, and challenging process due to regulation constraints. Scientific paper analysis showed low level of evidence for the AMS 800™ in women with severe urinary leakage. Furthermore, the efficacy results of this device are disparate, and the 24-h PWT is an objective tool to measure these outcomes, which could help solve the issue. Finally, transscrotal and transperineal techniques are comparable in terms of efficacy, quality of life and device survival. In the clinical-meet engineering design study, the knowledge that the OC took only 1 cc when pressurized was very useful for the design of an electronic urinary sphincter. We were then able proceed to pre-clinical studies showing novel device implantation feasibility, demonstrated the device could be activated and deactivated, and no serious adverse events were reported. The next step is to consider larger pre-clinical studies prior to the first implantation in humans of the smart device.

POPULÄRVETENSKAPLIG ÖVERSIKT PÅ SVENSKA

Bakgrund

Urinläckage berör miljontals vuxna män och kvinnor över hela världen och påverkar deras sociala samspel, värdighet, livskvalitet och familj. De vanligaste orsakerna är förlossning, missbildningar, neurologiska sjukdomar, ingrepp i lilla bäckenet och strålbehandling. Många patienter måste bära inkontinensskydd och är inte alltid medvetna om att kirurgi kan hjälpa dem att bli torra. För män är den kirurgi som utgör standardoperation med AMS 800 (Boston Scientific - Marlborough, Massachusetts, USA), en artificiell urinrörssfinkter (AUS), som utvecklades på 70-talet för att behandla omfattande urinläckage hos män efter prostatakirurgi (PPUI). Hos kvinnor betraktas denna anordning som ett andrahandsval efter att andra förfaranden misslyckats, som till exempel operation med stödjande band (MUS), som är det första rekommenderade alternativet vid måttligt till omfattande läckage. Även om anordningen har visat sig vara effektiv har den flera problem, som att den inte kan anpassas till patientens fysiska aktivitet, att den inte är helt användarvänlig och att den är föremål för hög frekvens av revisionskirurgi.

Syfte

För att åtgärda svagheterna med AMS 800™ skapades en ny elektronisk urinsphincter i Frankrike 2007. Denna avhandling berättar om utvecklingen av en ny smart anordning för behandling av svåra urinläckage hos både män och kvinnor, samtidigt som tre mål uppfylls: 1) att göra en litteraturgenomgång av nuvarande AMS™ för att identifiera litteraturluckor, 2) att fastställa och analysera data från bänkförsök och kliniska studier och 3) att genomföra prekliniska genomförbarhets-, prestanda- och säkerhetsstudier på mänskliga kadaver och djur före FIM-försök. De sex delartiklarna kommer att visa resultaten av en omprövningsprocess, från vad vi vet i dag genom den vetenskapliga litteraturen (***artiklarna I-III***), till utformningen av en ny anordning (***artikel IV***) och till prekliniska studier som förberedelse för kliniska prövningar (***artiklarna V-VI***), som leder till CE-märkning.

Material och metoder

I artikel I granskade vi internationella vetenskapliga artiklar från de senaste 30 åren och undersökte AMS 800:s kort- och långsiktiga effekt och komplikationer hos vuxna kvinnor med svår urininkontinens. ***I artikel II*** studeras 24-timmars läckagemätning som ett verktyg för att mäta urinläckage för att bedöma hur effektiv AMS 800 är. Detta är viktigt för att standardisera publicerade resultat i vetenskapliga artiklar men kan också hjälpa oss att definiera de primära målen för FIM. Vi analyserade det här testet hos 180 män som primärt genomgick AMS 800-kirurgi för omfattande urinläckage efter prostatacanceroperation. För det andra tittade vi på förhållandet mellan 24-timmars läckagemätning och livskvalitet. I ***artikel III*** jämförde vi de långsiktiga resultaten av urinläckage och säkerhetsprofilerna för två olika sätt att operera in AMS-800 hos män, varav den ena ger åtkomst av urinröret via pungen (transskrotalt) och den andra via mellangården (transperinealt). Metoderna studerades hos 183 män som opererats för PPUI vid en och samma klinik. Vi jämförde också de två teknikerna med avseende på deras inverkan på livskvaliteten. I ***artikel IV*** mättes den exakta volym vätska som AMS 800-ocklusionsmanchetter (OC) kunde rymma efter dess trycksättning, hos 67 män som behandlades för PPUI. Efter dessa tester fortsatte vi med prekliniska studier för att testa om den senaste prototypkonstruktionen var lätt att implantera, om operationen var genomförbar och om anordningen var funktionell. Vi ville också visa dess prestanda, säkerhet och biokompatibilitet. I prestandastudien använde vi urodynamiska undersökningar för att studera de tryck som genereras av anordningen och jämförde dem med AMS 800. Genomförbarhetstester för implantation utfördes på 4 avlidna personer som donerat sina kroppar till kirurgisk forskning och prestanda på ytterligare 4 som en del av en pilotstudie (***Paper V***). Ytterligare djurförsök på två kastrerade baggar utfördes i enlighet med gällande FDA- och EU-förordningar om nya medicintekniska produkter under utveckling (***Paper VI***).

Resultat

I ***artikel I*** sammanställdes 12 artiklar där slutsatsen var att bevisnivån är mycket låg. Vi behöver ytterligare väl utformade studier med ett större antal patienter. Vi understryker också vikten av studier efter marknadsintroduktionen för patientsäkerheten. I ***artikel II*** drog vi slutsatsen att 24-timmars läckagemätning var tillförlitligt, reproducerbart, objektivt och starkt korrelerat med livskvalitet. Studien i ***artikel III*** visade inga signifikanta skillnader mellan de två teknikerna när det gäller långsiktiga effektresultat, livskvalitet och livslängd för anordningen. Den transperineala tekniken hade dock sämre långsiktiga säkerhetsresultat, troligen på grund av att anordningarna som implanterades suttit på plats under längre tid. Resultaten i ***artikel IV*** visade att ju större manschetten var, desto mer volym kunde den ta emot, dock som högst 1ml. Denna information hjälpte ingenjörerna att slutföra utformningen av den slutliga prototypen, ett viktigt utvecklingssteg. Kadaverstudien (***artikel V***) bekräftade att anordningen lätt kunde implanteras. I prestandastudien visade den nya anordningen att den kunde generera urodynamiska slumpmässigt erhållna urinrörstryckprofiler, med ett maximalt urinrörsstängningstryck som var likvärdigt med AMS 800. Slutligen ville vi i det sista steget före FIM-studien (***artikel VI***) fastställa den nya anordningens funktionalitet och säkerhet i en pilotstudie på djur med hjälp av implantation i två kastrerade baggar. Studien visade att modellen var lämplig, att anordningen var lätt att implantera och att inga komplikationer rapporterades.

Slutsats

Utvecklingen av en ny artificiell urinrörssfinkter är en lång, dyr och utmanande process på grund av regelverkets begränsningar. Analysen av vetenskapliga artiklar visade låg bevisnivå för AMS 800 hos kvinnor med svårt urinläckage. Dessutom är effektresultaten för denna anordning disparata, och 24-timmars läckagemätning är ett objektivt verktyg för att mäta dessa resultat, vilket skulle kunna bidra till att lösa problemet. Slutligen är transskrotala och transperineala tekniker jämförbara när det gäller effektivitet, livskvalitet och överlevnad av anordningen. I studien om klinisk och teknisk design var kunskapen om att manschetten endast tog 1ml som mest, mycket användbar för utformningen av den elektroniska prototypen. Vi kunde sedan gå vidare till prekliniska studier som visade att den nya anordningen var möjlig att implantera, visade att anordningen kunde aktiveras och avaktiveras och att inga allvarliga biverkningar rapporterades. Nästa steg är att överväga större prekliniska studier före den första implantationen av den smarta anordningen i människor.

ABSTRACT

Background

Urinary incontinence (UI) plagues millions of women and men worldwide, leading to social stigma, low self-esteem, poor quality of life, and affects their loved ones. In women, frequent causes include childbirth, and in men prostate surgery for benign or malignant disease. In both genders congenital anomalies, neurological diseases, pelvic surgery, and radiation therapy are incriminating factors. Many patients struggle daily with pads and/or diapers, often unaware of the existence of a surgical cure. Since the seventies, the AMS 800™ (Boston Scientific - Marlborough, Massachusetts, USA) artificial urinary sphincter (AUS) has been the reference to treat severe male stress UI (SUI) secondary to intrinsic sphincter deficiency (ISD). In women, it constitutes a second-line option, the mid-urethral sling (MUS) being recommended as first-line surgical therapy in moderate to severe cases. However, although efficient, it has several drawbacks, namely poor ergonomics, untailored status to patients' physical activities, high revision and explantation rates.

Aims

To solve the above issues, a novel electronic AUS was incepted in France in 2007. This thesis tells the modern developmental journey of this device for severe SUI treatment. The objective is three-fold: to conduct a review of the current AMS™ in both genders to identify potential literature gaps to identify and analyze data resulting from bench tests and clinical studies, and to conduct pre-clinical feasibility, performance and safety studies on human cadavers and animals prior to FIM studies. The 6 constituent papers present the results of the process rethinking the current AMS 800™ known today, from State of the Art (***papers I-III)*** to the design stages (***paper IV***) and subsequent pre-clinical implantation phases (***papers V and VI***) prior to the First in Man study, which eventually leads to the obtention of CE marking.

Material, Methods, and Results

In ***Paper I,*** a systematic literature review of AMS 800™ implantation in women with non-neurogenic severe SUI, non-extant to date, was performed. The 12 articles included showed a very low level of evidence, result heterogeneity in performance and safety outcomes and highlighted the need for post-market studies. ***Paper II*** addressed the absence of standardized continence outcome measurement tool, essential to homogenize functional reported outcomes data, but also crucial for defining the primary outcomes of the FIM study. We retrospectively assessed the 24- hour pad weight test in 180 men treated with primary AUS for PPUI. Secondarily, its correlation to quality-of-life was analyzed. Thirdly ***(Paper III***), we retrospectively evaluated long-term continence and safety results of transscrotal versus transperineal (TP) primary AUS implantation in 183 men with PPUI in a single center. No statistical difference in performance outcomes was seen; however, the TP technique appeared to present worse long-term safety results. In ***Paper IV***, we dimensioned the novel AUS by prospectively measuring the exact *in vivo* volume taken by the AMS 800™ occlusive cuff after its pressurization at implantation. We found that the larger the cuff, the greater the accommodated volume, which did not surpass 1 cc. Therefore, the final prototype could be designed, an essential developmental milestone. In ***paper V*** the usability and performance of the novel AUS was established, in accordance with current FDA and European regulations on AIMDs in development. The device's usability and performance were shown in 8 anatomical subjects, using randomly obtained urodynamic maximum urethral closure pressure ranges, equivalent to those of the AMS 800™. In ***Paper VI,*** we ascertained the novel device's feasibility of implantation and histopathological safety in an animal pilot study using two wether models. The study showed the suitability of the models, the device's ease of implantation and the absence of peri-or postoperative, and histopathological adverse events. We could therefore safely consider a Pivot study.

Conclusion

Developing a novel AUS is a lengthy, expensive, and regulatory challenging process. In the '*State of the Art*', essential to assess the 'Gold standard', we identified three literature gaps relevant for the

risk analysis and evaluated similar competing devices. We showed a fine example of the application of '*in vivo'* clinical study to the design of the smart AUS device. These initiated the required pre-clinical studies prior to FIM trials, demonstrating device feasibility, performance, and safety. the importance of post-market studies was also highlighted, and we strive to soon deliver a safe and efficient electronic device, tailored to the patient's needs, whilst abiding to current regulations.

Keywords: Active Implantable Medical Devices, Artificial Urinary Sphincter, Stress Urinary Incontinence

LIST OF CONSTITUENT PAPERS

I. **Performance and Safety of the Artificial Urinary Sphincter (AMS800™) for Adult Women with Non-Neurogenic Stress Urinary Incontinence Secondary to Intrinsic Sphincter Deficiency: A Systematic Review.**
C. Reus, V. Phé, A. Dechartres, N. Grilo, E. Chartier-Kastler, P. Mozer
Eur. Urol. Focus. 2020 Mar 15;6(2):327-338. Doi: 10.1016/j.euf.2018.10.009. Epub 2018 Oct 30.

II. **Evaluation of the 24-H Pad Weight Test as Continence Rate Assessment Tool After Artificial Urinary Sphincter Implantation for Post-Prostatectomy Urinary Incontinence: A Swedish Retrospective Cohort Study.**
C. Reus, I. Brattås, D. Volz, F. Sydén, Pierre Mozer, L. Renström Koskela
Neurourol Urodyn. 2021 Aug;40(6):1585-1592. Doi: 10.1002/nau.24723. Epub 2021 Jun

III. **Performance and Safety Outcomes of Transverse Scrotal Versus Transperineal Approach for Primary Artificial Urinary Sphincter Implantation in Patients with Post-Prostatectomy Urinary Incontinence: A Retrospective Follow-up Cohort Study.**
Christine R. Reus, Izabelle Brattås, Daniela Volz, Filip. Sydén, Katarina Hallén Grufman, Lotta Renström Koskela
Manuscript

IV. **Prospective AMS 800™ Peri-bulbar Occlusive Cuff Volume Measurements After Pressurization: Clinical routine perspective and dimensioning a Novel Urinary Sphincter.**
Christine Reus, Aurélien Beaugerie, Emmanuel Chartier-Kastler, Pierre Mozer
Manuscript submitted

V. **Novel Electronic Urinary Sphincter: Feasibility and Performance Study in Human Cadavers**
Christine Reus, Aurélien Beaugerie, Emmanuel Chartier-Kastler, Pierre Mozer
Manuscript

VI. **Implantation Feasibility, Device Function and Safety of the novel UroMems Electronic Urinary Sphincter (eUS) in the Wether Model**
Christine Reus, Aurélien Beaugerie, Emmanuel Chartier-Kastler, Pierre Mozer
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

AAALAC	American Association for Accreditation of Laboratory Animal
ACT	Care Active Continence Therapy
AE	Adverse Events
AMS	American Medical Systems
AUS	Artificial Urinary Sphincter
CBP	Control/Battery Pack
CE	European Community logo (Communauté Européenne)
CP	Clinician Programmer
CTCAE	Common Terminology Criteria for Adverse Events
CU	Control Unit
DD	Device Deficiency
DOA	Detrusor overactivity
DRAE	Device related adverse Events
eAUS	Electronic Artificial Urinary Sphincter
FDA	Food and Drug Administration
FIM	First in Man
ICI-RS	International Consultation on Incontinence Research Society
ICS	International Continence Society
IFM	Institut Le Fer à Moulin
IM	Internal Magnet
ISD	Intrinsic Sphincter Defeciency
LE	Level of Evidence
MEMS	Myo-electro Mechanical System
MRI	Magnetic Resonance Imaging
MUCP	Maximum Urethral Closure Pressure
MUI	Mixed Urinary Incontinence
MUS	Mid-urethral Sling
NSAE	Non-serious adverse event
NIH	National Institutes of Health
OC	Occlusive Cuff
PPUI	Post-prostatectomy urinary incontinence
PRB	Pressure Regulating Balloon
PRC	Patient Remote Control
PROMs	Patient Reported Outcome Measures

PTFE	Poly Tetra Fluoro Ethylene
PWT	Pad Weight Test
RALP	Robotic assisted Laparoscopic Prostatectomy
RCT	Randomized Controlled Trials
RP	Radical Prostatectomy
SADE	Serious Adverse Device Effects
SAE	Serious Adverse Events
SNRI	Selective Serotonin and Norepinephrin Reuptake Inhibitor
SU-ACT	Sphincter Urinaire-Active Continence Therapy
SUI	Stress Urinary Incontinence
TP	Transscrotal
TS	Transperineal
TVT	Trans-vaginal tape
UI	Urinary Incontinence
UPP	Urethral Pressure Profiles
USDA	U.S. and Department of Agriculture
UUI	Urge Urinary Incontinence

1 INTRODUCTION

In Medical School, Urology was considered a General Surgical sub-specialty. It was reserved for a very select few imbued with this specific vocation, which I did not possess at the time, or so I thought. I then confidently embarked on a journey to become a well-rounded General Surgeon, in the traditional sense. Little did I know Urology would choose me when I landed a stand-alone training post as a Urology ST-trainee on the Isle of Wight, UK. There I met a Urology Consultant who convinced me otherwise and encouraged me to pursue a urological career in Sweden, propelling me into a world of clinical and academic possibilities. Through the most improbable and fortunate set of circumstances, and the support of my department at Karolinska University Hospital, I accepted a Fellowship at La Pitié-Salpêtrière University Hospital in Paris, which would launch the collaborative endeavor this thesis stems from.

During my Urology training, I recalled the unpopularity of the management of urinary incontinence amongst my peers. Robotic surgery for cancer pathologies was certainly trendier and more glamourous. Truth be told, our exposure to artificial urinary sphincter surgery was limited, owed to the fact that it is only performed by few urologists worldwide. As I met patients suffering from urinary leakage in clinic, I heard a recurring mantra, regardless of gender: '*I feel forgotten, alone, unheard, the medical profession isn't interested in my problem… it affects my intimate life, is there anything that can be done*?' I did not truly understand this plight until a friend and her totally urinary incontinent wheelchair-bound husband came to visit in Paris. I realized her incredible workload, composed of numerous daily washes from soiled garments and beddings, not mentioning the unpleasantness of the situation they faced daily. My eyes and ears were opened.

Did you know that in France, over 1000 of artificial urinary sphincters (AUS) surgeries in men and over 300 in women are performed per annum, with around 1/10 of that proportion at La Pitié Salpêtrière University Hospital? In comparison, about 150 cases in men/year are carried out in Sweden, the procedure being less offered in women. Consequently, my exposure as a Urology Fellow in Neuro-Urology and Reconstructive Surgery in Paris increased considerably. One day, my Main Supervisor Professor Pierre Mozer told me the story of his patient who, despite benefitting from the AUS, was completely dependent on his spouse for its manipulation and voiding, due to decreased hand function over time and weight gain, preventing him from visualizing and manually reaching the device. The struggle of this elderly couple prompted and motivated him to design a novel electronic device, aiming to offer a personalized continence, tailored to the patient's physical activities, functional and with less adverse events. The *'Smart AUS' p*roject was born. I was asked if I wished to be part of the adventure: my answer was '*Yes, of course*…'

The novel device's inception began in 2007. This thesis will take you through some of its developmental processes, from conception, literature review to risk analysis, device design and pre-clinical studies leading to the eve of its implantation in a First in Man (FIM) Trial. I will regale you with how a novel electronic implantable device saw the light, based on what is currently known of the 'Gold Standard'. Through its various developmental stopovers, I was guided by my patients, my exceptional supervisors, incredible Team of engineers, and Urology Staff Members, towards my growth into a better human being. I became a more insightful, compassionate surgeon/clinician and scientist, thanks to the knowledge and critical thinking process acquired along the way. My hope is to help my patients regain their continence, confidence, quality of life and most of all their dignity.

2. BACKGROUND AND STATE OF THE ART

2.1 Definitions

In the '7th *International Consultation on Incontinence-Research Society'* (ICI-RS), one defines **urinary incontinence** (UI) as "*Involuntary loss of urine that is socially and hygienically problematic".* UI may further be categorized into **urge incontinence** (UUI), known as "I*nvoluntary urine leakage accompanied or preceded by urgency"* and **stress urinary incontinence** (SUI) defined as "*Involuntary urine leakage on exertion or effort, or on sneezing and coughing"*. **Mixed urinary incontinence** (MUI) logically combines both UUI and SUI symptoms(1).
This thesis will focus on the surgical management of severe SUI secondary to intrinsic sphincter deficiency (ISD), defined by the ICS (International Continence Society) as 'A very weakened urethral closure mechanism'(2), described by a very low maximum urethral closure pressure (MUCP) on urodynamic evaluation.
Moreover, urethral hypermobility, otherwise known as bladder neck hypermobility (BNH), is not per se pathological and its etiology is poorly understood, therefore some authors have concluded that there was no real need for its definition (3,4). We must further define uncomplicated SUI in women, for this purpose, based on EAU guidelines 2020 definitions, as 'Women with no prior history of surgery, neurogenic lower urinary tract (LUT) dysfunction, bothersome genitourinary prolapse, and women not considering further pregnancy'. Whereas finally, complicated SUI will be defined as women with the presence of the above-mentioned conditions (5).

Surprisingly, there is no consensus to date regarding the objective cut-off values for clearly defining mild, moderate, or severe SUI, and neither is there a strict definition of cure after SUI surgery. Some authors have used a definition of cure rate of 'Less than 2 grams' when using the 24-hour pad weight test (PWT) as an assessment tool (6). This is largely owed to the fact that the 'Pad count', inaccurate to measure the exact quantity of urine leakage per day, has historically been used in urology practice. The '0-1 pad/day' or 'Social continence' and 'Zero pad/day' definitions have long been used in the literature to evaluate continence rate as primary outcome after SUI procedure. As a result, these considerations have contributed to a heterogeneity in published continence outcome data, as illustrated by published systematic reviews in both men and women, where none of the studies analyzed used the 24-hour pad weight test (PWT) instead of the pad count (7, 8).

To address this issue, a limited number of recent studies, have begun to use the 24-hour PWT for consistency in baseline continence evaluation and post-operative efficacy outcome assessment when considering continence as a primary endpoint, as illustrated by the MASTER study(7,8). The 1-hour pad weight test, shorter to obtain in practice and more standardized, may also be used but is less accurate, as it does not reflect the patients' symptoms during daily activities(9). Furthermore, the FDA (Food and Drug Administration, USA) has long recommended the use of the 24-hour PWT as a reliable tool for quantitative continence outcome assessment in trials using novel active implantable medical devices (AIMDs) for the treatment of moderate to severe SUI. This is stated in 'Guidance for Industry and Food and Drug Administration Staff Clinical Investigations of Devices Indicated for the Treatment of Urinary Incontinence' published on March 8, 2011(10).

2.2 Prevalence, and risk factors

Indeed, urinary leakage is a significant taboo health issue worldwide impacting health-related quality of life (HRQoL) in both genders (11,12). Today, depending on the chosen definition, prevalence

increases with age, 16-18% in women, and 5%-39% in males over the age of seventy (4–7). Quality of life is a recently evaluated concept, using validated questionnaires and patient reported outcome measures (PROMs), with however no existing consensus to date, as to which ones should be suited for research evaluating SUI surgery(17,18).

In men, radical prostatectomy or transurethral resection of the prostate are the leading causes for SUI, whilst in women vaginal delivery is the principal risk factor. Additionally, both men and women may be affected by obesity, neurological conditions such as stroke, diabetes mellitus, Parkinson's, or multiple sclerosis (MS), pelvic radiation therapy and pelvic trauma, all causative factors(19,20).

2.3 Pathophysiology of stress urinary incontinence

In women, two pathophysiological mechanisms are incriminated to explain SUI. The first is bladder neck insufficiency and urethral hypermobility due to a weak urethral support provided by the pubo-urethral ligament (PUL), and levator ani muscles via their relationship with the endopelvic fascia (21). The second is intrinsic sphincter deficiency (ISD). Both elements may coincide. However, many women with urethral hypermobility may not necessarily display UI symptoms (3). These pathophysiological considerations are intricately connected to complex fascia, muscles, and nerve supply to these structures. Any damage to the above may lead to urine leakage.

In men, complex combination of neuromuscular and anatomical factors is at play. The *internal sphincter* is responsible for passive continence and earlier return of continence after prostate surgery, promoting bladder neck sparing during RALP [LE 3, EAU guidelines 2020]. Similarly, the pelvic support, provided by *membranous urethral components*, i.e the pubo-prostatic and pubovesical ligaments, improve post-operative sphincter function, and therefore continence [LE 1b–3, EAU guidelines 2020]. Additionally, the *posterior musculofascial plate of Denonvilliers,* also known *as posterior fibrous raphe,* is reconstructed during surgery, thereby also improving PPUI [LE 2a–2, EAU guidelines 2020](22,23). Furthermore, *Fibrosis* is thought to play a role in the early onset of PPUI, through its negative influence on external urethral function (24,25). The *urothelium* is also essential for sphincter function, whose elastic structure affects urothelial coaptation (presumably around 5-10 mm) to ensure adequate continence, although we have little evidence to support this fact(22,25,26). Finally, various nerves also play a role, such as the pudendal nerve, the neurovascular bundle, the cavernous nerves, and the afferent innervation(9).The anatomical considerations of SUI applied to men and women are represented in figure 1. The full European guidelines are available on https://d56bochluxqnz.cloudfront.net/media/EAU-Guidelines-on-Urinary-Incontinence-2020.pdf.

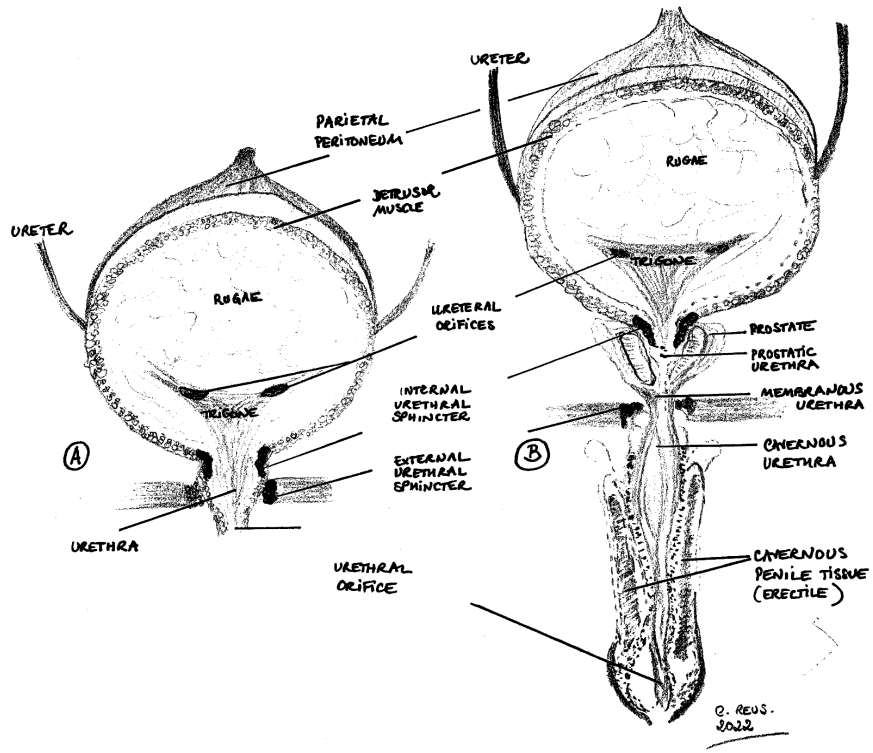


Figure 1. Frontal section of the female urethra (A) and male urethra (B)[1].

2.4 Diagnosing stress urinary incontinence

Typically, the patient suffering from SUI presents with urinary leakage on physical exertion, coughing, and any activity increasing intra-abdominal pressure, such as gardening or carrying heavy loads. Men having undergone RALP often describe a worsening of their symptoms towards the end of the day, when the external urinary sphincter is more 'fatigued'. Classically, patients also report the absence of urinary leakage when lying down. Invariably, they are restricted in their daily activities, and this has an impact on their quality of life.

Therefore, evaluating SUI includes thorough history taking, voiding diaries completion, objective quantification of UI by performing a 1-hour or preferably a 24-hour pad weight test to assess the severity of the pathology, and completing validated quality of life questionnaires, as a baseline reference.

A careful clinical examination should be performed, focusing on hand function and cognitive evaluation, previous inguinal hernia surgery scars, as well as perineal assessment that may impair AUS implantation. A flow rate and post-voidal residual must also be conducted to exclude overflow incontinence secondary to urinary retention for example or identify a pattern pathognomonic of urethral stricture.

[11] https://www.brainkart.com/article/Elimination-of-Urine_18828/

Complementary investigations may include a cystoscopy, to exclude urethral stricture, bladder neck stenosis, malignancy or urolithiasis that may need addressing prior to UI surgery. In women, care must be taken to seek a positive TVT-sign and/or urethral hypermobility, which could orientate towards the choice of a MUS or an AUS(27). Finally, urodynamic investigations may help identify the existence of pre-operative detrusor overactivity (DOA) typical in MUI, manageable pharmacologically and confirm ISD, where the maximum urethral closing pressure is very low. However, this is not routinely recommended. The findings of the above, along with the current literature knowledge, will help the clinician to provide proper pre-operative patient information, informed consent, and counselling, as well as manage the patient's post-operative expectations(28,29).

2.5 Management of SUI

In general, *mild* SUI responds well to conservative management, which include pads [LE 1b, EAU guidelines 2020], urinary catheters, external collection devices (convene) and penile clamps for men. Pelvic floor muscle training (PFMT), [LE 1b; EAU guidelines 2020] (30), lifestyle changes, such as weight loss [LE 1b, EAU guidelines 2020], smoking cessation [LE grade A], caffeine intake reduction [LE Grade B] and oral fluid intake measures [LE Grade C] may be recommended. Medications, such as anticholinergics or SNRIs may also be considered (31–34). *Severe* SUI usually tends to be refractory to conservative options. A 2015 Cochrane review (6 RCTs) showed that pelvic floor muscle training PFMT may speed recovery and showed short-term efficacy but not after 6 months (30). Pharmacological management such as anticholinergics is another aspect which showed no superiority of one agent over the other in terms of QoL improvement (31).

Other less invasive options include improving the coaptation of a weakened urinary sphincter by injecting a ***bulking agent*** around the bladder neck. This can be performed in outpatient clinic or in day surgery settings. For women suffering from *moderate or severe* SUI, with or without urethral hypermobility (LE 1a, EAU guidelines 2020), mid urethral slings (MUS) are currently recommended as a first-line surgical option(35). However, bulking agents [LE 1b, EAU guidelines 2020], or external non circumferential urethral compressive Adjustable Continence Therapy, such as the ACT® balloons (Uromedica, Plymouth, MN, USA) [LE 3; EAU guidelines 2020](30) may also be considered(36,37).

- *In Women with uncomplicated SUI*

A Cochrane review of fourteen RC or quasi-randomized controlled trials including 1,814 patients having undergone intraurethral injection of 7 various products (the most used being hydrogel, known as Bulkamid©), showed a tendency for short-term symptom improvement, although with higher complication rates, such as urinary infection or urinary retention(36,38–42). Additionally, two RCTs comparing bulking agents with open surgery for SUI demonstrated better efficacy with, however, more complication rates for open surgery (29,43)

- *In Men with SUI*

There is currently little evidence to support its efficacy in the surgical management of PPUI (44–46), with only one prospective trial, showing limited efficacy (47). Furthermore, there is weak evidence in favor of bulking agents improving QoL in men suffering from PPUI [LE3, EAU guidelines 2020].

The AUS on the other hand, is considered a second line surgical option, when all the above have failed. Today however, with the recent FDA recall on Mesh complications following prolapse surgery, the debate on AUS indication in women with moderate to severe SUI as a first line surgical option is very much alive (48). Although several high-volume centers (mainly in France where its first implantation began in the late 80's and has been since authorized by the French Health Authorities, Haute Autorité de Santé (HAS)), have published good long-term performance and safety outcomes (49,50), its practice remains limited worldwide to highly specialized centers (51). Its status is branded '*Off-label'*, as mentioned in the 2015 ICS Consensus conference report(52,53), with [LE 3; EAU guidelines 2020](30).

In 2017, when this thesis project began, there were no published systematic reviews analyzing female AUS implantation, whilst such review for male SUI had already been addressed by Van der Aa et. al in 2013(33). Female AUS surgery is now considered a subject worth of interest and is suddenly in the spotlight. This is illustrated by the rise in ongoing high-quality studies such as the *SU-ACT Trial*, a *'Prospective multicenter randomized controlled study comparing ACT® balloons to AUS'* in two parallel arms launched at La Pitié-Salpêtrière Hospital, Paris in 2015 (*ClinicalTrials.gov identifier: NCT02490917)* to provide much needed evidence on both therapies. The results should be published soon. Furthermore, the *VENUS trial,* led by the Leuven Team (Van der Aa), a '*Registry for patients undergoing AUS for Female SUI due to ISD*' commenced in October 2019 and should have been completed in February 2022 (*ClinicalTrials.gov identifier: NCT04114266).* This shift in practices paves the way for a novel AUS, which would also address female SUI.

Following a similar logic, *moderate* male UI may also be managed with ProACT® balloons (Uromedica, Plymouth, MN, USA))(54). The male sling is usually advocated in men with *mild to moderate* SUI and we evolved from a low level of evidence [LE 3, EAU guidelines 2020] (54,55) to high LE, thanks to the *MASTER trial,* a '*Noninferiority RCT comparing AUS to male slings'* published recently, which showed no difference in both procedures when using a 'Strict definition' of urinary incontinence. The authors reported that, men who benefit from the sling should however be informed of a higher re-catherization risk at 12 months post-surgery, are more likely to leak despite the surgery, and may be less satisfied compared with the AUS (7).Therefore, when considering *severe* male SUI, the AMS 800™ remains the 'Gold Standard', albeit with limited evidence [LE 2b, EAU guidelines 2020]. There is only one other RCT, comparing AUS with bulking agents (47); one French prospective study (56) and one systematic review (33), accounting for the low level of evidence in the literature(29).
It is worth highlighting the fact that, from an innovation perspective, there are no current ongoing trials registered with *ClinicalTrials.gov.* regarding AUS implantation. The MASTER trial is the very latest of high relevance. Interestingly, the *RELIEF II trial* (*ClinicalTrials.gov Identifier: NCT02288455*) assessed the 'Novel' GT urological AUS, later known as Aroyo®, a novel device in clinical phase, registered in 2014, which has gone bankrupt (57). Finally, the *SATURN trial*, the male equivalent to the *VENUS trial,* i.e., a multicentric prospective registry for men undergoing SUI procedures, launched in 2017. The preliminary results were published last year, and the authors concluded the study will be valuable to assess long-term performance, safety, and quality of life after SUI surgery in the coming years(58). The creation of patient registry fits the current need for sound post-market follow-up for implantable devices, to avoid similar scandals, as seen with Prolapse Mesh mentioned above, or more recently, the PIP breast implants. The management of SUI is summarized in figure 2. The surgical options used for the treatment of moderate to severe SUI will be described in detail in paragraph 2.8. '*Identifying the competition'.*

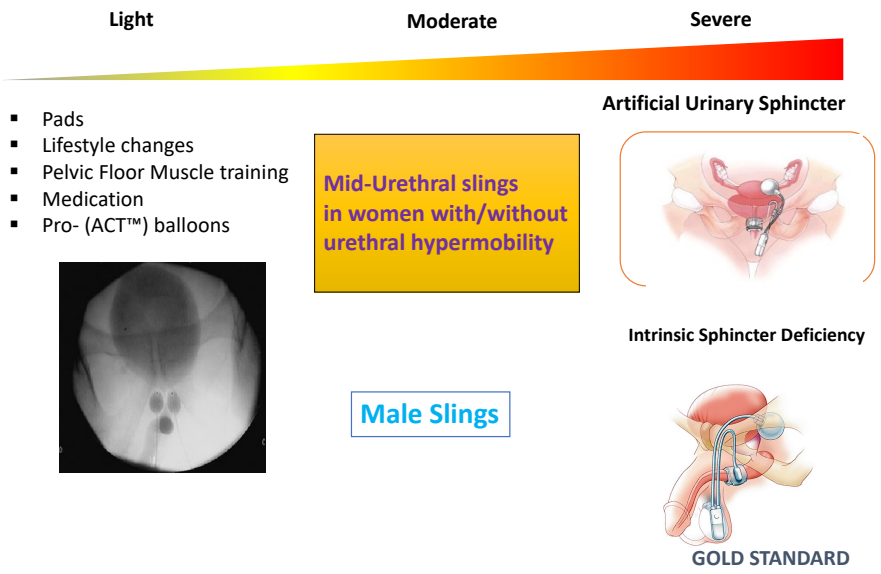


Figure 2. Management of stress urinary incontinence (SUI) in men and women[2].

2.6 The conundrums of the 'Gold Standard'

2.6.1 *The AMS 800 ™*

We have established that the AMS 800 ™ is the device of reference for the surgical treatment of severe male SUI, offering the advantage over all other SUI surgical procedures to allow the patient to preserve the perceived ability of normal micturition. This three-piece AUS consists of a fluid-filled inflatable occlusive cuff (OC) inserted around the bladder neck (in women, and male neurogenic patients) or the bulbar urethra (in men). A hydraulic control pump located in the scrotum (in men) or labia majora (in women), and a pressure-regulating balloon (PRB) placed pre- or intra-peritoneally complete the device, all pieces being connected with one another by kink-resistant tubings during surgery. The PRB is available in various pressures, 51-60 cmH_2O (rarely used); 61-70 cmH_2O (recommended and most implanted); 71-80 cmH_2O, 81-90 cmH_2O and 91-100 cmH_2O. Different cuff sizes exist, ranging from 3.5-11cm. The patient deflates the OC by pressing the pump manually, thus transferring the fluid contained in the OC to the PRB. Thanks to a pressure gradient from the PRB via a pump-located resistor, the OC refills passively, and closes around the urethra, thereby providing continence. An acute pressure transmitted from the PRB to the OC is prevented by this valve-like mechanism (figure 3). This device was described by Scott et al. In 1973(59).

Two major modifications later altered the initial device design over the years. The first was the creation of the narrow-backed cuff in 1987 responsible for a decrease of urethral erosion by 10%, solving only partially the issue(60). The second improvement was the introduction of an antibiotic coated version in 2008, the InhibiZone® (61). Contrary to the former improvement, and as opposed to penile prosthesis, the second failed to show any significant advantage compared to the non-coated model (53,62).

[2] ProACT™ X-ray image courtesy of Prof. E. Chartier-Kastler; female and male AUS: Copyright© granted by Boston Scientific.

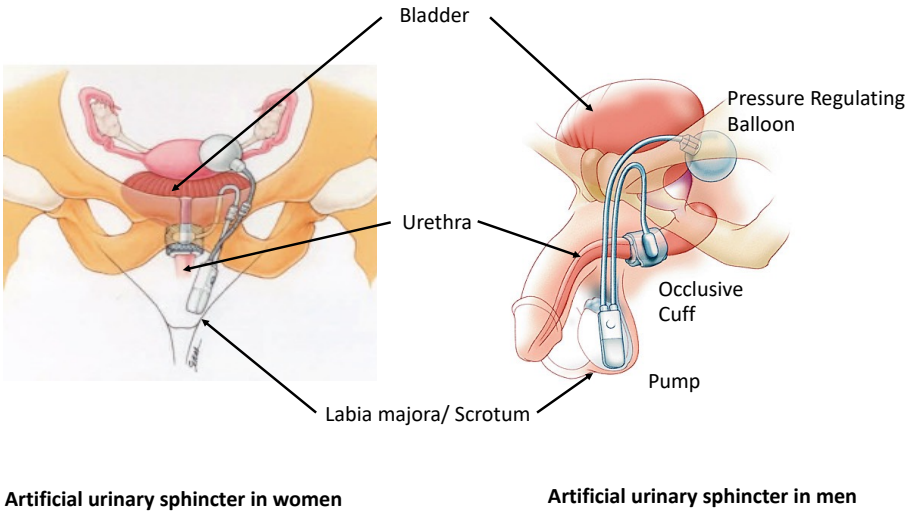


Figure 3. The AMS 800™ and its components (American Medical Systems, Boston Scientific, Minnetonka, MN, USA). Copyright© granted by Boston Scientific[3].

2.6.2 The issues of the AMS 800™

Although the AUS has proven its performance and safety over the years, it presents several inconveniences worth addressing(63,64) when designing a novel AUS device:

a) ***A Lengthy intra-operative device preparation***

AUS device components preparation prior to implantation are currently time consuming. Reducing this step would also decrease the overall procedure length, therefore minimizing intraoperative bacterial contamination of the operating field and implant itself.

b) A Challenging procedure

Implanting the AMS 800™ is complex, in part due to the difficulties of its assembly stated above, costly, and mostly reserved to a few high-volume centers worldwide.

c) It's a mechanical device!

The AMS 800™ is made of high-quality silicone and Titanium components in the pump. It is therefore exposed to increased infection risks (3-27%), as well as mechanical failures (2-13.8%) responsible for up to 25-30% device revisions at 3 years (33). As such, it doesn't escape limited longevity, with an average device survival of 8.7 years in men and 11.2 years in women (65), leading to high overall intervention rates of 25% at 3 years, 50% at 5 years and 100% at 10 years in men(33).

[3] Female AMS 800™ implantation reproduced from *Roupret M, Chartier-Kastler E, Richard F. Sphincters urinaires artificiels chez la femme: indications, techniques, résultats [Artificial urinary sphincters in women: indications, techniques, results]. Prog Urol. 2005 Jun;15(3):489-93. Copyright © 2005, published by Elsevier Masson SAS. All rights reserved.*

d) Poor ergonomics

Many patients find the fact of touching their genitals to manipulate the pump every time they need to pass water very uncomfortable. In women, merely pressing the pump a couple of times results in urine leaking on their fingers before they can void. Additionally, the implant is not suited for patients with hand function impairment (as in arthritis/arthrosis), poor eyesight or cognitive impairment. In short, the device is not user-friendly and excludes patients that could benefit from it (63,64).

e) Occlusive cuff erosion and urethral/spongiosal atrophy

Furthermore, the system applies a *constant* peri-urethral pressure in the OC, defined perioperatively at around 65cmH_2O (61-70 cmH_2O), untailored to the patient's position or physical activities. As a result, *urethral atrophy* occurs over time, most likely secondary to decreased urethral vascularization of the spongial urethra, responsible for ischemia of the underlying corpora spongiosum, which may eventually lead to urethral erosion.

This phenomenon was long imputable, in the literature, to solely *'Urethral atrophy'*, and further research is needed to elucidate whether the urethra or the corpus spongiosum or both are affected by ischaemia-attributed atrophy(64,66,67).

Consequently, the OC ultimately no longer adequately fits around a smaller urethral diameter and therefore, insufficient occlusive pressure is conveyed, resulting in gradual recurrent UI onset(67). There follows a clinically significant reintervention rate of 25%, that cannot be overseen(33). However, there are additional causes for progressive recurrent UI after AUS surgery, such as patient-related factors, peri-operative choice of OC and the loss of pressure in the PRB with time. Indeed, some authors showed that spongiosal atrophy could also be related to prior radiotherapy and prolonged timeframe between prostate cancer management and AUS surgery(57). Oversizing the OC during primary AUS implantation can equally account for persistent post-operative UI(69). Other authors were first to attribute recurrent UI to the inability of the PRB to generate enough pressure to ensure continence secondary to an intrinsic loss of pressure over time, possibly related to increased porosity of the silicone with time, rather than merely urethral atrophy. When conducting a capsulotomy during AUS revision, the urethra would regain its normal diameter(67,70). This is one of the main issues the novel AUS from this thesis will aim to address. We will develop this in another paragraph.

f) Sitting and Persistent UI

Depending on the definition used, the AMS 800™ provides 59-90% continence rate when adopting the *'Zero to 1 pad/day'* definition and only around 60% when using the dry continence rate or *'Zero pad/day'* definition (33,71). In clinical settings, most men complain of residual urinary leakage, albeit in minimal quantities, in orthostatic settings (from sitting to standing for e.g.). Indeed, being seated on a hard surface induces an increased applied pressure to the OC, causing fluid transfer from the cuff to the PRB via the pump resistor, leading to temporary UI when the patient rises. This illustrates another situation where the AMS 800™ cannot adapt peri-urethral pressure to the patient's activity or change in intraabdominal pressure, as is the case here. The authors demonstrated that the effect and the time required to repressurize the OC depended on the duration of the compression. And so, for 5 seconds of compression at 150 cmH_2O, 68 seconds were required for full cuff re-pressurization and for twenty seconds of compression at 250 cmH_20, an entire 207 seconds were needed for the pressure in the OC to normalize (61,62). Therefore, many men will still wear a *'Security pad'* for such occurrences. This knowledge will help the urologist to reassure the patient and give counsel to avoid sitting on hard surfaces for instance.

g) Iatrogenic urethral erosion due to traumatic urethral catheterisation

Despite all the above-described scenarios, the most usual etiology for urethral erosion remains however iatrogenic traumatic urethral catheterization, often by untrained health care professionals, ignorant of the fact that the AUS device requires deactivating prior to the procedure. This unfortunately accounts for a high number of unnecessary and onerous device explantations every year that could easily have been avoided(74,75).

h) MRI compatibilty

MRI compatibility is the bane of all active implantable medical devices. The AMS 800™ is labelled *'MRI conditional'*, meaning it has not shown any hazards when placed in a specified MRI setting, with well-defined circumstances of use. One strives for a novel AUS to be labelled as *'MRI safe'*, only possible should the device be biological, which is impossible to consider today. Therefore, all AIMDs strive to be at the very least *'MRI conditional'* (64). Figure 4 summarizes the problems all novel AUS will attempt to solve for the design of the ideal AUS.

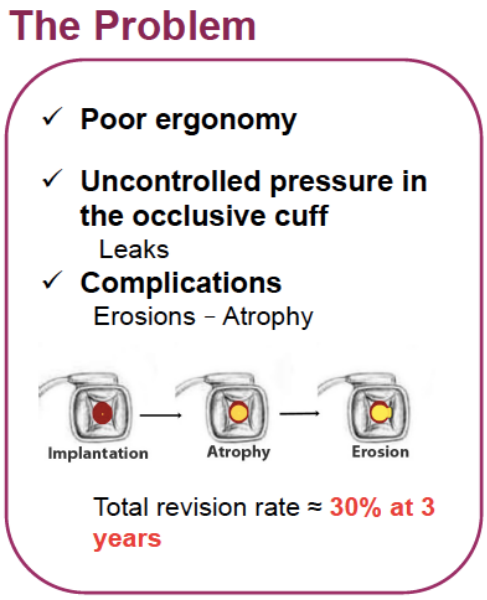


Figure 4. Summary of the main issues presented by the AMS 800™[4] -

2.7 A Smart Solution: A novel electronic AUS (eAUS)

To overcome the obstacles of its direct competitor the AMS 800™, a novel electronic artificial sphincter or eAUS, is currently being developed. Its concept is based on dynamic adjustments of the occlusive peri-urethral cuff pressure tailored to the patient's activity. The device comprises a pacemaker-sized control unit (CU) that automatically detects circumstances of increased bladder pressure and controls the peri-urethral occlusive pressure.

Demonstration that automatic urethral occlusion and continence could be achieved was established thanks to *in vitro* and *in vivo* experiments on isolated goat urethra(76). From the AMS 800™ the device has kept the Occlusive Cuff principle, placed either around the bulbous urethra (male) or

[4] Image courtesy of Professor P. Mozer.

bladder neck. However, both control pump and PRB are replaced by a mecatronic device i.e., a battery-powered myo-electro-mechanical system (Mems), contained in the CU, which is implanted sub-cutanously. Thus, the device adapts the pressure applied to the urethra to the patient's activity and therefore claims to improve safety by decreasing erosion risks and improving ergonomics. The pressure generated by the device is controlled by the patient via a handheld *Remote Control (PRC)*. The implanted device can be programmed by a clinician using the *Clinician Programmer (CP)*. An Accessory Kit (AK) is also provided, which includes surgical tools required for device implantation. (Figures 5-6).

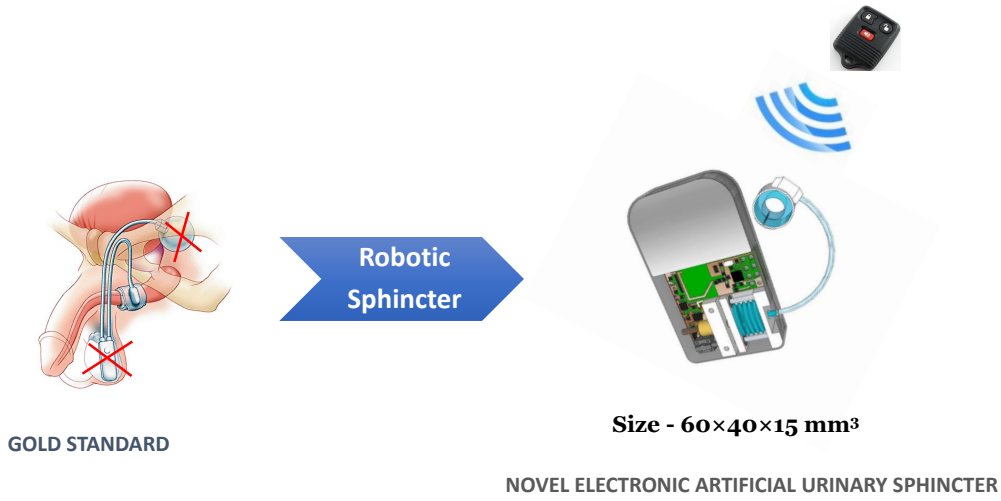


Figure 5. The novel electronic Artificial Urinary Sphincter (eAUS)[5]

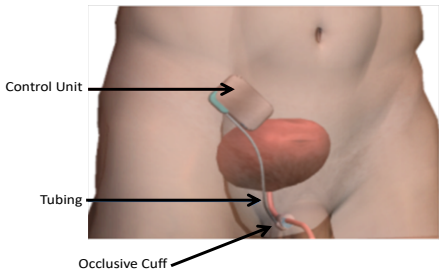


Figure 6. The implanted UroMems device and its components

The device comes with several patented functions to prevent potential adverse events as outlined above and thereby addressing the drawbacks of the AMS 800™:

[5] Image courtesy of Professor P. Mozer - Copyright© obtained from Boston Scientific.

1. ***UroActive®:*** is a function that adapts peri-urethral pressure to the patient's physical activity. At night the pressure applied would be at its minimum. This function aims to reduce ischemia-related urethral atrophy and erosion(33,64,66,67,69,70)
2. ***UroCath®:*** opens the OC automatically by detecting the catheter intra urethrally and therefore aims to minimize iatrogenic catheter-related OC erosions (33,74,75).

The eAUS aims to improve ease of implantation and manipulation whilst offering optimal continence with maximum safety, and in so doing revolutionize the existing options for the management of SUI.

2.8 Identifying the competition

In this step, a closer literature analysis of other passive and active devices for the management of SUI in both men and women allows for the novel AUS to identify which surgical options it is up against, not only from a developmental and surgical technique viewpoint, but also from a marketing perspective.

2.8.1. Slings

- *In Women with uncomplicated SUI: Mid-urethral slings*

MUS are the most frequently performed in Europe for surgical management of female SUI. These can be non-autologous (made of polypropylene non-absorbable monofilament microporous mesh) or autologous (derived from the rectus abdominis aponeurosis or fascial slings). Short-to midterm safety outcomes in a population-based study showed similar complication rates when comparing mesh and non-mesh surgery for UI (78). This is further supported by a Cochrane review from 2017, which backed these findings, regardless of the route adopted(78). However, despite a good short-midterm safety profile, there is a lack of published long-term efficacy and safety data. The E-TOT study, a RCT published in 2017 showed a patient-reported success rate of 71.6%, regardless of being performed inside-out or outside in, an overall 8% re-do procedure with tape extrusion/erosion rate of 4.5% at 9 years follow-up (29,79,80)

According to the 2016 Cochrane review, *colposuspension* showed overall comparable continence rates of 85-90% at five years after surgery with *MUS*, with however, no difference in objective efficacy outcomes (81). When comparing colposuspension with *autologous fascial slings*, 5-year continence rates were higher in the fascial sling group, 24% and 31% respectively with higher satisfaction rate in the latter and comparable adverse events rates of 10% in each group, as shown in a RCT(82). However, post-operative LUT dysfunction seems to be higher in the MUS group (81).
A Cochrane meta-analysis of MUS for the treatment of female SUI, as well as the TOMUS trial, a RCT comparing retropubic versus transobturator MUS, showed comparable subjective short-to midterm cure rates in both groups(83,84).

Finally, there is no evidence that adjustable MUS are more effective to treat or improve SUI in women compared to standard MUS, neither is there evidence that single incision MUS have more, or less adverse events rates as opposed to conventional MUS(30).

- *Male slings for the treatment of mild to moderate SUI*

Introduced to treat PPUI, these are inserted sub-urethrally and fixed via a retropubic or a transobturator approach. Tension adjustment occurs peri-operatively and is definitive. They offer the advantage to be less invasive, allow spontaneous micturition, and are more affordable compared to the AMS 800™(85). Two types of male slings are described: the *fixed* and the *adjustable* sling. Their

mechanism of action can further be subdivided based on continence obtention by *urethral compression* or by *urethral bulb repositioning*.

- In *fixed male slings* category, we explore:

a) *Continence by urethral compression:* ***Istop TOMS*** *(CL Medical, France)*

As previously mentioned, the fact that there is no consensus on cure rate definition makes it difficult to compare efficacy outcomes across studies due to their heterogenic nature. There are no RCT supporting its long-term efficacy, patient satisfaction or adverse outcomes. Three prospective single center French studies with limited patient number and variable end-point definition show success rates of 82.4% and 87% at 12 months follow-up(89–91).

b) Continence treatment by urethral bulb repositioning: ***AdVance*** *(Boston Scientific, USA)*

A recent systematic review with meta-analysis showed significant efficacy outcome heterogeneity. The AdVance sling constitutes 31% of implanted slings with *'Objective cure rates'* ranging between 9-87%(86). It presents post-operative LUT dysfunction between 1.3-5.7%, and overall failure rate of 20%, with negative prognostic outcomes in patients having undergone salvage radiotherapy(86,89,90).

- *Adjustable male slings*

Designed to adapt the tension of the sling after the procedure, to decrease post-operative LUT adverse events, they are positioned at the bulbar urethra proximally, with traction sutures surgically inserted in a retropubic fashion. Three main systems exist, the Remeex® Sling System (Neomedic International, Terrasa, Spain), the Argus® system (Promedon, SA, Cordoba, Argentina) and the ATOMS system (Agency for Medical Innovations. A.M.I., Austria). Again, there is poor evidence regarding their long-term efficacy due to the largely prospective/retrospective nature of published data, variable follow-up, and lack of consensus on cure rates definition. They constitute 23.6% of implanted slings according to a recent systematic review and meta-analysis(86).

  - *Remeex® and ATOMS® systems*

There are no RCT to assess its long-term efficacy and safety outcomes. However, another systematic review and meta-analysis comparing ATOMS® and REMEEX® published last year showed efficacy outcomes using '*Dryness rate'* as definition for ATOMS of 69.3% compared to 53.4% with REMEEX. There was a significantly higher complication rate of 35.8% for REMEEX system as opposed to 18.9% for ATOMS as well as higher explantation rates for REMEEX versus ATOMS of 13.9% and 5.5% respectively. The paper cited once again heterogeneity in outcome reporting rendering it complex to compare data(86,91).

  - *Argus® system*

There is, again, very few data reporting long-term efficacy and safety outcomes for this adjustable system. Success rates, based on *'Subjective cure'*, ranged between 17-91.6%, with reported readjustment rates ranging between 22.9-41.5%, infection rates of 5.4- 8%, erosion rates of 5-10% and explantation rates of 10-15%(86,89,92–94). The results of a multicentric prospective study will be presented at the next EUA 2022 meeting (results are currently unavailable on Embase for discussion) (95).

In summary, the evidence is too scarce to support that, adjustable slings cure or improve PPUI, or prove one sling type's superiority over another (LE 3).

2.8.2 Urethral compression devices for the treatment of complex SUI

These may be categorized into '*Non-circumferential'* and '*Circumferential'* devices:

- *Non-circumferential adjustable compression devices*

  - *In women*

in Europe, these devices are still currently indicated for the management of recurrent SUI after previous UI surgeries were unsuccessful. This is often the case of women with severe SUI, a positive TVT test and the absence of urethral hypermobility on clinical examination. The most routinely used is the adjustable compression therapy **(ACT©)** device (Uromedica, Plymouth, USA), in which, under ultrasound or fluoroscopic guidance, two inflatable spherical balloons are inserted on each side of the bladder neck. The volume of each balloon is adjusted several weeks post-operatively via a subcutaneous port located within the labia majora. This device is considered investigational by the FDA in the USA.

Once more, the level of evidence for its use in complex SUI is low (LE 3)(29), all case-series based reporting an 'Objective' cure rates from 47% to 100%, with patients requiring nevertheless several volume adjustments to reach the desired continence effect. Reported explantation rates of 21%, elderly women and those with prior radiotherapy being particularly at risk (27,43,48,96–98).There is only one systematic review on the subject(99).

Whether the ACT© is better than the artificial urinary sphincter in terms of long-term efficacy and safety outcomes is a question for the ongoing *SU-ACT trial*. A small cohort study seemed to be in favor of the AUS, but the nature of its design does not allow for conclusions to be drawn at this stage(100).

  - *In men*

The equivalent in men is the **ProACT®** system (Uromedica, Plymouth, USA), also considered investigational by the FDA, composed of two balloons placed on either side of the bladder neck via a small perineal incision. Similarly, the balloons are gradually filled with an isotonic solution through the tubing connected to an accessible titanium port, which is implanted subcutaneously on the posterior aspect of the scrotum. Post-operative balloon volume adjustments are done through the ports.

As previously stated for women, the level of evidence for this device in men is also low (LE3), with reported functional outcomes of 68%, explantation rates ranging between 11-58%, with however up to 50% experiencing persistent UI(101–103). More recently, a retrospective multicentric study including 515 men showed a statistically significant reduction in pad weight at 24 months follow-up, with however persistent UI after the procedure of 123 g/day and high complication rates of 22.5%, namely balloon failure(104)

- *Circumferential compression device*

The AUS presents the advantage over other SUI surgeries to preserve the sensation of being able to pass urine normally (105), and is classified as an active implantable medical device AIMD of class III (which bulking agents, slings and adjustable balloons are not, since they are passive). The AMS 800 ™ being the Gold Standard' in this category, it is therefore logical this device will constitute the reference against which the eAUS device will be compared to. Although it is important to be

acquainted with the existing surgical alternatives for SUI, a closer analysis of other circumferential compression devices is of relevance.

- *In women*

Interestingly, only the AMS 800™, the ARTUS/MyoPowers, the Uricontrol® and the UroMems devices will cater to SUI in women. From the following literature review, it became apparent that we did not have enough data regarding the AMS 800™ long-term efficacy and safety profile to complete a risk analysis on its implantation in women. We have addressed the issue by conducting a systematic review with a meta-analysis, which will be further detailed in the next paragraphs composing this thesis.

At the time this thesis begun there was a paucity of data to support the use of AUS in women. All published information is of retrospective nature with often limited cohort numbers, with heterogenous efficacy outcomes definitions and variable follow-up lengths(106). The largest cohort was published by Costa et al. with a cohort of 344 women, presenting a dry rate of 85.6%, a 5- and 10-year device-survival of 88.6% and 69.2% respectively at 9 years follow-up(27). Long-term safety outcomes report mechanical failure requiring revision and explantation (5.9-1.5%), with worst outcomes described with older age, previous Burch colposuspension and pelvic radiation(107). Common adverse events also include perioperative urethral, bladder, vaginal, and rectal injuries (27).

This begs to ask the question whether the AUS should be offered to a selected group of women, i.e., those with severe SUI, negative TVT test and fixed urethra, as a primary SUI procedure to avoid overly complex and morbid AUS insertion in multiple operated women(48). The debate is open.

Some centers in France have reported laparoscopic AUS implantation in women, however the evidence to support its safety compared to open surgery is too thin(108). Similarly, some large-volume centers have even begun to perform robotic AUS revisions as day-case procedures with promising results. Long-term data and prospective trials are needed to corroborate these findings(50,109–112).

- *In Men*

Invented by Mr Scott and Gerald Timm (who later became the founder of GT-Urological) the **AMS 800™** (Boston Scientific, Marlborough, MA, USA, formerly AMS, USA) has been the reference for the treatment of PPUI refractory to conservative management [LE 2b, EAU guidelines 2020] and has been on the market since 1973(29,33,59). The main question relevant for the development of the novel AUS is "*What are the adverse events reported in the literature to date?"*. This is essential to complete a thorough risk analysis of potential adverse events to be expected with the novel device.

One systematic review by Van der Aa et al., summarized the literature findings on the efficacy (continence outcomes) and safety features (adverse events) of the device. These findings would be extrapolated to the eAUS device and help conduct the risk analysis. Based on heterogeneous data due to varying definitions of cure rates, as well as variability in follow-up periods, the reported **efficacy outcomes**, i.e., dry rate ranged from 4.3-85.7%. Depending on the definition used, the reported '*0-1 pad'*/24h rate was 79% and the '*0 pad'*/24h rate was 43.5%. **Safety outcomes** according to the same systematic review, showed an overall of 8.5% infection/erosion rates, 6.2% mechanical failure rates, 7.9% urethral atrophy, 26% re-intervention rates (33).

Furthermore, the *MASTER non-inferiority RCT* comparing male slings and AUS results helped us consolidate the Risk Analysis, using the 24-h pad weight test as efficacy assessment tool. This study

included 380 men and showed at 12 months comparable continence rates of 87% for male slings versus 84.2% for AUS, few serious adverse events (SAEs) and high satisfaction rates in both groups(7).

2.8.3 Novel AUS devices in pre-clinical development phase

Like the eAUS urinary sphincter device, innovative devices strive to address the limitations of the AMS 800™ as previously outlined, by offering a patient-personalized, surgeon-friendly, safe, efficient, functional, and affordable AUS. In the seventies, novel devices were not subject to today's regulatory constraints. Therefore, to develop a novel AIMD today takes an extraordinary amount of time, is onerous, and can unfortunately fail, as illustrated by the TMOD (GT-Urological). The bankruptcy of the latter has further highlighted the importance of *post-market follow-up studies* to ensure long-term patient safety. All AIMDs in development wish to obtain the *CE marking* for marketing access purposes, with the promise of equivalent/higher *reimbursement* possibilities to the device of reference. But first, these devices currently in development *must* establish at least an efficacy/performance and safety profile comparable to the 'Gold Standard'.

We have compiled the following AIMDs showing potential as future PPUI treatment options and/or SUI treatment in women: 1. the *VAD* ; 2. *Uricontrol*® (Implantica AG, Zug, Switzerland); 3. *ARTUS MONO* (Myo- Powers Medical Technologies); 4. *Magnetic Artificial Sphincter* (MARS); 5. *The Politano-Sayet-Sutherland Flow Control Device* (PSS-FCD, Precision Medical); 6. the *Novel remotely-controlled artificial urinary sphincter*; 7. *TMOD* (Tape Mechanical Occlusive Device (GT Urological LLC); and 8. *the Magnetically controlled Endourethral Artificial Urinary Sphincter*. Pre-clinical pilot/pivot studies are necessary to obtain CE marking

2.8.3.1 VAD

In summary, this AUS *two-piece* device includes a sensor automatically adept in detecting bladder pressure variations circumstances and subsequently adjusts the peri-urethral occlusive pressure. That urethral occlusion and continence were achievable was demonstrated during *in vitro* and *in vivo* experiments on isolated caprine prior to the start of the thesis (76). Pre-clinical pilot studies in human cadavers and wether model are at the core of constituent papers V and VI, which will be covered in the relevant sections.

2.8.3.2 UriControl® (Implantica AG, Switzerland)

This device was developed by Implantica AG, a company founded by Peter Forsell, a Karolinksa Institute graduate, General surgeon turned billionaire, known for its lead CE marked product RefluxStop™, a 'Passive medial implant for gastro-oesophageal reflux'. Like the VAD device, it is a remote-controlled smart, urethral closure pressure-regulating system also catering to both genders with refractory SUI, claiming to reduce complications, improve ergonomics and device efficacy. However, contrary to the VAD device, the rechargeable wireless AIMD seems to be implantable under the skin. There is no information whether the occlusive cuff is similar to the AMS 800™ or, if not, which materials constitute the OC. There are, however, no published bench experiments or pre-

clinical studies to date. According to the company's website, cadaver studies are ongoing[6]. The device is represented in Figure 7.

Figure 7. UriControl® (Implantica AG, Switzerland); Copyright® granted by Implantica AG[7].

2.8.3.3 ARTUS MONO (MyoPowers, France)

The ARTUS MONO AUS possesses a silicone urethral cuff which is cable-controlled by an electromechanical implant placed in the lower abdomen. Its remote opening function enables the patient to void. A wireless interface allows the clinician to make post-operative, personalized, non-invasive modifications. Like the above-described AUS, it aims to decrease the constant peri-urethral pressure application, responsible for the ischemia-induced urethral atrophy, by exerting of sequential pressures. Pre-clinical studies in 19 sheep demonstrated that the device could ensure continence(113) and further studies in six human cadavers have established its feasibility and ease of implantation(114). A clinical study was conducted in 2018 in 3 female patients in one French center for feasibility of implantation, safety, and efficacy evaluation. The device was 'Temporarily' implanted in patients due to undergo 'Anterior pelvic resection' for bladder cancer. The study was registered on Clinical Trials.gov (*NCT03703843)* and is now completed. The results of this trials have not yet been published[8]. Another safety and clinical Performance '*Interventional, prospective, non-randomized open-label single arm multicentric'* study prior to obtaining CE marking has been registered on Clinical Trials. Gov (*NCT04827199)* and recruitment process is yet to commence[9].

2.8.3.4 MARS

This magnetic AUS is meant to be inserted (or removed) endourethrally, in a minimally invasive fashion, as a day case. Like the above devices, it is also intended for both male and female patients. The prototype is composed of an internal magnet (IM) and a 'Unidirectional polymeric valve' constituting its core, capable to adapt the opening pressure. An external magnet controls the IM, thus regulating the urine flow. During Bench tests (simulation experiments), opening, closing, and holding forces were calculated. X-ray images confirmed that the system did indeed open/close. *Ex vivo* studies on human cadaver have been conducted and according to the authors, showed that the system could provide continence, as well as modulate the urine flow at will(115). The advantage of the device would be to require a less invasive procedure, to potentially decrease mechanical failure rates and not

[6] https://www.implantica.com/media/press-releases/2021/implantica-successfully-performs-cadaver-implantations-of-pipeline-products-and-several-related-tests-at-the-cadaver-lab/.
[7] https://www.implantica.com/product-pipeline/prioritized-products/urology/urinary-incontinence/
[8] https://clinicaltrials.gov/ct2/show/NCT03703843?term=artificial+urinary+sphincter&cond=Urinary+Incontinence%2CStress&draw=2&rank=4.
[9] https://clinicaltrials.gov/ct2/show/NCT04827199

to be dependent on manual dexterity. There have been no further developments regarding pre-clinical animal biocompatibility and/or performance studies since 2017.

2.8.3.5 PSS-FCD (Precision Medical),

The Politano-Sayet-Sutherland Flow Control Device has gone through six prototype stages. It is a fluid-free, remote-controlled, *three-piece* AUS composed of a control/battery pack (CBP), a cable/valve element with anvil/cap segment, consisting of a plunger placed around the urethra and a wireless Bluetooth operated remote control. The plunger is opened and closed by the CBP, which is adaptable, by telemetry, to 10 different closure force settings. In a healthy urethra, normal closure pressure ranges from 75-100 cmH2O and the external urethral diameter is estimated at 8mm (24Fr). The PSS-FCD can clamp the urethra over a surface of 75 mm^2. The clamp force may also be adjusted to obtain fluid flow occlusion. According to the authors, Phase I, IIa and IIb implants, as well as bench tests, enabled the improvement of Bluetooth telemetrically activated AUS/valve. Also, animal studies performed on dogs have established histologic compatibility, ease of feasibility and performance/safety on 4 animals without reported complications over a 1-year period(116,117).

2.8.3.6 The novel remotely- controlled AUS

This is *four-piece* AUS also uses Bluetooth technology. The authors claim it to be affordable, functional, hydro-mechanical, and AMS 800™ components-compatible. It consists of a small electronic pump implanted close to the PRB, aims to minimize energy expenditure, and decrease mechanical failure with subsequent revision rates. This newest AUS would offer ease of implantation and remote peri-urethral pressures adjustments. The authors have demonstrated that continence could be achieved during animal testing. Nevertheless, additional *in vitro* and *in vivo* animal studies for histocompatibility, performance and safety studies are necessary. No additional data has been published since 2013(118).

2.8.3.7 TMOD

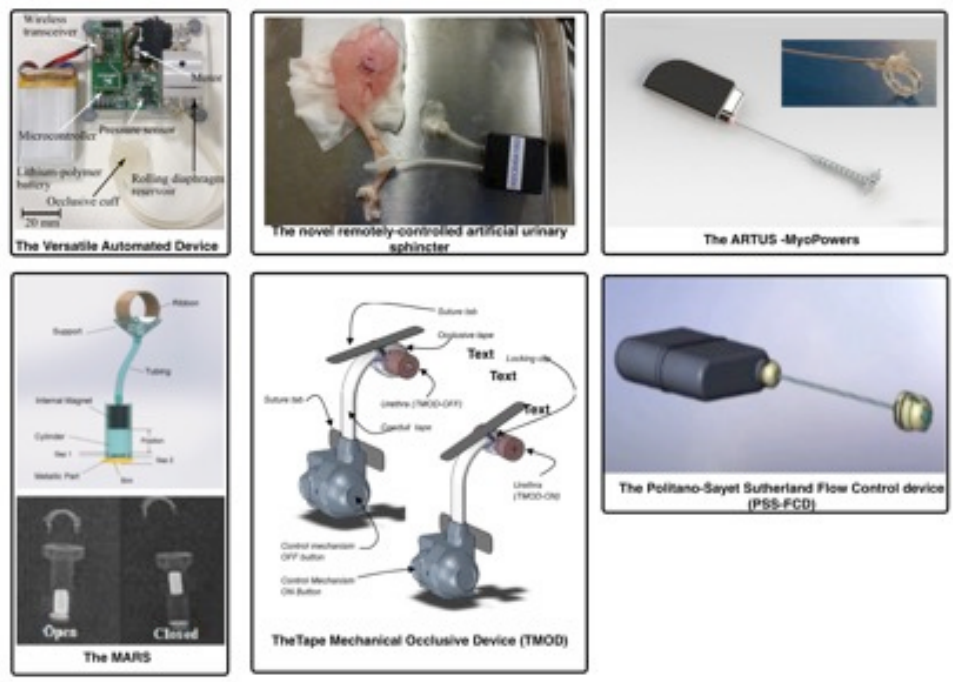
The Tape Mechanical Occlusive Device is a single-piece, non-hydraulic AUS, which is in fact the precursor of the GT-Urological. Hand-controlled by the patient, thanks to an on/off switch, it consists of occlusive tapes made of Poly Tetra Fluoro Ethylene (PTFE) and a control boot coated with silicone, containing a spring composed of a nickel-cobalt chromium alloy. The pressure around the urethra can be adjusted thanks to an injectable port. A peri-urethral pressure of 50–80cmH2O is applied through the occlusive tape, when the switch is ‘on’. When the switch is ‘off’, the pressure around the urethra diminishes, allowing the patient to pass urine. The authors claim that intraoperative injuries to the urethra could be avoided, since the narrow occlusive cuff may need less dissection, therefore facilitating the device’s implantation.

Pre-clinical animal studies in three bitches with the TMOD device implanted around the bladder neck have been previously conducted. Device functionality was established at two- and nine-weeks post-device implantation. The AUS was activated at two weeks postoperatively and was deactivated for three- and 30-minutes periods per day. No macroscopic or histological features of infection, erosion or necrosis were reported. Pre-clinical studies in three male cadavers have also been completed. No macroscopic or microscopic infection, erosion or necrosis signs were reported. Further pilot studies for performance and safety evaluation will be described in the GT-Urological/Aroyo prototype(119).

2.8.3.8 Magnetically controlled Endourethral Artificial Urinary Sphincter

Like the MARS, this novel AUS is made of a valve in polymer and a magnetically energized system constituting its core, able to adjust opening urethral pressures, therefore modulating its pressures to the patient's physical activity and increased intra-abdominal pressures. The authors claim its ease of implantation in day surgery settings thanks to minimally invasive endoscopic procedure. Bench tests and pre-clinical studies on a female cadaver showed the device's implantation feasibility and functionality, but also demonstrated that continence could be achieved; urination could be prevented for intra-vesical pressures reaching 16 kPa (163.15 cmH_2O)(120).

This device has several drawbacks, namely biocompatibility for its aluminum alloy, Polydimethylsiloxane or PDMS, and the Nitinol components that need to be demonstrated. Furthermore, pre-clinical trials assessing the device's valve durability, performance and safety are required. Finally, there is the issue of device migration into the bladder, necessitating the design of a functional distal anchoring system. Also, if the device claims to cater to both genders, additional studies in male cadavers are necessary. No further trial results have been published since 2017. Novel devices in pre-clinical phase are summarized in figure 8.



Reus, Grilo, Chartier-Kastler, *BJUI Knowledge* (2019)

Figure 8. Novel AUS devices in pre-clinical development phase[10]

2.8.4 Novel AUS Devices in Clinical development phase

The devices in clinical phase include: 1. The ***VICTO™*** **/VICTO PLUS™**, previously known as *FlowSecure™*(Sphinx Medical, Bellshill, UK/Promedon, Cordoba, Argentina)(106,121–125), 2. The

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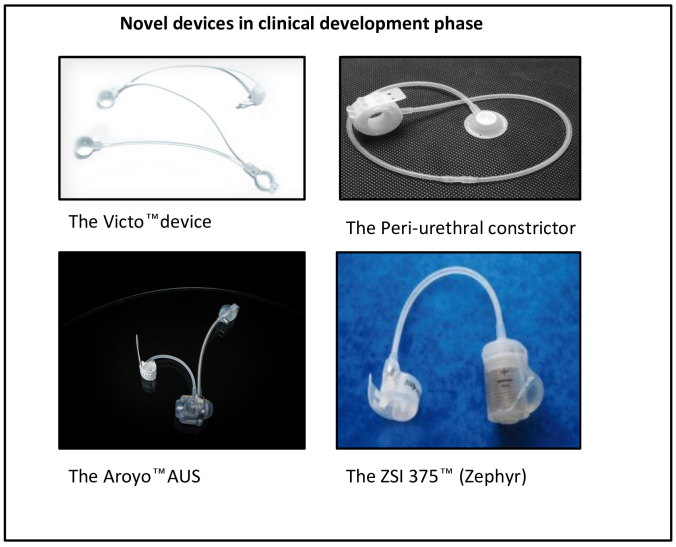
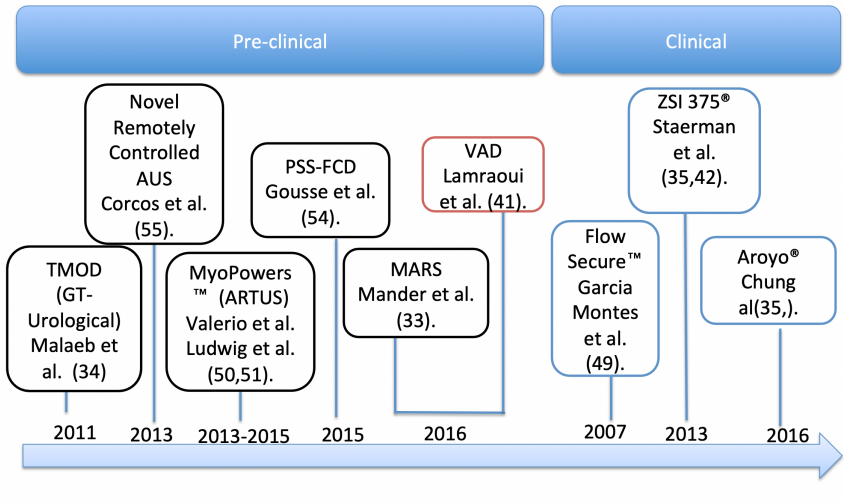
Periurethral Constrictor or PUC (Silimed, Rio de Janeiro, Brazil)(126–129), and 3. The ***ZSI 375*** (Zephyr Surgical Implants, Switzerland) (126–129) and finally the ***Aroyo ™***. We will not address the PUC in detail, for its design is commercialized in developing countries and is subject neither to EU nor US regulations. We will describe the above novel AUS devices considering the way they attempt to solve the drawbacks of the AMS 800™. They are represented in Figure 9. and their historical timeline is presented in Figure 10.



Reus, Grilo, Chartier-Kastler, *BJUI Knowledge* (2019)

Figure 9. Novel AUS devices in clinical development phase[11].



Reus, Grilo, Chartier-Kastler, *BJUI Knowledge* (2019)

Figure 10. Novel AUS in Pre-Clinical and Clinical Development Phases: Historical Timeline[12].

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2.8.4.1 VICTO™ and VICTO PLUS™

This novel AUS device was designed in the nineties, before the wireless technology era, to address the shortcomings of the AMS 800™, namely its inability to adjust the peri-urethral pressure according to the patient's intra-abdominal variations and daily physical activities. Throughout the years, it has undergone several prototype modifications, the FlowSecure™, the VICTO™ (devoid of stress balloon) and finally the current VICTO PLUS™ design, comprising a stress balloon and a new cuff pattern.

A ready-to use, pre-filled with 30mL of normal saline, *single-piece* system, it has four components connected by silicone tubings: 1) a *PRB* delivering basal occlusive pressure, 2) a stress-release balloon (*SRB*) inserted outside of the peritoneum, which transmits intermittent intra-abdominal pressures, to an occlusive cuff around the urethra, tailored to stress scenarios, 3) a circumferential peri-urethral occlusive cuff, and 4) a high-volume control pump.

The injection or retrieval of fluid in the system through a titanium port allows for individualized adaptation of the regulating pressure between 0-100 cmH2O ranges. A resistance valve within the control pump permits swifter manual inflation of the occlusive cuff, which also contains a 'Self-sealing port', allowing for internal pressure adjustments.

In 2006, the authors demonstrated preliminary overall improvement of the '*Continence Index'* for the Flowsecure™ (defined as: ([100 x Vv]/[Vl + Vv]: volume voided (Vv), volume leaked (Vl)) from 54- 97% twelve months post-operatively. However, 4/9 patients only achieved continence through further complication-free pressurization (121,124). A third study reported mechanical failure of 6%, infection rates of 5%, and pump assembly malfunction rates of 9% in hundred patients after a short to intermediate follow-up period.

Giammò et al. published the results of a retrospective, multicenter implantation of the VICTO™ or VICTO PLUS™ in 17 patients between 2017-2019 suffering from moderate to severe SUI after RP. At 15 months follow-up, dry rate using the 24-h PWT was 76.4%, and the reported Clavien-Dindo class I complication rate of 17.6%, with no difference between the two device versions(130). Later last year, the results from the implantation of the VICTO™ or VICTO PLUS™ in 96 patients (cumulated between 2016-2020), of which 51% had received salvage radiation, were presented at the EAU 2021 meeting. The authors reported this time a social continence rate (i.e., 0-1 pad) of 74% and an explantation rate of 8.3% after a follow-up of 23.5 months(131).

To conclude, the VICTO™ aims to offer ease of implantation, thanks to its single-unit design, with a potential for lower ischemia-related erosion due to its adjustable peri-urethral pressure features. However, it would be interesting to see how this device will stand the test of time, especially in this wireless technology dominated era.

2.8.4.2 The PUC

This is an affordable and simpler design developed for pediatric neurogenic UI in 1996 in emerging countries. It was neither granted CE marking nor FDA approval and is therefore unauthorized in Europe or the US(127).

Its principle is based on providing continence via a fixed periurethral pressure, enabling urethral catheterization without cuff deflation. This two-*piece* silicone AUS has an occlusive cuff, linked to a

hydraulic self-sealing port in the scrotum thanks to a 20 cm modifiable tubing. To provide suitable peri-urethral compression the cuff has 2 layers: an internal one made of polyurethane and an external modulable polyester layer. Consecutive system re-filling for the purpose of additional titration may be required post operatively, which can be done in clinic.

This device offers a cheaper, easily implantable, functional AUS alternative where expensive versions cannot be afforded. However, there is no advantage regarding the avoidance of ischemia-related urethral erosion, since the periurethral pressure is kept constant. There are few publications on the use of the PUC in PPUI, but the available data ascertain its unsafe profile. Some authors have reported 80% continence rates at 18 months(129). Furthermore, two retrospective studies showed 41% explantation rates, 63% reservoir malfunction rates, of which 20% needing additional revision after median follow-up of 27.5 months(126,128).

The PUC device illustrates the importance of the cost, which in emerging countries are entirely at the patient's expenses, in the absence of an adequate social security system.

2.8.4.3 Aroyo™

Like the VICTO™ this is a *one-piece* hybrid mechanical/hydraulic device, which the patient controls manually using an *on/off* switch, described in the paragraph covering its ancestor, the TMOD, which completed both function and biocompatibility requirements at the time. An innovating stainless steel locking clip securing the occlusive tape modified the design, simplifying its retrieval and repositioning when revision was required. CE marking was granted in January 2015.

A Multicenter, prospective, single arm feasibility and performance *pilot study* (RELIEF I trial) analyzed 10 men suffering from PPUI or transurethral prostate resection between 2013-2015. After a mean 12-months follow-up, with a primary endpoint defined as '*The change in 24-hour pad weight from device activation at three months*', 90% of the patients completed the trial. One device malfunction and one explantation due to intra-operative adverse event was reported(132).

After obtaining the CE marking, the RELIEF II trial, a prospective, multi-center Pivot study was conducted. '*The change in 24-hour pad weight from pre-implant screening to month three post-activation'* constituted its primary endpoint. Composite safety features determined on device-related adverse events and/or outcomes at 3-months after AUS activation (infection, erosion, urethral atrophy, device reposition/revision/removal) constituted the secondary endpoints. The authors reported that an intra device pressure of ≥80cmH_2O could induce a 24-hour pad weight reduction of ≥80%. They also alleged that 15% of the reported serious adverse events (SAE) could compare to the 5-53% revision and explantation rates of the AMS 800™(57).

Sadly, in 2017, the company went bankrupt, illustrating that CE marking does not guarantee access to the actual market.

2.8.4.4 ZSI 375

Like the VICTO™ and the Aroyo™, this is also a *one-piece* silicone elastomer AUS. It is made of a pressure-regulating tank located in the scrotum, capable of adjusting pressure ranges from 60-70cmH_2O to 90-100cmH_2O, thanks to three components: an activation button (causing the piston to move the fluid from the cuff to a hydraulic circuit at rest), a hydraulic system and a compensation chamber. An occlusive peri-urethral inflatable silicone cuff in different sizes (3.75-5cm) completes

the ensemble. When the system is activated, the fluid movement from hydraulic circuit to the compensation chamber, causes the cuff to inflate.

Emulating the VICTO™, this device modulates the peri-urethral pressure through fluid injection/re-aspiration from the compensating chamber. Also, its single-piece feature, and retropubic placement aim to decrease bladder injury and device migration. Nevertheless, periurethral pressure adaptations to intra-abdominal pressure fluctuations are not possible, therefore the device does not address the erosion risks. Additionally, increased infection risks and pressure-regulating tank degradation, owed to frequent postoperative pressure adjustments are significant, as illustrated by published results(123,133).

A retrospective multicenter study analyzed a cohort of 36 patients between 2009-2011. After a mean follow-up of 15.4 months, 11% complications (4/36) necessitating device explantation was reported. The authors also published a 79% continence rate (defined as *'0 or 1 pad/day'*) and 13% device failure at 12 months, comparable to the AMS 800™(134) . Furthermore, Kretschmer *et al*. showed poor device results with 30.8% device-related adverse effects, an overall explantation rate of 61.5%, a 15.4% infection rate, and erosion rates of 7.7% at 13.5-months follow-up. Another recent retrospective, multicenter study including 106 men reported overall continence rates of 79% at 12-months, decreasing to 51% at 24-months and a 20% erosion rate(135).

In terms of quality of life, Otrowski and colleagues have conducted a prospective, non-randomized multicentric study between 2013-2019 in 86 men. Functional outcomes using the pad count, defining total continence as '*0 pad use'* and social continence as '*0-1 pad use'*, as well as quality of life were assessed. They reported a very low 8.1% total continence rate, 69.8% social continence rate, 17.5% complication rate (12.8% of which were secondary to urethral erosion) and a significant QoL improvement after 12 months follow-up(136). These results fail to convince this device's superiority over the AMS 800™ considering its high complication rates after short-to mid-term follow-up.

The outcomes of the novel devices in clinical phase are summarized in Table 1[13] below whilst the financial aspects of the development of a novel AUS are considered in Table 2[14] (64).

Table 1. Summary of the outcomes of the different AUS in clinical development

Device	AMS 800	Victo	PUC	Aroyo	Zephir ZSI 375
Company	Boston Scientific	Promedon	Silimed	GT Urological	Zephir SI
Overall incontinence	75–80% at 10 years	89% at 12 months	30% at 8.6 years	Unknown	94% at 20 months
Revision rate	10-15% at 10 years	Unknown	41% at 8.6 years	15% serious adverse events at 3 months	61.5% explantation at 13.5 months
Erosion/Infection rate	<2% at 10 years	14% (with initial prototype)	30% at 6.8 years	Unknown	Erosion 7.7% Infection 15.4% at 13.5 months
Satisfaction rate	>75%	Unknown	Poor	Unknown	Unknown
Explantation rate	26%	28%	41%	10%	61.5%
References	[2, 12]	[4, 13, 15, 16, 18, 34	[21, 22, 23, 34]	[25, 26]	[4, 27, 29, 34]
Remarks	Gold standard	No further data since 2012	PPUI data Emerging countries	Bankruptcy Pooled RELIEF I and preliminary RELIEF II results	30.5% device failure at 13.5 months

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Device	Country	Approval	Reimbursed	Key decision maker	Costs (including hospital stay)
AMS 800	USA	FDA in 2001 and in 2006 for InhibiZone	Yes	Unknown	Unknown
	France	CE (class IIb)		HAS and AGEPS	*8 686.12€
	Sweden			Hospitals (users, purchasers)	86500 SEK (~8400€)
	Germany			Hospitals (users, purchasers)	10620.38€
	UK			Hospitals (users, purchasers)	8068 £ (~11 428€)
PUC	USA	None	No	N/A	Commercialised in Brazil 2000€ in Italy [34]
	France				
	Sweden				
	Germany				
	UK				
Victo	USA	None	No	N/A	None PILOT study awaited
	France	CE marking in 2012			
	Sweden				
	Germany				
	UK				
Aroyo	USA	None	No	N/A	N/A The company filed for bankruptcy in 2017 after completing PILOT and PIVOT studies
	France	CE marking in 2015			
	Sweden				
	Germany				
	UK				
ZSI 375	USA	None	No	N/A	N/A PIVOT study awaited
	France	CE (class IIb) marking obtained			
	Sweden				
	Germany				
	UK				
Artus	USA	None	No	N/A	N/A PILOT study awaited
	France	CE (class IIb) marking obtainied			
	Sweden				
	Germany				
	UK				

Chartier, Reus, *BJUI Knowledge* (2021)

Table 2. Novel AUS devices in clinical development: financial considerations

2.8.5 Future perspectives

With the 21st century we step into a new era of global electronic, mechanical, and technological prowess, as well as communication innovation. Over the last 5 years, newer miniaturized devices have made their entry in urology. The *Axonics Sacral Modulation Systems ™* (Axonics, California, USA) and the newly FDA approved *Interstim X™ system (Medtronic, Minnealpolis, MN, USA)*, for instance, are the newest miniaturized CE marked AIMDs benefitting from the latest wireless battery recharging technology for the treatment of OAB with sacral nerve modulation(137). Similarly, another AIMD, a leadless cardiac pacemaker was introduced on the cardiac surgery market in 2016(138). With these recent advances, we are on the verge of the creation of an electronic wireless AUS.

Breaking down the AMS 800™ disadvantages, one could easily envisage how the future AUS may possibly look like. Firstly, yes, ***size*** does matter in the world of AIMDs: *the smaller the device, the better*! Both patients and urologist are attracted to a device that takes the least amount of space in the body and would therefore be quicker to implant. Second, due to the silicone and titanium components of the AMS 800™, the ideal solution would be a ***biological AUS***; promising tissue engineering research on animal models using *autologous stem cell therapy* are paving the way(139–141). Therefore, successful human stem cell therapy is the next logical future landscape. Third, ***wireless/BlueTooth technology*** seems inevitable, as it best addresses the question of ergonomics, but can also provide a solution regarding a more intermittent and adaptable peri-urethral pressure, thus avoiding ischemia-related erosion. It is less conceivable today to imagine how novel AUS using volume/pressure adjustments through manual port injection would compete with wireless alternatives. Finally, all these considerations point towards the development of an MRI- safe novel AUS device, most devices having achieved MRI-conditional status (64).

In summary the ideal future AUS would be biological, if not, miniaturized, made of biocompatible material, functional and able to provide personalized peri-urethral pressures with less erosions. The device would also be easily implantable, affordable, safe, and efficient. In the meantime, we look forward to following the promising journey of the above devices. Summary of current AUS issues and future AUS devices perspectives are summarized in Table 3[15].

AMS 800 drawbacks	Clinical implications	Solutions	Future perspectives
Mechanical device	1. Limited device survival in time (10 years) 2. Mechanical failure 3. Revisions rates 30% at 3 years 4. Erosion/explantation	1. InhibiZone 2. Narrow-backed cuff 3. 1- or 2-piece devices: VAD, ZSI 375, VICTO™/VICTO PLUS 4. Biological AUS: Tissue engineering, currently on animal models	Autologous stem cell therapy in humans
Constant applied periurethral pressure	1. Urethral atrophy & erosion due to decreased vascularisation 2. Recurrent UI over time 3. High revision rates	1. Applied periurethral pressure adapted to the patient's physical activity decreasing urethral atrophy risk: VAD, ARTUS 2. Nocturnal device deactivation 3. Non – circumferential urethral cuff: ARTUS	VAD: Feasibility/performance on animal and cadaver study results are ongoing ARTUS: launch of multi-center clinical trial 2020 (AFU 2018, Paris, France)
Poor ergonomics	Scrotal pump manipulation	Remote controlled device using Bluetooth technology – 2-piece/1-piece device: VAD, the ARTUS, the PSS-FCD, the novel remotely controlled AUS (both using communicating Bluetooth technology) have the potential to improve ergonomics	Awaiting clinical trials results
Persistent urinary incontinence whilst seated & increased UI upon physical exertion	Dry rate/0-pad rate of 60%	Automatic orthostatic pressure adjustment of applied periurethral pressure: VAD ARTUS	Awaiting clinical trials results
Simplifying AUS implantation procedure	1. Shortens device component preparation prior to implantation 2. Decreases infection risks 3. Shortens operating time	ZSI 375 VAD ARTUS	Awaiting clinical trials The optimal AUS will be simple to prepare, quick & easy to implant maximum safety and efficacy
MRI conditional	Possibility to have an MRI in specific conditions	No information available regarding current AUS in pre-clinical and clinical development	Aiming for 'MRI safe' in the future: biological AUS
Iatrogenic urethral catheterisation	Iatrogenic urethral erosion leading to explantation	Automatic cuff opening upon detection of a catheter in the urethra: VAD	Awaiting clinical trials

Chartier, Reus, *BJUI Knowledge* (2021)

Table 3. Summary of the current AUS issues and potential corresponding future perspectives

2.9 Identifying literature gaps

Conducting this literature review has allowed us, not only to build a clearer picture of the ideal novel smart eAUS devices must strive to become, but it also helped identify *three literature gaps*.

1. First since the eAUS aims to cater to both genders, it was of the utmost importance to analyse the ***long-term efficacy and safety outcomes of the AMS 800™ in women suffering from non-neurogenic severe SUI***, another missing information in the literature. This knowledge would help us complete the risk analysis necessary for the developmental stages but also required for regulatory purposes.
2. Second, the review highlighted the need for data evaluating the ***24-hour pad weight test as an efficacy assessment tool*** for UI, in order to clearly define the primary efficacy outcomes of the First in Man study, in accordance with the FDA requirements. Furthermore, this tool

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will help minimise heterogeneity in efficacy outcome reporting in the literature, thus facilitating comparison between various devices.

3. Third, some centres in the world use the transscrotal approach as a mode of AMS 800™ implantation, which is the case in the USA and in Karolinska University Hospital. This implies that the eAUS device could potentially be implanted using both techniques. Consequently, a paucity of data in the literature regarding a comparative analysis in terms of long-term performance and safety between transscrotal and transperineal implantation techniques was required for the purpose of a thorough risk analysis.

Armed with a meticulous State of the Art, the comprehensive risk analysis requested for regulatory aspects could be completed. Furthermore, the drafting of the Clinical Investigation Plan (CIP) and summary for the FIM clinical studies, with the help of professors Mozer and Eric Vicaut could also be achieved.

2.10 From 'Gold standard' to novel AUS: navigating the regulatory waves

At the time of its creation back in the seventies, the AMS 800™ was not subjected to the developmental regulations and restrictions we know today. These have increasingly been tightened in the past decade, justly so, in the light of scandals that have shaken the world of passive and active medical implants, such as the PIP implants or the prolapse meshes, to name but a few. Furthermore, AIMD regulation is at its infancy in Europe compared to the USA, where the FDA has legislated for far longer. Indeed, due to regulatory, financial, and political obstacles, developing a new AIMD is a time-consuming affair, where a minimum of 15 years is expected, from inception to the beginning of the first clinical studies.

More restrictive quality and regulatory directives, as well as new requirements from the International Continence Society (ICS) Consensus for novel AUS, are transforming the landscape of novel AUS device development process(52,53). As we have stated earlier, CE marking does not guarantee device commercialization, as showed by the fate of GT-Urological, an event that further highlighted the need for post-market studies to ensure patient safety.

The FDA granted approval for the AMS 800™ in 2001, although the results of the pivot study including 85 patients after a 24-month follow-up, remained unpublished. Today it is the only AIMD for the treatment of PPUI, that was granted both FDA and CE approval, and achieved reimbursements in the USA, as well as many European countries. The AMS 800™ is also the only AUS with the 'Open label' status for female SUI treatment in America, which was approved by the Haute Autorité de Santé (HAS) for this specific indication in France.

Consequently, industrials developing a novel AUS must complete the following important steps to comply with current EU regulations (142,143):

1. ***Pre-clinical phase***: *in vitro* biocompatibility, bench, animal, and cadaver testing must be completed to establish feasibility, ease of implantation and biocompatibility profiles.
2. ***Clinical phase***: a *FIM*, then a *Pilot study* analyze, with few patients, the AUS' feasibility, technical performance, and safety (SAEs), but also assesses the patient selection criteria and surgical technique.

3. ***Provision of the medical device phase***: a *Pivot study* performed on a cohort of subjects, with well-defined objectives, primary and secondary endpoints; inclusion/exclusion criteria are determined, a control treatment if a comparative study is applicable (in the current case the novel AUS is compared to the reference, i.e., the AMS 800™) is chosen. The experimental plan is outlined, and finally investigational centers (multi-center studies) are defined.
4. ***Post-market study***: after *Pivot study* completion, long-term efficacy, and safety outcomes of the device are followed-up.

The novel device's clinical use must imperatively be approved by the country's ethical committee and preceded by multicentric-controlled studies. Once the AUS is granted CE marking, reimbursement, and device prices depending on the country and the applied healthcare system are negotiated. We have summarized these considerations, based on the information we have of 4 countries in table 2. Reported tariffs may be subject to further adjustments, based on negotiated agreements between hospitals, health care providers and the relevant companies(143).

To conclude, from the *State of the Art* several research questions were raised: 1) *What is the level of evidence supporting the use of an AUS for non-neurogenic SUI in women? 2) How do we evaluate the 24-h PWT as an efficacy assessment tool, and how does it correlate with quality of life after AUS implantation in patients with PPUI?* 3) *Does the AUS surgical implantation technique used influence long-term efficacy and safety outcomes in men with PPUI?*

The answers to these three questions would help complete a thorough *risk analysis*, necessary to construct a solid regulatory base for the new eAUS device. Furthermore, it would allow us to define the primary performance/functional outcome criteria, determine the sample size and draft the *Clinical Investigation Plan of the FIM study*. Finally, we could move to the *Design Phase* of the AUS device, bringing up another question 4) *How can we dimension the pump of the device, to finalize the prototype?* Once the final device design was agreed upon, we could consider the pre-clinical development stages, human cadaver, and animal studies, required to answer the final two questions prior to the FIM study: 5) *How do we demonstrate the device's feasibility and performance against the 'Gold Standard*'? 6) *How can we establish the animal model's suitability, the device's implantation feasibility and short-term safety profile prior to a Pivot study?*

3. RESEARCH AIMS

Overall aims:

The objective of this project is three-fold:

- First, to establish a *State of the Art* of the current AUS of reference or '*Gold Standard'* for the treatment of severe SUI in both genders in order to identify and address potential *literature gaps* relevant for the *Device Design*, the completion of the Risk Analysis (i.e. extrapolated adverse events), the preparation of pre-clinical and clinical trials (FIM). These will be explored in constituent **papers I-III**.
- Second, to identify and analyse the relevant data resulting from bench tests and clinical studies. These enable to define the novel device's specifications and *finalize the device's design* that will be used in pre-clinical studies. This will be studied in constituent **paper IV**.
- Third, to perform *pre-clinical feasibility, performance and safety studies* on human cadavers and animals prior to conducting FIM clinical trials preceding CE marking. These will be analysed in constituent **papers V-VI**.

Objectives of paper I

- To establish the level of evidence regarding the use of the AMS 800™ in female non-neurogenic SUI by analysing the long-term efficacy and safety outcomes in this group through a systematic literature review.

Objectives of paper II

- To primarily assess the 24-h PWT as a functional/performance outcome evaluation means, and secondarily to analyze its correlation to current validated quality of life questionnaires.

Objectives of paper III

- To retrospectively study the long-term functional and safety results of transverse scrotal versus transperineal AMS 800™ implantation in men suffering from non-neurogenic PPUI.

Objectives of paper IV

- To prospectively measure the exact volume taken by the AMS 800™ Occlusive Cuff at the time of its pressurisation in order to dimension a novel AUS device.

Objectives of paper V

- To demonstrate the feasibility of implantation of the smart UroMems AUS and to evaluate its performance in human cadavers.

Objectives of paper VI

- To show the suitability of the wether model and the novel AUS' feasibility and short-term safety profile in the chosen animal model.

4. MATERIALS AND METHODS

4.1 Study design

This study is built based on the development steps of a novel AIMD for the treatment of severe SUI in men and women, starting from concept to device design, and finally to the preparation of the FIM trial. A solid regulatory and quality foundation for the new device, based on a thorough product *Risk Analysis* is required, drawing performance and safety information on the device of reference, i.e., the AMS 800™, from the literature. Thereafter, perfecting the AUS design, based on prospective *in vivo* clinical studies, prior to pre-clinical studies was the next step. Finally, designing and conducting pre-clinical human cadaver and animal studies that would lead to the FIM trial would conclude this thesis. It was also important that the thesis mirrored the collaborative work between two institutions, the Karolinska University Hospital/Institute in Stockholm, Sweden, and La Pitié-Salpêtrière University Hospital/La Sorbonne, in Paris, France.
In **paper I,** a systematic literature review was carried out to assess the long-term efficacy and safety results of the AMS 800™ in adult women suffering from severe non-neurogenic SUI. For this purpose, a systematic search of Embase (PubMed/Medline) and the Cochran Central Register of Controlled Trials was conducted, including data from 1987-2018. The studies included had to have published information on functional outcomes after AMS 800™ surgery in minimum five adult females, with the above-stated criteria, and had at least a six-month follow-up. The research protocol was registered on PROSPERO 7 (CRD42017056576) and the PRISMA statement (Preferred reporting Items for Systematic Reviews) was followed. Keywords used were the combination of '*Urinary incontinence*' (Medical Subject Headings [MeSH] AND U*rinary sphincter'*, '*Artificial*' [MeSH] AND '*Female*' [MeSH] with no restriction of language.

Paper II primarily retrospectively analyzed the 24-h pad weight test as a performance evaluation tool and secondarily its correlation to patient quality of life validated surveys, collected from institutional Electronic Medical Records (EMRs) in a single center.
To conclude the literature review, in **Paper III,** a retrospective comparison of efficacy and safety between transscrotal and transperineal AMS 800 **™** implantation in men suffering from PPUI was performed, also using data from a single center's Electronic Medical records.

In the following *Device Design* step, a non-interventional, prospective single center peri-operative cohort study from *in vivo* measurements of implanted peri-bulbar AMS 800 **™** occlusive cuff volumes after pressurization at the time of implantation was conducted. This was covered in **paper IV.**

The final stages included *Pre-clinical Studies* in human cadavers (**Paper V**) and animal studies (paper **VI)**. In the former, a pilot study on eight human cadavers assessed the novel AUS device's feasibility of implantation and compared its performance with the AMS**™**. In the latter, a pilot study in two whether models to evaluate the model's suitability, but also to assess the device's implantation feasibility, biocompatibility, performance, and safety.

4.2 Study population

Paper I

A systematic literature review was carried out to assess the long-term efficacy and safety results of the AMS 800™ in adult women suffering from severe non-neurogenic SUI. For this purpose, a systematic search of Embase (PubMed/Medline) and the Cochran Central Register of Controlled Trials was conducted, including data from 1987-2018. The studies included had to have published information on functional outcomes after AMS 800™ surgery in minimum five adult females, with

the above-stated criteria, and had at least a six-month follow-up. From 12 articles we included 886 adult female patients suffering from severe non-neurogenic SUI secondary to ISD, refractory to conservative management and previous anti UI surgery, who had undergone AMS 800™ implantation between 1987-2018.

Inclusion criteria were as follows: adult women aged ≥ 18 years, suffering from non-neurogenic SUI and/or urogenital malformation (i.e., vesical extrophy/epispadias, urovaginal fusion, imperforate hymen, cloacal and anorectal anomalies) undergoing open, laparoscopic, or robotic AMS 800 implantations. We also considered co-existing augmentation cystoplasties in non-neurogenic bladders. In the event of heterogenous cohorts (with both neuro and non-neurogenic SUI) only studies comprising at least 80% of non- neurogenic SUI cases were included.

Studies reporting < 80% of non-neurogenic cohorts and pooled results, case reports of less than 5 female patients, studies reporting neurogenic UI, pediatric and male populations, or cadavers and animal studies were excluded. Any surgical technique other than the AMS 800™ or transvaginal AMS 800™ procedures were also excluded.

Paper II

In this study we retrospectively analyzed 221 patients and included 180 adult men aged ≥ 18 years with PPUI secondary to ISD who benefitted from an AMS 800™ implantation between 2005 and 2018 at Karolinska University Hospital. Pediatric patients, men suffering from neurogenic SUI, and secondary AUS implantations were excluded.

Paper III

We retrospectively investigated a total of 183 adult men who underwent primary AMS 800™ implantation for non-neurogenic PPUI at Karolinska University Hospital between 2005 and 2018. In 130 men, the transscrotal approach was adopted and in 53 the transperineal technique was used.

Paper IV

Examined 67 men suffering from non-neurogenic PPUI due to ISD, who underwent a transscrotal peri-bulbar AMS 800™ insertion at La Pitié-Salpêtrière University Hospital between October 2016 and November 2018. Thus, the volume of 67 peri-bulbar cuffs were measured at the time of their pressurization.

Paper V

Considered eight human cadavers (one female and seven males) in this non-clinical pilot study, in which the AMS800™ and the new eAUS Device were implanted between June and July 2018. In four anatomical subjects (including the female subject), implantation feasibility was assessed and in the other four a performance study was conducted.

Paper VI

Investigated two castrated rams, otherwise known as wethers in a non-clinical pilot feasibility, biocompatibility, performance, and safety study, in which the novel eAUS device was implanted. The subjects used were of the *Ovis aries*, Grivet breed weighing 63 and 87 kg at implantation. Both specimens were assessed to be healthy by the CRO's official certified veterinary prior to AUS implantation.

4.3 Methods

In **Paper I,** abstracts, and full texts (when available) were analyzed by two independent researchers with a third researcher intervening when a consensus was required. Thereafter, data regarding study design (RCT, non RCT, prospective, retrospective ect.), patient characteristics, adopted surgical AUS implantation mode (open, laparoscopic, or robotic), performance outcomes and mean AMS 800™ survival were extracted. Furthermore, for risk bias assessment, the '*Newcastle-Ottawa scale for non-RCT*' and the '*NIH study Quality Assessment Tool for case series'*[16] were used(144,145). Main performance outcome was defined as *'Zero pad'* rate for complete continence, based on the FDA AEs classification system ("FDA Guidance for industry and Food and Drug Administration Staff Clinical

Investigations of Devices Indicated for the Treatment of Urinary Incontinence" issued on 8 March 2011, applied to Class III Active Implantable Medical Devices such as the AMS 800)[17].

For **Paper II,** data from a two-day micturition diary including a 24-h PWT, as well as the ICIQ-UI SF "*International Consultation on Incontinence Questionnaire Short Form*"[18], and the I-QoL "*Incontinence Quality of Life*"[19](146) were retrospectively collected before surgery and at 3-6 months following AUS device activation from a single center EMRs from 2005-2018.

Like in paper II, a retrospective gathering of information from single institutional EMRs, from 2005-2018, were carried out in **paper III**. This time, we focused on *pre-operative* patient profiles (age, BMI, co-morbid factors, prior history of anti-UI or urethral/anastomotic stricture procedure, previous radiation treatment and pre-existing detrusor overactivity). We equally collected data on *peri-operative* elements, which included the AMS 800™ surgical mode (TS, TP and transcorporal occlusive cuff placement), AUS profile regarding cuff diameter used, PRB volumes and pressures, as were recorded complications. Finally, *Post-operative* information about short and long-term adverse events (AEs), as well as device longevity were analyzed.

In **Paper IV**, a prospective intra-operative, non-interventional measurements of the OC volumes during a classic transperineal AMS 800™ implantation (as described in the AMS 800™ Operating Manual 2017)[20], in men suffering from PPUI were performed by four experienced surgeons, whilst a 14 French urethral catheter was in situ. This was done by attaching a 5 ml Luerlock seringe to the tubing leading to the OC after pressurization thanks to a 15-gauge blunt needle supplied by the Manufacturer's Implantation Kit. We then completed the remaining steps of the routine procedure, without modifying it in any way, although it was prolonged by 5-10 min.

For the human cadaver study in **paper V**, several data were gathered from the *feasibility of implantation* and from a *novel AUS performance standpoint*. In the former, the basic eAUS device automatic functions were first tested in 4 cadaver (of which 1 female) to assess their operationality, namely the '*Priming*', '*Get atmospheric pressure*' and '*Calibration'.* Once these were ascertained,

[16] https://www.nhlbi.nih.gov/health-topics/ study-quality-assessment-tools

[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-investigations-devices-indicated-treatment-urinary-incontinence-guidance-industry-and-fda.

[18] https://iciq.net/licences

[19] http://depts.washington.edu/seaqol/

[20] https://www.bostonscientific.com/content/dam/Manuals/us/current-rev-en/92116964 01A_AMS_800_ORM_en_s.pdf

we proceeded to the device's implantation, following the same procedural steps as for the insertion of the AMS 800™ previously described (AMS 800™ Operating Manual 2017). Information about OC sizes and possible intra-operative AE were recorded.

In the latter, evaluation of the eAUS device was done against the AMS 800™. The *Maximum Urethral Closure Pressure* (MUCP), in cmH_2O determined the principal performance criterion. This was obtained through urodynamic investigations, performed using the GOBY™ urodynamic station (Laborie, Canada), the UDS120 Goby software and the Bohler 2 ways 10F (Peters®) urethral catheter. The protocol was based on the UPP measurement protocol described in '*Accuracy of pressure measurements obtained by an air-charged transducer balloon catheter system (Tdoc®) for urodynamic testing*' by Le normand et. Al(147). Patency of the urethra was confirmed by performing a cystoscopy, then the subject was catheterized with a 18Fr catheter. Comparative pressure flow studies between the eAUS device and the AMS 800™ were then carried out to obtain the MUCP, by randomly selecting a PRB (with pressure ranges: 51-60 cmH_2O; 61-70 cmH_2O; and 71-80 cmH_2O). Random pressures were given to the eAUS Control Unit (CU) from 10-150 cmH_2O in +10 cmH_2O increments. For each pressure value a MUCP measurement was carried out to show that the novel device was able to provide similar pressure ranges to the 'Gold Standard'.

Finally, in the animal study, covered in **paper VI,** the eAUS device was implanted in two wethers under general anesthesia between December 2018 and January 2019. The implantation protocol was identical to the one described in the cadaver study. *Implantation feasibility* and novel eAUS characteristics were assessed, and potential intra-operative AEs were recorded. Thereafter, the (OC) was left open to allow urethral healing for 4 weeks before the device's activation (closure of the OC), which was carried out 6 times/day for a fifteen-minute period: at 8:45 am, 10:45 am, 12:45 pm, 2:45 pm, 4:45 pm and 6:45 pm. The device also remained deactivated at night from 8:45 pm – 7 am to allow the animals to void. A necropsy was done 4 weeks after device activation.

The smart functions eAUS device and CU data were analyzed every week. Daily clinical evaluation of the wethers was conducted, as were voiding observations for one week post-operatively until activation, then once daily thereafter. The novel eAUS device's safety was assessed by pre-operative, during anesthesia, at activation and at termination blood analysis, tested for electrolytes and renal function. The veterinary inspected the surgical sites daily. Histopathology assessment of tissue for adverse events was carried out after the necropsy. Because no *in vitro* nor computer simulated models exist to assist us in mimicking potential AEs, we extrapolated these to be mechanically and/or biologically related. Thus, anticipated device-related AEs gathered were device migration/malposition, mechanical dysfunction, and infection. Expected clinical AEs included wound infection, genito-urinary AEs, Pain/discomfort. Tissue AEs encompassed macroscopic qualitative variations observed at necropsy, local tissue reaction or infection, and allergic reactions.

4.4 Data analysis and statistical methods

Paper I

According to the 7th ICI's (*International Consultation on Incontinence*) clinical research guidelines, each study included was described, on the basis of its design, patient and procedure characteristics, and performance outcome assessments (1). Primary functional outcomes were defined as '0 pad' and '0-1 pad' rates. Safety outcomes encompassed the following, according to the *CTCAE terminology*,

from the US department of Health and Human Services, NIH/National Cancer Institute[21]: *Non-Serious Adverse Events* or NSAE (which also include procedure adverse event or PAE) and non-serious adverse device effect or NSADE, in which device deficiency (DD) was also categorized. In *severe adverse effects* or SAE rates, one included *procedure serious adverse event* or PSAE rate and serious adverse device effects (SADEs), which may be unanticipated and anticipated (i.e., infections/erosions).

The results of each outcome were graphically represented using forest plots. The R version 3.4.3 (R Core Team: R: a language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria [2017], https://www.R-project.org/) was used.

Paper II

We used the Stata/SE 15.0 software. Descriptive statistics for 24-h pad weight, were calculated. We defined $p < 0.05$ as being statistically significant for all investigations. For paired comparison we used Wilcoxon signed rank test when comparing pre- and post-operative data, expressed as median values and interquartile range (IQR). A Spearman's correlation (r_S) evaluated the relationship between the 24-h PWT, I-QoL, and ICIQ-UI SF. A weak correlation was defined as $r_S = 0.2–0.39$; moderate as $r_S=0.4–0.59$; strong as $r_S=0.6–0.79$; and very strong as $r_S= 0.8–1.0$.

Paper III

The *Stata/SE 17.0 (*StataCorp, College Station, Texas, USA) software was used for all statistical analysis. We used mean and standard deviation (SD) or median and interquartile range (IQR) when applicable to summarize numerical variables. The two-sample t-test was used when comparing the equality of means between two groups. When between three groups, the analysis of *variance (ANOVA)* was applied.

Quantile regression was used when comparing the equality of medians for continuous results. We summarized categorical variables as frequencies and compared them adopting the *Pearson χ2 test*. A log binomial regression estimated binary outcomes and their 95% confidence intervals (CIs). The *Aalen-Johansen estimator* assessed device revision cumulative incidence function, whilst the *Cox proportional hazards regression* estimated cause-specific hazard ratios (HRs) and their 95% CIs.

Comparison of association of TS against TP cohorts and the outcome(s) was carried out in a main analysis. Secondarily, comparison of TS and TC to TP cohorts was performed. The analyses were further stratified into previous radiation, DOA, anti-UI surgery and procedure for urethral/anastomotic stricture. All tests performed were two-sided, with a level of significance defined as $p < 0.05$.

Paper IV

We used the XLSTAT 2019.1.2.56804. software for descriptive statistics and sub-group analysis. An unpaired sample t-test was applied for subgroup analysis, with a significance level of 0.05 for a one-tailed hypothesis.

Paper V

For descriptive statistics, the XLSTAT 2019.1.2.56804. software was used.

Paper VI

The XLSTAT 2019.1.2.56804. software was used for descriptive statistics.

[21]https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

4.5 Ethical considerations

Paper I was a systematic literature review which required no ethical permit. We followed the Preferred Reporting Items for Systematic Reviews (PRISMA) statement, as stated above and we registered the protocol as required on PROSPERO 7 (CRD42017056576).

Papers II and III
Ethical approval was obtained from the Regional Ethical Review Committee. Data was collected, pseudonymized, and stored according to national, institutional confidentiality and security guidelines.

Paper IV
The study conformed with current European Medicines Agency Clinical Trials and Good Clinical Practice guideline[22]. The hospital's ethical committee (*Comité de Protection des Personnes* (CPP)) Ile de France VI, Groupe Pitié-Salpétrière) granted ethical approval. The patients received the hospital's standard patient information form and signed a written consent prior to their inclusion in the study. Patient anonymity was preserved in stance with the above.

Paper V
For this study, anatomical subjects were used. This research was conducted at the Surgical School 'Institut Le Fer à Moulin' IFM (UMR-S 1270 / Inserm / Sorbonne Université, Paris, France), who follows the Human Cadaver Studies French legislation, as stipulated in Article R2213-13 of the "*Code Général des Collectivités Territoriales*"[23] and Article 16-1-1, Paragraph 2, of the Civil Code (The legal and ethical framework governing Body Donation in Europe[24] (Riederer et.al. Eur J Anat, 16(1):1-21(2012)[25]. The IFM also adhered to the Body Donation Chart[26].

Paper VI
This study was carried out on animal subjects by NAMSA, an international Contract Research Organisation (CRO) for Medical Device testing, ISO 9001:2015 certified and ISO/IEC 17025:2017 accredited. The CRO has been certified by the French Department of Food and Agriculture, has received full AAALAC (American Association for Accreditation of Laboratory Animal Care) certification and follows the U.S. and Department of Agriculture (USDA) regulations. The study protocol's approval by the NAMSA Ethical Committee was granted. Each protocol is reviewed on a five year-basis by the French Ministry of Education, Higher Education and Research, and is part of a project authorization. Prior to conducting this study, any significant changes to the protocol were approved. *Husbandry, Housing and Environment* conditions complied with the EU legislation (Directive EU/2010/63). Only previously healthy animals were included for this study. The wethers were kept under required laboratory conditions at 10-24°C, with 12-hour light and 12-hour dark cycles under automatic timer control. They were cared for by trained and qualified personnel and were provided standard veterinary medical care. Sedation, analgesia, and anesthesia were used throughout this study.

[22] https://www.ema.europa.eu/en/human-regulatory/research- development/compliance/good-clinical-practice.
[23] https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000023512733/
[24]https://www.legifrance.gouv.fr/codes/section_lc/LEGITEXT000006070721/LEGISCTA000006136059/#LEGISCTA000006136059
[25] https://eurjanat.com/v1/journal/paper.php?id=120001br. df.
[26] https://www.enseignementsup-recherche.gouv.fr/sites/default/files/content_migration/document/Rapport_mission_don_du_corps_1416820.pdf.

5 RESULTS

Paper I.

We identified 345 records from which 15 duplicates were removed, leaving 175 records for screening. Further 122 were excluded and thus, 53 full text articles were assessed for eligibility. Fifteen studies remained for inclusion in the meta-analysis. None of the studies followed the 7th ICI recommendations and not one was a RCT. Most studies were single-center and retrospective in nature. A single study conducted in 2017 by Peyronnet et al. was retrospective and multicentric, analyzing the outcomes of female robotic AUS implantation(148).

Patient and AUS implantation characteristics

There remained 12 articles for selection and included **886** adult female patients suffering from severe non-neurogenic SUI secondary to ISD, refractory to conservative management and previous anti UI surgery, who had undergone AMS 800™ implantation between 1987-2018. Mean *age* (years) ranged between 54-70.5 years. Information on *pre-operative pad use* of at least 3 pads/day in >70% of patients was reported in a single study by Vaileux et.al(149). *Pre-operative* negative *MUS/Marshall* test was investigated in 9 studies, reporting 48-100% of patients with non-hypermobile urethra and one study reporting a 4% of patients displaying urethral hypermobility. Equally, urodynamically confirmed *ISD* was reported in 9 studies (75%) in 82-100% of women. *Prior anti-UI procedures* were reported in 11/12 studies (92%) and ranged from 76-100% of patients; however, the number of these interventions were only reported in 50% of studies, with 21-73% having had more than one procedure. 75% of studies reported on open AUS implantations, since laparoscopic and robotic techniques have only been performed recently. Patient characteristics are summarized in the Table 4. below.

Study	*N*	Mean age (yr)	Median follow-up (mo)	Preoperative negative Marshall/ sub-MUS test, *n* (%)	ISD (MUCP <40 cmH_2O or VLPP <60 cmH_2O), *n* (%)	Previous anti-UI surgery, *n* (%)	>1 Anti-UI surgery, *N* (%)	Surgical approach
Beaujon (2010) [21]	27		26.1	NR	27 (100)	NR	NR	Open
Biardeau (2015) [32]	11	67.5	17.6	NR	9 (81.8)	11 (100)	8 (72.7)	Robotic
Costa (2013) [15]	344 (376)[a]	57.2	115.2	344 (100)	NR	260 (75.6)	135 (39.2)	Open
Chung (2011) [35]	29	54.5	106.1	29 (100)	NR	29 (100)	6 (20.7)	Open
Ferreira (2016) [17]	49	69.1	37.5	49 (100)	49 (100)	39 (79.6)	NR	Laparoscopic
Fournier (2014) [22]	6	65.0	14.3	6 (100)	6 (100)	5 (83.3)	2 (33.2)	Robotic
Petero (2006) [24]	55	54.5	134.4	49 (89.0)	48 (87.7)	49 (89.0)	39 (71.0)	Open
Phé (2014) [23]	34 (26)	56.5	204.0 (1)	34 (100)	34 (100)	33 (97.0)	18 (52.9)	Open
Vayleux (2011) [20]	215	62.8	72.0	103 (47.8)		191 (88.8)	NR	Open
Revaux (2011) [36]	50	59.0	67.2	50 (100)	50 (100)	50 (100)	NR	Open
Peyronnet (2018) [13]	49	70.5	18.5	49 (100)	49 (100)	42 (85.7)	NR	Robotic
Sayed (2017) [25]	17	57.0	64.0	NR	15 (88.0)	15 (88.0)	NR	Open

ISD = intrinsic sphincter deficiency; MUCP = midurethral closing pressure; MUS = midurethral sling; UI = urinary incontinence; NR = not reported; VLPP = Valsalva leak point pressure.
[a] Devices (not number of patients).

Table 4. Patient Characteristics[27]

Patient Follow-up

The studies reported a median follow-up of 69.0 months, with 5 studies reporting a high dropout rate related to a longer follow-up period in an elderly population, where AUS procedure-unrelated deaths occurred.

Performance and safety

A UI cure rate defined by ***'0 pad'*** rate was analyzed in 12 papers, with heterogenous proportions ranging from 42-86% reported in 83% (10/12) of studies. ***'Zero-one pad'*** rate was reported in 58%

[27]Reus et al. Performance and Safety of the Artificial Urinary Sphincter (AMS 800) for Non-neurogenic Women with Urinary Incontinence Secondary to Intrinsic Sphincter Deficiency: A Systematic Review. Eur Urol Focus. 2020 Mar 15;6(2):327-338.

(7/12) of studies, with proportions ranging from 58-100% and ***'One pad rate'*** was reported in 50% of cases, with again, heterogenous proportions ranging from 7-17%. The cure rate outcomes are represented in the Figure 11.

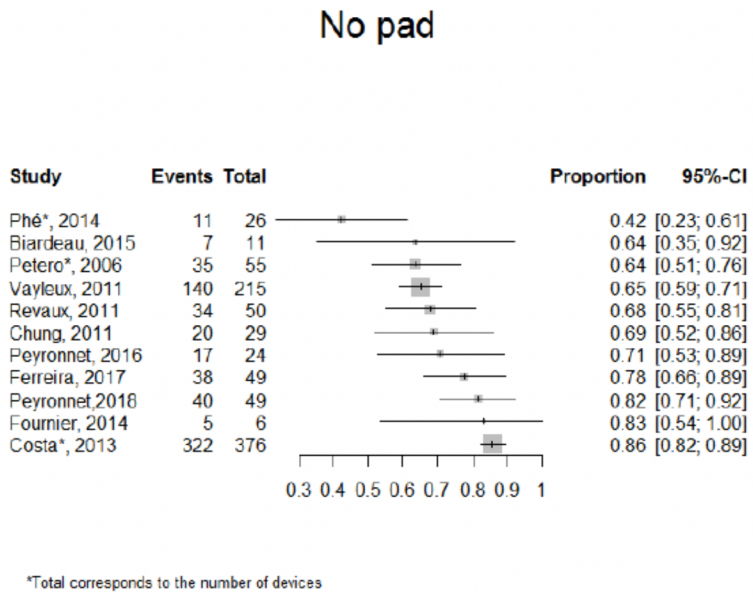

Figure 11. UI Cure rates with *'0 pad'* used as definition for cure

When analyzing safety outcomes expressed in ***AE* rates**, we considered ***SAE rates*,** namely ***PSAE rates,*** which include intra operative urethral, vesical, or vaginal injuries, which were reported in 50% (6/12) of studies, with heterogenous rates ranging from 2-54%. ***NSAE rates*** were reported in 58% (7/12) with equally heterogenous proportions ranging from 6-36%.
SADE rates including infection and/or erosions leading to *explantations* were reported in 75% (9/12) of studies, with rates ranging from 2-31%. This was mirrored in 67% (8/12) studies reporting 2-26% *infection rates* and 75% (9/12) studies reporting *erosion rates* ranging from 0.5-27%. These findings have been compiled in the table 5 and figure12.

	Adverse Events	Adverse Device Effects
Non Serious	**AEs** (6-36%) (Including PAEs)	**ADEs** (Including DD) Revision rates (6-45%)
Serious	**SAEs** (2-54%) (Including PSAEVs)	**SADEs** (Including USADEs & ASADEs) Explantation rates (2-31%) Infection rates (2-26%) Erosion rates (0.5-27%)

AEs = Adverse Events
PAEs = Procedure AEs
SAEs = Serious AEs
PSAEs = Procedure SAEs
ADEs = Adverse Device Effects
DD = Device Deficiency
SADEs= Serious ADEs
USADEs = Unanticipated SADEs
ASADEs = Anticipated SADEs

Table 5. Summary of Adverse Events (AEs)[28]

[28]https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

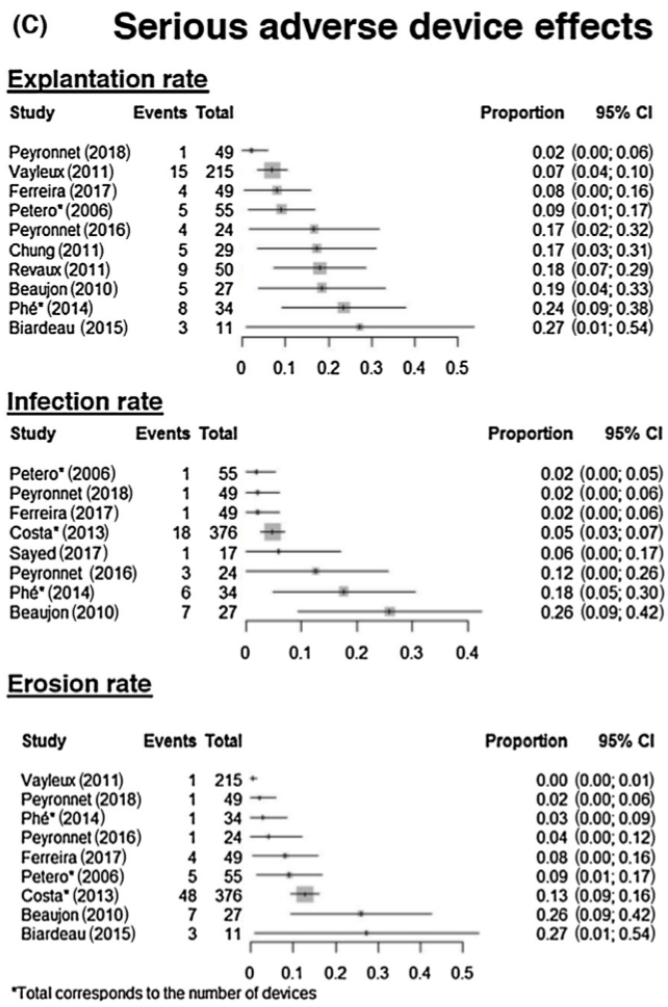

Figure 12. Serious Adverse Device Effects (SADEs)

Grading of evidence and level of evidence

Based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (150,151)the level of evidence regarding performance and safety outcomes resulting from this systematic review was low.

Paper II

Patient-related outcomes

From the 221 patients from our EMR records who benefitted from an AMS 800™ implantation between 2005-2018 analyzed, 41 patients were excluded: 3 female patients, 23 neurogenic SUI, 12 secondary AUS implantations, 2 patients with no reported pre- and post-operative information on the 24-h PWT or QoL surveys and 1 patient where the procedure was abandoned due to intraoperative urethral injury. A total of 180 men were included in this study.

Efficacy outcomes

The great majority, 99.5% (179/180), had completed a *pre-operative* 24-h PWT, with values of 494 (IQR: 304–780) g and 88% (158/180) completed a post-device activation test, with values of 7.0 (IQR: 0–25) g. This meant that 87% (157/180) of men correctly filled out the PWT both pre-and postoperatively. In these 157 patients a paired comparison was conducted, which demonstrated a statistically significant improvement in continence, equivalent to the data obtained for all measurements, $p < 0.001$. The results are summarized in figure 13.

QoL outcomes

I-QoL survey: reported pre-operative compliance was 76.7% (138/180) and 65.6% (118/180) post-AUS activation, with only 54.4% (98/180) of men correctly completing the survey on both occasions. The median pre-operative I-QoL index of 33.5 (IQR: 19.3–63.6) raised to 86.4 (IQR: 73.9–94.3) points post-operatively, showing a significant improvement of 52.9 points ($p<0.001$). There was no significant difference in QoL improvement when conducting a paired comparison using all measurements, $p < 0.001$ (Figure 13).

ICIQ-UI SF survey: reported pre-operative compliance was even less, with 68.3% (123/180) responders and 21.7% (39/180) postoperatively. The percentage of responders on both instances was very low, at 20% (36/180). Median pre-and postoperative ICIQ-UI SF measurements reduced significantly from 20 (IQR: 17–21) to 5 (IQR: 3–9) points, with 15 points increase ($p < 0.001$). We completed a paired comparison on the 20% who adequately filled in the survey on both occasions and found a statistically significant amelioration, comparable to the obtained values when applying all measurements, $p < 0.001$ (Figure 13).

Correlation between 24-h PWT and patient quality of life

I-QoL survey: to analyze the link between 24-h PWT and I-QoL, we conducted a Spearman's rank correlation (r_S) in the 98 men who adequately completed the survey pre-and post AUS surgery. We found a statistically significant strong negative correlation between the 24-h PWT and I-QoL, with $r_S = - 0.74$, $p < 0.0001$ (Figure 14).

ICIQ-UI SF survey: furthermore, we also ran a Spearman's rank correlation (r_S) to evaluate the existing link between 24-h PWT and ICIQ-UI SF, applied to the 35 patients who correctly completed the survey pre-and postoperatively. We found a statistically significant strong positive correlation, with $r_S = 0.91$, $p < 0.0001$ (Figure 14).

These findings showed a monotonic relationship between QoL amelioration and the reduction of urinary incontinence.

Finally, a Spearman's rank correlation (r_S) was carried out on the 36 men who adequately completed both QoL questionnaires on both occasions, to assess the relationship between I-QoL and ICIQ-UI SF. This showed again a very strong negative correlation, with $r_S = -0.84$, $p < 0.0001$ (Figure 14).

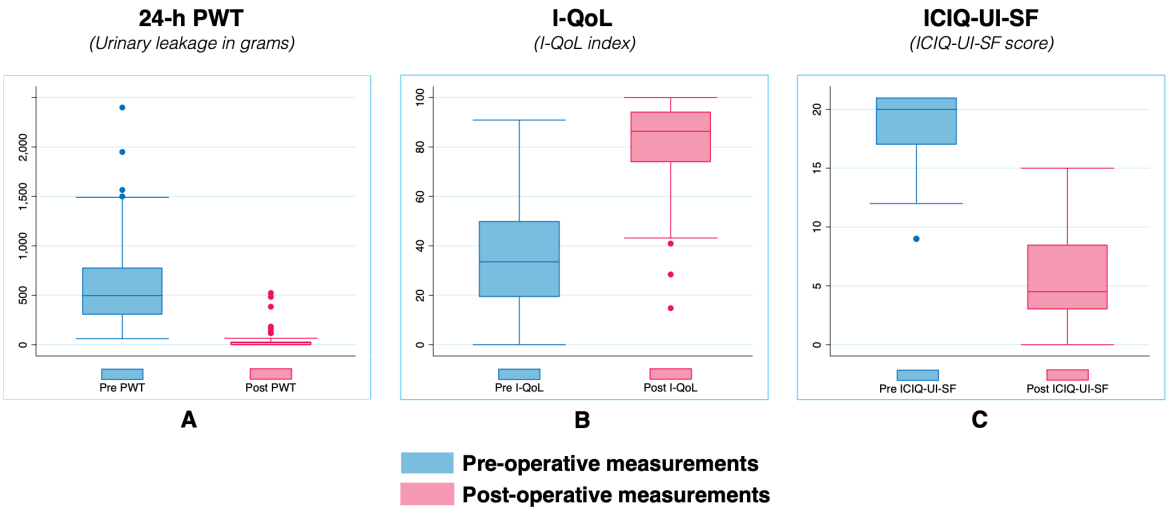

Figure 13. Pre-operative versus post-device activation continence and qualitative outcomes

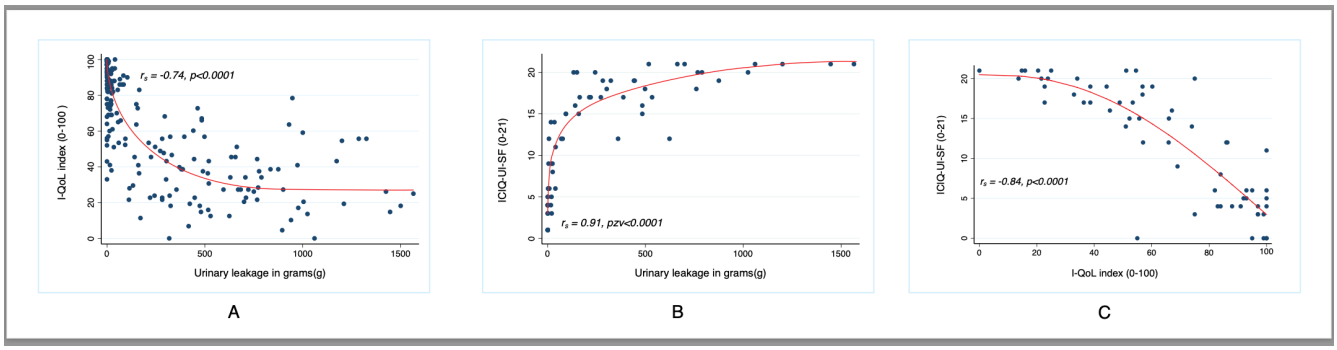

Figure 14. Correlation between 24-h pad weight test and qualitative questionnaires, I-QoL and ICIQ-UI SF

Paper III

In this study the performance and safety of transscrotal (TS) was compared to transperineal (TP) primary AUS implantation in men suffering from PPUI.

Patient characteristics

The study included 183 men with a mean age at the time of surgery of 70.0 years (SD=5.16), the mean BMI was 26.4 (SD=3.04). Of these men, 7.7% (14/183) suffered from diabetes mellitus and 6.0% (11/183) were on anti-coagulant medication. Both groups (TS/TP) were similar in terms of co-morbidities (*p=0.356* for diabetes and *p=0.999* for anticoagulants) and regarding their pre-operative concomitant DOA profile (41.5% for TP and 43.1% for TS group). More than twice the proportion of men in the TP group had had previous UI surgery (28.3% compared to 11.5% in the TS). Prior urethral/anastomotic stricture procedure was noted in 1.5 more patients in the TP cohort (30.2%) compared to the TS (19.2%). More noteworthy, double the proportion of men had previous salvage radiation in the TS group (26.2%) compared to the TP (13.2%), as shown in Table 6.

	All N=183 (mean, SD)	TP N=53 (mean, SD)	TS(ink TC) N=130 (mean, SD)	p-value	TP N=53 (mean, SD)	TS-TC N=101 (mean, SD)	TC N=29 (mean, SD)	p-value
Age (years)	70, 5.2	69, 4.4	70, 4.5	p=0.091	69, 4.4	70, 5.5	71, 5.0	p=0.121
BMI	26.4, 3.0	26.0, 3.0	26.6, 3.0	p=0.187	26.0, 3.0	26.5, 3.1	27.1, 2.1	p=0.103
	N, %	N, %	N, %	p-value	N, %	N, %	N, %	p-value
DOA	78/183 (42.6%)	22/53 (41.5%)	56/130 (43.1%)	p=0.905	22/53 (41.5%)	42/101 (41.6%)	14/29 (48.3%)	p=0.779
Previous UIS	30/183 (16.4%)	15/53 (28.3%)	15/130 (11.5%)	***p=0.004***	15/53 (28.3%)	13/101 (12.9%)	2/29 (6.9%)	***p=0.016***
Previous USS	41/183 (22.4%)	16/53 (30.2%)	25/130 (19.2%)	p=0.169	16/53 (30.2%)	19/101 (18.8%)	6/29 (20.7%)	p=0.363
Previous RT	41/183 (22.4%)	7/53 (13.2%)	34/130 (26.2%)	***p=0.045***	7/53 (13.2%)	5/101 (5%)	29/29 (100%)	***p<0.001***

TP: Transperineal
TS: Transscrotal
TC: Transcorporeal
DOA: Detrusor overactivity
UIS: Urinari incontinence surgery
USS: Surgery for urethral/and or anastomotic stricture
RT: Radiation therapy

Table 6. Summary of patient characteristics

Performance outcomes

Overall, in the 86.3% (158/183) of men adequately completing pre-and postoperative 24-h PWT, we found a significant decrease in UI, with a median of 478.5 (IQR: 280–747) g pre-operatively and 7 (IQR:0-25) g post-device activation. When comparing TP versus TS cohorts, a similar proportion of men had filled the 24-h PWT on both occasions, 83% and 87.7% respectively. Equally, no difference in median pad weight decrease was shown when comparing both groups, neither was there any in the TS/TC versus the TP group, -1.0 (95% CIs: -10.9, 8.9), p=0.842 (Table 7). Similarly, no difference was observed when these measurements were stratified into DOA, prior UI, and urethral stricture surgery, as well as previous salvage radiation therapy.

Median 24h-pad weight test before and after surgery as well as the median reduction i leakage (A). There was no difference in medians between patients operated with a transscrotal incision as compared to those operated with the transperineal approach (B). Furthermore, no differences was seen when sub-grouping in regard to patients in the transscrotal group that had recieved a transcorporeal cuff placement(B). Median pre- and post-operative I-QoL index as well as median increase in I-QoL index (A). For the I-QoL index there was no difference in medians between patients operated with a transscrotal incision as compared to those operated with the transperineal approach (B). Furthermore, no differences was seen when sub-grouping in regard to patients in the transscrotal group that had recieved a transcorporeal cuff placement(B).

Table 2A

	Total			TP			TS including TC			TS excluding TC			TC		
	N	Median	IQR	N	Median	IQR	N	Median	IQR	N	Median	IQR	N	Median	IQR
24h pad weight test															
Pre-surgery	158	492	300.00, 767.00	44	494	324.00, 784.50	114	489	282.00, 767.00	93	450	280.00, 714.00	21	630	370.00, 940.00
Post-surgery	158	7	0.00, 25.00	44	8	0.00, 25.50	114	7	0.00, 25.00	93	7	0.00, 25.00	21	9	0.00, 20.00
Diff. post- and pre-surgery	158	-479	-747.00, -280.00	44	-482	-756.50, -320.00	114	-479	-743.00, -261.00	93	-442	-683.00, -243.00	21	-590	-940.00, -358.00
I-QoL Index															
Pre-surgery	98	35	22.00, 51.00	30	29	22.00, 45.00	68	39	22.00, 52.50	56	39	22.50, 54.50	12	35	14.00, 45.00
Post-surgery	98	86	74.00, 94.00	30	78	68.00, 86.00	68	88	75.50, 95.00	56	89	75.00, 97.00	12	88	84.00, 92.50
Diff. post- and pre-surgery	98	47	31.00, 58.00	30	43	30.00, 54.00	68	48	35.50, 59.00	56	47	32.00, 57.50	12	50	43.50, 66.50

Table 2B

	Crude difference of medians				Adjusted difference of medians*			
	Diff	95% CIs		p-value	Diff	95% CIs		p-value
Difference between post- and pre-surgery 24h PWT								
TS including TC vs TP	10,00	-155,42	175,42	0,905	-1,00	-10,92	8,92	0,842
TS excluding TC vs TP	48,00	-124,42	220,42	0,583	-1,01	-11,49	9,48	0,850
TC vs TP	-100,00	-349,92	149,92	0,430	2,07	-13,09	17,22	0,788
Difference between post- and pre-surgery I-QoL index								
TS including TC vs TP	6,00	-4,95	16,95	0,280	6,27	-1,37	13,92	0,107
TS excluding TC vs TP	5,00	-6,18	16,18	0,377	6,12	-2,01	14,25	0,138
TC vs TP	10,00	-6,88	26,88	0,242	9,51	-2,65	21,66	0,124

* Adjusted for the pre-surgery measurement of the same outcome

TP: Transperineal
TS: Transscrotal
TC: Transcorporeal

Table 7. Comparative functional and qualitative outcomes between TS and TP approaches

Quality of life outcomes

I-QoL questionnaires

Overall, in the 53.6% of men who adequately completed both pre-and post-operative surveys, a median increase of the I-QoL index of 47 points (IQR: 31- 58) pre-and post-AUS activation was shown, p<0.001 (Table 7/Table 2A).

Comparing *TP versus TS groups*, correct survey completion was seen in 56.6% and 42.3% respectively, with a greater median pre-and post-operative I-QoL index in the TS cohort. However, both groups were identical in terms of median I-QoL index increase (adjusted difference in medians 6.3 (95% CIs: -1.4, 13.9), p=0.107), nor was there any in the *TS/TC versus TC cohort* and the *stratified analysis in TS versus TP group*. Although, a greater median I-QoL index increment was seen in the TS group having previously undergone surgical treatment for urethral/anastomotic stricture (Table 7/Table 2B).

ICIQ-UI SF questionnaires

Overall, only 19.7% of men had adequately completed the surveys on both pre-and post-device activation occasions, with 5.7% in the TP cohort and 25.4% in the TS, and therefore the small numbers did not allow proper comparison.

Safety outcomes

Early adverse events

We reported only 12% (22/183) early (< 90 days) AEs, mostly in Clavien-Dindo Class I-II in all groups, with 7.5% (4/53) in the TP, 5.4% (7/130) in the TS (which also included TC OC insertions). We noted that 10.3% (3/29) of non-serious AEs appeared in the TC group alone. Nevertheless, we observed more serious AEs in the TP group 11.3% (6/53), compared to 3.8% (5/130) in the TS (of which 3.4% (1/29) occurred in the TC group. One patient incurred a peri-operative urethral injury in the TP group, precluding him from any device implantation, and primary injury repair was achieved (Table 8).

CLAVIEN-DINDO CLASSIFICATION	SYMPTOMS	MANAGEMENT	AUS IMPLANTATION TECHNIQUE			
			TP (n=53)	TS (n=101)	TC (n=29)*	Total (N=183)
I	Pain, hematoma, urinary retention, superficial wound infection	Analgesia, urethral catherisation	3 (5.7%)	4 (4.0%)	3 (10.3%)	**10 (5.5%)**
II	Urinary Tract infection	Antibiotics	1 (1.9%)	0 (0%)	0 (0%)	**1 (0.5%)**
IIIa	Bleeding	Re-operation with diathermia	0 (0%)	1 (1.0%)	0 (0%)	**1 (0.5%)**
IIIb	Migration of device parts	Revision	2 (3.8%)	1 (1.0%)	0 (0%)	**3 (1.6%)**
	Implant infection within 90 days	Explantation	4 (7.5%)	1 (1.0%)	0 (0%)	**5 (2.7%)**
	Urinary retention	Revision (cuff re-sizing)	0 (0%)	0 (0%)	1 (3.4%)	**1 (3.4%)**
	Erosion	Explantation	0 (0%)	1 (1.0%)	0 (0%)	**1 (0.5%)**
IV-V			0 (0%)	0 (0%)	0 (0%)	0 (0%)
TOTAL			10 (18.8%)	7 (6.9%)	4 (13.7%)	22 (12.0%)

* All TC approaches have been performed using the TS technique.

TP=Transperineal approach
TS=Transscrotal approach, excluding transcorporeal cuff placement
TC=Transcorporeal cuff placement
AUS= Artificial urinary sphincter

Table 8. Early complications - Clavien-Dindo Classification

Late adverse events (>90 days)

Excluding the patient with the urethral injury, 31.9% (58/182) long-term AEs were reported over 17 years. Overall, 4.4% (8/182) of men developed AUS *infection,* 9.3% (17/182) had device *erosions* and 21.4% (39/182) mechanical failure. Consequently, 31.8% (58/182) of re-operations were conducted, including 19.7% (36/18) *revisions* and 12.1% (22/182) AUS explantations. Looking more closely into *mechanical failures* we showed a 40.5% OC-related device failure, 29.7% PBR-related complications, 13.5% tubing defects, 10.8% pump malfunction, and unspecified cause in 5.4%.

We observed a **lower** *infection* (RR=0.24 (95% CIs: 0.06, 0.99), p=0.048), *explantation (*RR=0.72 (95% CIs: 0.36, 1.45), p=0.360), *mechanical failure* (RR=0.43 (95% CIs: 0.25, 0.75), p=0.003), and *revision* (RR=0.42 (95% CIs (0.25, 0.72), p=0.002) risks in the **TS cohort** as opposed to the TP.
A **higher** *erosion* risk (RR=1.33 (95% CIs: 0.45, 3.88), p=0.608) in the TP group was also reported.
When analysing **TS with TC versus TP cohort**, as expected, the TC group was responsible for greater *erosion* risks (RR=3.20 (95% CIs: 1.02, 10.02), p=0.046) leading to higher explantations risks, with however wider CIs (RR=1.43 (95%CIs: 0.64, 3.23), p=0.383) (Table 10). The TS technique displayed lower hazard of device revision, albeit with large confidence intervals (HR=0.61, 95% CIs: 0.31, 1.20, p=0.154).

When conducting the stratified analysis for DOA, prior salvage radiation, previous anti-UI surgery and procedures for urethral/anastomotic stricture, the contrast in RR for TS as opposed to TP within the strata was small, although low estimate precision could not exclude a chance occurrence (Table 10). The AUS implantation mode seemed to have no obvious effect on device survival in the stratified analysis (Figure 15).

Over all rates of infection, erosion, mechanical failure, revision and explantation for different surgical approaches (A). Risk ratios and risk differences between the groups (B).

A	Total		TP		TS including TC		TS excluding TC		TC	
	N=182		N=52		N=130		N=101		N=29	
	N	%	N	%	N	%	N	%	N	%
Infection	8	4,40	5	9,62	3	2,31	3	2,97	0	0.00
Erosion	17	9,34	4	7,69	13	10,00	6	5,94	7	24.14
Mechanical failure	37	20,33	18	34,62	19	14,62	15	14,85	4	13.79
Revision	39	21,43	19	36,54	20	15,38	16	15,84	4	13.79
Explantation	28	15,38	10	19,23	18	13,85	10	9,90	8	27.59

B	Risk ratios				Risk difference			
	RR	95% CIs		p-value	RD	95% CIs		p-value
Infection								
TS including TC vs TP	0,24	0,06	0,99	0,048	-7,13	-15,41	1,16	0,092
TS excluding TC vs TP	0,31	0,08	1,27	0,104	-6,46	-15,00	2,07	0,138
TC vs TP								
Erosion								
TS including TC vs TP	1,33	0,45	3,88	0,608	2,45	-6,33	11,24	0,584
TS excluding TC vs TP	0,79	0,23	2,67	0,701	-1,61	-10,08	6,87	0,710
TC vs TP	3,20	1,02	10,02	***0,046***	16,59	-0,53	33,71	0,058
Mechanical failure								
TS including TC vs TP	0,43	0,25	0,75	***0,003***	-19,35	-33,47	-5,22	***0,007***
TS excluding TC vs TP	0,44	0,24	0,80	***0,007***	-19,11	-33,62	-4,60	***0,010***
TC vs TP	0,41	0,15	1,09	0,073	-20,17	-38,06	-2,28	***0,027***
Revision								
TS including TC vs TP	0,42	0,25	0,72	***0,002***	-21,15	-35,64	-6,67	***0,004***
TS excluding TC vs TP	0,43	0,24	0,77	***0,004***	-20,70	-35,60	-5,80	***0,006***
TC vs TP	0,38	0,14	1,00	0,051	-22,75	-40,88	-4,61	***0,014***
Explantation								
TS including TC vs TP	0,72	0,36	1,45	0,360	-5,38	-17,63	6,86	0,389
TS excluding TC vs TP	0,51	0,23	1,16	0,108	-9,33	-21,52	2,86	0,134
TC vs TP	1,43	0,64	3,23	0,383	8,36	-11,12	27,83	0,400

TP: Transperineal
TS: Transscrotal
TC: Transcorporeal

Table 10. Summary of late adverse events comparing TS and TP techniques

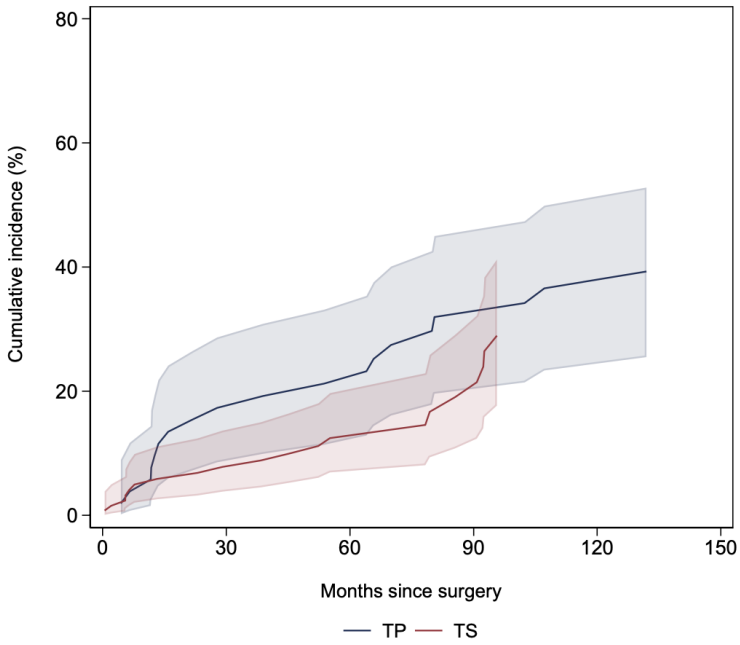

Figure 15. Device revision cumulative incidence in men who underwent TP and TS procedures.

Paper IV

We analyzed 67 men with a mean age of 70.2 years (SD= +/- 10.0), who underwent AUS implantation for non-neurogenic PPUI using a transperineal technique, with a bulbar urethral occlusive cuff placement, at La Pitié-Salpêtrière University Hospital between October 2016 and November 2018. Consequently, the volume of 67 peri-bulbar cuffs were measured at the time of their pressurization. The measurements were conducted whilst the patients had a 14Fr urethral catheter in situ.

Implant characteristics

All men received a 61-70 cm H2O PRB. The measured *OC sizes*, using the cuff sizer provided in the Accessory Kit, were as follows: 3.5cm (n=1); 4.0cm (n=29); 4.5cm (n=26); 5.0cm (n=9); 5.5cm (n=1); 6.0cm (n=1). We observed that 43.3% of occlusive cuffs measured 4.0cm 38.8% and 4.5cm. We found the median measured cuff volume at pressurization to be 0.3cc (interquartile range [IQR]: 0.2– 0.5) and the mean volume of 0.34 (SD+/- 0.19). No significant volume difference in OC volumes in a subgroup analysis between 4.0cm and 4.5cm sizes was shown (*p<0.05).* Furthermore, we must take into account that the 14 French catheter was in the urethra, and since the OC is an incompressible cylinder measuring 16mm high, its calculated volume (*V*) using the formula $V = \pi r^2 xh$ *(π:pi; r:radius; h:height*), at the time of pressurization is 0.27ml. We demonstrated that, the larger the cuff, the larger the accommodated volume required, which, did not exceed 1ml. (Figures 16 and 17).

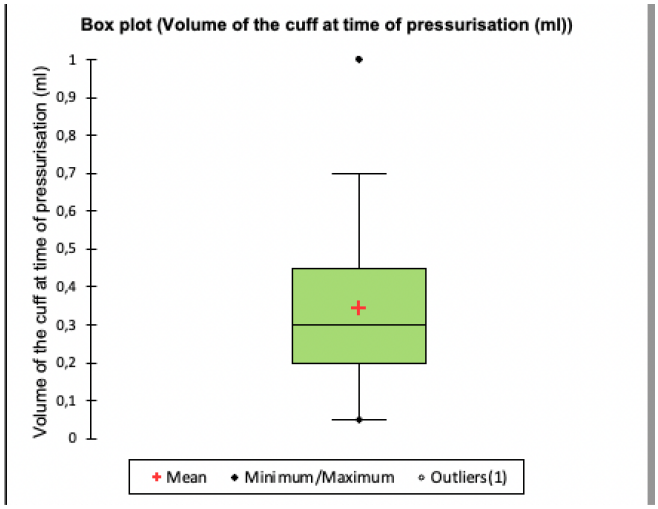

Figure 16. Peribulbar OC volumes measured at pressurization

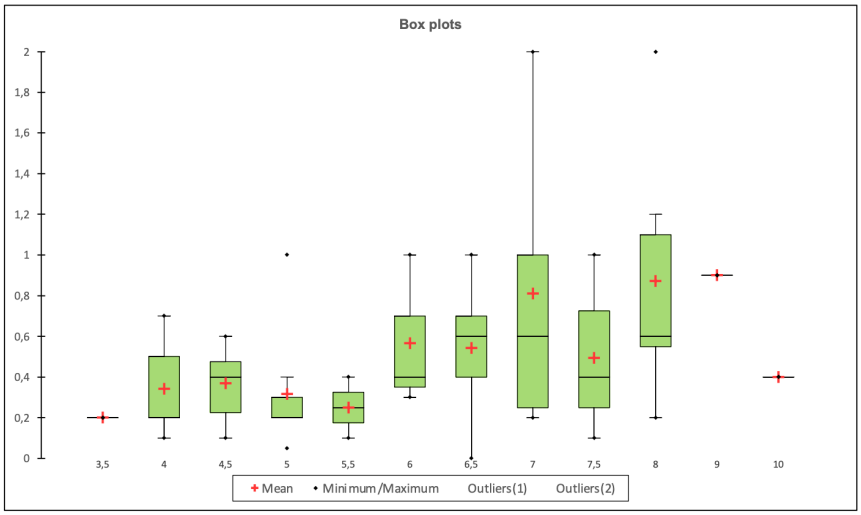

Figure 17. In vivo Peri-operative OC volume measurements at pressurization

Paper V

In this pilot study we wished to establish the feasibility of implantation of the novel eAUS device and to demonstrate its performance in human cadavers.

Novel AUS device feasibility of implantation

Four human cadavers (3 males and one female) were implanted with the novel eAUS device for feasibility evaluation purposes.

An engineer tested the software functions of the CU, and the device was primed.

The incision to fit the CU was slightly larger, about 10 cm in length compared to the one routinely performed for the AMS 800™ balloon. The operation steps were shortened since the AMS 800™

components preparations were automatically achieved by the novel eAUS device. We implanted 4.0 cm OC in the 3 male and a 6.0 cm for the female subjects (Table 11).

Feasibility study summary	Subject 1	Subject 2	Subject 3	Subject 4
Gender	Female	Male	Male	Male
Implantation technique	Open technique Bladder neck occlusive cuff placement	Trans-perineal incision Bulbar urethra occlusive cuff implantation		
Implantation duration	20-25 minutes			
OC Size (cm)	6.0	4.0	4.0	4.0
Peri-operative complications	None observed			
Basic UroMems device functions **1. Priming** **2. Get atmospheric pressure** **3. Calibration**	All functions were operational			

Table 11. Summary of novel AUS feasibility of implantation study

Performance evaluation

Four male human cadavers were implanted with the novel eAUS device for performance evaluation. Automatic CU functions were operational prior to implantation. The implanted OC sizes were 4.0 cm (n=1) and 4.5 cm (n=3). Measuring the MUCP in cadavers was feasible and very similar to standard clinical practices.

The CU could provide MUCP ranges above and below those of the AMS 800™ PRBs (51-60 cmH_2O, 61-70 cmH_2O and 71-80 cmH_2O) provided for the occlusive cuff to close around the urethra.

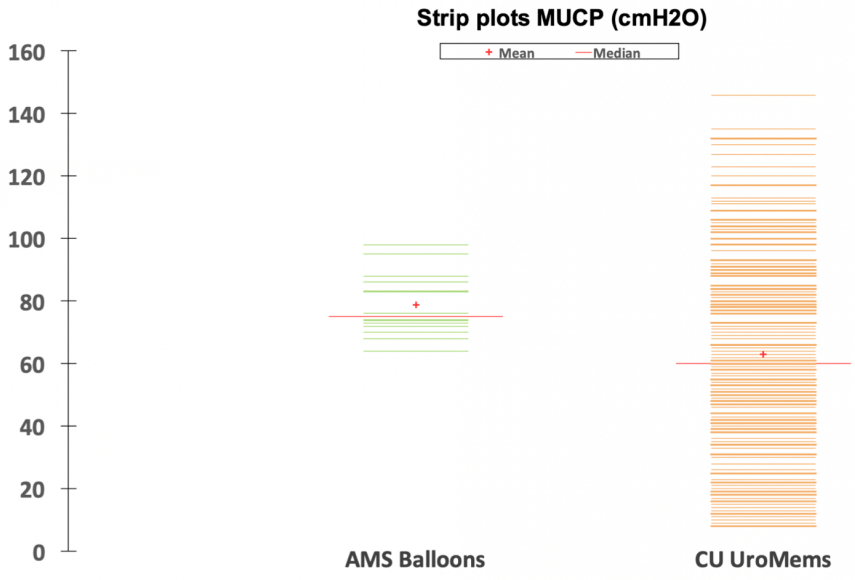

Figure 18. Performance study showing the novel device provided similar MUCP ranges than the randomly selected AMS 800 PRBs, i.e., between 20-120 cmH_2O.

Paper VI

In this study we wished to evaluate feasibility of implantation, performance, and safety of the novel eAUS device in a wether model.

Wether characteristics

Wether-1 weighed 63kg and wether-2 87 kg at Day 0 (on the day of implantation). The weight loss in Wether-1 was statistically insignificant post operatively, registered weights being 61kg at week 4 and 8. Wether-2 incurred a 10% weight loss at termination, recorded weights being 87 kg at week 4 and 78 kg at week 8 post-device implantation.

Surgical characteristics

We report no intraoperative AES. No difficulty was incurred during the procedure. Operating time was 84 min for Wether-1, which was fitted with a 4.0 cm OC and 70 min for Wether-2, which received a 4.5 cm OC. A 42 cm tubing length for Wether-1 and 43 cm for wether-2 were implanted and connected the OC to the CU (Figure 19). The device was operational and the CU functional, since it automatically opened and closed the OC at the end of the implantation.

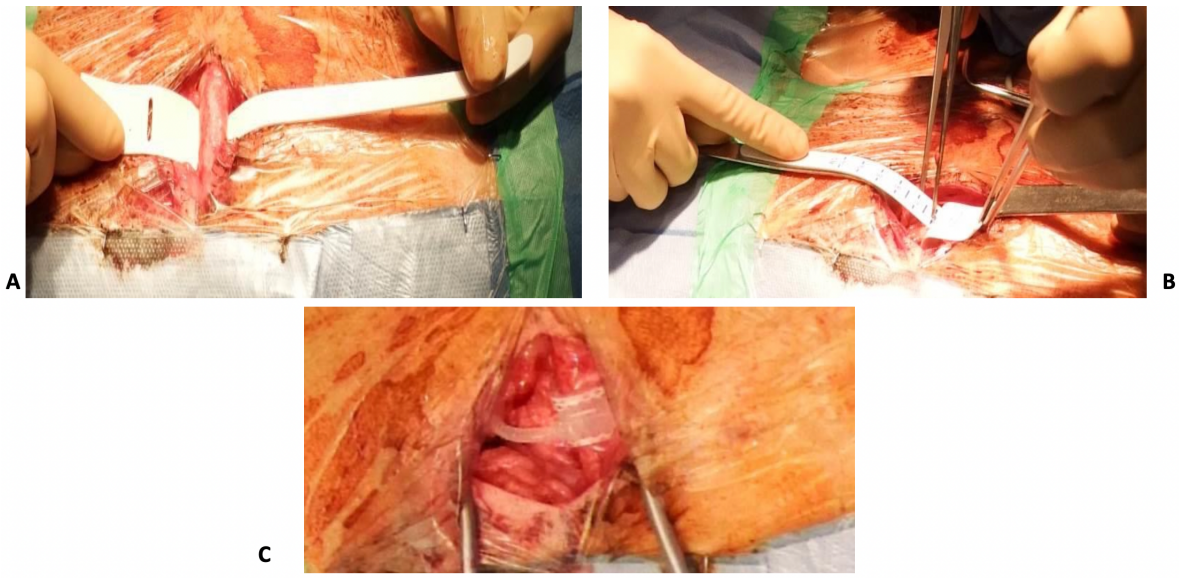

Figure 19. Surgical implantation of the novel eAUS device in a wether model

A. Dissection of the urethra – **B**. Urethral diameter measurement **C.** Peri-urethral insertion of the OC

Clinical parameters

There were no systemic or local infection observed between Day 0 and week 8, nor were any significant signs of infection, discomfort/pain. The wethers displayed stable biochemical parameters, with no signs of intra-or post-operative blood loss, raised white cell count, or impaired renal function during the study. However, slight decrease in white cell count in both wethers between Day 0 and Week 4 after novel AUS activation was reported. Also, both wethers showed mild oedema with or without seroma in the tissues around the CU, the tubing, or the urethra, which was expected as part of the post-operative physiological response, and therefore had no bearing on the study results as these events spontaneously resolved.

The bedding of the cage was moist daily, attesting the animals could urinate. Both wethers appeared clinically normal for the duration of the study.

Device function

Both AUS devices were operational at the end of the surgery and could be activated/deactivated at the end of the anesthesia. The OC remained opened to allow urethral tissue healing. Four weeks post-implantation, the device was easily calibrated, and the implant could be successfully activated in both wethers.

Necropsy analysis

At 8 weeks post-device implantation, no soft tissue abnormality around the OC or the tubing was reported, corroborated by histopathological assessment, showing light to moderate inflammatory reaction. Surrounding the CU, a white grayish capsule measuring 2-5 mm with pink to dark red tissue discoloration by the CU borders were described. Also slight to moderate hemorrhage and marked fibrosis were found. No device/tubing erosion, kink, damage, or migration were observed.

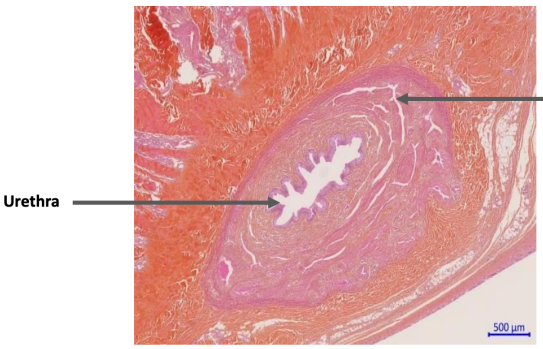

Figure 4a. Cross section showing partial endoluminal occlusion of the urethra

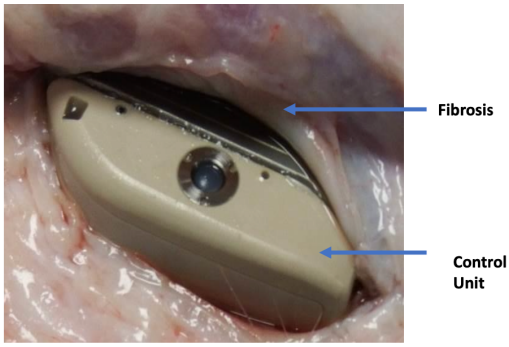

Figure 4b. Fibrotic tissue around the control unit

Figure 20. Histopathological and necropsy findings

Histology analysis

A fibrous capsule of 4-6 mm thickness was seen, without features of necrosis, degeneration or infection around the CU and the tubing. No noteworthy tissue reaction was identified between the connecting and central part of the tubing. A <1 mm fibrous capsule also covered the OC. No cuff defect nor leakage was identified. Zero to mild necrosis signs was shown, at the connecting part of the tubing but not at the OC interphase.

Summary of findings of papers I-VI

In the *systematic review*, the information on 886 female patients from 12 articles were analyzed. None of the reported studies were RCT or prospective in nature. We showed result heterogeneity regarding long-term performance outcomes, expressed as *'0 pad'* rate, from 42-86%, but also long-term safety results, with revision rates of 6-44%, mechanical rates of 2-41%, PSAE rates of 2-54% and SADEs

rates of 2-27%. The review showed that the level of evidence for AUS implantation in women with non-neurogenic SUI is very low.

Furthermore, the 24-h PWT is an objective AUS device performance assessment tool, which correlated with validated quality of life questionnaires, and could help decrease the heterogeneity in reported outcomes in the literature. Overall, urinary incontinence decreased significantly by 489.5g (99.1%), p<0.001, with median pre-and post-device activation *24-h PWT* measurements of 494 (interquartile range [IQR]: 304–780) and 7 (IQR: 0–25) g respectively. Similarly, we showed a significant 52.9 points improvement of quality of life mirrored in the *I-QoL* surveys, which presented incremental values from 33.5 (IQR: 19.3–63.6) to 86.4 (IQR: 73.9–94.3) points, (p<0.001). This was also the case of ICIQ-UI SF surveys, where median pre-and post-device activation measurements decreased significantly by 15 points, from 20 (IQR: 17–21) to 5 (IQR: 3–9) points, (p < 0.001).

Additionally, our study comparing TS (n=130), of which 29 had a TC cuff, and TP(n=53) AUS implantations in 183 patients, showed that both techniques had similar long-term efficacy and safety profiles, with potentially more mechanical failures in the TP cohort. Indeed, no significant difference in 24-h PWT decrease nor was there in I-QoL index increase when comparing both groups (p=0.842 and p=0.107 respectively). When analyzing long-term complication rates, we observed 4.4% overall infection rate, with a lower infection risk in the TS cohort (RR=0.24, p<0.05). However, an overall erosion rate of 9.3% of men was identified, with a *greater* risk in the TS group (RR=1.33, p=0.608) due to a larger proportion of radiated patients in this cohort. Finally, we found a lower mechanical complication rate and consequently lower revision rates in the TS group (RR=0.43, p=0.003).

The clinical prospective *in vivo* measurements of the peribulbar occlusive cuff showed that larger cuffs would accommodate larger volumes, but that these volumes did not go beyond 1cc, even considering the additional 0.27cc urethral catheter volume. This information was crucial to dimension the novel electronic AUS device.

In the pre-clinical studies, pilot cadaver studies showed that the novel AUS was easily implantable, that its automatic functions were operational and that it could procure similar MUCP ranges on urodynamic investigations from 20-120 cmH_2O as the 51-60 cmH_2O, 61-70 cmH_2O and 81-90 cmH_2O AMS 800™ PRBs. Similarly, pilot wether studies demonstrated device ease of implantation, with no intraoperative AEs, no post-operative SAEs and device operationality. The device could successfully be activated and deactivated as programmed. Tissue biocompatibility showed no major AEs, and the clinical follow-up of the animals did not show any signs of infection nor renal function impairment 8 weeks after device implantation.

6 DISCUSSION

This thesis was a collaborative endeavor between two institutions with the aim to accompany some of the developmental stages of a new electronic AUS device for the treatment of severe non-neurogenic SUI in both men and women. When conducting the *Risk Analysis* of the novel AUS, it became apparent that there was a paucity of information pertaining to long-term efficacy and safety profiles of the AMS 800 implantation in female patients. We therefore wished to address this point by conducting a *systematic literature review* on the subject, which had not yet been done at the time the thesis began, for thorough risk analysis completion.

In parallel, preparations for the FIM implantation commenced at a very early stage, especially the Clinical Investigation Plan for the study design, where defining primary outcomes is essential. Planning has not only regulatory, quality, and financial impacts on the AIMD development timeline, but is also important from a patient safety perspective. In accordance with the FDA guidance[29] for the development of new AIMD for UI, the primary efficacy endpoint should, i.e., evaluate the device's performance, measured using the 24-h PWT. However, it appeared that there were very few studies reporting the efficacy of this tool. The Karolinska University Hospital had a long history of using the 24h-PWT instead of the pad count to measure qualitative post-operative outcomes of men suffering from PPUI since 2004. Similarly, the institution has also used validated questionnaires such as the I-QoL and the ICIQ-UI SF to evaluate the qualitative outcomes. Therefore, it was only logical to perform a retrospective analysis of the 24-h PWT as an efficacy assessment tool of UI results after AUS surgery that would, not only provide further published data, but also help decrease the reported heterogeneity in AUS performance outcomes in the literature.

Furthermore, for risk analysis completion's sake, there was also little known in the literature regarding long-term efficacy and safety of transscrotal AUS implantation, a technique used at Karolinska University Hospital but also in many centers of the USA, compared to the transperineal approach, largely performed, including at La Pitié-Salpêtrière University hospital. We therefore also conducted a retrospective analysis of TS versus TP performance and safety outcomes, which would complete the chapter of the identification of literature gaps relevant for the development of the novel smart eAUS device.

Simultaneously, the design of the novel AIMD progressed, with bench and in vitro tests being completed. Another question, which the clinical world could help resolve was the maximum volume the OC could accommodate at the time of its pressurization. This information was crucial to dimensioning one of the components of the new eAUS device. To provide the answer, we conducted a prospective intraoperative *in vivo* OC volume measurement in men undergoing AUS implantation at La Pitié-Salpêtrière hospital. This would constitute a fine example of clinical and engineering collaboration for an AIMD development.

Additionally, pre-clinical human cadavers and animal studies needed to be carried out to validate bench, *in vitro*, and in *vivo* tests. We conducted pilot studies in the first instance, assessing the device's implantation feasibility, record any perioperative AEs, ascertaining the device's automatic functions and ensuring it could be activated/deactivated, thereby showing its capacity of providing continence as safely as possible. Tissue biocompatibility testing were demonstrated on wethers.

[29] https://www.fda.gov/media/71054/download

In so doing, we have been able to accompany the design in the risk analysis, design specification and validation, as well as its pre-clinical developmental processes.

6.1 Literature gaps

Systematic literature review

We conducted the first systematic literature review analyzing long-term performance and safety outcomes of the AMS 800™ implantation for severe non-neurogenic SUI in adult women. We showed that the data was based on low evidence and highlighted disparateness in methodology across the studies analyzed.

Performance outcomes were difficult to evaluate owed to the fact that results from neurogenic and non-neurogenic outcomes were often indiscriminately reported, which partially accounted for the heterogeneity in reported functional outcomes (42-86%) using the '0 pad' rate definition. Other factors include various follow-up periods and surgical modes. Drawing conclusions on the long-term functional impact of robotic or laparoscopic AUS implantation is premature at this stage since these techniques are recent. We identified the need to implement a core set of performance outcomes for evaluating female AUS surgery in well-designed prospective, multicentric or RC trials for more accurate assessment.

Furthermore, *safety outcomes*, namely PSAEs were significant in some studies, emphasizing the importance that female AUS implantation should be reserved to specialist centers with expertise only (with more optimal learning curves and therefore less complication rates), as stated by key opinion leaders in the field(112). From this review, the outcomes of Transoburator MUS in women with confirmed ISD AND absent urethral hypermobility were similar, although information on the status of urethral mobility was only reported in 1/3 of studies(152). Information on *urethral mobility* should be more systematically reported in trials to help with surgical decision making, MUS versus AUS. The question is, should AUS be offered as a first line surgical option to women with fixed urethra, instead of subjecting these patients to several anti-UI procedures, invariably leading to higher intra-operative PSAEs when offered AUS as a last resort? Indeed, the number of UI procedures prior to AUS surgery contributes to reduce device longevity(27). Regardless, mean AUS survival of 14.7 yrs. compared to 6.9 years in men, in a cohort where 46.5% of women underwent prior Burch surgery was reported (65).

Finally, the retrospective data precludes to draw any conclusions on SAEs, which may well be underestimated. More prospective, multicentric or RCTs are required to assess additional risk factors, which would include the surgeon's learning curve or the impact of previous radiation therapy. This systematic review therefore plays a role in identifying future research questions.

From an AIMD perspective, because of the Mesh controversy and FDA recall previously mentioned, there will be increasing scrutiny by regulatory bodies, industrials and surgeons will be under more pressure to provide adequate AIMD quality control and post-market registries to optimize patient safety. Therefore, a particular effort to create multicentric national AUS patient registries would be the way forward, to facilitate prospective data collection, patient follow-up, and increase post-operative safety.

The 24-h PWT study

This study was the first large follow-up retrospective cohort study assessing the performance outcomes of the AMS 800™ using the 24-h PWT in men with PPUI in a single tertiary center, which decreased selection bias. From a functional perspective, the significant post-operative reduction of 24-h PWT after AUS activation was within similar reported ranges in the literature, where the '0-pad' rate definition was used(71,153). However, its retrospective design constitutes its main inevitable weakness. Very few centers world-wide use the 24-h PWT routinely as an effectiveness assessment tool after AUS surgery, preferring to use the less reliable pad count, rendering it difficult to collaborate to obtain multi-centric data. Therefore, the retrospective approach is the initial step to help identify factors that will pave the way for better designed prospective and randomized trials.

Furthermore, the use of surveys highlighted the question of *compliance.* In our study the compliance for pre-and post-device activation 24-h PWT completion was 87.8%, which supports its feasibility, reproducibility, and reliability as a tool to assess AUS performance, in line with previous statements(153–155). Similar findings were reported in the recently published MASTER trial, one of the few existing RCT evaluating AUS outcomes, a non-inferiority controlled comparative study between male slings and AUS. The authors found an overall preoperative survey completion of 83.7% (159/190) but a mere 27.8% (44/158) postoperatively using the 24-h PWT as an UI assessment tool. In comparison, we achieved greater pre-and postoperative survey responses of 99.5% and 87.8% at 3 months respectively. Of course, comparing these findings after a follow-up of at least 12 months would be more relevant.

To conduct a comparison between pad count and 24h-PWT would have brought strength to our study, but unfortunately the information of pad count from our records was poor. This is because the 24h-PWT was adopted directly when we started implanting AUS in our institution. On the contrary, compliance rates for pre-and post-operative quality of life questionnaires were surprisingly much lower. We observed a fall from 76.7% for I-QoL and 68.3% for ICIQ-UI SF pre-operatively to 65.6% and 21.7% post-device activation respectively. Several factors may explain this phenomenon: clinically low patient survey completion and return is well known. Poor post-operative outcome or sufficient satisfaction after surgery may decrease patient motivation. Also, research and data collection awareness among clinicians may play a role, as do clerical archiving errors. These findings strengthen our study, as they will help us improve patient response rates and clinician awareness in future studies. Online questionnaires can be implemented, bearing in mind that poor digital literacy, impaired eyesight, or hand function may constitute a deterrent factor. Mobile applications are also worth considering, although confidentiality issues may be a limiting factor.

However, the study showed a significant QoL improvement, although comparison with other studies remains challenging since various types of questionnaires are used such as the Lickert scale. Also, QoL is a new research concept in Urology, which explains the lack of data in the literature. Additionally, our results are short to mid-term(33,156,157).

Regarding secondary outcomes, we showed a direct correlation between the 24-h PWT and QoL. In other words, the dryer the patient, the more satisfied he will be, and even a small quantity of urinary leakage may significantly affect the patient's QoL. These findings mirror those by Nitti et al(158). We also found no differences in functional or safety outcomes when comparing patients who correctly filled the pre-and post-activation qualitative surveys to those who did not. Interestingly, patients reporting a 'Zero gram' performance outcome did not report highest I-QoL index levels. This could be partially explained by other factors unrelated to UI, but more AUS related, such as device ergonomics, or persistent erectile dysfunction. This was a valuable information to improve data

gathering when evaluating AUS qualitative outcomes. Consequently, from a research design point of view, it would be worth including ED questionnaires and AUS satisfaction related questionnaires to further elucidate the matter in future studies.

Finally, to complete the research angle, RCT or multicentric prospective trials are expensive and not always achievable in functional urology, where there is limited funding to finance such trials, in particular qualitative assessments. However, patient registries including on-line QoL, and ED questionnaires, as stated above are worth implementing. Also, owed to the fact that not all centers use the 24-h PWT, one should be able to draw comparisons between pad count and pad weight in a prospective manner in larger cohorts, thereby bridging another literature gap.

From an innovative AIMD perspective, this study paves the way to implement practice behaviors changes amongst clinicians, encouraging the adoption of the 24-h PWT as per FDA guidance for AIMDs. This could also facilitate post-market data collection and improve patient functional outcome assessment in a more homogenized and standardized fashion.

TS versus TP AUS implantation study

In this third paper, we conducted the largest retrospective comparative cohort follow-up study, using the 24-h PWT as a performance outcome assessment tool, investigating long-term efficacy and safety outcomes of primary TS versus TP AUS implantation in men with PPUI. Like the previous study, selection bias was reduced because the procedures were performed in a tertiary center. Another strength of this study is its stratification analysis, using DOA, salvage radiation, previous UI surgery and/or urethral stricture procedures to further investigate their impact on both techniques. Finally, a third strong suit of the study consisted in the comparative elements of qualitative outcomes in both techniques, something that has not yet been explored in the literature to date.

Nevertheless, the very retrospective character of the study analyzing a limited number of patients constitutes its weakness. Indeed, AUS implantation is only limited to a few centers across the globe and a minority of patients are offered this type of treatment.

The transperineal approach is more widely used than the TS technique, described by Wilson et al. in 2003, and improved in 2010(3,159). The latter was developed to obtain more proximal OC positioning and to render it quicker and more technically accessible for urologists. We started out with the TP technique in 2004 but evolved into adopting the TS technique in 2010, albeit using a two-incision approach to decrease PRB related complications. Therefore, it would be expected to find higher mechanical failures and consequent revision rates in the TP group, since the AUS devices had been implanted in the patient for longer.

Both groups were identical when analyzing long-term *performance outcomes* measured by post-operative 24-h PWT and were comparable to a recent study presented at an international meeting in 2019 with similar demographics. This paper investigated 125 men, 64% which underwent a TS and 36% a TP AUS implantation, although the authors used the '*1 pad/day'* definition (160). However, a much smaller cohort study including 21 men, 12 TP and 15 TS, using a 'Completely dry' rate definition showed a higher continence rate for the TS group, 66.7% compared to 50% (p=0.767) for TP group at 10 years(161). The exact opposite was reported by a third study of 126 men with 50% of TP and 50% of TS approaches, perhaps explained by a more distal OC insertion, which was often described in the early days of TS AUS surgery(162).

Similarly, no differences in *QoL outcomes* were seen when comparing both groups, with significant improvement in qualitative outcomes. We had no other study exploring these findings in TS AUS implantation to compare with and found our results to be in line with those published by Van der Aa, the Mayo Clinic in the US and the MASTER trials (7,33,68). This highlights the lack of standardization in QoL questionnaires and the recent awareness, as mentioned earlier, of the impact of QoL after AUS surgery.

Furthermore, no significant differences in short-term AEs were identified between the two groups, although we noted higher SAEs rates in the TP group, like the MASTER trials reported results on TP AUS implantation. As for long-term safety outcomes, 4.4% overall *infection rate*, with lower infection risk in the TS cohort (RR=0.24, $p<0.05$) was seen. It is difficult to attribute our result to our practice of pre-, peri-, and post-operative antibiotic prophylaxis regime and the use of Inhibizone, used in the institution since 2008. However, overall *erosion rate*s of 9.3% was reported, with a *greater* risk in the TS group (RR=1.33, p=0.608) because this group included a greater number of radiated patients (TC, n=29). Finally, lower mechanical complication rates and subsequent lower revision rates in the TS group (RR=0.43, p=0.003) was described, a fact we have explained above. These findings are in line with Singal et al. and Henry et al. (160,163). Once again, it was difficult to compare our 13-year results to similar cohorts' sizes owed to their significant shorter follow-up interval. Equally, the risk of AUS device complication rates increases with its longevity. Overall *explantation rates*, with increased RR in the TP group, were comparable to results reported in the literature.

When comparing TS versus TP *Device Survival*, there was no statistical difference between both techniques, as previously shown by Henry et al. (163). We adopted the more precise Aalen-Johansen estimator, a version of the Kaplan-Meier estimator, to investigate survival process related hazard.
Finally, no statistical difference in functional outcomes when performing a stratified analysis for the above-mentioned factors was seen. Our findings related to the TS/TC group i.e., salvage radiation cohort are comparable to the radiated TP group from Viers et al from the Mayo Clinic (164).

Once again, with this retrospective analysis, we could only pinpoint areas of data gathering that needed to be improved in future long-term multi-centric prospective studies or whenever financially possible, RCTs. Gathering these data allows us to compare our results with other centers and ensure that we offer the best level of care possible with the evidence-based medicine available. We contributed to improving information on TS AUS implantation, which would also be relevant for the Risk analysis conducted for the development of the new eAUS device.

6.2 Device design: prospective peribulbar OC measurements and novel device dimensioning

To our knowledge, this is a rather unique study, where clinical *in vivo* investigations have a direct engineerial application in the design of a novel AIMD and is, the largest prospective study collecting the data of 67 men undergoing AUS implantation for PPUI. Consequently, we have no comparable data in the literature to measure against.

We identified the maximum volume the OC could accommodate at pressurization, in relation to its size, a volume which did not exceed 1cc, even when adjusting this volume to the 0.27 cc represented by the 14Fr urethral catheter. With this knowledge, the size of the dimension of an electronic pump could be determined, an important step for the design. This further illustrated the significance of clinical and engineering collaboration for the betterment of patient QoL.

For constant pressure range of 61-70 cmH_2O, the bulbar occlusive cuffs sizes implanted were 4.0-4.5cm. Furthermore, this study shed additional light on the concept of pressurization step, and the reason why it can be skipped for smaller cuffs, as recommended by the manufacturer. Since we obtained valuable information on peribulbar cuffs, future research could include larger OCs as seen in female and male neurogenic AUS implantation.

The limitation of the study resides however, in the limited cohort and monocentric nature. A multicentric study would have provided larger cohorts, which time and cost constraints on the design timeline did not allow. Moreover, it would be clinically relevant to establish a possible correlation between continence, OC size and OC volume, which could be explored in future studies. Indeed, there are very few published prospectively conducted *in-vivo* data from a combined engineering and clinical perspective. This illustrates how challenging the path to obtaining the CE marking for a Class III AIMD is. Without the design completion, performance and safety testing cannot take place in pre-clinical and later in clinical studies, as these are central to ascertain the device's effectiveness for ulterior marketing application.

6.3 Pre-clinical studies

Human cadaver study

In this pilot cadaver study, we demonstrated the ease and feasibility of device implantation in both male and female subjects. We ascertained the device's automatic functions operationality. We showed that the device could provide similar MUCP ranges, using urodynamic investigations between 20-120 cmH_2O, equivalent to the randomly chosen AMS 800™ pressure regulating balloons, 51-60cmH_2O; 61-70cmH_2O and 81-90 cmH_2O, thus decreasing bias, could deliver. We therefore showed the AIMD could provide the pressures required to occlude the urethra and therefore achieve continence even at lower pressures. We also showed that the device's automatic functions help bypass the lengthy AMS 800™ component preparations prior to the device's implantation. We report no intra-operative complications, such as urethral or bladder injuries.

The main limitation of the study is related to the subjects. There are no ideal models to speak of to mimic the human urethra and avoid these pre-clinical steps, essential to establish the device is functioning before we implant it in patients in future clinical studies like the FIM. There are attempts at computer-generated models, but these have not been validated by the FDA. Implantation in human cadavers is therefore a pre-clinical step an AIMD cannot forego if it wishes to comply to current EU/US standards. This has been illustrated by the **ARTUS** (MyoPowers™ Medical Technologies St. Louis, France SAS), implanted in 6 subjects(165), the **TMOD** (Tape Mechanical Occlusive Device, GT Urological LLC, Minneapolis, MN, USA)(119) and the **Magnetically controlled Endourethral Artificial Urinary Sphincter (AS**, Italy), implanted in one human female subject (120). All novel devices must follow current AIMDs regulations, which include the completion of bench, in vitro, biocompatibility testing, and pre-clinical studies on cadaver and animals evaluating feasibility and device performance. Thereafter, clinical steps, the FIM and a pilot study, will assess the novel AUS' safety and effectiveness in clinical settings. As a final step the medical AIMDs provision phase will follow, where the device will be implanted in a larger number of patients as part of a Pilot multicentric study(142).

Today, the regulations are increasingly strenuous to guaranty patient safety. Moreover, obtaining the CE marking does not necessarily lead to market access as illustrated with GT-Urological (AroyoTM) in 2017. Additional requirements have been implemented by ICS Consensus for novel AUS development (1). All these obstacles complexify the innovation process of novel AUS devices. Cost is also a limiting factor. Nevertheless, it is reassuring that much is done to improve patient safety. Historically, the AMS 800™ was not subject to such developmental constraints. Regardless, we enter an era of personalized AUS for the management of SUI, where we wish to develop a safe device that delivers optimal qualitative and functional outcomes, every urologist's dream.

Animal study

This pilot wether study established ease of device implantation without intraoperative AEs, nor serious post-operative complications, and ascertained the device's function. Calibration and automatic functions were operational. We showed that the device was successfully activated/ deactivated as programmed and the wethers could pass urine during the day. Tissue biocompatibility tests showed no major AEs, and clinical wether follow-up showed no infections or renal function impairment at 8 weeks post-eAUS implantation. No device-related complication was reported. Clinical follow up showed a 10% weight loss in wether-2, which could not be explained. However, this study is a short-term pilot study which would require a larger Pilot study prior to its implantation in humans, as shown by Valerio et al. (113), to standardize device implantation. Historically, the TMOD, was tested in 3 female canines(119).

Histology investigations showed the beginning of the formation of a pseudo-capsule around the CU and OC, which are normal findings in clinical context, with no macro or microscopic signs of infection, erosion, or necrosis. These findings are in line with published data, which stated that the ARTUS was implanted in 17 rams in 2013(113). The PSS-FCD, was implanted in 6 animals in a phase IIb study, however, the authors did not specify which animal model was used (117). The MARS, the 'Novel remotely controlled artificial urinary sphincter' and the Magnetically Controlled Endourethral Artificial Urinary Sphincter have not proceeded to animal studies for biocompatibility testing(115,120).

As already stated above, animal studies are an unavoidable step for the evaluation of novel AIMD implantation feasibility, performance and prior to their use in humans.
There is however no consensus on the ideal animal model. We therefore used an animal that could mimic as closely as possible the human urethra, by its related environmental and physiological characteristics, and could offer a predictive model of clinical setting. This step allows the identification of local tissue reaction to any novel AUS components, which could be addressed prior to clinical trials. These informations are not given during bench tests or cadaver studies. Initially, a short-term 8-week pilot study in two wethers confirmed the animal model choice, ascertained implantation feasibility, optimized the surgical technique, and assessed the short-term safety profile of the novel electronic AUS. The completion of this step paved the way to future FIM studies.

7 FUTURE PERSPECTIVES

In **paper I**, we ascertained the lack of evidence regarding AUS implantation in women with severe SUI. The first prospective multicenter RCT comparing in two parallel arms the ACT balloon and AMS800™, the SU-ACT trial (ClinicalTrials.gov, identifier: NCT02490917)[30], is now completed. This RCT will shed more light on the surgical management of SUI secondary to ISD and will present the results of prospective data from a pure cohort of women implanted with either AUS or ACT. These highly anticipated findings will hopefully provide the urologist with additional information relevant for better patient counselling. Furthermore, increasing awareness of the female AUS among gynecologists, general practitioners and women in Sweden will help widen AUS indications in this group. From a clinical standpoint, although open female AUS surgery has previously been performed at Karolinska University Hospital, robotic AUS implantation was launched last year. This has broadened SUI management armamentarium. In parallel female patient's registry-based prospective data collection is worth considering in future research endeavors.

Paper II- Similarly, the ongoing PROSPECT study[31], is another randomized prospective international study investigating the efficacy and safety of the Ustrap device versus the AMS 800™ for the treatment of PPUI, which uses the 24-h PWT as UI assessment tool. With the MASTER study, we hope that the knowledge gap regarding the 24-h PWT as a performance assessment tool and complement our contribution on the subject. Meanwhile, our study endeavors to help decrease heterogeneity in published performance outcomes across studies. Additionally, there are promising ongoing prospective multi-centric registry-based studies such as SATURN (58) and VENUS projects, a '*Registry for patients undergoing AUS for Female SUI due to ISD*' completed in February 2022 (*ClinicalTrials.gov identifier: NCT04114266)*[32]. Moreover, this study helped with the design of the FIM in defining primary outcome measures, i.e., post-novel device implantation performance evaluation using the 24-h PWT as an outcome tool. From a more immediate clinical prospective viewpoint, the creation of national patient registries for UI implant surgery will ameliorate data collection, contribute to post-market evaluation, and improve patient post-operative safety. These studies could include comparison between pad count and 24h-PWT, erectile function questionnaires, and device satisfaction related surveys to further elucidate additional factors explaining the reason why, a good functioning AUS does not correlate with maximum I-QoL indexes.

Paper III- We are hoping that this paper, like paper II, will help bridge the gap on the knowledge pertaining transscrotal implantation. Further patient registry prospective trials like the ones mentioned above are certainly the way forward to consolidate long-term knowledge on both TS and TP AUS implantations both nationally and internationally.

Paper IV- The study has truly emphasized the collaboration between clinicians and engineers in the design process of a novel electronic device. As previously mentioned, further studies on female and male bladder neck OC placements could provide additional cuff volume information that could have a clinical impact. Also, analyzing a correlation between OC size, volume and continence could equally be clinically relevant. These questions could be explored in future prospective, possibly multi-centric studies.

[30] La Pitié-Salpêtrière University Hospital, Prof. E. Chartier-Kastler
[31] https://clinicaltrials. gov/ct2/show/study/NCT03323554
[32] https://clinicaltrials.gov/ct2/show/NCT04114266

Papers V and VI- These pre-clinical studies have been the precursors of the FIM trials. The ideal AUS would have homologous tissue characteristics, using stem cell technology, which could provide safe personalized urinary continence. However, this is not yet in the realm of achievable and in the meantime, a one-piece or two-piece automated wireless AUS device, that is functional, easy to implant, safe and efficient will be the way to the future. Furthermore, there is still a promising research space for further male/female urethra computational, mechanical, and biophysical modeling, to improve available models that can mimic clinical settings when applied to AIMD development, since this has yet to succeed (166–168).

8 CONCLUSION

The level of evidence provided in this first systematic review of AUS implantation for adult non-neurogenic female severe SUI is very low and intraoperative PSAEs rates are high. Results from the SU-ACT trial, and the VENUS studies are highly anticipated to improve patient counselling and quality of care. Additionally, this study has also highlighted the importance of post market registry and follow-up to ensure patient safety after novel AUS device implantation. We live in an era where change in industrial, clinical, and surgical practices are necessary to offer the best level of care possible.

Moreover, the second paper, a retrospective cohort study, showed that the 24-h PWT as a performance assessment tool after primary AUS implantation in men with PPUI is reliable, objective, and reproducible. It could be used to help standardize UI definition and contribute to decrease disparity in published functional/performance outcomes across studies. Strong correlation between 24-h PWT and validated QoL questionnaires was also established. Consequently, its use over the pad count should be used for accurate and objective continence outcomes evaluation in research and clinical settings. These findings are in line with the FDA guidance on AUS device evaluation for the treatment of UI and helped define primary outcomes for the upcoming FIM study.

Additionally, in the third paper, this retrospective single centre cohort study did not show any significant difference in long-term performance and qualitative results when comparing TS and TP AUS implantation techniques. Both techniques were also similar when performing a stratified analysis for DOA, radiation therapy, previous UI/urethral stricture surgery and showed no impact on performance. However, increased RR of infection, mechanical failures and revisions were found when investigating long-term safety outcomes. Moreover, device survival and erosion risks were similar in both approaches. We identified that long-term follow-up, as well as well-designed multicentric prospective studies were required using PROMS to improve long-term device performance and safety. This paper shows that the novel electronic device could be used using both techniques.

Furthermore, the fourth paper showed that the maximum volume accommodated by the peri-bulbar OC at pressurization was 1cc, helping dimension a novel AIMD for the treatment of severe SUI in men and women. This was a fine demonstration of a pre-CE marking prospective *in vivo* study application to the design of a novel AUS. Subsequent long-term erosion rates in relationship to cuff volumes would also be a future research angle with clinical relevance.

Finally, in the pre-clinical papers, the cadaver study ascertained implantation ease and feasibility, as well as operationality of basic automatic functions of the device. Performance evaluations showed that the device provided similar MUCP ranges than the PRBs of the AMS 800. The animal study confirmed the device's feasibility of implantation and functionality. The device could be activated and deactivated as programmed and no SAEs were reported during and after surgery. Histocompatibility testing showed no infection, erosion, or necrosis. The device is therefore ready for the relevant pilot studies on a larger number of specimens, paving the way to the FIM study.

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