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Future Directions for Ureteral Stent Technology: From Bench to the Market

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Ureteral stents are broadly used for the treatment of a wide range of pathologies, with different complexities and characteristics. Despite being efficient, the morbidity associated with stents, such as bacterial infection and pain, limits their therapeutic action and often represents an increase in healthcare costs. As no single solution fits all problems, there is still a need to improve these medical devices. Throughout this review, the most recent innovations are outlined and suggestions regarding future directions for ureteral stent technology are formulated with respect to materials, coatings, and designs of these devices. As highlighted here, during the process of passing these innovations to the growing market of ureteral stents, one of the biggest challenges is to increase the predictive value of the in vitro assays and, consequently, reduce the number of in vivo tests needed. Thus, recommendations concerning in vitro standard testing of these devices are provided, with focus on medium, flow conditions, and microbiological parameters. Additionally, the reader is also presented with insights about a crucial but rarely discussed topic, the bureaucratic part of the bench to market process, particularly the product certification legislation in Europe.

1. Introduction

The term "stent" arose when in 1850s Charles Thomas Stent, a London dentist, developed a material used for dental impression, which was named "Stent's compound."[1] During the First World War, this material was used to stabilize the skin grafts of soldiers,[2] and, since then, the word "stent" was extended to different medical specialties, including urology, to designate supporting devices. In 1949, when ureteral tubes were first described, they were made of polyethylene, a promising material due to its endurance and water-repellent nature.[3] Ever since, stent technology has undergone many developments regarding the bulk material, surface coatings, and design, mostly to tackle problems related to stent migration, infection, and encrustation. In the 1960s, silicone started to be explored as stent material due to its

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thermal resistance, which allows sterilization, and, consequently, decreases the potential for infections.[4] Advances on the stent surface, as hydrophobic and peptides coatings, were made to improve stent tolerability, and prevent encrustation and infection, by inhibiting bacterial adhesion.[5] Over the years, the ureteral stent design evolved from a straight tube to a tube with a distal bulb to prevent dislodgment, and, in the 1970s, to single J and double J stents.[6] Nowadays, the most common ureteral stents are 22–24 cm long flexible tubes made of polymeric materials, namely polyurethane or silicone, with strategic side-holes and double J ends.[6–8]

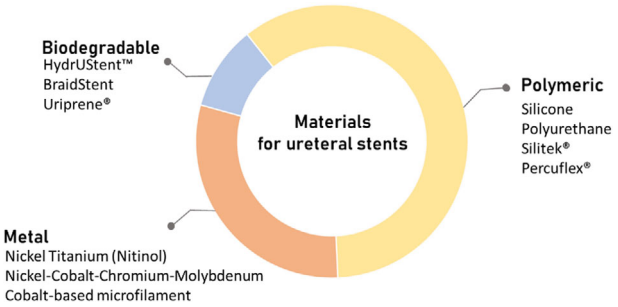


Figure 1. Most common used materials for ureteral stents.

2. Clinical Need

In clinics, urological stenting is the standard procedure frequently done to restore compromised urological function caused by disorders of the urinary tract, such as kidney stones, strictures, and tumors.[7,9] These devices are effective for the relief of upper urinary tract obstruction, prevention from stricture formation, support of ureteral healing, and management of urinary leakage.[10] Annually, over 1.5 million ureteral stents are used worldwide; however, it is estimated that more than 80% of patients suffer from a wide variety of stent-associated complications, whose prevalence is directly proportional to treatment duration.[11] Listing stent-related problems is key to identify current needs . This will guide the future directions for ureteral stent technology development and improve the overall stent function and patient care.

In long-term treatments, biofilm formation may occur, which may promote the onset of urinary tract infections (UTIs), encrustation and pain. In these cases, biofilm formation arises due to the deposition of a urinary conditioning film, composed by urinary proteins, ions and crystals at the stent's surface, which favors the interaction and adhesion of bacteria to the stent surface.[12,13] Within biofilm environment, microorganisms are protected from the action of host defenses and antibiotics.[14] In a clinical study, it was found that the most common bacteria found on urinary stent surface biofilms are *Escherichia coli*, *Enterococcus* spp. and *Staphylococcus* species.[15] Bacterial colonization on stents can exceed 90% of patients, however only 20–45% of patients develop symptomatic urinary tract infection.[15–17] This pre-existing bacterial colonization can promote encrustation, a late complication that may affect the indwelling of the stent, and in some cases, might require surgery to facilitate stent removal.[18,19] Reported encrustation development rates were 9.2%–26.8% before 6 weeks, 47.5%–56.9% between 6 and 12 weeks and 75.9%–76.3% thereafter.[10,20] The most decisive factor for the appearance of encrustation is the stent dwell time, however different factors can affect stent encrustation and contribute to the heterogenous reported rates, including urine composition and pH, stent's material, surface topography, stent dwell time, and urine flow dynamics.[21] Besides bacterial infection and encrustation, different clinical disorders associated with stents were also reported, as physical distress, misplacement, stent fracture, and forgotten stent syndrome.[18] Moreover, around 58% of patients reported decreased work performance, and 32% expressed sexual dysfunction.[11] As a consequence of these hurdles, stent failure may occur, which leads to a significant negative impact on a patient's quality of life and represents an increase in healthcare economic burden.[11]

3. Advances in Ureteral Stent Technology

In order to reduce the abovementioned morbidity associated with ureteral stents and improve the performance of these devices, three key aspects need to be addressed, namely, constitutive material, coatings, and design of stents. In this section, these features will be reviewed and future directions for ureteral stent technology will be outlined.

3.1. Materials

To date, a gold standard material for ureteral stents in terms of mechanical performance, surface roughness, biocompatibility and cost-effectiveness fabrication has not yet been identified. Although there are biodegradable materials on the market, most stents are based on nondegradable polymeric and metallic materials, such as silicone, polyurethane, and nickel/titanium mixed alloys[8] (**Figure 1**).

As previously stated, one of the main drawbacks associated to ureteral stent procedure is their long-term persistence causing

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patient discomfort and pain, and the need of a surgical procedure to remove the device. In this context, completely bioabsorbable stents may represent a solution, providing temporary urinary drainage and avoiding surgical removal.[22] In the last 20 years, many efforts were devoted to the development of completely biodegradable stents based on synthetic and natural polymers or metals.[5,23–26] Among these, biodegradable shape memory polymers (SMPs) are an interesting class of materials for the ureteral stent field. Shape memory materials are defined as materials able to keep a temporary shape, as a consequence of the application of a stimulus, which may return afterwards to the original permanent shape. In 2009, Neffe and co-workers[27] reported a drug delivery ureteral stent based on biodegradable shape-memory polyurethane, where the device, due to its temporary shape, could be easily inserted, anchoring in situ after recovering to its permanent shape.

The biodegradable SMPs are associated with cutting-edge printing technology. 3D printing techniques were introduced in the 1980s and gained an ever-growing interest in several application fields, ranging from space to biomedical sciences. The 4D printing process was first introduced in 2014, by Skylar Tibbits,[28] to add time-dependent properties to 3D objects. This technique combines smart materials, such as the mentioned biodegradable SMPs, and additive manufacturing techniques for rapid fabrication using computer-aided design models.[28] Ly et al.[29] developed a protocol to obtain stents with a 1.75 mm filament starting from shape memory polyurethane mixed with carbon nanotubes which were processed by fused deposition modeling technique. The stimuli-responsive shape memory polyurethane was retained after 3D printing process, leading to a wider range of applications of SMPs and encouraging research in this direction. Among the additive manufacturing techniques, stereolithography allows to achieve high resolution substrate surface finishes, being limited by the narrow range of employable materials. Choong et al.[30] described the use of stimulus responsive *tert*-butyl acrylate (tBA)-*co*-di(ethylene glycol) diacrylate (DEGDA) network as shape memory resin for stereolithography technique. The stimulus-responsive mechanism arouses from the ultraviolet crosslinking of tBA monomers and DEGDA crosslinkers, using phenylbis (2,4,6-trimethylbenzoyl) phosphine oxide (BAPO), as photoinitiator. The shape memory performance of the printed objects was demonstrated, and optimal resin composition allowed to obtain full shape recovery. Ge et al.[31] synthesized different methacrylate polymers to develop a material platform with varied ranges of physicochemical and mechanical properties. Multiple SMPs, formed by blending different methacrylate constituents and forming strong interactions between them, were processed through projection microstereolithography in 3D structures, which exhibited interesting time-dependent properties. The first example of 4D stent-like structure was proposed by De Marco et al.,[32] by developing an indirect 3D printing approach, through the fabrication of a 3D sacrificial template exploiting the direct laser writing (DLW) technique. DLW enables the production of high-resolution 3D architectures with heights ranging from a few hundred nanometers up to several millimeters and layer thicknesses below 1 μm. A commercially available shape memory material (NOA63) was chosen to produce stents with two different complex structures. A positive photoresist was deposited on a silicon substrate, then the 3D shape was obtained through DLW equipment, followed by NOA63 casting and ultraviolet irradiation. Both stent-like structures showed a temperature-responsive behavior, being capable of recovering their original shape when immersed in water solution at 40 °C.

From the biomaterial engineering point of view, the 4D printing process represents an innovative tool able to overcome conventional manufacturing processes limitations. 4D printed stents were successfully produced for cardiovascular[33] and tracheal[34] applications. The processing of biodegradable SMP by 4D printing technique is a promising approach for low-cost mass production of ureteral stents, able to be easily applied, limiting patient's discomfort.

3.2. Coatings

The modification of the stent surface has been proposed to improve the stent performance and to add new functionalities. Among all the proposed strategies, here we will review the used materials for ureteral stent coatings, dividing them by their nature (organic/inorganic), highlighting the future perspective for each case. **Table 1** summarizes the most relevant studies made on ureteral stent coatings and their major conclusions.

Among the organic materials used as coatings for ureteral stent surfaces, hydrophilic/hydrophobic polymers represent the majority. Nowadays, hydrophilic coatings are commercially available in the ureteral stent market, as AQ from Cook Medical, SL-6 from Applied Medical, HydroPlus from Boston Scientific, and heparin-based coating Endo-Sof Radiance, from Cook Medical. The working principle is based on the water trapping within the polymeric structure, which decreases the friction coefficient of the surface and prevents encrustation, by reducing adhesion phenomena at the biomaterial–tissue interface. [8][35] Nevertheless, various studies also pointed out that, due to the absorption of urinary solutes, hydrogel-coated stents could have the same[36] or even a higher risk[37] of becoming encrusted, comparing with uncoated ones made of the same substrate polymer. Moreover, other hydrophilic coatings, using polymers as the antifouling agents as poly(vinyl pyrollidone) (PVP) or 3,4-dihydroxyphenylalanine (DOPA) conjugated polyethylene glycol (PEG), are able to inhibit or destabilize biofilm formation, while also bestowing a beneficial lubricious effect.[38,39] On the other hand, hydrophobic coatings, as polytetrafluoroethylene (PTFE) and corethane, have also been studied for ureteral stent coating application, and their effectiveness in preventing the luminal occlusion caused by urothelial hyperplasia has already been proven.[40,41] Concerning organic approaches, the future research must involve more detailed studies regarding biomolecule-based coatings, which attempt to impart biomimetic and biocompatible properties to the stent surface. These strategies follow a similar rationale as the one made for the already approved heparin-based coating, however, apart from polysaccharides (heparin), other biomolecules can be applied. Among proteins, immunoglobulins[42] and oxalate-degrading enzymes[43] are interesting examples, being associated with less encrustation and reduced bacterial adhesion. For a quite innovative and distinct purpose, cells can also be used as "living" coating for ureteral stents.[44] The results demonstrated that this kind of design can

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Table 1. Most relevant strategies for ureteral stent coatings.

Strategy		Coating	Material	Major remarks	Ref.
Organic	Hydrogel Hydrophilic	Poly(*N*,*N*-dimethylacrylamide) (PDMAA) Poly(vinyl pyrollidone) (PVP) 3,4-Dihydroxyphenylalanine (DOPA)-conjugated polyethylene glycol (PEG)	Polyurethane Silicone polyurethane	Higher lubricity and less friction. Significant reduction of the adherence of *E. coli*. Reduction of the side effects and complications on patients with hydrogel-coated stents. Reduction of encrustation than the uncoated ones. Reduction of attachment of uropathogens, in vitro. In vivo, using rabbit model, it was reported a reduction of 75% in the number of stent adherent *E. coli*.	[54,55][a] [38] [56][b]
	Hydrophobic	Polytetrafluoroethylene (PTFE)	Metal	Avoid obstruction by urothelial hyperplasia, supporting its safety and applicability in ureteral stricture.	[57][b], [58][a]
		Corethane	Metal	Prevention of obstruction in vivo.	[59][b]
	Biomolecule-based "Living" coating	Immunoglobulins	Polyurethane	Reduction of *E. coli* adhesion.	[42]
		Oxalate-degrading enzymes	Silicone	Reduction of encrustation without exhibiting toxicity.	[43]
		Chondrocytes	Polyglycolic acid mesh coated with 50:50 polylactic-co-glycolic acid	Macroscopic examination of the engineered stents showed the presence of cartilaginous tissue. Biomechanical tests demonstrated that the cartilaginous cylinders were readily elastic and withstood high degrees of pressure.	[44][b]
		Bladder epithelial cells	poly (L-lactic acid)	Promotion of cell proliferation, aiming for ureteral reconstruction.	[45][b]
Inorganic	Amorphous carbon	Diamond-like carbon	Polyurethane	Reduction of bacterial adhesion and prevention of struvite encrustation. In ten patients, DLC coating strongly limited the formation of an extended biofilm and showed a lower friction coefficient that further facilitated the placing and removal of the stent.	[46][c], [60][a]
	Metals	Zinc oxide (ZnO) particles Copper (Cu)-based coatings Molybdenum disulfide (MoS_2) and tungsten disulfide (WS_2) nanostructured coatings, gold, SiO_2, TiO_2	Silicone/polyurethane	Great antimicrobial activity and biocompatibility. Capability to limit encrustation.	[48,49,50][b], [51]

[a] Clinical trial; [b] In vivo study.

promoted cell proliferation, suggesting that it could serve as alternative cell carrier for tissue engineered ureters.[45]

Among inorganic materials, the use of carbon-based materials as functional coatings for ureteral stent devices was also considered. Diamond-like carbon (DLC) coatings, especially due to their inert surface chemistry, were able to limit the formation of deposits and encrustations during long-time indwelling both in vitro and in vivo.[46,47] As the UTIs in treated patients were significantly reduced, nowadays DLC coating is a commercial option in the ureteral stent market (Ureteral Stent Set–CarboSoft). In addition, different inorganic material-based solutions using metals are being proposed. Recently, zinc oxide (ZnO) gained considerable attention in the biomedical field due to its intrinsic antimicrobial activity and biocompatibility.[48] Copper (Cu)-based materials have also been investigated in the field of ureteral stent fabrication due to their antibacterial properties, and the prevention/limitation of encrustation, comparing with control samples.[49,50] Other novel materials also recently

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considered include molybdenum disulfide (MoS_2) and tungsten disulfide (WS_2) nanostructured coatings.[51] Apart from the abovementioned strategies, many other materials, especially those belonging to the class of metals (as gold) and oxides (silicon dioxide (SiO_2), titanium dioxide (TiO_2)) are rising as potential candidates for the fabrication of inorganic coatings with improved functionalities.[52,53] These materials show very interesting physical and chemical properties, which are tunable once externally activated.

Additionally, in the last decades, several advances have been obtained in urinary catheters (UC) seeking to reduce pathogen colonization. Although ureteral stents and UC are different devices, with distinct idiosyncrasies, the progress made on UC can be helpful for the development of new antimicrobial coatings for ureteral stents as these devices share a number of features: i) the fluid surrounding their surfaces is the same (urine), ii) the etiological agents that infect the devices are essentially the same (although some may be more deleterious than others, depending on the device), and iii) the range of shear forces caused by urine flow in a stent comprises the average shear value determined in UC (see Section 4). In this context, we will review some of the surface coatings that have been successfully tested in UC, and may, therefore, indicate the direction for ureteral stents advances. **Table 2** describes the anti-biofilm strategies of different material coatings and their potential against several bacterial and fungal species. Surface coatings were grouped into four categories: i) release of antimicrobial agents, ii) contact-killing, iii) antiadhesive, and iv) biofilm architecture disruption.

The success of antimicrobial release coatings is frequently associated with the high local concentrations of antimicrobial agents released at the potential site of colonization and their high effectiveness against the target pathogen.[61] Antimicrobial release strategies include the use of metals (e.g., silver and noble metal alloys), antibiotic and antifungal agents, and disinfectants. Up till now, several studies have reported the effectiveness of silver-coated films in the reduction of microbial adhesion and biofilm formation. The mechanism of action of silver is already well characterized, and its application in UC was already approved by the Food and Drug Administration (FDA).[61,62] Since 1980,[63] numerous studies have evaluated the in vitro efficacy of 1) silver (ions/nanoparticles),[64–67] 2) silver–polymer nanocomposites,[68–74] and 3) silver conjugated with antibiotic agents.[75] Silver and its formulations were studied in different polymeric surfaces, including silicone, polyurethane, and latex, and tested against a broad spectrum of Gram-positive and Gram-negative bacteria, in both in vitro and in vivo studies. [67,68,74,76–79] For all these reasons, silver is a promising coating for ureteral stent devices, and it has been widely investigated for coating application in the urinary tract context. Nonetheless, contradicting studies already described the ineffectiveness of this strategy, reporting no significant advantages against UTIs.[80,81]

Antimicrobial agents/disinfectants were also introduced as a strategy to inhibit or delay the onset of biofilm formation, showing efficacy in vitro and in vivo studies.[70,75,82–89,90–92] Even though these options appear to be promising, a careful evaluation should be performed. Over the years, studies undertaken with antimicrobial agents/disinfectants show that prophylactic use of those components as a systemic therapy can trigger the development of further microbial resistance, without avoiding the adhesion of the already resistant uropathogens.[93] In 2016, FDA banned the use of triclosan (an antibacterial and antifungal agent used for UC coatings) in health care antiseptics, ceasing to be classified as "generally recognized as safe and effective." After a meta-analysis study, it was demonstrated that the use of antibiotics is effective for short-term implants, however for long-term implants, this strategy favors the development of microbial resistance. This phenomenon is explained by the release profile of this type of compounds, with an initial burst release followed by concentrations that are not inhibitory, creating an infection even more difficult to treat.[94]

In the last decade, antimicrobial peptides (AMPs) have emerged as contact-killing coatings for UC and are currently one of the most promising alternatives to conventional antimicrobial agents. AMPs display a broad-spectrum activity, targeting pathogens by several mechanisms of action.[95–100]

Since microbial adhesion depends on the charge, roughness, and topography of the surface, antiadhesive coatings have been optimized to change these physicochemical properties and, thus, prevent the initial microbial adhesion. Several polymers, including 1) hydrogel, 2) polyzwitterionic polymers, 3) cationic polymers, 4) hydrophilic polymers, 5) amphiphilic polymers, and 6) polymer brushes, have been explored as antiadhesive coatings for UC. The hydrogel capability to decrease bacterial adhesion of Gram-positive and Gram-negative bacteria has been reported by several authors. [101,102] In turn, polyzwitterionic polymers demonstrated high prevetion of bacterial adhesion and biofilm formation,[103–105] which is due to their resistance to nonspecific protein adsorption through electrostatic and steric repulsion.[61,106–108] Cationic polymers also showed effectiveness as antibacterial contact-active coatings. This type of coatings adsorbs both proteins and bacterial cells by electrostatic interaction through the negatively charged bacterial membrane, exerting an antimicrobial and anti-biofilm effect, simultaneously.[61,109,110] Both hydrophilic polymer-coated films[111] and catheters coated with amphiphilic polymers[112,113] demonstrated a high capability to reduce bacterial adhesion and subsequent biofilm formation. Lastly, polymer brushes have been developed to prevent microbial adhesion by limiting the contact of substratum with living microorganisms.[114,115] Nowadays, different approaches are also emerging, aiming to disrupt the architecture of biofilm through matrix degradation or by quorum sensing interruption.[116–119]

Although the results are promising, most of the antimicrobial and anti-biofilm strategies are far from clinical application. Among the reviewed studies, only 15.7% (8/51) were performed in vivo. On the other hand, about 60.5% (26/43) of the in vitro studies were performed under dynamic conditions, increasing their predictive value.[120] However, since most of the studies did not provide shear stress or shear rate values, it was not possible to fully compare the effectiveness of the different coatings. Overall, these data provide important clues that should be considered during the development of new ureteral stent coatings.

3.3. Design

Currently, the most common design of ureteral stents consists of a tube with double J extremities. Despite the acceptable performance, this design is associated with vesicoureteral reflux

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Table 2. Coatings successfully tested for urinary catheters that are promising for ureteral stents.

Strategy	Coating	Material	Microorganisms	Major remarks	Ref.
Release of antimicrobial agents	Metal (ions/nanoparticles)				
	Silver	Silicone Polyurethane Latex	Gram-positive and Gram-negative bacteria	Inhibition of bacterial adhesion by 30%–99.9%; and biofilm formation by 1–6 Log, depending on the species. In vivo studies demonstrated that silver-coated catheters reduced CAUTIs incidence by 27%–47%.	[63][a], [64][c], [65, 66][c], [67,68][c], [69, 70][71][c], [72][c], [73][c], [74,75][c], [76][a], [77][b], [78][b]
	Noble metal alloy	Silicone Latex		Reduction of CAUTIS incidence by 1.5%.	[79][a], [121][a], [122][a]
	Antimicrobial agents/disinfectants				
	Antibiotic agents	Silicone Polyurethane	*B. subtillis* *E. coli* *E. faecalis* *P. aeruginosa* *P. mirabilis* MRSA *S. aureus* *S. epidermidis*	Delay on the onset of biofilm formation up 12 consecutive weeks; Reduction of bacterial adhesion by 85–91%, with potent antimicrobial activity (83%–96%).	[85][b], [86][c], , [70], [75][c], [87][c], [88]
	Antifungal agents	Silicone	*C. albicans*	Reduction of fungal adhesion on coated films by approximately 3 Log CFU.	[89][c]
	Disinfectants	Silicone PolyurethaneLatex	*C. albicans* *C. parapsilosis* *E. coli* MRSA *P. aeruginosa* *P. mirabilis* *S. aureus*	Reduction of microbial adhesion by 83%–99.8% and biofilm formation by 2 Log CFU. Resistance to encrustation was increased up to 7 days.	[90–92][c], [82][c], [83][c], [84][c], [86][c]
Contact-killing	Antimicrobial peptides (AMP)				
	Synthetic AMP	Silicone Polyurethane	*C. albicans* *E. coli* *P. aeruginosa* *S. aureus*	Reduction of bacterial adhesion by 92%–100% and biofilm formation by 75%–90%; AMPs killed by contact most of the adhered bacteria (99%).	[95–97][b),c], [98][b],[99,100]
Antiadhesive	Polymers				
	Hydrogel	Silicone Polyurethane	*E. coliP. mirabilis* *S. aureus* *S. epidermidis*	Extension up to 13 h of the patency of coated catheters and reduction of biofilm formation up to 90%.	[101][c], [102][c]
	Polyzwitterionic polymers	Silicone	*E. coli* *P. aeruginosa* *P. mirabilis* *S. aureus* *S. epidermidis*	High resistance to bacterial adhesion, with an inhibition of biofilm formation by 80%–95%.	[103][c], [104,105][c], [107]
	Cationic polymers	Silicone	*E. coli* *P. aeruginosa* *S. aureus* MRSA VRE	Coated films with excellent in vitro and in vivo antimicrobial and anti-biofilm activities (>94.5%).	[109][c], [110][b]

(*Continued*)

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Table 2. (Continued).

Strategy	Coating	Material	Microorganisms	Major remarks	Ref.
Antiadhesuve	Hydrophilic polymers	Silicone	*E. coli* *P. aeruginosa* *E. coli* *P. mirabilis* *C. albicans*	Reduction of bacterial adhesion by 50%–90%. Reduction of biofilm formation by 30%–60%.	[111] [123]
	Amphiphilic polymers	Silicone Polyurethane	*E. coli* *P. aeruginosa* *S. aureus*	Reduction of bacterial adhesion up to eightfold.	[112][c], [113][b),c)]
	Polymer brushes		*E. coli*	Decrease of surface area coverage by 40%–60% and biofilm viability up to 80% compared to control (silicone).	[114][c], [115][c]
Disruption of biofilm architecture	Enzymes for EPS disruption				
	α-Amylase	Silicone	*E. coli* *P. aeruginosa* *S. aureus*	Inhibition of biofilm formation by 30%.	[116][b),c)]
	Quorum quenching				
	Acilase	Silicone Polyurethane	*P. aeruginosa*	Reduction of biofilm formation by 45%–80%.	[117][c),][118]
	Quorum sensing inhibitors				
	Organic compounds	Silicone Polyurethane Latex	*C. glabrata* *C. krusei* *C. tropicalis*	Total inhibition of *Candida* sp. adherence.	[119]

[a)] Clinical trial; [b)] In vivo study; [c)] In vitro study performed under flow conditions; *B. subtillis*, *Bacillus subtilis*; *E. coli*, *Escherichia coli*; *E. faecalis*, *Enterococcus faecalis*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *P. mirabilis*, *Proteus mirabilis*; MRSA, methicillin-resistant *Staphylococcus aureus*; *S. aureus*, *Staphylococcus aureus*; *S. epidermidis*, *Staphylococcus epidermidis*; *C. albicans*, *Candida albicans*; *C. parapsilosis*, *Candida parapsilosis*; VRE, vancomycin-resistant *Enterococci*; *C. glabrata*, *Candida glabrata*; *C. krusei*, *Candida krusei*; *C. tropicalis*, *Candida tropicalis*.

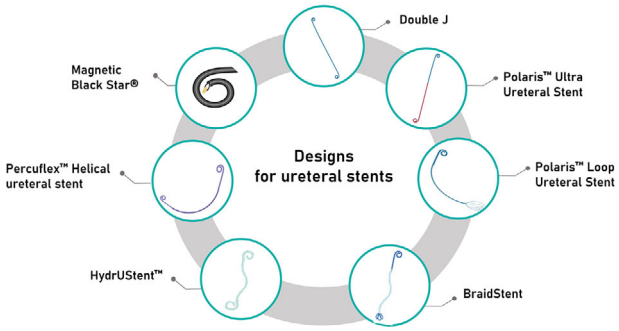


Figure 2. Most relevant designs for ureteral stents.

(VUR), as it prevents closure of the ureterovesical junction. Besides that, irritation of the bladder mucosa by the bladder coil of the ureteral stent is frequent, especially at the trigone, an area of high density of nerve fibers, with alpha-1 adrenergic receptors.[124] This urothelial irritation leads to a symptomatology known as lower urinary tract symptoms, causing discomfort to patients, and sometimes demanding earlier stent removal. Therefore, research into new ureteral stents designs is mainly focused on reducing the morbidity associated with the current double J ureteral stents (**Figure 2**).

To avoid VUR, the high rate of backflow of urine to the kidney, and the associated flank pain, a variety of antireflux stents have been described. In this concern, bladder coils have been modified to make them softer via changes in the composition of the polymers in this distal coil (e.g., Polaris Ultra Ureteral Stent, Boston Scientific Corporation, Natick, MA.) (Figure 2).[125] There are also changes in the design of this bladder coil, modifying the vesical pigtail to a unique bladder loop design (Polaris Loop Ureteral Stent, Boston Scientific Corporation, Natick, MA), with an average of 69% less material in the bladder than with standard stents (Figure 2). These stents have been reported to have some clinical advantages over the traditional ones, however there is still no strong evidence that these two kinds of stents improve the quality of life of patients. In fact, although there is less vesical polymeric material, there is still material that causes patients' discomfort.[126]

The latest antireflux ureteral stent design employs 3D printing to incorporate a flexible polymeric flap valve that can be attached at the vesical end of a standard ureteral stent. The valve consisted of two lip-like membranes and an inner cavity, designed to prevent backward flow with minimized reduction of the forward flow. Kim et al.[127] assessed the effectiveness of the polymeric flap valve attached to a standard double J ureteral stent in a porcine model. This stent design did not fully prevent VUR, mainly because periprosthetic VUR at the ureterovesical junction level was not avoided, being the partial success due to the VUR prevention through the internal lumen of the stent.[128]

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In recent years, a series of stents with intraureteral design has been settled, as the concept of material reduction within the bladder appears crucial to decrease bladder mucosal irritation. These show a distal anchoring system that replaces the bladder coil by nonrefluxing silicone end piece, or, in other cases, the bladder end is replaced by a thread for easy removal (MiniFiland CIU-SP).[129–131] All clinical studies have shown, with statistical significance, that intraureteral stents might decrease ureteral stent discomfort, however, these devices can be associated with stent migration.[129,130] A new purely intraureteral stent design (BraidStent) was evaluated in an animal model with encouraging results.[132] Soria et al.[132] reported that this design gathered the expectations of a current double J ureteral stents, in terms of passive ureteral dilatation, avoiding VUR completely and decreasing significantly macroscopic and histologic damage at the ureterovesical junction. Furthermore, the internal scaffold effect of the stent was tested in a ureteropelvic junction obstruction model, treated by minimally invasive surgery techniques and the posterior placement of the BraidStent.[133] The selective intubation of the healing area provided by this design allowed proper ultrasonographic recovery of the kidney and tissue healing with acceptable surgical success rates, suggesting ureteral surgery as one of the conditions that may benefit from this antireflux design.

Considering the difficult removal of an intraureteral biostable stent and the current need for biodegradable ureteral stents (BUS), after the studies that presented the proof of concept for the antireflux design of BraidStent,[132,133] this approach was also studied using biodegradable materials (Figure 2). The subsequent evaluations in a porcine model of the biodegradable BraidStent revealed a predictable and controlled degradation rate of 6 weeks, without any obstructive phenomena.[134,135] The BUS maintained the features validated in previous studies. Moreover, the authors described the persistence of ureteral peristalsis beneath the distal tip of the stent in 58%–83% of ureters, which would likely avoid ureteral spasm, one source of pain in patients. However, this biodegradable design presented higher migration and bacteriuria rates than the ones obtained with the biostable BraidStent.[135] On the other hand, Jin et al.[11] and Zhang et al.[12] assessed their BUS design in dogs. Jin's stent provided equal drainage as a standard double J ureteral stents and degraded completely by the 5th week of follow-up, although bulky fragments of the stent were observed during the degradation.[136] Zhang et al.[12] also validated their braided thin-walled single-J biodegradable stent, which triggered a tissue reactivity similar to a standard stent, but lacked radiopacity and the degradation resulted in nonobstructive fragments in the renal pelvis and bladder. As expected with a BUS, mechanical properties, such as resistance to compression and radial force, decreased as the degradation took place.[137] The preclinical evaluation of a double pigtail BUS developed by Barros et al.,[138] HydrUStent (Figure 2), evidenced promising results as the degradation was homogeneous without any repercussion in urine flow. The porcine renal units stented with the BUS showed improved pathological conditions than the one with the commercial double J ureteral stents.[138] In the case of double J ureteral stent Uriprene BUS,[139] with the aim to overcome the pitfalls encountered during the assessment of the first generation of the device, Chew et al. developed and tested in the porcine model the second- and third generations of Uriprene.[22,140] Proportion and conformation of materials were changed in order to obtain shorter degradation times while at the same time providing an adequate stiffness. Both second- and third-generation Uriprene presented enough axial and radial strength for their correct placement.[22,140] The degradation of third-generation Uriprene started on the 14th day and was completely attained at the end of the 28th day, which is more similar to clinical indwelling times of ureteral stents.[22,124,140] Unlike the first-generation Uriprene, these two generations did not produce obstruction.[22,140] Other biodegradable tubular ureteral stent with no coil in each end of the stent, made from poly(ϵ-caprolactone) (PCL)/poly(lactide-*co*-glycolide) (PLGA), has undergone evaluation in two different animal model.[141,142] Histocompatibility of the stent was confirmed via implantation in the dorsal muscle of the rabbit, and the safety and degradation were analyzed in the porcine model. This later study revealed that degradation started on day 28th at the distal end of the stent and advanced proximally until the 70th day.[142] Moreover, PCL/PLGA stent caused significantly less hydronephrosis and urothelial inflammation in comparison to a standard double J ureteral stent.[142]

Another innovative design, more adapted to the ureter shape in order to better accommodate patient movements, is Percuflex Helical ureteral stent (Boston Scientific Corporation, Natick, MA), a spirally cut flexible stent (Figure 2). Its spiral-cut design allows it to better accommodate to the movements and shape of the ureter, due to the flexibility provided by its design along the entire length of the stent. A comparative clinical study showed a significant reduction in the total of analgesics required in the Percuflex Helical stent group compared to standard double J ureteral stents.[143] Unfortunately, the assessment of this stent has only been carried out in a small group of patients, and the comparative study showed no difference in pain scores. On another hand, to avoid cystoscopy, which is the classic system used for the removal of double J ureteral stents, a new design was developed, Magnetic Black Star ureteral stent, Urotech, Germany (Figure 2). Since cystoscopy is performed under anesthesia, this magnetic innovation is particularly more advantageous for pediatric patients than the current clinical procedure. Moreover, this design has been shown to significantly reduce pain at removal. As a clinical limitation, the removal of these stents may be in some cases challenging in male patients with prostatic hyperplasia.[144]

For future ureteral stents, it is important to address the weaknesses that currently characterize their design and that distance them from the concept of the ideal ureteral stent. First, it may be necessary to overcome the idea that a single design can meet all urological needs. In this respect, intraureteral stents could avoid the side effects of current designs by preventing VUR and inflammation of the bladder mucosa. In some cases, patients that require permanent intubation of the ureteral orifice may benefit from an intraureteral design.[129,130,133] Besides that, one of the most promising features that new designs should consider is the ability to biodegrade in urine, thus avoiding the removal of these medical devices. The limitations are now evident, as it is indispensable to provide BUS with adequate mechanical properties that facilitate drainage, with a controlled and predictable rate of biodegradation, avoiding obstructive fragmentation.[135] The combination of the biodegradable design with drug-eluting technology may also contribute to upgrade ureteral stents performance. In this way, in addition to the scaffold function and the

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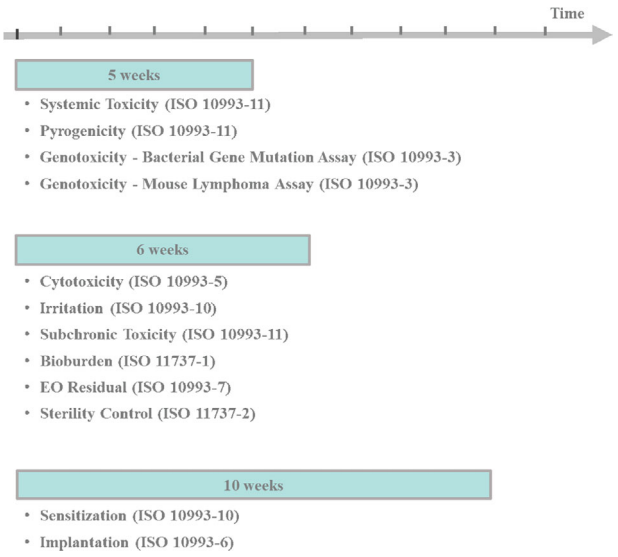


Figure 3. Timeframe of tests usually carried out to fully evaluate ureteral stents.

promotion of urinary drainage, stents would become carriers for topical drug delivery (analgesics, anti-inflammatory drugs, cytostatics, etc.). This feature could avoid the systemic administration of drugs to the urinary tract, which could increase their effectiveness and reduce their side effects.[145,146] Moreover, applying computational fluid dynamics simulations and microfluidics studies (see Section 4), better designs can be developed, and features, as the optimal stent thickness and the shape of side-holes, can be optimized, thus improving the drainage capacity of the stents and avoiding complications such as encrustation.[147]

4. Steps to Go Through to Bring New Stents into the Market

Product certification and safety are characteristics that consumers increasingly take for granted. These procedures are especially critical for medical devices, where biocompatibility and cytotoxicity testing must be ensured, always under the light of international standards. The certification of ureteral stents requires a cluster of well-established guidelines that can take a few months to complete (**Figure 3**). In vitro testing of new materials, coatings and designs is crucial for the development of more efficient stents. Although in vitro test systems are highly simplified assays that not entirely reflect the true behavior of a surface when placed inside the human body (for instance, the immune response is omitted), if they are carefully designed, they can often predict the outcome of in vivo tests. This will lead to an important reduction in the number of in vivo experiments, reducing costs and animal suffering. In vitro tests can, therefore, be considered as simplified assays where a trade-off is made between complexity and throughput.

The ISO 10993, which focuses on the biological evaluation of medical devices, is of one the most important guidelines, with 6 of its 20 parts being recommended to evaluate ureteral stents, namely, Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity; Part 5: Tests for in vitro cytotoxicity; Part 6: Tests for local effects after implantation; Part 7: Ethylene oxide sterilization residual; Part 10: Tests for irritation and skin sensitization; and Part 11: Tests for systemic toxicity. The set of important guidelines also includes the ISO 11737, regarding the sterilization of health care products, microbiological methods, Part 1: Determination of a population of microorganisms on products; and Part 2: Tests of sterility performed in the definition, validation, and maintenance of a sterilization process. The mentioned standards are a general set of test methods, without pass/fail criteria, in order to avoid a false sense of security. This makes them suitable for diverse types of devices, yet it also makes them unspecific for certain assessments. A more unambiguous standard, ASTM F1828, standard specification for ureteral stents, was created in 1997 and reviewed after that to describe more suitable in vitro methods to evaluate the safety and effectiveness of single-use ureteral stents. Nonetheless, the demand for alternative in vitro platforms to test and evaluate stent performances is constantly growing. To reduce the number of in vivo tests and better mimic physiologic environment, dynamic in vitro models can be developed. Cauda et al.[36] compared the performance of three different double J stents for up to 6 months employing a dynamic bioreactor with an artificial urine reservoir, allowing sterile conditions, continuous agitation and physiological temperature. To guarantee the same continuous pressure under continuous urine flow, stents were placed in parallel channels. Results confirmed that such a test platform was suitable to evaluate the urinary stent ability to inhibit the inorganic encrustation formation.

Analyzing the models that have been developed over time, one can verify that when setting up a relevant in vitro test for this type of application, several parameters must be considered, including medium, flow conditions and microbiological specifications (species and strains to be used and their respective concentrations).

The ideal testing medium for ureteral stents is urine, nevertheless human urine is inherently variable in different individuals and also shows variation within the same individual.[148] Some researchers have used pooled urine from volunteers, but even then, there is poor reproducibility, particularly when the same test is repeated in different groups, as a normalized fluid composition between batches is difficult to attain. Thus, artificial urine formulations, presented in the mentioned ASTM F1828, should be used so that more reliable and comparable results can be obtained.[149,150]

Flow conditions are another critical aspect during testing, as flow affects the transport of microorganisms from the bulk flow to the stent surface, the nutrient transport to the biofilm, and also the shear forces that adhered cells (at the beginning of the colonization) or biofilms have to withstand.[151] Thus, hydrodynamics affects cell adhesion and retention,[152] biofilm growth, and architecture[153] and can also impact biofilm resistance to chemical treatment. Several available in vitro platforms enable testing under flow conditions, including agitated microplates, the drip flow reactor, the center for disease control biofilm reactor, and the rotating disk reactor.[154] Although standardized methods exist for some of them,[155] the fact is that they have a number of limitations when the objective is to test surfaces in highly controlled hydrodynamic conditions. For instance, some of these platforms cannot be used to test different materials at the same time, others have reduced sampling areas, or the flow pattern inside them

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changes in time (or it is difficult to control), making it hard to run assays in defined hydrodynamic conditions.[120] Taking into account their respective advantages and limitations,[154] the testing systems that enable a better control of the hydrodynamic conditions are modifications of the Robbins device, flow chambers, and microfluidic systems.

The Robbins device consists of a pipe with several holes, where coupons are mounted on the end of screws and become in contact with the fluid. The main advantage of this system is that coupons can be removed independently, for instance, at different experimental times. A further modification of this design (modified Robbins device or MRD) uses a square channel where coupons are aligned with the inner surface, so as not to disturb the flow.[154] MRDs have been operated in conditions that mimic the flow in UC[156] and stents[53] and they are particularly useful as they enable the simultaneous testing of different surfaces.

In terms of flow chambers, many models were initially designed to enable direct observation of biofilm development in real-time.[154] Particularly when used with transparent surfaces, these systems enable monitoring of initial adhesion, which has been used to test surfaces for UC[157] and novel surfaces for stents.[114]

Additionally, microfluidic systems are increasingly being used for in vitro surface testing, since it is well known that fluidic dynamic processes play a significant role on the initiation and growth of encrustations on stent surface. These systems have reduced volumes and work at very low flow rates, even when used in broad dynamic ranges. This means that medium consumption is minimized, which is beneficial in long-term experiments. Likewise, dead volumes are minimal, and there is great flexibility in channel design.[151,158,159] Although these systems are traditionally made from silicone other surfaces can be tested due to advances in lithography methods.[160] Microfluidic devices could also be used to monitor the influence of stent architecture and materials on surface crystal formation. "Stent-on-chip" (SoC) models[161] are used to mimic urinary stent environment. Mosayyebi et al.[147] exploited SoC models to analyze how stent shape and thickness affect stent performance in terms of crystal formation and encrustation, confirming that the fluidic dynamic based approach can be successfully applied in this field.

Although these three platforms enable testing at broad dynamic ranges, it is of particular importance that the operator makes sure that the flow has stabilized in the area of the flow system, where the surfaces are placed. In all of these systems, entry effects are observed due to the fact that significant expansions or contractions exist where the velocity field is unstable.[152,160,162] Thus, a stabilization length must be considered prior to placing the surfaces so that reproducible results can be obtained with these systems.[120] The length of this stabilization region depends on the geometry of the flow system, on the operating conditions (namely the flow rate), and the properties of the fluid (which change with environmental factors such as temperature). Although several commercial versions of these flow systems exist,[154] the information about the flow dynamics inside them is often not available to researchers. One strategy to obtain a detailed knowledge of the hydrodynamics of each flow system is to use computational fluid dynamics, which is able to simulate the flow inside the device[159,162] but requires further validation.

Two major characteristics of flow in contact with surfaces are the wall shear rate and the shear stress. The shear rate (designated by σ and with units of s^{-1}) is a measure of change of the fluid velocity near the wall in the perpendicular direction of the surface. The shear rate is related to the force which the fluid flow exerts on the wall, expressed as the shear stress (designated by τ and with units of Pa), according to $\tau = \mu \times \sigma$, with μ being the dynamic viscosity of the fluid.[120] Once researchers make sure that their setup enables testing in defined hydrodynamic conditions, they should adjust the flow rate to operate at shear stresses between 0.01 and 0.02 Pa, as shear stresses in this rage were found critical for encrustation in ureteral stents.[161] In UC, the reported value for the shear rate is 15 s^{-1}.[163] Assuming laminar flow conditions, one can use the relationship described above between the shear stress and shear rate, and estimate the shear stress in UC. Several authors have used the dynamic viscosity of water at 25 °C (1 mPa s) or 37 °C (0.692 mPa s) with this relation since the viscosity of water is not very different from urine.[164] Although the properties of urine are highly variable even in the same individual,[148] dynamic viscosity values in the range 0.635–0.797 mPa s have been reported,[165] since viscosity changes not only with temperature but also with physiological conditions, including the occurrence of a UTI.[166] When using any of the referred values with the expression above, shear stress values close to 0.01 Pa can be obtained, which is the critical shear stress for ureteral stents. This means that studies evaluating the performance of new materials or surface coatings for UC that were performed at a shear rate of 15 s^{-1}, using urine medium and relevant strains, may be useful for ureteral stent research. This further emphasizes the need for a careful design of in vitro testing so that experimental results can be used for a different application, as outlined in Section 3.2.

Concerning microbiological considerations, there are no standard tests available for testing the antimicrobial efficacy of urinary stents. Ideally, while designing in vitro experiments, the microorganisms should be selected as a representative of a clinical situation, so that they can predict the outcome of in vivo tests. However, at this time, suitable clinically significant model strains for testing the efficiency of antimicrobial materials for the urinary stents have not yet been fully identified.[10] The most commonly isolated strains associated with stent-related urinary infections are *E. coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, along with *Proteus mirabilis*, *Staphylococcus aureus*, and *Candida albicans*.[11] The recommended microbial strains for antimicrobial testing of long-term urinary devices are *P. aeruginosa* and *P. mirabilis*, and *C. albicans* for yeast models.[10] The density of bacteria should be 10^{7-9} CFU mL^{-1} and for *C. albicans* 10^5 CFU mL^{-1} in the experimental design.

Despite the undeniable contribution of science to the development of both valid in vitro tests and proper medical devices, the passage from the bench to the bedside can also be challenging due to legal reasons. The number and the increasing complexity of the features of such devices have added challenges to the governments, responsible for the fail equilibrium between the entrance of the earliest innovations in healthcare versus the demand for an accurate safety profile. Therefore, health authorities have been updating regulation to be more stringent, and more prepared to evaluate the new technologies that have aroused in the last years. A new regulatory landscape concerning medical

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devices in Europe has emerged, laid down by Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices. This substitutes the past Medical Devices Directive (MDD) 93/42/EC of 14 June 1993. The new regulation presents 22 rules, 4 more than the previous directive, and its demands have obliged the reclassification or even upclassification of products.

In order to determine the proper classification of the urinary stents, the classification rules of Annex VIII of Medical Device Regulation (MDR) have to be considered, as well as other criteria such as the duration of contact with the patient, the degree of invasiveness and the parts of the body affected by the use of the device. As urinary stents are invasive devices that will be inserted into the body through the urethra, they could be considered either Class IIa (if used for more than 2 h but up to 30 days) or Class IIb (if used for more than 30 days), according to Rule 5 of MDR. If a device incorporates as an integral part a pharmacological substance that is liable to act on the body with ancillary action to that of the device, then the urinary stent should be classified as a class III medical device, regardless of the duration of use (following Rule 14 of MDR). It is important to note that independently of the urinary stents being classified as Class IIa, IIb or III medical devices, the CE marking of the stent will need to follow a conformity assessment procedure with a notified body (NB). CE marking of a device implies that compliance with its applicable requirements has been demonstrated. Regulatory requirements concerning the safety and performance of medical devices for CE marking (General Safety and Performance Requirements, GSPRs) are listed in Annex I of MDR.

Early identification of applicable GSPRs is critical to ensure a regulatory-compliant development of a stent and optimize time to market. Demonstration of conformity can be evidenced in different ways:

i. The first and easiest way is by complying with relevant European Harmonized Technical Standards. Harmonized standards are published periodically by the EU Commission on a list, and grant presumption of conformity to the corresponding requirement(s) during the assessment conducted by the NB. Reporting stent compliance with these standards will automatically be considered by the notified body that the related GSPRs are met.
ii. Complying with other (nonharmonized) Technical Standards. These standards, although not directly presuming conformity, may help in demonstrating conformity to the related GSPRs, particularly when there are no European harmonized standards available. Technical standards are consensus documents, frequently based on the industry practice in specific areas.
iii. Referring to published scientific literature in case compliance with particular GSPRs could be demonstrated by bibliographic data. In this case, it is advisable to include full copies of the referred scientific articles in the Technical Documentation.
iv. Using in-house methods, validated/verified for the particular stent. Method validations/verifications must be included in the Technical Documentation.

The Technical Documentation should compile all the data that supports the stent conformity of the correspondingly applicable regulatory requirements. In general terms, the Technical Documentation should include: Product description and intended use, Product design data, Medical device classification (and justification), a statement of the conformity assessment procedure that has been followed, description of production phases (including process controls), product specifications (raw materials, packaging materials and final product), analysis and risk management (including the documents that testify for risk reduction and safety studies), assessment of Quality Management System (accordingly to EN ISO 13485:2016, and that enclose the Risk Management System–EN ISO 14971). The technical documentation is necessary to demonstrate that the product meets the essential requirements and, therefore, justify and support an EU declaration of conformity. One needs this documentation in order to affix the CE marking to the product. An EU declaration of conformity (DoC) is a mandatory document that the manufacturer or the authorized representative need to sign to declare that products comply with the EU requirements. With this documentation, it is then possible to ask for a conformity assessment procedure with a NB and complete the CE marking procedure.

5. Ureteral Stents Market

Urinary stenting expenses can be divided in i) direct costs, which include the cost of the stent, its insertion and removal, and ii) indirect costs, which are associated with health-related quality of life, outpatient hospital care, drug costs, absence from work, and resuming normal physical activities.[9] In 2016, an economic study, made on St. Gallen Cantonal Hospital, St. Gallen, Switzerland, concerning ureteral stent-related problems stated that although the ureteral stent costs were around US dollars (US$) 100, the total costs amounted to a fourfold higher cost per patient, a median of US$ 455 for the entire treatment.[167]

In 2018, the global ureteral stent market was valued at US$ 359.9 million, and it is forecasted to exceed US$ 564.4 million by 2026, with a projected compound annual growth rate of 5.8% between 2018 and 2026.[168] The technological advancements in stent composition and the presence of key players, whose aim is to find solutions to bypass common limitations, support the growth of the ureteral stents market. Additionally, improvements in healthcare infrastructure, enlargement in healthcare investment in developing countries, and the creation of ureteral stent tracker products are expected to boost market growth. Otherwise, problems associated with stent placement and lack of skilled professionals are the flagship factors that might significantly limit market growth. Geographically speaking, North America is expected to be the most lucrative region, as a result of the high rate of diagnosis and treatment of urological disorders, and the facilitated access to ureteral stents due to the presence of major players in the region.[168]

A careful analysis of the patent landscape can provide us important information regarding the pertinence of this subject in a global framework. The great interest in the ureteral stents area originates scientific knowledge and innovations, which can later become important patents for the field. To perform a structured and reliable analysis, The Lens.org platform, an open global

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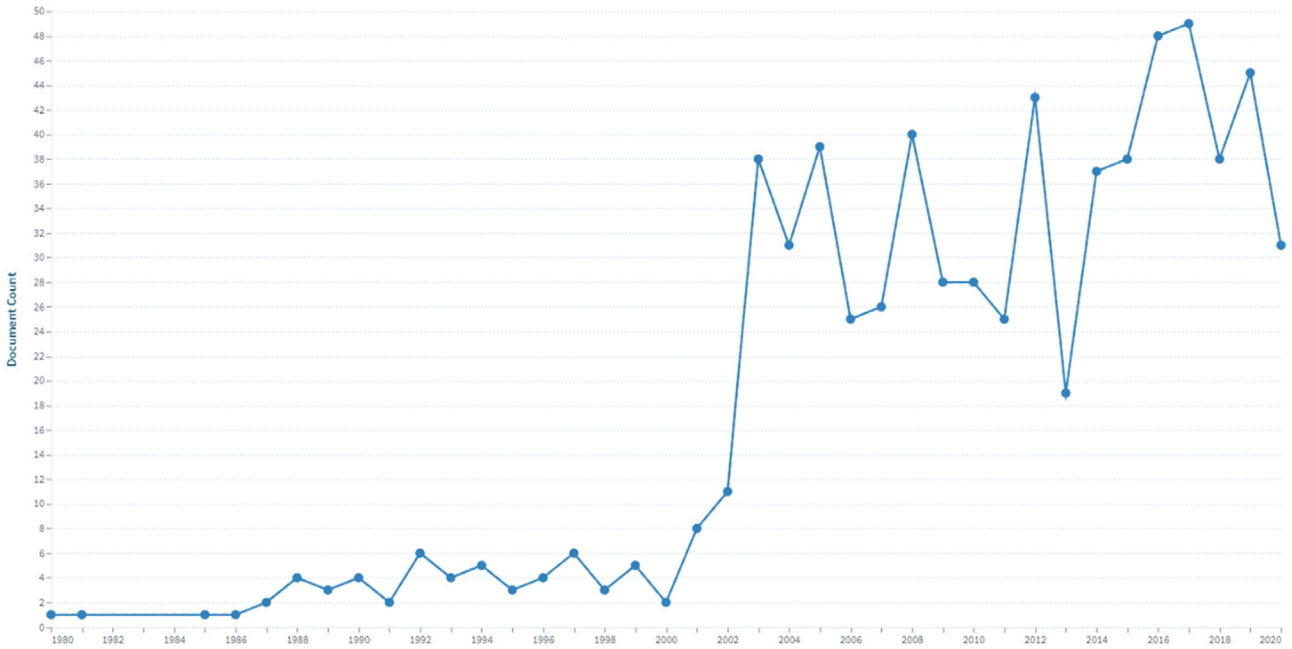


Figure 4. Number of patents related to ureteral stents, by year. Reproduced with permission.[169] Copyright 2021, The Lens.org platform.



Figure 5. The main patent applicants in the ureteral stent field up to 2021. Reproduced with permission.[169] 2021, The Lens.org platform.

cyberinfrastructure for innovation, was extensively explored. At the time of this search, there were registered 635 patents with proven mention of ureteral stents on their claims.[169] In terms of scientific content, a great number of these patents are related to drug-eluting technology; however, there is no drug-eluting stent commercially available, conceivably due to concerns regarding its long-term safety and complex pharmacodynamic. More than 60% of the total documents are patent applications, and less than 40% are granted patents. At the beginning of the millennium, there was an increase of more than 100% in the total number of published patents, and the records from the past 20 years suggest that there is a tendency to increase the number of total registered documents (**Figure 4**).

In terms of jurisdiction, USA has more than 60% of the ureteral stents related patents (406), followed by the World Intellectual Property Organization (WIPO), which has 138, and European countries, which have 91 patents. Although there are more than 300 different applicants, Boston Scientific Scimed Inc. stands out as the major applicant in this field, with more than 20% of the total existing patents (**Figure 5**). The second most relevant applicant is Scimed Life Systems Inc, with 40 documents, which represents 6% of the total documents. Boston Scientific Ltd, Tepha Inc and Cook Medical Technologies llc have less than 5% of the total documents, each. The fact that these companies are based in the USA corroborates the observations described above, namely the evidence that USA is the country with the greatest power of jurisdiction in this area, combining the great capacity to develop innovative technologies with elite healthcare institutions.

6. Conclusions

The most recent advances on the ureteral stent field aim to reduce the device-associated complications, as bacterial infection, and minimal/mild encrustation. Despite benefiting from pioneering materials and techniques, the progress towards finding suitable solutions has been slow, with almost immutable clinical outcomes, over the past few years. The future involves using cutting-edge technology, as 4D printing and innovative designs, to achieve better stent performance and, consequently, provide a better quality of life for patients. Besides the commercially available hydrophilic and DLC coatings, in the promptest future, ureteral stents market can profit from studies already made for UC, as the ones with metals as antimicrobial agents. However, since there is no single standard method with controlled hydrodynamic conditions and established microbiological species to test the response of materials, coatings and designs already created, the comparison of results is hampered. Thus, it is urgent to develop adequate standard assays to enable reliable and comparable results, which will contribute to the development

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of new and better advances in the field. With this in mind, and in order to reduce the number of in vivo tests and better mimic physiologic environment, we suggested the use of dynamic in vitro models, with controlled medium and flow conditions, in combination with the recommended microbial strains for antimicrobial testing of long-term urinary devices, as *P. aeruginosa, P. mirabilis,* and *C. albicans*. These standard protocols will facilitate the passage of these innovations to the ureteral stent market, further promoting its upward growth trend in the coming years.

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Conflict of Interest

The authors declare no conflict of interest.

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in vitro testing, innovations, markets, ureteral stents

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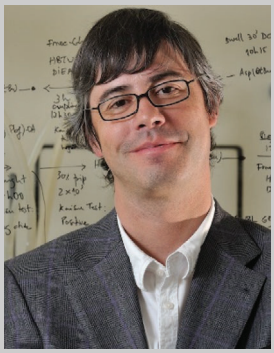
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