9.4.29. Clinical Evidence

iVascular iVolution self-expanding peripheral stent system was certified according to the Medical Devices Directive 93/42/CEE by the Notified Body 0318. The clinical evaluation was carried out in line with guideline MEDDEV 2.7.1 rev 3. Data was generated through literature search and it was compared to equivalent devices to demonstrate the acceptable performance and safety (article 6.1 of MEDDEV 2.7.1)

Report ID13-046 *Relevant Scientific Literature concerning self-expanding peripheral stent system* demonstrates the clinical benefit in terms of efficacy and safety of commercialized equivalent devices through results of clinical trials collected over the history of this type of stent. *iVolution* does not present any scientific novelty regarding the equivalent devices currently commercialized, so in the above report it is demonstrated the clinical, biological and technical equivalence of *iVascular iVolution* compared to mentioned devices.

This report is regularly updated in order to evaluate new clinical data or any significant change in the medical device.

Regarding this device currently is an on-going registry conducted in Belgium:

EVOLUTION. Registry iVolution stent in real life

The objective is evaluating the outcome of treatment in femoropopliteal stenotic or occlusive lesions. The primary endpoint is primary patency at 12 months, defined as freedom from >50% restenosis at 12 months.

The end of recruitment is planned for end of October. The preliminary results are included in the corresponding section

REPORT FROM RELEVANT SCIENTIFIC LITERATURE ABOUT SELF-EXPANDING PERIPHERAL STENT SYSTEM

iVascular iVolution

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Documentary Technic
LVD BIOTECH

Report Nº: ID-13-046

15/07/2013

1. GENERAL INFORMATION

1.1. Product name: iVolution

Equivalent products:

MANUFACTURER	PRODUCT NAME
Abbott	Absolute Pro
Biotronik	Pulsar 35
Cook	Zilver 635/Zilver Flex
Cordis	S.M.A.R.T./S.M.A.R.T. Control
Covidien	Protégé EverFlex
CR Bard	LifeStent /LifeStent XL
Medtronic	Complete SE
Medtronic (Invatec)	Maris Plus
Terumo	Misago

Table 1. Main equivalent approved comercial products

Equivalent products are considered those self-expanding stent pre-mounted into a delivery system for 0.035" guide wire and whose intended use is the treatment of atherosclerotic lesions in peripheral arteries of lower limbs and/or palliation of malignant stenosis in biliary ducts (indications for use analogues to those of **iVolution)**; the stents mentioned above are manufactured from a Nitinol tube and do not are coated.

Available technical information related to equivalent products can be consulted in annex I of this report.

1.2. Codes:

62 references are requested (see Table 2)

Reference codification is divided in five sections:

1. Product type: **SPN** = (**S**tent **P**eripheral **N**itinol).
2. Main characteristics: **BC35** = stent **B**are **C**oaxial for 0.0**35**" guide wire.

Product dimensions:

3. Catheter's total length: it is given in centimeters. 3 digits are provided. Two lengths are requested: **080**cm and **140**cm.
4. Stent's nominal diameter: given in decimals of millimeter. Requested references go between (**050**) and 10 (**100**) mm, with a difference of 1 mm.
5. Stent's length: it is given in millimeters 3 digits are provided. Requested reference in the present product are between 40 (**040**) and 100 (**100**) mm, with a difference of 20mm. Together with previous lengths, in the case of diameter 8 mm, the 150mm length is requested and finally for diameters 5, 6 and 7mm are requested 150 and 200mm.

Parts 1-2 are common in all references; while parts 3, 4 and 5 change depending on the reference: **SPC BC35 XXX YYY ZZZ,** where X points the useful length of the catheter and Y and Z refers to diameter and length of the stent respectively.

Example: SPN BC35 080 050 040. Self-expanding stent system, coaxial, for 0.035" guide wire, Catheter's useful length is 80cm, stent's nominal diameter 5mm and length 40mm.

Ø	LENGTH (mm)					
mm	40	60	80	100	150	200
5.00	SPN BC35 080 050 040	SPN BC35 080 050 060	SPN BC35 080 050 080	SPN BC35 080 050 100	SPN BC35 080 050 150	SPN BC35 080 050 200
6.00	SPN BC35 080 060 040	SPN BC35 080 060 060	SPN BC35 080 060 080	SPN BC35 080 060 100	SPN BC35 080 060 150	SPN BC35 080 060 200
7.00	SPN BC35 080 070 040	SPN BC35 080 070 060	SPN BC35 080 070 080	SPN BC35 080 070 100	SPN BC35 080 070 150	SPN BC35 080 070 200
8.00	SPN BC35 080 080 040	SPN BC35 080 080 060	SPN BC35 080 080 080	SPN BC35 080 080 100	SPN BC35 080 080 150	
9.00	SPN BC35 080 090 040	SPN BC35 080 090 060	SPN BC35 080 090 080	SPN BC35 080 090 100		
10.00	SPN BC35 080 100 040	SPN BC35 080 100 060	SPN BC35 080 100 080	SPN BC35 080 100 100		

Table 2a. Requested references of the self-expanding stent system, iVolution, for catheter length 80cm.

Ø	LENGTH (mm)					
mm	40	60	80	100	150	200
5.00	SPN BC35 140 050 040	SPN BC35 140 050 060	SPN BC35 140 050 080	SPN BC35 140 050 100	SPN BC35 140 050 150	SPN BC35 140 050 200
6.00	SPN BC35 140 060 040	SPN BC35 140 060 060	SPN BC35 140 060 080	SPN BC35 140 060 100	SPN BC35 140 060 150	SPN BC35 140 060 200
7.00	SPN BC35 140 070 040	SPN BC35 140 070 060	SPN BC35 140 070 080	SPN BC35 140 070 100	SPN BC35 140 070 150	SPN BC35 140 070 200
8.00	SPN BC35 140 080 040	SPN BC35 140 080 060	SPN BC35 140 080 080	SPN BC35 140 080 100	SPN BC35 140 080 150	
9.00	SPN BC35 140 090 040	SPN BC35 140 090 060	SPN BC35 140 090 080	SPN BC35 140 090 100		
10.00	SPN BC35 140 100 040	SPN BC35 140 100 060	SPN BC35 140 100 080	SPN BC35 140 100 100		

Table 2b. Requested references of the self-expanding stent system, iVolution, for catheter length 140cm.

See available information regarding approved references of equivalent commercial proiducts in the annex I

1.3. **Manufacturer:**

LIFE VASCULAR DEVICES BIOTECH S.L.
Camí de Can Ubach, 11
Pol. Ind. Les Fallulles
08620 St. Vicenç dels Horts

2. GENERAL DESCRIPTION AND INTENDED USE

2.1. Brief description of the device

iVascular iVolution self-expanding peripheral stent system, as all equivalent marketed products[a], is a single-use device designed for endovascular treatment of peripheral arteries under aortic arch and for palliation of malignant stenosis of bile ducts, which comprises:

- A self-expanding metal peripheral stent manufactured from an equiatomic metal alloy of Nickel and Titanium (NiTinol), premounted into a coaxial delivery catheter. It is a flexible prosthesis that reaches its maximum diameter when, once it is placed in the artery, the delivery system is withdrawn. The stent is adapted to the artery exerting a constant radial force which allows the maintenance of blood flow.

  The stent **iVolution** is manufactured by laser cutting of a metal tube. Once the stent is cut, it is submitted to several treatments in order to obtain a final smooth and shiny finish. At each end of the stent there are 4 radiopaque markers which indicate its length and aid to position the stent in the artery. The stent is supplied in several lengths and diameters.

Fig 1. Design of iVolution.stent

- A delivery system is a coaxial catheter for 0.035" guide wire (0.89mm) and compatible with a 6F introducer. It comprises an inner tube, an intermediate tube, a retractable sheath, an outer sheath and handle for control the delivery:
  - The ***Inner tube:*** is the lumen of guide wire passage; it goes from the tip of the catheter to the more proximal part of the handle, which ends in a luer lock connector. The stent is loaded in the outer distal part of this tube.
  - The Intermediate tube is a reinforcement and containment tube and it is called ***support tube***. This tube extends from the distal part of the handle to the proximal end of the stent with two functions:
    1. Stiffen the catheter to increase its pushability;
    2. Contain the stent between the tip and the distal part of the tube to prevent the stent from moving.
  - The ***retractable sheath*** extends from the catheter tip to the more distal part of the handle covering the stent. This sheath compresses the stent in such way that the stent remains in a low profile for its insertion and trackability. In the moment that, with the aid of the handle, the sheath is moved back, the stent is released and expanded.
  - Finally the ***outer fixed sheath***, is placed over the retractable sheath covering it, in order to prevent that retractable sheath can be manipulated.

[a] See part 1.1: Table 1.

- ***The delivery handle:*** allows the withdrawal of retractable sheath. It has a security system to avoid that stent was delivered or moves inside the sheath during handling previous to delivery. The delivery system is a dual one:
  - *Slow delivery system*: allows begin the deployment of the stent accurately.
  - *Fast delivery system*: once placed the first millimeters of the stent, this system allows the insertion in rapid way.

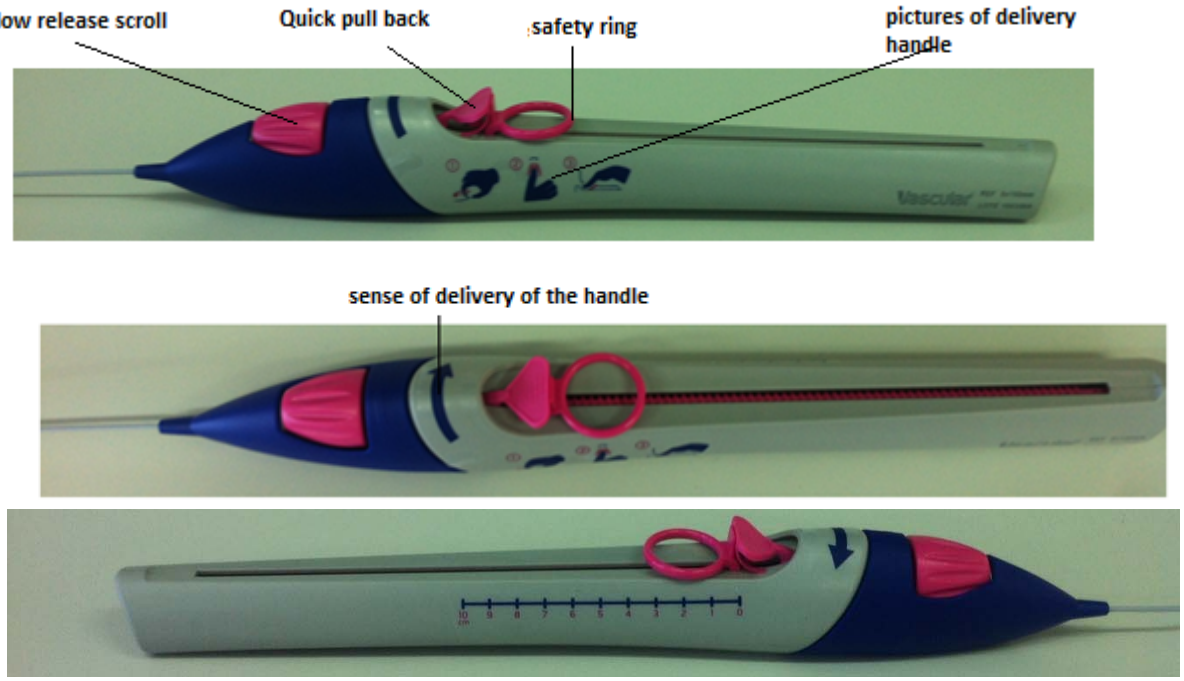


Fig. 2 Details of delivery system.

The system ends in a soft and atramautic tip to avoid damaging the artery during its advance

2.2. Use of the device

The self – expanding peripheral stent system **iVolution**, is indicated for treating:

- *de novo or restenotic* atherosclerotic lesions located in peripheral arteries below the aortic arch, that is, iliac, femoral popliteal arteries with nominal diameter between 4.5 and 9.5 mm

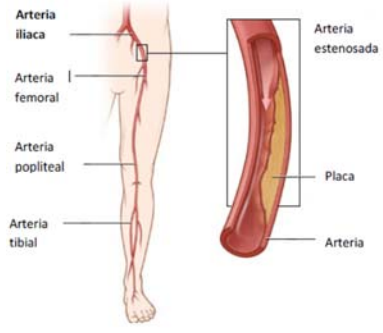


Fig. 3 Main implantation area of self-expanding nitinol stent.

- palliation of malignant stenosis affecting bile ducts with nominal diameters between 4.5 and 9.5 mm.

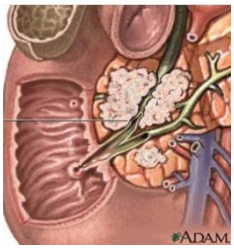


Fig. 4 Obstructed bile duct by a pancreatic tumor. This treatment is only palliative, in cases where tumor is non-operable.

These indications are the same as ones included in equivalent products' instructions for use (*See Annex I*).

According to the standard procedure, the stent mounted into the delivery system is introduced in the stenosed/narrowed artery or bile duct and it is passed until reaching the lesion. Once it is placed the retractable sheath is removed and the stent is expanded recovering its initial shape (elastic expansion mechanism since the stent is released from the cover that keeps it compressed and mechanism of thermal expansion due to shape memory upon reaching body temperature).

2.2.1. Relevant technical data

Stents require for their proper design a compromise between structural characteristic and thermomechanical properties of the material, a constant external soft force that allows a gradual relaxation of the narrowing in the artery and a high resistance to radial compression that prevents from collapse due to any external action.

The material used in stent manufacture as well as its design are important factors when it comes to getting the required features[1-8].

Functional performance

- Suitable support:
  - Enough radial strength to hold or keep the artery opened: if it is insufficient, stent collapses.
  - Lumen adaptability, for engaging the arterial anatomy
  - Ratio between stent surface – lesion as small as possible since it determines the grade of thrombus formation and / or restenosis; but it has to be enough to keep the radial force
- Small wall thickness to achieve the smallest possible profile and to avoid restenosis and distortions in circulatory flow.

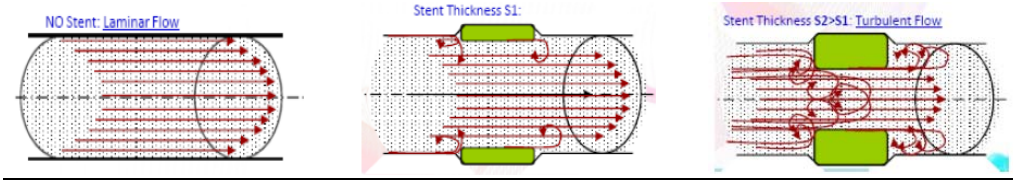


Fig. 5 Distortion flow vs stent thickness

- Reliable fixation to prevent migration

- Minimal obstruction of normal circulatory flow
- Minimum tissue proliferation

Ease of use

- Low profile;
- flexibility;
- pushability;
- trackability;
- high radiopacity to be visible under fluoroscopy
- release technique / easy implementation

The choice of materials affects the main features of the stents, such as radiopacity, strength, flexibility, etc. For treating peripheral arteries can be chosen, depending on lesion location and complexity, between stents with expanding balloon (BE) or self – expanding (SE). Manufacture and features are different:

- For stents BE materials such as stainless steel (SS 316L) or chromium alloys (e.g CoCr L605) are used. These stents are manufactured from a tube which is subsequently subjected to two plastic deformations: 1st crimping and then expansion. Both deformations are induced, first by the crimping machine and afterwards by balloon inflation (the elongation of these materials increases and decreases proportionally to the applied force). They are indicated for protected arteries.
- SE stents are of a nickel-titanium alloy known as Nitinol (NiTi), this material allows designing devices in which the material undergoes elastic deformations 10 time higher than those of BE steel stents and deformation is non linear, this elastic behavior, unlike the foregoing materials, is similar to the natural materials forming the body. NiTi stent is manufactured in its final shape, which acquires when it is deployed from the inside of the shealth containing it.

  NiTi is a shape memory material (SMA: Shape Memory Alloy), which is characterized because after an apparently plastic deformation at low temperature, recover its original shape spontaneously upon heating to the temperature range to which it has been configured during manufacture. The properties that allow this behavior are effects due to phase shift occurring in this solid state material (thermoelastic martensitic transformation):

  - *Termal shape memory or shape memory effect :* allows the generation of force or movement and is the capability of these materials to remember one shape, even after severe deformation, and
  - *Elastically memory or superelasticity:* allows storing energy and makes it resistant from kinking.

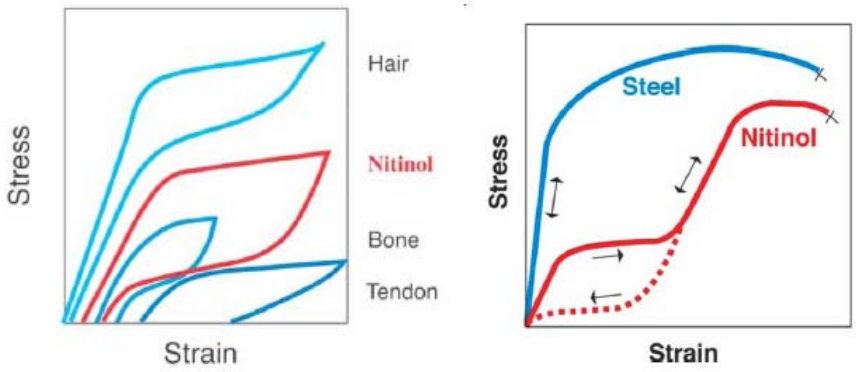


Fig. 6 Left. Comparative curve stress - deformation nitinol vs natural components of the human body.

Fig. 6 Right. Comparative curve stress- strain stainless Steel vs Nitinol.

Nitinol is the most widely used and preferred material for the manufacture of vascular devices (self-expanding stents, filters, cardiac valves structures, occlusion devices …) due to its high stability in cycling, biocompatibility, corrosion resistance and ability to recover large deformations. X-ray visibility of NiTi is similar to the SS316L, but lower than CoCr one's, therefore a radiopaque marks are placed at the ends of the stent to improve visibility.

Balloon expandable stent	**Self-expanding stent**
▪ Made on a tube which is crimped and expanded to vessel diameter by balloon inflation ▪ Can collapse if the critical external pressure is exceeded. Collapsing strength depends on eccentricity of the lesion, local irregularities and if it is a protected lesion. ▪ Resists the expansion of the ball. ▪ After balloon deflation recoil or elastic recovery takes place. ▪ Direct stenting is usual. The stent is advanced into the lesion and expanded. ▪ Are crimped on the balloon, although this is rarely, can be evicted during its release. ▪ They adapt worse blood morphology and even modify the artery. ▪ Has more radial strength or support.	▪ Manufactured slightly above the vessel diameter, mounted and constrained to a smaller diameter until the release site is reached. ▪ Do not have strength limitations and it elastically recovers before collapsing completely. ▪ Ideal for superficial locations such as femoral arteries and carotids; unprotected arteries as the impact returns it to its shape. ▪ Attend vessel expansion. No recoil after implantation. ▪ If properly overdimensioned, the stent still applies a force to expand the artery remodeling profile thereof. ▪ Do not have enough rigidity or strength to directly open calcified lesions. Pre dilatation or post dilatation is necessary. ▪ It is placed in a delivery catheter ▪ It adapts to the arterial morphology supporting twists and stretches (femoral artery) ▪ More difficult to release.

Table 3. Comparative features balloon expandable stent vs nitinol self-expanding stent.

On the next page a table summarizing the main characteristics of **iVolution** and equivalent products (information from published technical data for the corresponding trading house (see annex I)) are included.

Stent characteristics

The especial characteristics of the NiTi stent (superelasticity and shape memory) make that usually the stent used has a diameter 10 -15 % greater than the diameter of the artery to treat. Once released the stent attempts to recover its original shape so it perfectly fits the diameter of the treated artery and exerts a small constant strength against the artery walls since it has not reached its original diameter.

Regarding the length of the stent, it must be slightly greater than the total length of the plaque in order to ensure as homogeneous as possible dilation of the treated area. In clinical practice, a stent whose length exceeds the distal and proximal length of the lesion is chosen.

Based on the above, for optimum results it is necessary to choose a stent with length and diameter according to lesion location and characteristics. In this case, iVolution and equivalent products are marketed with a diameter between 5.0 – 6.0 and 10 mm with 1 mm variability, which is set to the normal diameter of the arteries in the area.

Depending on the trading house and the indications for use, stent lengths range from initial lengths of 20-40 mm and 100-120 mm final lengths if it is only indicated for iliac arteries or to 150-220 mm whether it is also indicated for the femoropopliteal segment with an approximate variability of 20 mm between the different references. These dimensions fit the normal casuistry of the lesions to treat. In section 3.2, anatomy of the areas to be treated, it is justified the choice of stent diameters and lengths **iVolution** according to the anatomical area to be treated.

Name	Company	Indic. Use	Ø (mm)	Length (mm)	Leng. catheter (cm)	Num radiopaque markers ; composition[b]
iVolution	LVDB	Peripheral bile	5-10	40-200	80; 140	8; Ta
Absolute Pro 0.035	Abbott	Peripheral bile	5-10	20-100	80; 135	12; Ni-Ti alloy
Absolute Pro LL	Abbott	Peripheral bile	5-8	120-150	80; 135	12; Ni-Ti alloy
Pulsar 35	Biotronik	Peripheral (SFA, BTK)	5-7	30-200	90; 135	12; Au
Epic	Boston	Iliac	6-12	20-100	75; 120	Na; Ta
Zilver 635	Cook	Iliac			80; 125	Multiple; Au
LifeStent /XL	C.R. Bard	SFA & PPA	6-10	20-200	80; 130	12; Ta
S.M.A.R.T. / S.M.A.R.T. Control	Cordis	SFA/PPA iliac	6-10	20-150	80; 120	12; Ta
Protégé EverFlex	Covidien	Peripheral bile	6-8	20-200	80;120	NA; NA
Maris Plus	Medtronic	SFA /Iliac	6-12	30-150	80; 120	2; Ta
Complete SE	Medtronic	SFA/PPA Iliac	4-10	20-150	80; 130	8; Ta
Misago	Terumo	Iliac/femoropopliteal	6-10	40-150	135	6; Au

Table 4. Comparative data iVolution stent system (guide 0.035", compatible with 6F introducer) technical characteristics.

[b] Ta: Tantalum; Ni: Nickel; Ti: Titanium; Au: gold; NA: Not available

Release system characteristics

Except for Misago system (Terumo), the release system of **iVolution** and the other equivalent products is a coaxial catheter (multi lumen from the distal tip to the proximal connector, the guide wire goes through all along the catheter inside) for a 0.035" guide, compatible with introducer 6F. Two catheters lengths (aprox. 80-90 and 120-135 cm) are marketed to cover the two types of access, anterograde and retrograde, which are widely practiced.

Unlike the rest, the Misago release system is Rapid Exchange (RX), maintaining compatibility with 0.035" guide and 6F introducer. As it is a RX system, only the greatest length (135 cm) is marketed.

In catheters that treat peripheral leg arteries, it is necessary to have two lengths because depending on the access performed, it takes longer or shorter length to access the lesion:

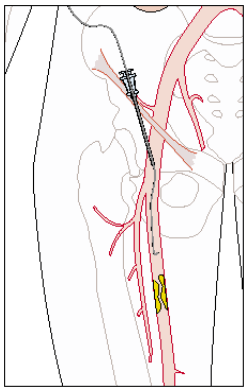


Fig 7. Antegrade access

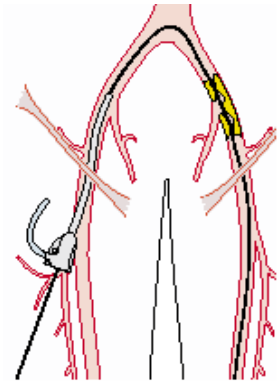


Fig 8. Retrograde or contralateral access.

Antegrade access is performed with the flow, it requires less catheter length since it is carried out in the leg where the lesion is located. Retrograde access is performed against the flow, it is normally necessary in narrowed lesions where catheter needs much support; as access is in the opposite leg to the one with the lesion, catheter shall be longer. The rapid exchange system characteristics only allow retrograde access.

In conclusion, all peripheral self-expanding stent systems, including **iVolution**, have the same materials for stent and radiopaque markers manufacture, have similar stent dimensions (length and diameter) and catheter length, use the same release system (except Misago) and have the same indications for use.

2.2.2. Biological relevant data

Biocompatibility[c] requirements for a stent are [1-8]:

- Low thrombogenic response
- Corrosion resistance; and
- Not interfering with normal physiological processes.

Both in **iVolution** stent system and in equivalent products materials used are medical grade and homologated for this use.

The stent is manufactured by laser cutting from a tube of Nitinol (aprox. 55% nickel and titanium). Nickel is a heavy metal that can causes allergic reactions, but NiTi is not an alloy itself, but an

[c] Capability of materials to do not present toxicity during the implanted period.

intermetallic compound where Ni is bonded to Ti in a stronger way than to SS316L elements. Furthermore, treatments to which stent is subjected after laser cutting cause the formation of a titanium oxide layer on device surface that prevent nickel from release. Therefore, Nitinol is a biocompatible and suitable material for the manufacture of vascular grafts.

NiTi, with rare exceptions, is the SMA material of choice when it comes to manufacture vascular devices because of its stability, biofunctionality[d], biocompatibility and resistance to corrosion (the last two, comparable and better respectively than SS316L).

NiTi stents are known and used to treat atherosclerotic lesions in peripheral arteries and palliation of malignant stenosis in bile ducts for more than 20 years, consequently their biocompatibility with bloodstream is proved.

The materials used to manufacture the release system are medical grade such as nylon, Pebax, polyimide and polyethylene, whose biocompatibility is demonstrated and used in both angioplasty balloons and balloon expandable stents release systems. All these materials are also used to manufacture current SE stents systems already marketed.

Specifically the materials used in **iVolution** manufacture are:

- Stent: NiTinol
- Lumen guide: Polyimide
- Support tube: Mesh polyimide
- Tip: PEBAX
- Retractable sheath: Teflon; mesh; nylon 12
- Fixed sheath: Polyethylene

[d] Capacity of materials to perform the desired functions for the expected period in the body.

3. THERAPEUTIC AND DIAGNOSTIC INDICATIONS AND CLAIMS

3.1. The disease

IVolution is specially indicated for percutaneous treatment in peripheral arteries located in lower extremities; and to palliate malignant non-operable tumor that block the bile ducts. In this case, the diseases that lead to the use of this device are completely different.

3.1.1. Peripheral arteries diseases

Peripheral vascular disease (PVD) is a slow and progressive disorder of the bloodstream[9-10], which includes all the vessels of the circulatory system, except the coronary ones. When the affected vessel is an artery, it is called PAD (peripheral arterial disease).

PAD occurs due to the build-up of plaque (atherosclerosis) in the arterial system that carries blood to the extremities and vital organs, arteries fail to receive adequate blood flow to operate causing ischemia in the tissues supplied by the affected vessel.

The anatomical regions of particular interest in EAP are the lower extremities, as the prevalence of the disease in this area is 90% of cases and affects three major segments: aorto-iliac area, femoro-popliteal are and infrapopliteal area (mainly tibial arteries).

Clinical manifestations of PAD are: intermittent claudication, chronic and critical ischemia. They are a major cause of acute and chronic disease associated with a decrease in functional capacity and patients' quality of life and may lead to amputation of the affected limbs and increase the risk of death. Patients suffering PAD, often, have associated an increased risk of cardiovascular and/or cerebral ischemia, since the nature of the arteriosclerotic process contributes to the development of this disease in the arteries of the heart and brain[e]. It is estimated that 40% of people suffering from this disease, whose main symptom is intermittent claudication[f], will die or suffer a stroke within five years after diagnosis.

Causes and sources[9-10]

PAD includes a diverse group of disorders that lead to stenosis (narrowing) or progressive obstruction, or to an aneurysmal dilatation of the aorta and its non-coronary branches, being atherosclerosis, among other pathophysiological processes, its principal cause.

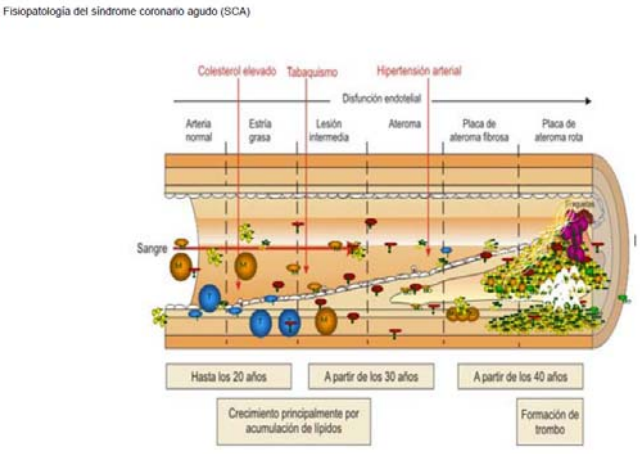


Fig 9. Evolution atherosclerosis formation vs age.

[e] PAD is associated with a high mortality rate for coronary artery disease, which leads to 50% of patients' death after 10 years. There is also 10% of deaths caused by stroke.

[f] Limb pain that occurs when walking but at rest disappears, due to a decreased flow in the arteries.

Atherosclerosis is a disease in which a waxy substance inside the arteries is formed.

This substance is called plaque and is composed of cholesterol, fats, waste products from the cells, calcium and clotting substances.

Plaque narrows the passage of blood flow and may block completely the artery. During the plaque formation, the artery wall loses its elasticity and cannot react to tissues demand causing ischemia in tissue supplied by the affected artery. Two types of plaque have been identified:

- Heavy plaque (stable): high content of fibrous elements and even calcification.
- Soft or vulnerable plaque (unstable): high content of cholesterol and macrophages.

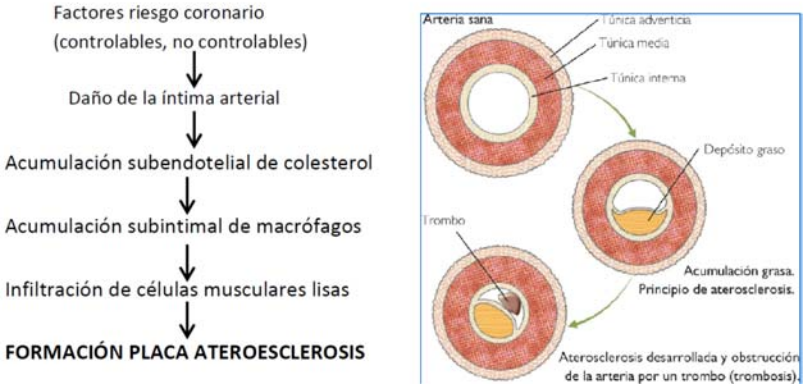


Fig. 7 Sequence of a formation of an atherosclerotic plaque

PAD treatment[11-17]

The main aim is to reduce vascular events as myocardial infarction, stroke or vascular death risk.

Intermittent claudication: in this case, patient's quality of life improvement is the additional purpose to the previous one. Conservative therapy (change in lifestyle, exercise, pharmacological therapy) is the first choice, only if no improvement is achieved, revascularization will be considered.

Critical limb ischemia (CLI)[g]: ulceration and gangrene appearance threatens limb integrity, so salvage of the affected limb becomes the aim of the treatment. Patients with CLI are candidates to revascularization, by either surgical bypass[h] or endovascular procedures[i]. If it is practicable, the first option is endovascular revascularization (balloon angioplasty + stent implantation or direct stent implantation).

Acute limb ischemia (ALI): In these patients, there is an unexpected decrease in limb perfusion mainly due to thrombus, and revascularization must be performed urgently. The different revascularization options (percutaneous or surgical) include thrombus removing.

Lesion features (localization, length, number of lesion, occlusion grade) and patient's conditions (life expectancy and possible risk factors), are the factors that determine the choice of treatment.

[g] Final stage of the disease where the pain does not stop while resting and ulceration and gangrene may be produced

[h] Surgical bypass (CABG): procedure consisting on reroute blood flow around the narrowed vessel through a tube made of a synthetic material or a section of a healthy vein of the patient, so that connects the vessel above and below the obstruction allowing blood to flow around it.

[i] Minimally invasive technique wherein the interventionist introduces a device (balloon/drug eluting balloon/stent) through a small incision in the femoral artery to the injured artery, and then it is inflated to reopen the vessel.

Aortoiliac segment treatment

Studies endorse a high technical success rate, a high long-term patency and a high limb salvage percentage. Treatment choice in this segment is between direct stenting or angioplasty + stenting.

The characteristics of this segment, large vessels and protected area, allow implantation of a balloon expandable stent as well as a self-expanding stent, being the results comparable in both cases: high technical success of the procedure and high long-term patency. Given the large size of these arteries in case there is some proliferative growth that results in restenosis, it is minimal and does not affect the long-term results in the same way as if it is a short artery.

Clinical trials seem to indicate that angioplasty followed by stenting achieves better results, but there is not any consensus and in practice, it depends on the interventionist. BE stent is more often used in short lesions, in the common iliac, aortoiliac bifurcation and calcified lesions where accurate deployment and a higher radial force are required and always performed in protected arteries. While SE stent is more used in the external iliac, in long lesions or in tortuous vessels where greater flexibility and adaptation to arterial morphology is necessary and the artery is not protected against potential impacts.

Femoropopliteal segment treatment

This area is one of the longest in the body, superficial femoral artery (SFA) which is fixed by two point with high flexion such as hip and knee. Therefore, it is an area that during movement is exposed to different forces: flexion, lateral and longitudinal compression, torsion and which is also subjected to external compressions during muscular activity.

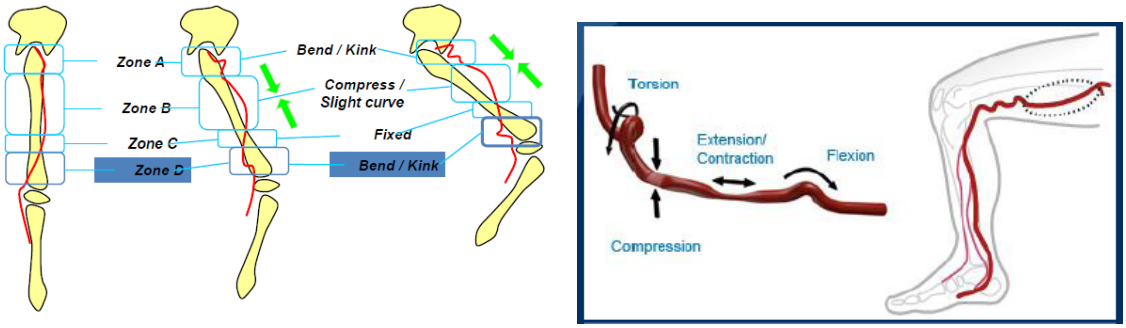


Fig 11. Forces/deformations to which AFS is submited.

The treatment of femoropopliteal area with angioplasty balloon is successful in the first instance, but revascularization rates due to restenosis are very high, thus stenting shall be resorted. To choose the type of stent used in this area it shall be taken into account that it is a superficial area with high flexion, subjected to considerable tensions both internal and external affecting the stent. The characteristics of the stent, lower radial force than BE, superelasticity, shape memory (impact resistance with initial shape recovery), etc…, allow perfect adaptation to the particularities of this area getting better clinical outcomes and lower rate of stent fracture than in BE stents.

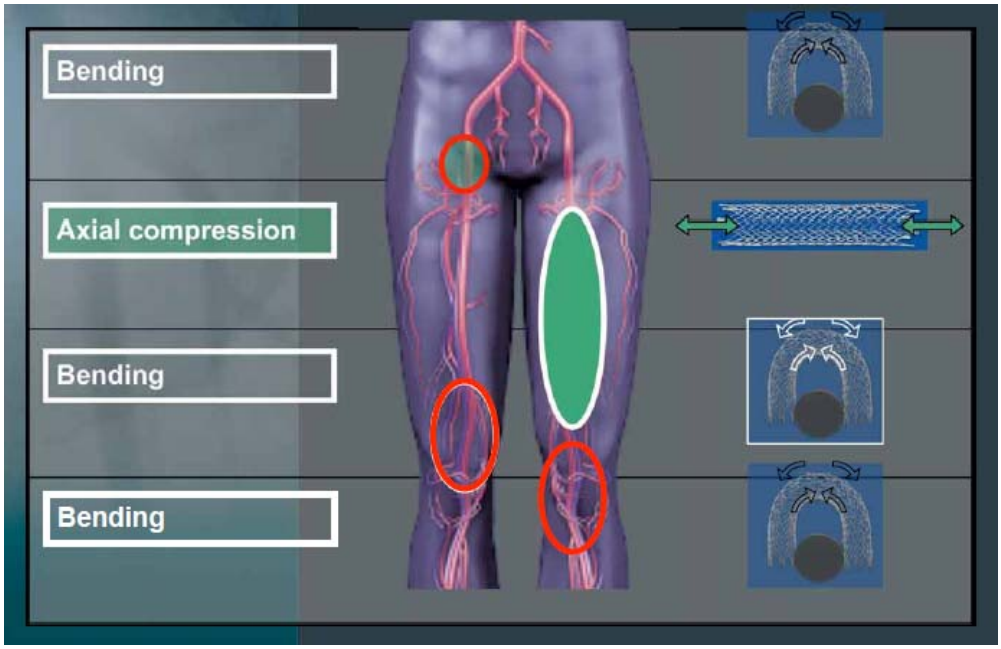


Fig. 12. Deformations to which the stent is subjected depending on the implantation area.

3.1.2. **Bile duct obstruction**[18-19]

Bile duct obstruction is a direct consequence of produced carcinomas at this area: bile and non-bile carcinomas such as pancreatic tumors, liver metastasis, etc. These tumours are usually detected at very advanced stages and they are located in difficult access areas, which makes complex its surgical intervention, thus they are associated to high mortality and bad prognostic.

Obstruction is caused by the compression exerted by theses tumours to bile duct, blocking the bile flow and preventing bile from reaching the intestine normally. Bile is a fluid that helps with fat digestion during meals, it is produced in the liver and it flows through the bile ducts to the gallbladder where it is stored. When it is necessary, the gallbladder contracts and delivers bile through the bile ducts to the small intestine or duodenum. Consequences of the bile flow blockage are jaundice, cholecystitis, anorexia or liver failure amongst others.

First symptoms of cancer are produced at an advanced stage and surgical resection is the only curative treatment. When it is not practicable, non-surgical palliative treatments can only be applied with the aim of bile flow restore and patients' quality of life improvement. These patients' life expectancy is limited so minimally invasive techniques to restore duct patency are preferred, due to short hospital stay and few complications are involved, and thus they represent an improvement for a patient whose life expectancy is short.

<u>Palliative treatment</u>

The treatment consists on the percutaneous introduction of a stent (PTBS: percutaneous transhepatic biliary stenting) in the blocked duct and the expansion thereof, so the duct is dilated and the flow restored. Approved stents for bile system can be metallic, either balloon expandable or self-expanding, or made of plastic. Both of them tend to re-occlude, which involves obstruction effects reappearance; but metal stents need more time than plastic ones. In addition, metal stents can be introduced by a smaller catheter, its internal diameter is larger and they remain fixed at the position they are placed.

Although both stents, BE and SE, can be implanted, SE implantation is much more widespread.

Thus, major late complication of this treatment is re-obstruction when the patient is still alive, which implies stent removal and replacement in case it is made of plastic, or intra-stent stenting when it is metallic.

3.2. Anatomía[21]

3.2.1. Peripheral arteries below the aortic arch or limb arteries:

Aortic artery is the main artery of human body and it origins the rest of the human body arteries comprised at the circulatory system except pulmonary ones. Its function is to transport and distribute oxygen-rich blood to all these arteries.

At the part of the aorta artery known as descending aorta peripheral arteries are originated, which are the focus of performance of **iVolution** self-expanding metallic stent and its equivalent products:

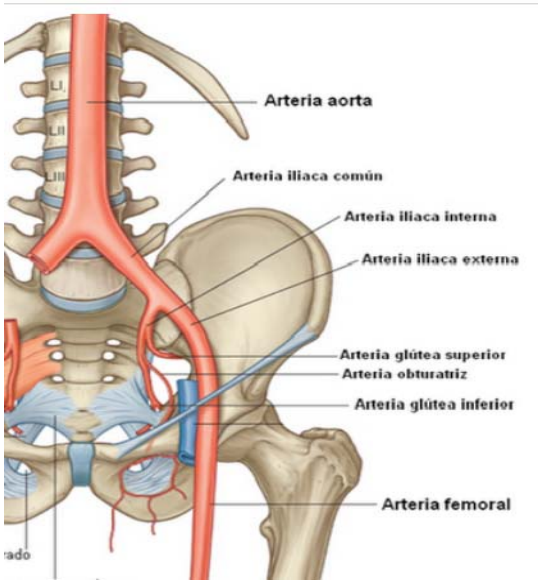


Fig. 13 Aortoiliac zone anatomy

Common or primitive iliac artery (CIA): right and left ones, which are the terminal branches of abdominal aorta and bifurcate in external (EIA) and internal (IIA). Once EIA inguinal ligament, which irrigates viscera and pelvis walls, is overstepped, it becomes femoral artery; which gets blood to lower limbs. IIA, at the same time, is branched in different terminal vessels that supply several pelvic muscles and tissues' structures, gluteal muscles and external genitals.

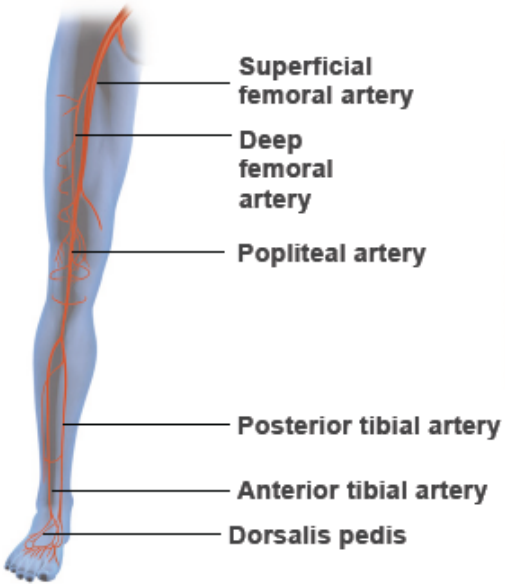
CIA is a high caliber artery whose diameter can be greater than 10mm, although **average diameter is between 7-10mm**, right CIA used to be slightly larger than the left one, **5 and 4 cm** average, respectively (3.5-7.5cm).

EIA, as main prolongation of CIA, is also a high calibre artery whose maximum diameter is approximately 10mm, average oscillates between **6 and 8 mm**, and its length is established at **8-10 cm**.

Finally, **IIA** is smaller than EIA, both in diameter and length. Its average length is estimated to be **4 cm**, while its diameter is about **5-6 mm**.

So, diameters between 5 and 10 mm and length of almost 100 mm are required for stenting this area.

Femoral arteries: They pass near the outer surface of the upper thighs and are divided into smaller branches to provide blood to muscles and superficial tissues in the thighs. They also supply the skin of the groin and lower abdominal wall. One of its branches it the deep femoral artery, the main artery of the thigh since it caters to the juncture of hip, femur and several muscles in the thighs.



The superficial femoral artery (SFA) is the artery most frequently affected by peripheral artery disease (50% of cases) because it is one of the longest vessel surrounded by two important flexion points (hip-knee) so developed lesions are more diffuse and extended. The length of these arteries is related to the patient's height, particularly with the length of the leg from the groin to the knee that can exceed 400 mm, whereas the average diameter of the healthy artery is between 5 and 10 mm.

It is the main focus of SE stents use as it is an unprotected artery subjected to multiple movements.

Fig. 14 Femoropopliteal area anatomy

Popliteal artery: when the femoral artery reaches the space behind the knee, it becomes the popliteal artery (starting in the inner edge of the femur and ending in the soleus ring where it bifurcates into two terminal branches: tibial arteries). The branches of this artery also join a network of nerves in the knee connectors to be helped to have alternative ways in case of arterial obstruction. The average length varies between 17 and 18 cm and the average diameter remains around 7 mm.

In the femoral-popliteal area is where largest lesions occur since it is where the largest vessels of the body are placed. For that reason, sometimes stents larger than 200 mm and with diameters between 5 and 10 mm are required.

Clinical justification for the requested presentation variants

Required lengths are between 40 and 200 mm. Smaller lengths (up to 100-120 mm) are to cover lesions in the iliac or short lesions in femoropopliteal area, while lengths between 100-200 are use only in the femoropopliteal area due to length and forces they are subjected to. In cases of long lesions, the best obtained results are by using a single stent implantation, as stent overlapping increases the probability of losing flexibility in the area. Moreover overlapping stents increases the materials in the area rising the restenosis risk. It shall be kept in mind that a single stent implantation is economically more profitable than implanting several stents in tandem.

In general, if lesions are located in the iliac arteries and are short, BE stent is normally chosen as it has a greater radial strength and this is a protected area that does not receive external impacts. On the other hand long and diffuse lesions in the iliac arteries (where a BE stent will increase stiffness too much) and in femoropopliteal area a SE stent will be chosen because it is more flexible and adapts better to the arteries anatomy.

The diameters of these arteries range from 5 to 10 mm, depending on patient's height, weight and age, so stent diameters between 5 and 10 mm fit the dimensions of the arteries.

3.2.2. Bile ducts:

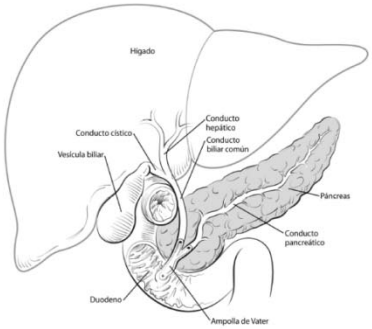


Fig. 15 Bile ducts anatomy

Bile is produced in the liver and it flows to the hepatic duct. At this point, it can go to the common bile duct (choledochal), which flows into the duodenum, or it can go to the gallbladder, for its storage. Simultaneously, when it is required, bile comes out of the gallbladder to the duodenum through the common bile duct. The **bile duct diameter** is between **4 and 6mm**, although it can reach 10mm, and an **average length of 100 mm**.

Clinical justification of the requested references

Although balloon expandable stents can be used as well, especially in short lesions, to treat this area self-expanding stents use is more widespread.

Stent lengths used in this area are mostly in the range between 40 and 100 mm, and stent diameter between 6 and 10 mm, mainly 10 mm.

3.3. Indications for use and contraindications

a. iVolution therapeutic indications

iVolution stent system is indicated for:

- treatment of *de novo or restenotic* atherosclerotic lesions in peripheral arteries located below the aortic arch, mainly iliac, femoral and proximal popliteal arteries.
- Palliation of malignant stenosis affecting bile ducts.

In both cases, artery / duct diameter must be between 5 – 10 mm.

b. iVolution contraindications

iVolution stent system is contraindicated in the following cases:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated
- Patients with clear diagnosed heavy metal allergy, especially to nickel
- Patients with haemorrhagic disorders
- Presence of a recent non dissolved and disorganised thrombus or from embolic material
- Renal failure or contrast media allergy
- Severe ascites
- Threat of vital side branches occlusion

c. Comparison to equivalent products

Equivalent product indications and contraindications, which are compiled in the available instructions for use, are included in annex I. **iVolution** indications and contraindications are equivalent to those products.

Procedure and technique for implantation

Implantation in peripheral arteries

The procedure is conducted by specialist physicians in hemodynamic/radiology rooms or sometimes in an operating room.

The patient is monitored to control its heart rate, blood pressure and pulse.

Before the procedure

The area where the stent will be inserted is cleaned and a local anaesthetic is applied.

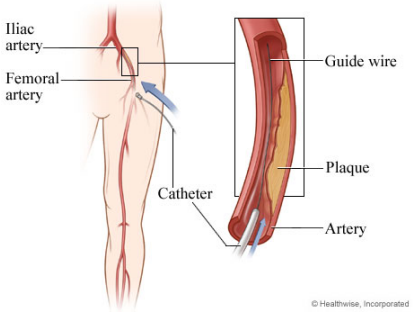
A small puncture is made in that area where a needle is introduced, and a short guide wire is passed through it. The needle is removed and an introducer is inserted, which remains ready to allow access to all used devices during the procedure.

During the procedure

The procedure will begin with an angiography to determine the artery diameter and the exact location and number of lesions in order to avoid unwanted risks: a diagnostic catheter guided by X-ray is introduced and placed in the aortic artery entrance, before iliac arteries bifurcation. The diagnostic catheter tip is left downwards, towards the iliac arteries. Then contrast liquid is injected through this catheter and an angiography of the leg peripheral arteries is taken to determine lesions location.

With this information the implantation starts. Depending on the area and type of lesion, stenting can be preceded by balloon angioplasty for lesion pre-dilatation. The used angioplasty balloon catheter and the stent diameters and lengths depend on the artery diameter and the lesion length.

Before inserting both the balloon catheter or the stent, a 0.035" guide wire is introduced and placed crossing the lesion. The folded devices are inserted through this guide wire until reaching the suitable place using radiopaque markers. Once at its place, the balloon is inflated until reaching the desired dilatation either by plaque compression against the artery walls or plaque rupture, without exceeding in any case the vessel diameter.



The balloon is deflated and removed. The stent pre-mounted on a balloon catheter is introduced. Once placed in the lesion, the sheath that covers the stent is removed and stent is released. The stent remains expanded against the artery walls as a structural support.

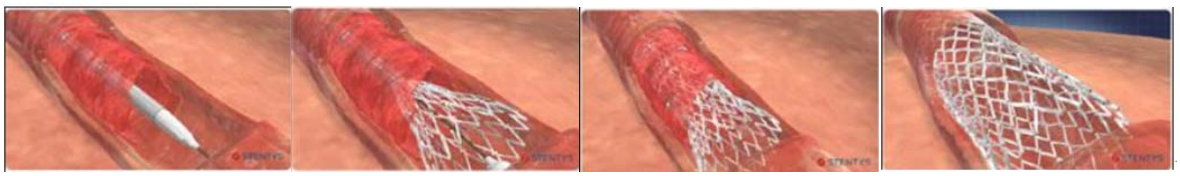


Fig. 16 Se stent release in the artery

Following the deployment of the stent, a balloon is inserted and inflated to help the total stent deployment and apposition against the vessel wall, taking care not to exceed the vessel diameter.

Procedure time is variable depending on lesion complexity.

Generally the patient is awake during the procedure and only mild sedation is administered.

At the end of the procedure, the introducer is removed and pressure applied to stop any bleeding. The opening performed on the skin is covered with a bandage. No sutures are needed.

The patient will remain in the hospital for 1-2 days after the procedure and must follow a treatment with antiplatelet drugs during the time indicated by the doctor.

Implantation in bile ducts

Paliative treatment of malignant stenosis includes three steps:

- Bile drainage
- Balloon dilatation
- Prosthetic implantation

Bile drainage

- The patient is punctured with a needle in a lateral access between the posterior and media axillary lines, accessing the liver
- Contrast liquid is injected to obtain a cholangiography[j], used to choose the access to the bile duct in order to place the drainage catheter
- Through the needle a 0.018" guide is introduced as distal as possible
- The puncture needle is removed, the arterial introducer will remain throughout the procedure. The guide wire is also removed and a 0.035" guide is introduced.
- Over the guide the catheter drainage is introduced and placed in the blockage site
- Once the catheter is properly positioned, the guide is removed and the greatest possible amount of bile aspirated. Subsequently the drainage catheter is removed.

Balloon catheter dilatation / Stent implantation

- 0.035" guide wire is placed again and, a balloon catheter that is inflated until blockage dilatation.
- Afterwards the self expanding stent system is introduced and released in the blocked area in the same way as in previous section, to maintain the duct opened so that bile drain into the intestine.

3.4. Complicaciones durante la Implantación

Severe complications[k] are uncommon, but they can occasionally occur[l]:

At the insertion point:

- Any procedure that involves placing a catheter in a blood vessel implies certain risks. This includes: blood vessel damage, bruising or bleeding in the site where the needle is placed, and infection.

[j] Diagnostic test in which images of the gallbladder and bile ducts are obtained by ducts opacification with contrast medium and viewing through an X-ray screen.

[k] Complications are related to the procedure and the type of device, independently from the used stent platform.

[l] Available instructions for use of the equivalent products are included at annex I of this report. Described complications at these instructions for use meet with the information included in this part and in the **iVolution** instructions for use (see part 6.1 of this dossier).

- A little bruising in the site where the balloon is inserted is common (usually in the groin). In severe cases, this may require a transfusion and/or surgery and a longer stay in hospital.
- Artery block in the insertion site
- A pseudoaneurysm may also occur. One of the reasons that occurs is because difficult puncture with bad compression. It normally closes spontaneously.
- Finally, arteriovenous fistula is the least common complication. Only in case it does not close spontaneously or it may not respond to ultrasound-guided compression, surgical treatment will be required.

Arteries damage:

- There is a small risk of artery damage at the dilatation point (rupture or perforation requiring surgery).
- Abrupt obstruction or blood vessel occlusion / thrombosis / embolization of the stent. This obstruction occurs in the area treated with balloon angioplasty within 24 hours after the procedure. If this occurs, a drug could be administered to the artery to dissolve blood clot. In some cases, an emergency bypass surgery may be necessary. This is the most risky complication, as it may result in a myocardial infarction.
  Rarely, some of the calcareous substances (atheroma) that obstruct the artery may break off and obstruct a blood vessel in other site.
- Low risk of blood clot formation or artery tearing.
- Endoprosthesis migration/bad placement/partial deployment
- Reoclussion of the treated area: restenosis
- Artery spams

Systemic complications[m]:

- Allergic reaction to device materials, used medications in the intervention or contrast material.
- Bleeding due to antiplatelet/anticoagulant medicines.
- Brain attack (ictus/emboli/thrombus): thrombus that may form on the catheters can reach the brain. Administered anticoagulants during the procedure reduce its risk.
- Angina
- Endocarditis
- Arrhythmia
- Hemodynamic deterioration
- Infections
- Hypo-hypertension
- Acute myocardial infarction.
- Death risk.
- Emergency CABG.

[m] Systemic complications are not inherent to the medical device, but may be due to a bad candidate choice.

Bile use specific complications

In case of bile use, in addition to the previously mentioned complications at the insertion point, it can cause:

- Abcess
- Additional intervention due, but not limited to: endoprosthesis migration, misplacement or partial deployment
- Bile duct occlusion/obstruction
- Bile duct perforation
- Cholangitis
- Pancreatitis
- Peritonitis
- Sepsis

4. RELEVANCIA DE LOS DATOS

4.1. Aim

The aim of this bibliographic report is to identify, select, collect and revise relevant clinical trials related to peripheral arteries dilatation located below the aortic arch, stenosed or obstructed, and bile ducts, through PTA with a Nitinol self-expanding stent for 0.035" guide.

It will be demonstrated by literature that the aforementioned device is an already well-known and used product in hemodynamic or radiology interventional rooms that improves the patient's quality of life allowing the blood flow restoration in partial or total obstructed peripheral arteries or narrowed bile ducts due to inoperable malign tumours.

The initial aim is to demonstrate by literature **iVolution**'s technical, clinical and biological equivalence against other self-expanding stent systems for 0.035" guide used in the same type of lesions and which are already approved by a notified organism.

The final aim is to perform an assessment and analysis of the clinical data related to products with marketing approval in order to verify its clinical utility and safety under its intended use conditions, and so, to be able to ensure **iVolution** clinical utility and safety.

4.2. Process methodology and bibliographic search

The followed procedure to identify, select and collect data has been: searching (1) in recognized cardiology journals, (2) conferences and (3) currently marketed metal self-expanding stents.

(i) Data search date: May-June 2013.

(ii) Name of the person who collected the data:[n] Àurea Roca

(iii) Period covered by the search: from the technique origins to present.

(iv) Used sources to identify clinical data in the literature:

a. SciFinder: a powerful global database daily updated. It provides citations and abstracts of journal articles, technical reports, PhD Theses, presentations at conferences, patents, etc. about multiple scientific disciplines.

It comprises Chemical Abstract Service (CAS) databases; which include Chemical Abstracts since 1967, and MEDLINE database from the National Library of Medicine (since 1958). It involves:

- more than 10000 current publication references,
- patents from more than 62 authorities, and
- Scientific advances since the mid-1800s to the present.

In order to make the selection of published articles, the search has been done using keywords related to the product, the procedure and location of the lesion, the search was focused on articles relating to clinical trials and/or the state of the art.

b. Conferences: LINC; PCR and TCT[o]

[n] Degree in Chemistry and documentalist with 6 years of experience in the medical device industry.

[o] Main congresses on interventionist surgery. LINC: Leipzig Interventional Course; TCT: Transcatheter Cardiovascular Therapeutics, USA; PCR: Paris Course Revascularization, Paris.

c. Registered clinical trials databases:

ClinicalTrials.gov (http://clinicaltrials.gov/)

d. Web pages of the companies with equivalent products.

(v) Selection and exclusion criteria

In order to set screening documents criteria, relevant data from recognized scientific publications have been taken. Representative data have been also chosen attempting not to duplicate information, for instance; different studies of the same product with similar results obtained.

From all the consulted bibliography, documents related to clinical trials with nitinol self-expanding stents without any kind of stent coating (pharmacological, passivating) have been selected, both studies using currently marketed products and historical ones that have allowed to establish the treatment validity have been also taken into account. The scope of the relationship between the literature and the specific characteristics of our product has been assessed.

Known companies that are already marketing nitinol self-expanding stent system have been taken into account.

4.2.1. Bibliographic search results

Searches for clinical literature identification have been conducted to identify clinical trials involving nitinol self-expanding stent to treat peripheral arteries and bile ducts, so used keywords have been: stent, nitinol, self-expandable, peripheral, iliac, femoral, femoropopliteal, biliary.

SciFinder conducted searches allow refining searches by document type, so "clinical trial" option has been selected.

Conducted searches have been summarized in the following table.

Database search	Keywords	Initial references	Selection	Final references
1. www.clinicaltrial.gov	Stent nitinol or self-expandable (1)	374	References in which self-expanding stent with balloon is exclusively studied are excluded. Also those that are duplicate in different databases, clinical trials protocols with unpublished results, trials with published results during less than 6 months and studies not including the stablished safety and efficacy parameters.	**13**
2. SciFinder	(1) + iliac	24		
3. Webpage of companies marketing equivalent products	(1) + femoral/popliteal	43		
4. LINC, TCT y PCR	(1) +biliary	79		

Table 5. Summary of conducted searches and obtained results on relevant clinical trials.

5. CLINICAL DATA SUMMARY AND ASSESSMENT

5.1. Clinical data assessment

All collected clinical trials have been carried out by specialist physicians and published on rated journals by prestigious databases, world renowned interventional conferences or WebPages of the companies.

The following criteria have been taken into account for the choice of the clinical trials to be analyzed:

Evaluation criteria on clinical trials suitability

All obtained data correspond to equivalent products to **iVolution**, both in indications for use and features.

All obtained data cases corresponds to device application in lesions whose type, length or diameter respond to **iVolution** use indications. The application procedure thereof is also the same.

Patient's group participating in all the trials is able to represent **iVolution** intended population.

Obtained data comprises enough information to quantify the devices safety and efficacy for the studied type of lesion.

Evaluation criteria to assess clinical trials data contribution

Trials analysed are randomized and non-randomized safety / efficacy studies and registers in which nitinol self-expanding stent for 0.035" guide use is assessed in de novo or restenotic lesions of peripheral arteries located in lower limbs or palliative treatment in bile duct obstructions, the design of which is appropriate in all cases.

Analysed studies have published results with at least 9 months' monitoring, which allows certifying long-term device safety and/or efficacy. Data on technical success, procedure success and device success has been obtained besides adverse effects, death, myocardial infarction, revascularization of the treated lesion and amputation up to 9-12 months' monitoring. Data after a very long time (3-6 years) is also available.

All studies contain statistical analysis which evaluates the results and conclusions noting the limitations that the study could have.

5.2. Relevant data from clinical trials

Trial name	Stent	Type of study Type of lesion	Initial data	Trials, results										Ref.
				Time	Patients	MAE, %	Death, %	MI, %	TLR, %	% amputation	Restenosis, %	Primary patency %	Comments	
CLINICAL RESULTS / ILIAC IMPLANTATION														
MOBILITY	Absolute Pro	Non randomized Prospective Multicenter Safety/efficacy in de novo and restenotic lesions in IC and IE 96.7% patients with calcific.mod.-severe. 3.6mm ≤RVD ≤9.1mm 10mm ≤ lesion length IC or IE ≤110mm 40mm≥total occlusion length IC	151 pac./181 Les. 76.0% IC 24.0% IC+IE/IE Calcification: 33.9% moderate 62.8% severe RVD: 7.6±1.8mm Long les: 28.8±18.9mm	9 months Technical success[p]: 87.3% Proc. success: 85.4% Dev. success.: 96.4%	149	6.1	2.7	1.4	1.4 (CD)	0.7	8.4%	90.9%	The aim is to improve %MAE published in literature (19.5%). It is posible to reduce this value significantly (p<0.0001)	22
BRAVISSIMO	Absolute Pro	Prospective Non randomized Multicenter Iliac lesions type TASC A, B, C & D	TASC A&B-190 pat (40/18%) TASC C&D 135 pat (17/25%) Lesions length: TASC A: 32mm TASC B: 50mm TASC C: 81mm TASC D: 149mm Grafts distribution 147 pat Aboslute Pro 151 pat. Omnilink Elite 27 pat both	12 months								Aboslute Pro: 96% TASC A: 94% TASC B: 96.5% TASC C: 91.3% TASC D: 90.2%	There are no significant statistical differences between TASC groups.	23
				24 months								Total: 87.9% Absolute Pro: 92.1% A-88% B-88.5% C: 91.9 D: 84.8		
ZIPS	Zilver	Pilot study Prospective Non randomized Multicenter Safety and efficacy PTA + stent Up to 2 stenotic lesions (≤10cm) or occluded (≤5 cm) in IC or in IE (de novo or restenotic lesions)	151 pat/177 les RVD: 7.4±1.5mm Long les: 32.9±18.8mm	9 months Proc. success Clinical success in 30 days	146 93.3 94.0	**7.5%**	3.0/5.3	0.0/0.7	0.7/0.7	0.0/0.7		92.9	The aim is to improve MAE in this indication set at 16%. Total MACE is 7.5%, whereas MACE due to the device or procedure is only 2.7%.	24
ORION	Epic	Prospective, Security and efficacy De novo or restenotic lesions in IC or IE. Max 2 stents lesion Lesion length ≤130mm 5mm ≤RVD ≤11mm	125 patients/166 lesions RVD: 7.69±1.79mm Les length: 31.04±22.13mm	12 months Technical success Proc success	113 100% 99.2%	N.D.	1.8 Card: 0.9	N.D.	4.0	0.0	5.6	94.4	The MAE to be achieve based on literature is 17%.	26
CRISP-US	SMART	Randomized Prospective Patients with CLI after PTA not optimal.	203 patients: 102 SMART 101 Wallstent (stainless steel)	9 months Proc. success	98.2/87.5	4.9/5.9	2.0/0.0	N.D.	2.0/4.0	N.D:	3.5/2.7	94.7 /91.1(12 months)		27
Complete SE iliac Registry	Complete SE	Prospective Non randomized Safety / efficacy De novo or restenotic in IC o IE RVD: 4.5-9.5; Leng ≤110mm	158 pat RVD: 7.0±1.1mm Les. length: 40.3±23.5mm	9 months	55	9.4	3.64		3.8	3.9	0.0	100		28
FEMOROPOPLITEA CLINICAL RESULTS														

[p] Dev. success.: cases % in which stent has been unfolded successfully. Tecnical success: cases % in which final residual stenosis is <30%; Procedure success: non complications (death, MI, Amputation, ST, TLR) 2 days after the procedure.

Trial name	Stent	Type of study Type of lesion	Initial data	Studies, results										Ref.
				Time	Patients	MAE, %	Death, %	MI, %	TLR, %	% amputation	Restenosis, %	Primary patency, %	Comments	
RESILIENT	LifeStent	Prospective Randomized 2:1 Multicenter PTA +Stent vs PTA in SFA and/or PPA, de novo or restenotic lesions RVD: 4.0-6.5mm Leng<150mm	206 pat/325 stents : 72 pat PTA/80 lesions 134 pat Stent/153 lesions RVD Stent: 5.2±0.8mm RVD SPTA 5.2±0.9mm Leng les Stent 61.3±42.4mm Leng les PTA 57.0±37.0mm	12 months (PTA/Stent) 24 months 36 months	198 pat	8.2 /6.9 13.4 / 11.1 15.7 /11.1	3.7 /2.8 7.5 / 5.6 9.0 7 6.9	4.5 71.4 6.0/. 5.6 7.5 /5.6	54.2/12.7 58.2/22.2 58.2/24.5 P<0.0001	0 / 4.2 1.5 / 4.2 1.5 / 4.2	N.D.	36.7/81.3 P<0.0001		25
ETAP	LifeStent	Randomized vs. PTA Prospective Popliteal No restrictions in lesions length	246 patients Leng les Stent 41.3±31.3mm Leng les PTA 43.2±28.1mm	12 months	97/97		3.9/2.1 P=0.68	1/0 P=1	15.4/50.4 P=0.0001	0/0 P=1	32.6/45.1 P<0.05	67.4/44.9 P<0.05		30
SUPER SL	S.M.A.R.T. Luminexx	Prospective Randomized TASC C&D in long SFA lesions	96 pat SMART 103 pat Luminexx RVD 5.3±0.67 /5.3±0.5mm Leng 77.8±73.7/65.8±63.2mm	12 months	96/103		2.1/7.8 P=0.103		18.1/24.7 P=0.349	2.1/1.9 P=1.0	34.8 vs44.2 P= 0.310			31
Complete SE SFA Study	Complete SE	Prospective Non randomized RVD: 4.0 -7.0mm Leng: 40-140mm	196 patients	12 months	196	11.0	0.0 (30 days)		8.4	0.5		72.6		32
DURABILITY I	Protégé EverFlex	Non randomized Prospective Efficacy in SFA De novo or restenotic lesions Leng. les max 140mm Max 1 stent	151 RVD 5.5±0.7mm Long les 96.4±26.8mm 50.4% patients stent 150mm	12 months Technical success	134 100%	N.D.	N.D.	N.D.	20.9	N.D.	N.D.	72.2		33
Durability-200	Protégé EverFlex	Lesions TASC C and D in femoropopliteal lesions treated with 200 mm stent.	100 patients/158 stents Leng: 160-450mm 27% popliteal							31.8		64.8		34
DURABILITY II	EverFlex	Prospective Non randomized Multicenter Safety vs efficacy SFA/PPA, large, complex and highly calcified lesions.	287 pat 73% stent >100mm 46.2% stent>150mm Av. length: 89mm	MAE 30d (security) Primary patency (efficacy) 12m			30d- 0%					77.2		35
MISAGO 2	MISAGO	Prospective Non randomized Long-term security in occlusive or stenotic lesions in SFA and popliteal. Stent diameter: 6-7mm Stent length: 40-100mm	744 patients RVD 5.3±0.6mm Leng les 63.9±37.4mm Total occlusions : 37.6% SFA : 80.8% SFA-Popliteals : 11.6% Lesions AB : 87.9%	12 months	671 paci̧t		2.4 Card-0.9		10.1		3.1	87.6		

Table 6. Summary of the obtained results on safety/efficacy clinical trials with nitinol self-expanding peripheral stent system.

6. DATA ANALYSIS

6.1. Background

6.1.1. Revascularization in iliac arteries lesions

Iliac arteries are vessels commonly affected by PAD, which can be treated by means of endovascular revascularization or surgery. In clinical practice, specialists opt for applying minimally invasive techniques, even in complex lesions, as it results in fewer complications (risk of infection or bleeding, mortality, etc) than surgery and the results are comparable. In fact, the best patency results after balloon angioplasty and/or stenting in peripheral arteries in lower limbs are obtained in the common iliac artery and effectiveness diminishes as it descends in the anatomy of this area.

Guidelines written by different experts groups (TASC II; ACC/AHA 2005 and ESC 2010), based on clinical trials and/or clinical experience endorse endovascular treatment choice against surgery for the treatment of lesions located in the protected arteries below the aortic artery due to the better benefit/risk* ratio achieved by the first one:

Class IA: benefit-risk favourable risk in the treatment of claudication in focussed occlusive lesions located in the aortoiliac area

Class IB: endovascular intervention for the treatment of claudication located in the iliac area

Class IB: provisional stenting is indicated in the iliac arteries as salvage therapy in case of non-optimal or failure results after PTA.

Class IB: stenting is effective as primary therapy in the treatment of stenosis and occlusions located in the common iliac artery

Class IC: stenting is effective as primary therapy in the treatment of lesions and occlusions located in the external iliac artery.

This classification reflects the assessment treatments on one side of the risk benefit demonstrated in the clinical practice (I, II, III); and type of clinical evidence that led to that conclusion (Level A, B, C)

Clase I**: reflects Benefit >>> risk. Evidence / general agreement among experts that a treatment / procedure is useful, beneficial and effective. **Procedure / treatment should be performed.

Clase IIa:** Benefit >>> risk. Evidence / opinión is in favor of usefulness / efficacy. Further studies with focused objectives are necessary. **It is reasonable to perform the procedure / treatment.

CLASE IIb:** Benefit ≥ risk. Usefulness / eficacy is less well stablished by evidence / opinión. **Further studies with larger goal and records are necessary.

***LEVEL A:** indicates that the data derived from multiple randomized controlled trials or meta-analyzes*

***LEVEL B:** indicates that data derived from a single randomized controlled clinical trial or non randomized studies.*

***LEVEL C:** indicates that data derived from the consensus of expert opinion, case studies or standards of care.*

Nowadays the procedure success is above 95%, being between 85 and 99% in balloon angioplasty and from 95 to 100% in stenting; and there have been reported competent long-term results for both primary patency (85-90% of stenosis, 60-70% of occlusions in 5 years) and limb salvage[8-9, 12-15, 17].

Historically conducted clinical trials to evaluate stenting suggested that angioplasty followed by stenting results were better. In clinical practice, stenting or not depends on the interventionist, though.

Lesion location/ Type	Trial	Conclusions / Comments	Ref
Aortoiliac occlusive	Metanalysis 6 PTA tests: 1300 pat. 8 stent tests: 800 pat.	Procedure success, similar complications and death rates are similar but slightly better in stenting. Long-term failure (4 years) is lower in the stent group.	38
Iliac TASC A-D	ATP vs ATP/stent 487 lesions 10 years follow-up	In PTA cases, there are differences in restenosis rate depending on the type of lesion. Stent allows obtaining good long-term results in TASC C/D lesions.	39
Iliaca	Dutch Iliac Stent Trial (DIST) Stent vs ATP + optional stent 279	PTA + selective stenting patients' group achieves better results. There are no differences with respect to quality of life. In case of stent, primary patency is about 83% in 6-8 years' monitoring and it is approximately 74% for PTA + optional stent.	40
Aortoiliac TASC C-D	Metanalysis 16 tests: 958 pat. 12 months follow-up	Results of these endovascular lesions treatment are acceptable and patency in primary stenting group is better than in selective implantation one (PTA + optional stent)	41

Table 7. Clinical and metanalysis trials that endorse stenting in all kind of lesions in the aorotoiliac area.

6.1.2. Revascularization in femoropopliteal segment

Lesions in this area are characterized for being large, diffuse and much calcified. This pattern is associated with failure of immediate balloon angioplasty in an elastic recoil, vascular dissection and high grade residual stenosis way.

Early attempts performed two decades ago with balloon expandable stents to avoid the problems of balloon angioplasty especially in complex lesions, did not show the expected results with high rate of in-stent restenosis and stent fractures. Because of this during more than a decade, stenting in this area was only used in case of balloon angioplasty failure.

The introduction of NiTi SE stents has allowed getting better patency rates in comparison with expandable balloon designs, thanks to its special features that enables a good radial strength and a shape recovery after an impact. The results of randomized clinical trials have endorsed the recommendation of nitinol stenting as a first option for treating intermediate-large lesions supporting large stents use. The permeability after 12 months is comparable to surgical revascularization, thus these devices are a good alternative to surgical revascularization especially in large lesions, in candidates with severe cardiovascular comorbidity and without

available saphenous vein graft. It is also the first option in CLI patients in which ulcer healing is more important than long-term patency, and for this they need optimal primary outcomes.

ESC 2010 practice guidelines, supports the use of endovascular revascularization in femoropopliteal lesions with the following recommendations:

Class IC: when revascularization is necessary, it is recommended as first strategy in all TASC A-C femoropopliteal lesions, endovascular revascularization.

Clase IIaA: in TASCB femoropopliteal lesions primary stenting is recommended.

Clase IIbC: Endovascular therapy can be considered as a first choice in TASC D lesions in patients with severe comorbidities and if an experienced interventionist is available.

These recommendations are based on results from randomized studies performed with SE stents that are currently used[q]:

Lesion location/ Type	Trial	Conclusions / Comments	Ref
SFA	ABSOLUTE: RCT Stent (46 pat.) vs. PTA (52 pat.)	Results after 2 years, primary SE stenting involves a morphological benefit and a trend towards clinical benefit BA + stent	42
SFA	RCT Stent (34 pat.) vs. PTA (39 pat.)	SE stent implantation to treat intermediate length lesions in SFA shows greater clinical and morphological benefit.	43
SFA/PPA obstructed lesions	RESILIENT: RCT Stent (134 pat.) vs. PTA (72 pat.)	SE stent implantation in moderate-large lesions is associated with better acute angiographic results and better patency.	44
SFA	FAST: RCT Stent vs PTA	Treated lesion <5cm; there are no significant differences between both techniques in short lesions.	45
SFA/PPA	Metanalysis: 4 RCT Stent vs PTA + optional stenting (Total 627 pat)	Technical success is significantly higher in stenting group (95.8% vs 64.2%). TLR after 12 months is better in the stenting group, although the difference is not statistically significant. Binary restenosis is significantly lower in the stenting group. Similar mortality in both groups.	46

Table 8. Clinical and metanalysis studies that endorse stenting in femoropopliteal lesions with medium-large length.

[q] In scientific literatura there are other publications including metanalysis of ranzomized trials regarding direct stenting vs angioplasty + optional implantation, which results show no benefit in direct stent implantation vs balloon angioplasty + stenting only in case of failure. Those results have not been taken into account as they were based in both BE and SE stent.

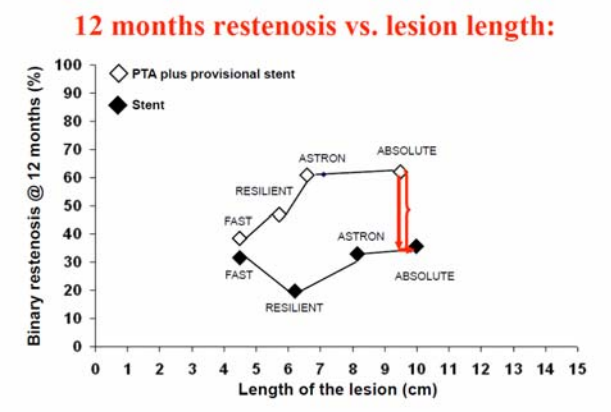


Fig. 17 Stenting vs angioplasty + optional stent benefit, based on lesion length.

The previous graph shows binary restenosis rate obtained by angioplasty balloon revascularization or with SE stenting. Although in all studies the binary restenosis % is lower with stenting, in short lesions the difference between both methods is not significant (FAST, average lesion length 4.5 cm). As the lesion length increases (ASTRON, average length 8.4 cm; ABSOLUTE, average length 13 cm), it is observed that binary restenosis rate increases as well, if balloon is used, while virtually it does not affect the obtained result with SE stent, therefore the difference between both methods is evident.

6.1.3. Restore of bile flow produced by inoperable malign tumors

Tumors incidence at the area affecting bile ducts is increasing and the difficulty of early diagnosis thereof implies that in 90% of cases the only available alternative for the patient is palliative treatment.

PTBS is a well-established technique in clinical practice that allows improving patients' quality of life. Clinical trials state that 90% of bile flow restore improvement is achieved in most of cases, although, this % may be reduced to 53% in case of severe obstructions. Regarding the surgery, this technique reduces by up to 40 % the complication risks, mortality after 30 days decreases and is less costly.

Clinical trials have allowed establishing that short-term results obtained with metallic stents, mainly self-expanding, and plastic stents are similar. However, SE stents present a lower reobstruction risk and consequently at medium-term these are better than plastic one when referring to higher patency, less number of complications and patients' quality of life improvement.

Trial	Conclusions / Comments	Ref
Metanalysis 2436 pat 24 RCT Surgery vs. Plastic or metallic stents	Plastic stents present a lower risk of complications but a higher risk of obstructions than surgery. SE stents results are similar but with a better patency rates than plastic stents.	47
Metanalysis 724 pat. 7 RCT Stents SE vs plastic	Metallic stents with a higher patency rate than plastic stents.	48

Table 9. Metanalysis RCT studies that endorse SE stent implantation to palliate malignant obstructive stenosis in bile ducts.

6.2. Clinical trials analysis performed in aortoiliac area by using currently marketed devices.

6.2.1. Studies characteristics

Studies with published results where currently marketed products' safety and efficacy in **de novo** or **restenotic** lesions located in the **common or external iliac artery** were evaluated have been analyzed. These studies have comparable number of patients, mean diameter of the treated arteries and mean lesion length.

Evaluated devices for the treatment of iliac arteries are: *Absolute Pro* (**MOBILITY** trial); *Zilver* (**ZIPS** trial); *EPIC* (**ORION** trial); *S.M.A.R.T.* (**CRISP-US** trial) and *Complete* (**COMPLETE SE** Iliac trial).

These studies specify lesion size (diameter and length) so used stent diameters and lengths can be easily extrapolated and thus, needed reference items to treat this kind of lesions can be justified. Keep in mind that the length of the stent must always be somewhat longer than lesion length, in order to cover it well, unlike BE stents where stent diameter should be as tight as possible. In SE stents, due to their thermo-mechanical properties that allow it to fit the stent anatomy the chosen diameter must be 1-2 mm greater that the diameter of the artery being treated. The following table provides lesion and possible stents used data in each trial[r]:

TRIAL Name	MOBILITY Absolute Pro	ZIPS Zilver	ORION Epic	CRISP-US S.M.A.R.T.	COMPLETE SE Iliac
Type of study	No RCT	No RCT	No RCT	RCT[s]	No RCT
Patients / Lesions	151/181	151/177	125/166	203/N.D.	50
Ø Treated lesion (mm)	5.8-9.4	5,9-8,9	5,9-8.8	5,77-9,63	5.9-8.1 4.5-9.5
Treated lesion leng. (mm)	9.9-47.7	14,1-51.7	8,91-53.2	7,21-41,99	16.8-63.8 <110
Ø available stents (mm)	7-10	7-10	7-10	7-10	6-10
Avail. lengths stents (mm)	20--80	20-80	20--80	20-80	20-120

Table 10 Summary type of study, lesion and implanted stents dimensions.

The dimensions (diameter and length) of the treated lesions in these studies justify the use of stents in the aortoiliac area up to 100 mm length, and whose diameter is between 5-10 mm.

The results of SE stent implantation in iliac according to the TASC[t] type of lesion, have been assessed in two studies: non-randomized study **BRAVISSIMO** (stent *Absolute Pro*) and **e-MISAGO** register (stent *Misago*). Unlike BRAVISSIMO study (see results in 6.2.3); e-MISAGO register is not focused only on iliac lesions but a register in which all patients are included regardless of the lesion location (iliac, femoral, popliteal), lesion complexity or patient' status. e-MISAGO results will be discussed in Section 6.3.

[r] Available stents size (lengths and diameters) of each company

[s] Randomized study vs steel stent (Wallstent), in this study the results regarding this stent have not been included for not being equivalent. The conclusion indicates that both stents have similar results, but with SMART a greater procedure, success is achieved and its release is more accurate.

[t] Lesions classification in the aortoiliac area, depending on location and complexity. TASC A and B correspond to short isolated stenosis; TASC C and D: stenosis or multiple occlusions.

6.2.2. Safety results

Long-term safety is evaluated by means of a composite rate: MAE (Major Adverse Effect), which is the sum of several factors that are considered as adverse events and which can be modified from one trial to others, but it usually comprises death, myocardial infarction, TLR and amputation rates.

Death, MI and amputation rates are assessed individually as analyzed studies do not define MAE with the same parameters.

Trial	Time	% Mortality	% MI	% Amputation
MOBILITY	9 months	2.7	1.4	0.7
ZIPS[u]	9 months	3.0/5.3	0.0/0.7	0.0/0.7
ORION	12 months	1.8	N.A.	0.0
CRISP-US	9 months	2.0	0.0	2.0
COMPLETE SE Iliac	9 months	3.64 (0.0 caused by proced. or dev)	N.A.	0.0

Table 11 Long-term safety results of clinical trials in aortoiliac area.

Obtained values are low for all parameters; including amputation, which allows achieving one of the main purposes that is limb salvage, proving graft safety.

The aim of the MOBILITY study is that adverse event % (MAE = mortality %, MI %, amputation % and TLR %) was lower than % registered in the literature (19.5%). The obtained results were 6.1%[v], therefore the purpose is widely achieved. Current devices have better clinical outcomes than those reported in the literature.

Conclusions:

High technical success rate obtained in these clinical trials certifies the used devices short-term safety, whereas long-term safety is demonstrated by the low death and amputation rates obtained in 9 months or more time.

6.2.3. Efficacy results

Acute efficacy is measured through the procedure success percentage (safe procedure without complications). In all assessed studies is above 85 %.

In these studies long-term efficacy has been only evaluated from a clinical point of view such as %TLR and/or primary patency which would be associated to in-stent restenosis absence (≥50%), although its definition varies among the different studies.

[u] Indicates % of events related with the procedure or device and % of relative and non-relative events.

[v] This result includes TLR % (according to the MAE definition stablished in this study), not include in analyzed results of table 11.

Trial	% TLR 9 months	% Patency 12 months
MOBILITY	1.4	90.9
ZIPS	0.0/0.7	92.9
ORION	4.0	94.4
CRISP-US	2.0 (TVR)	94.7
COMPLETE SE Iliac	3.9	100 (9months)

Table 12 Long-term safety results of clinical trials in aortoiliac area.

Revascularization rate is very low in all the studies, and patency rate at 12 months is above 90%, which is consistent with the accepted values for these devices in these types of lesions.

The BRAVISSIMO study is a non-randomized trial in which treatment of all types of iliac lesions based on TASC classification have been assessed, both with SE stent (Absolute Pro) and BE stent (Omnilink Elite). This study has only published patency results based on type of lesion and type of stent used.

Lesions		% primary patency	
	Lesion average length (mm)	12 months	24 months
TASC A	32	94.0	88.0
TASC B	50	96.5	88.5
TASC C	81	91.3	91.9
TASC D	149	90.2	84.8
Absolute Pro	147 patients	96.1	92.1
Omnilink Elite	151 patients	91.8	85.2

Table 13 Efficacy results according to TAS type of lesion.

These results are consistent with the type of lesion treated, better patency in less complex lesions. Even though, high patency obtained in lesions that are more complex can certify revascularization effectiveness in all type of lesions in iliac area with both SE stents and BE stents.

There are no statistical differences between the different TASC groups: neither TASC classification or lesion length are, in this case, predictors of restenosis.

If stents are separated by type, patency results got with SE stent are slightly better than BE stent ones.

Conclusions

The high success percentage after performing this procedure can certify the treatment and device acute efficacy.

It is proved that currently available devices on the market have the same or better long-term efficacy than devices that allowed certifying it at the beginning of the technique.

Likewise, technique efficacy is demonstrated regardless of the lesion type, for both simple and complex lesions.

6.3. Clinical trials analysis performed in femoral and femoropopliteal area with current marketed devices.

6.3.1. Study characteristics

The studies are directed basically to the treatment of PPA and/or SFA, since is where most lesions occur in this area. Both lesions, de novo and restenotic, are included.

As shown in the following table, the dimensions of the lesions treated in this studies, justify stent use in femoral and popliteal area with diameters from 5 to 8 mm and lengths between 40 and 200 mm.

Trial Stent	Study type Lesion loc.	Nº patients	Ø lesion (mm)[0] Ø stent (mm)	Leng. lesion (mm)[0] Leng. Stent (mm)
RESILIENT **LifeStent**	RCT[1] vs BA SFA/PPA	SE: 134 BA: 72	5.1±0.8 (4-6.5) 5.0-6.0-7.0	70±43.2 (≤150) 40-150
ETAP **LifeStent**	RCT[2] vs. BA popliteal	SE: 119 BA: 127	N.D. 6.0-10.0[3]	41.3±31.3 40-150
SUPER SL **S.M.A.R.T.** **Luminexx**	RCT TASC C /D SFA	96 103	4.7-5.9 6-10[4] N.D.	80-188 20-150 N.D.
COMPLETE SE SFA **Complete SE**	No RCT SFA/PPA	196	3.9-5.7 (4-7) 5-8	23.1-98.3 (<140) 20-150
DURABILITY I **Everflex**	No RCT Largas SFA	151	4.8-6.2 6-8	69.9-123.2 (<140) 100-150
DURABILITY II **EverFlex**	No RCT SFA/PPA	287	3.9-5.7(4.5-7.5)	64.6-154.6(4-18)
Durability-200 **Everflex 200mm**	No RCT SFA TASC C/D	100	4-6.5	160-450 (> 150) 200
MISAGO 2	No RCT SFA-PPA	744	5.4-7.4 6-7	30-180 40-100
MARIS PLUS	Registro SFA	998	N.D. 6-10[4]	N.D. 40-150[4]

Table 14 Summary study type, lesion and implanted stent dimensions.

[0] Indicates length and diameter of treated lesions based on all lesions average, data in brackets indicates length / diameter stablished as premise in the study.
[1] Randomized study: pre dilatation + stent (BS) vs balloon angioplasty (BA). Average length with stent: 99.2 mm; 1.6 stent/patient
[2] Randomized study POBA + provisional stent vs stent implantation
[3] No available data concerning lesion and stent diameter used in the study, stent diameters match with the ones included in the catalogue.
[4] No available data referring stent diameter and/or length used in the study, provided sizes match with catalogue references.

6.3.2. Safety results

The same parameters included in studies performed in iliac lesions are assessed (see section 6.2.2).

Trial Stent	Time (months)	Death, % SE/BA[1]	MI, % SE/BA	Amputation, % SE/BA
RESILIENT **LifeStent**	12	3.7 /2.8	4.5/1.4	0/4.2
	24	7.5/5.6	6.0/5.6	1.5/4.2
	36	9.0/6.9	7.5/5.6	1.5/4.2
ETAP **LifeStent**	12	3.9/2.1	1/0	3/3
SUPER SL **(SMART/Luminexx)**	12	2.1/7.8	N.D.	2.1/1.9
COMPLETE SE SFA **Complete SE**	12	0.0	N.D.	0.5
DURABILITY II	12	2.9	N.D.	0.7
MISAGO 2 **Misago**	12	2.4	N.D.	3.1
Maris Registry **Maris Plus**	12	0.4	0.0	0.2

Table 15 % Events related to safety parameters

[1] Only two facts are provided in randomized studies (first stent, then balloon), otherwise only fact regarding the corresponding stent is provided. In case of comparing two stents, values are in the same order as they are mentioned.

All studies have low and comparable rates concerning death and amputation in both femoral and popliteal area, and regardless of the lesion complexity. In randomized trials vs balloon angioplasty there is no significant difference between both groups in the safety parameters evaluated (p>0.5).

6.3.3. Efficacy results

The same parameters included in studies performed in iliac lesions are assessed (see section 6.2.3).

Trial Stent	Time (months)	TLR, % SE/BA	Primary patency, % SE/BA[1]
RESILIENT	12	12.7/54.9	81.5/36.7
	24	22.2/58.2	N.A.
	36	24.5/58.2	N.A.
ETAP	12	15.4/50.4	67.4/44.9
SUPER SL	12	18.1/24.7	N.A.
COMPLETE SE	12	9.4	72.6
DURABILITY	12	20.9	72.2
DURABILITY II	12	13.9	86.9
DURABILITY 200	12	31.8	64.8
MISAGO-2	12	8.6	87.6

Trial Stent	Time (months)	TLR, % SE/BA	Primary patency, % SE/BA[1]
MARIS PLUS	12	17.4	N.A.

Table 16 % Events related to efficacy parameters

[1] Only two facts are provided in randomized studies (first stent, then balloon), otherwise only fact regarding the corresponding stent is provided. In case of comparing two stents, values are in the same order as they are mentioned.

In randomized studies vs balloon (RESILIENT and ETAP), best results are obtained with stenting in both revascularization rate and primary patency, revascularization rates decrease and improved patency obtained with stent is significant ($p<0.001$). Therefore, SE stents efficacy is proved for treating the femoral (RESILIENT) and popliteal (ETAP) areas.

Patency results after 12 months are linked to the complexity of the lesion, being the results in TASC A-B lesions good and in TASC C-D acceptable.

Long length stents (150-200 mm) also demonstrate its effectiveness (Durability 200 study) obtaining results of TLR % and patency acceptable considering the complexity of the treated lesions for their length and type (TASC C&D).

6.3.4. e-Misago register results analysis

e-Misago[29] is a register performed with 3400 PAD patients using the efficacy and safety results after 12 months in the first 1000 patients. This register allows to evaluate the efficacy and safety of SE stent in the real world (all kind of patients, all kind of lesions, all locations).

Lesion	Patients Type of lesion TASC, %	Ø lesion (mm) Leng. Lesion (mm)	% Primary patency 12 months	Safety / efficacy results 12 months
Iliaca	346 A-B: 76.2 C-D: 22.8	5.0-7.6 5.2-124.6	98.9	Death: 1.9% Amputation: 0.9% TLR: 4.8%
SFA	525 A-B: 79.1 C-D: 20.9	4.9-6.5 7.2-146.2	90.0	
SFA-popliteal	123 A-B: 61.3 C-D: 38.7	4.9-6.3 12.7-156.3	N.A.	
Popliteal	95 A-B: 62.1 C-D: 37.9	4.8-6.0 45-61.4	N.A.	

Table 17 e-Misago register lesions location and classification (%).

Safety rates are low and comparable to those obtained in both iliac lesions studies and femoropopliteal lesions studies.

Patency values obtained depending on the location of the lesion are high and consistent with the results reported in the literature.

Results of this register endorse the use of stents in daily clinical practice.

6.4. Clinical trials analysis performed to palliate malignant stenosis in bile conducts.

6.4.1. Study characteristics

There are results from a randomized clinical trial performed to evaluate safety and efficacy of a device equivalent to **iVolution**: Zilver. This device is evaluated against Wallstent (SE stent elgiloy).

The dimensions of the stents used in this study correspond to Wallstent stents with 10 mm diameter and Zilver stents with 6 and 10 mm diameter. The stent length is chosen so that they are, at least 10 mm bigger than the obstruction.

6.4.2. Safety results[27]

The device was placed successfully in all patients without misplacement or stent migration. Neither complications related to stent implantation were detected.

	Ø, stent	Patients	Average survival
MOZART I Zilver vs Wallstent	6 mm Zilver	64	132.6 days
	10 mm Zilver	88	186.0 days
	10 mm Wallstent	89	170.0 days

Conclusions

Percutaneous implantation of SE metal stent is a safe procedure with a high % technical success.

6.4.3. Efficacy results

	Ø, stent	Patients	Average days stent patency	Reintervention due to stent occlusion	Average days until occlusion
MOZART I Zilver vs Wallstent	6mm Zilver	64	142.9	39.1%	141.3
	10mm Zilver	88	185.5	23.9%	155.3
	10mm Wallstent	89	186.7	21.4%	141.6

Conclusions

According to Zilver study, stent diameter may be a determining factor in occlusions rate, since in 6 mm group a large number of occlusions occurred, whereas there were no significant differences between the two groups with 10 mm diameter. Although life expectancy for these patients is very limited due to the advanced status of the disease, SE stent direct implantation as a palliative treatment of bile duct obstruction is an effective treatment that improves patients' quality of life.

6.5. Product information and instructions for use

iVolution is a nitinol self-expanding stent for 0.035" guide, indicated for increasing internal diameter in case of "de novo" or restenotic lesions located at the peripheral arteries and for palliation of malignant tumors located in bile ducts with nominal diameter between 4.5 and 9.5 mm in both cases.

The system, its requested references, materials and indications for use are analogue to those of the marketed devices with CE mark that have been presented at the clinical trial bibliographic research. *(Annex I).*

Used materials in **iVolution** manufacturing are medical grade and are currently used in analogue marketed devices manufacturing.

Requested references, indications for use and contraindications agree with the used references in clinical trials and with the claimed inclusion/exclusion data thereof.

7. CONCLUSIONS

The endovascular revascularization by ATP is a minimally invasive therapy to treat PAD patients suffering IC or ICE. The aim of PAD treatment in peripheral arteries in lower limbs is to eliminate symptoms, improve patients' quality of life and limb salvage in most severe cases. In case of bile ducts obstruction caused by non-operable malignant tumors, the objective is to restore bile flow and improve patients' quality of life.

The choice of treatment in both cases depends on the expected risk-benefit based on the type of lesion and patients conditions.

Since the origins, the technology has evolved rapidly and cases that are more complex can be treated. Initially, the technique consisting on balloon angioplasty, offered as major advantages a low rate of complications (0.5-4%), a high technical success even in long occlusions and a clinical acceptable short-term results.

Long-term clinical results of balloon angioplasty, were not so good due to the high rate of restenosis that in most cases lead to a reintervention of the treated lesion. The introduction of self-expanding stents has influenced in the long-term results increasing the patency rates. Along with its shape memory properties and superelasticity, these NiTi devices provide a good radial strength and shape recovery after crushing, making them indicated in unprotected lesions.

In iliac arteries, metallic stent implants have been used for approx. two decades. Both literature and clinical practice support endovascular treatment with these devices, as a first choice over traditional surgical bypass treatment for almost all patients including obstructions, large and complex lesions, due to benefit/risk balance is clearly favorable. The technique followed is primary stenting or balloon angioplasty followed by stenting. This balance is positive both short and long term thanks to a high technical and clinical success, a low risk of mortality, high rate of affected limb salvage and long term good patency. In this area the results between BE stents and SE stents are comparable, the choice depends on the artery, length and type of lesion; being SE stents more used in external iliac, tortuous vessels and large lesions.

The introduction of self-expanding stents for treating the femoropopliteal area has allowed improving the long-term patency. These material properties enable placing them in superficial areas submitted to high flexions with a low stent fracture rate. Improved stent design and long length, up to 200 mm, comercialization to treat this area, have also allowed improving efficacy long-term results even in complex lesions.

In short lesions there is no significant benefit between direct stent implantation vs balloon angioplasty + optional stent implantation. Nevertheless, direct SE stenting shows a clear improvement in long lesions and is an effective alternative to surgical revascularization especially in patient with high comorbidities or without grafts on the saphenous vein.

In bile ducts, the choice of minimally invasive techniques implies minimal complications caused by the procedure and a rapid improvement in patients' quality of life for those patients with a prognosis of short-term survival due to the disease.

The diversity of dimensions in lower limb arteries, lesions in iliac are usually short and short stents with large diameter are required, while in femoropopliteal lesions long stents with small diameters are usually used; is reflected in the diameters and lengths of stents marketed (see *Annex I*). This variety of marketed stents dimensions is in line with treated lesions dimensions included in clinical trials and with requested references for **iVolution**.

The results of the evaluated and analyzed clinical trials, conducted with nitinol self-expanding stents equivalent to **iVolution** in stenotic and restenotic lesions located in iliac and femoropopliteal arteries, certify that these devices are both safe, with low mortality and limb amputation rates, and effective with high rates of long-term patency in all kind of lesions, according to TASC classification.

SE stents are also safe and effective in restoring bile flow in patients with inoperable malignant tumors that cause bile duct blockage, improving the quality of life within the limitation of the disease.

References available in the market and requested for **iVolution** meet the criteria required by treated arteries anatomy and lesions characteristics that often take place in this area.

iVolution does not present any scientific novelty compared to already marketed devices with certification and CE approval, that are commonly used in hemodynamic rooms around the world in order to dilate de novo or restenotic lesions in iliac and femoropopliteal peripheral arteries.

As proved in this report, self-expanding stent systems for 0.035" guide manufactured from NiTi are useful, efficient and secure devices, and there is a clinical, technical and biologic equivalence between **iVolution** and CE/FDA marked devices.

For the aforementioned reasons, it can be concluded that percutaneous revascularization in peripheral arteries below the aorta and the obstruction of bile ducts caused by malignant tumors through percutaneous implantation of a self-expanding stent has a clear benefit of use with minimal risk to the patient.

ACRONYMS AND ABBREVIATIONS

CIA: common iliac artery

EIA: external iliac artery

IIA: internal iliac artery

PTA: Percutaneous Transluminal Angioplasty

BA: Balloon Angioplasty

BMS: Bare Metal Stent

IC: Intermittent Claudication

PVD: Peripheral Vascular Disease

ALI: Acute Limb Ischemia

CLI: Critical Limb Ischemia

LL: Late Loss

MAE: Major Advers Events

MI: Myocardial Infarct

OTW: Over The Wire

PTBS: Percutaneous Transhepatic Biliary Stenting

TLR: Target Lesion Revascularization

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ANNEX I

AVAILABLE REFERENCEES OF SELF-EXPANDING STENTS FOR PERIPHERAL ARTERIES TREATMENT

Ø (mm)	20	30	40	50	60	70	80	90	100	120	150	170	200
5,00	AP	AP	AP		AP		AP		AP	AP	AP		
	CM	CM	CM		CM		CM		CM	CM	CM		
			iV		iV		iV		iV		iV		iV
6,00	AP	AP	AP		AP		AP		AP	AP	AP		
	EP	EP	EP	EP	EP	EP	EP		EP	EP			
	SM	SM	SM		SM		SM		SM	SM	SM		
	Z6	Z6	Z6		Z6		Z6						
	LS	LS	LS		LS		LS		LS		LS	LS	
	EF	EF	EF		EF		EF		EF	EF	EF		EF
		MP	MP		MP		MP		MP	MP	MP		
	CM		CM		CM		CM		CM	CM	CM		
			MS		MS		MS		MS	MS	MS		
			iV		iV		iV		iV		iV		iV
7,00	AP	AP	AP		AP		AP		AP	AP	AP		
	EP	EP	EP	EP	EP	EP	EP		EP	EP			
	SM	SM	SM		SM		SM		SM	SM	SM		
	Z6	Z6	Z6		Z6		Z6						
	LS	LS	LS		LS		LS		LS		LS	LS	
	EF	EF	EF		EF		EF		EF	EF	EF		EF
		MP	MP		MP		MP		MP	MP	MP		
			MS		MS		MS		MS	MS	MS		
	CM		CM		CM		CM		CM	CM	CM		
			iV		iV		iV		iV		iV		iV
8,00	AP	AP	AP		AP		AP		AP	AP	AP		
	EP	EP	EP	EP	EP	EP	EP		EP	EP			
	SM	SM	SM		SM		SM		SM	SM	SM		
	Z6	Z6	Z6		Z6		Z6						
	LS	LS	LS		LS		LS						
	EF	EF	EF		EF		EF		EF	EF	EF		EF
		MP	MP		MP		MP		MP	MP	MP		
			MS		MS		MS		MS				
	CM		CM		CM		CM		CM	CM	CM		
			iV		iV		iV		iV		iV		
9,00	AP	AP	AP		AP		AP		AP				
	EP	EP	EP	EP	EP	EP	EP		EP				
	SM	SM	SM		SM								
	Z6	Z6	Z6		Z6		Z6						
	LS	LS	LS		LS		LS						
		MP	MP		MP		MP		MP				
			MS		MS								
	CM		CM		CM		CM						
			iV		iV		iV		iV				
10,00	AP	AP	AP		AP		AP		AP				
	EP	EP	EP	EP	EP	EP	EP		EP				
	SM	SM	SM		SM								
	Z6	Z6	Z6		Z6		Z6						
	LS	LS	LS		LS		LS	LS					
		MP	MP		MP		MP		MP				
			MS		MS								
	CM		CM		CM		CM						
			iV		iV		iV		iV				
12,00	EP	EP	EP	EP	EP	EP	EP		EP				

Abreviatura	Referencia
AP	AbsolutePro (Abbott)
EC	EPIC (Boston Sci)
SM	SMART (Cordis)
Z6	Zilver 635 (Cook)
LS	LifeStent (CR Bard)
EF	EverFlex (Covidien)
MP	MariPlus (Medtronic)
CM	Complete SE (Medtronic)
MS	Misago (Terumo)
iV	iVolution (LVD Biotech)