Engineering aspects of stents design and their translation into clinical practice

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Summary. The implantation of coronary stents is a relevant part of interventional procedures for percutaneous revascularization. The wide acceptance of coronary stenting was based on the results of two highly significant trials which have shown the superiority of stenting over balloon angioplasty in terms of reduction of angiographic restenosis and need for repeated intervention in focal lesions and large coronary arteries. Since then, the growing use of stent market was impressive. A rapidly increasing number of different stent type with different material and designs has been introduced in the market both for bare metal stent and drug eluting stent. This review will summarize the different components of stent design that are important in term of biological response of the arterial wall and clinical outcome. In addition, new stent platforms, mainly represented by the biodegradable stent will be shortly reviewed since it may provide in the near future a more "physiological" answer to stent implantation, reducing vascular injury and accelerating vessel healing with consequent improving in clinical outcome.

Key words: coronary artery disease, stent technology, drug-eluting stents, percutaneous intervention.

Riassunto *(Caratteristiche tecniche del disegno degli stent e risvolti correlati nella pratica clinica)*. L'impianto di stent nell'albero coronarico è una delle procedure più utilizzate nel campo della rivascolarizzazione meccanica percutanea della malattia aterosclerotica coronarica. L'ampia accettazione di questi dispositivi è venuta dai risultati di due *trials* clinici che hanno mostrato come l'utilizzo dello stent in arterie di grosso calibro ed in lesioni focali sia significativamente superiore alla sola angioplastica con palloncino in termini di riduzione della restenosi angiografica e di necessità di ripetere un'ulteriore procedura a distanza. Da allora la crescita dello stent nel campo della cardiologia interventistica è stato esponenziale. Un numero sempre crescente di differenti tipi di stent con diverso disegno e materiali utilizzati per la costruzione sono stati introdotti sia per gli stent metallici tradizionali che più recentemente per gli stent medicati. Questo lavoro vuole riassumere dal punto di vista ingegneristico i differenti componenti e materiali che caratterizzano il disegno dello stent e dal punto di vista clinico come un disegno dello stent "ideale" possa influenzare la risposta biologica della parete vasale ed il risultato clinico. In ultimo saranno brevemente rivisti le nuove piattaforme di stent ed in particolari gli stent biodegradabili, che in un futuro ormai prossimo saranno introdotti nel mercato con la speranza che il ridotto danno vascolare e l'aumentata risposta cicatriziale della parete che caratterizza questi stent di ultima generazione si possa tradurre in un maggiore beneficio clinico nei pazienti che si sottopongono alle procedure di rivascolarizzazione percutanea.

Parole chiave: malattia aterosclerotica coronarica, aspetti tecnologici degli stent, stent medicati, interventistica percutanea.

INTRODUCTION

The implantation of coronary stents is an integral part of most interventional procedures for percutaneous revascularization. The wide acceptance of coronary stenting was based on the results of the BElgian NEtherlands STENT (BENESTENT) [1] and the STent REStenosis Study (STRESS) [2] trials, which showed the superiority of stenting over balloon angioplasty in terms of reduction of angiographic restenosis and need for repeated intervention in focal lesions and large coronary arteries. Since then, the growing use of stents in ever more complex lesions and patients [3] has stimulated the introduction of a rapidly increasing number of different stent designs. Among the reasons why different designs have been proposed, there are concepts of physiological mechanisms: indeed a primary concern of stent development is the need to reduce device pro-

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files and to increase flexibility to facilitate safe delivery. A major caveat, almost completely resolved by double oral antiplatelet therapy, regards the possible occurrence of thrombotic episodes, hours to days after stent deployment, leading to relevant clinical events (sudden cardiac death or acute myocardial infarction). Other important issues are lesion coverage, to avoid plaque prolapse, and radial support, to prevent elastic recoil of the artery. Furthermore, the possibility to easily access side branches through the stent struts of a deployed stent in bifurcation lesions has progressively gained importance. Finally, radiological visibility is another important element to optimize the clinical benefits of a stent.

In clinical practice, the operator must decide which stent is most appropriate for the patient, and even more importantly, for the lesion that is going to be treated.

General characteristics pertaining to the "ideal" stent are reported in the following:

- flexible;
- trackable;
- low unconstrained profile;
- radio-opaque;
- thromboresistant;
- biocompatible;
- reliably expandable;
- high radial strength;
- circumferential coverage;
- low surface area;
- hydrodynamic compatible.

TYPES OF STENTS

Stents can be classified according to several engineering variables [4] which influence stent characteristics, biocompatibility and outcome *(Figure 1)*:

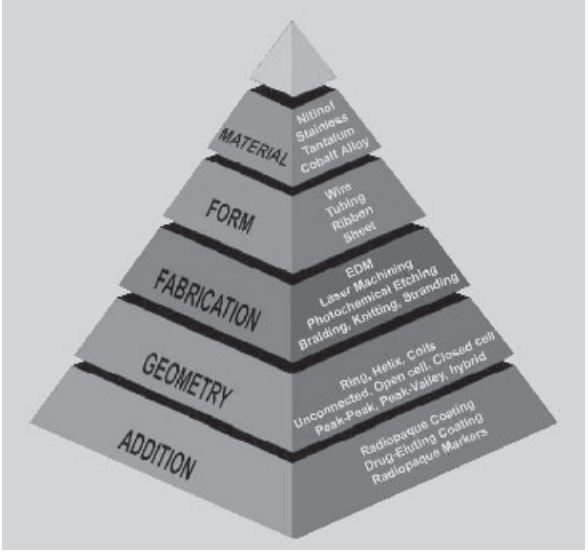

Fig. 1 | *Stent design pyramid with different material and construction characteristics.*

- mechanism of expansion (self-expanding or balloon-expandable);
- materials (stainless steel, cobalt-based alloy, tantalum, nitinol, inert coating, active coating, or biodegradable);
- forms (sheet, wire or tube);
- manufacturing methods (laser cut, water-jet cutting, photo-etching, etc.);
- geometrical configurations/design (mesh structure, coil, slotted tube, ring, multi-design, or custom design);
- addition to stent (grafts, radio-opaque markers, coatings, etc.).

MECHANISM OF EXPANSION

In general stents can be divided on the basis of the mechanism of expansion into two major types: self-expanding stents and balloon-expandable stents. Balloon-expandable stents are made from materials that can be plastically deformed through the inflation of a balloon; after the balloon is deflated the stent remains in its expanded shape, except for a slight recoil caused by the elastic portion of the deformation. Self-expanding stents, on the other hand, are manufactured in the expanded shape, then compressed and constrained in a delivery system. Upon release from the delivery system they spring back, *i.e.* self-expand, to the preset diameter.

MATERIALS

Materials for metallic balloon-expandable or self-expanding stents must exhibit excellent corrosion resistance and biocompatibility *(Table 1)*; they should be adequately radio-opaque, and create minimal artifacts during MRI. For balloon-expandable stents the ideal material for construction should have a low yield stress (to make it deformable at manageable balloon pressures), high elastic modulus (for minimal recoil), and work hardened through expansion for high strength.

Balloon-expandable stents are manufactured in the "small diameter", *i.e.* deliverable configuration, pre-mounted over a balloon, and they are deployed by balloon inflation (that permits them to obtain their expanded shape) at the target site inside the vessel. On the contrary, the function of self-expanding stents is based on the elastic properties of the material used. Ideally, the material should have a low elastic modulus and a high yield stress for large elastic strains. Alternatively, the shape-memory effect of nitinol can be utilized. Here, large strains can be achieved either super-elastically, or via the thermal memory of the material. The most widely used material for stents is stainless steel, typically 316L, a particularly corrosion-resistant material with low carbon content and additions of molybdenum and niobium. In its fully annealed condition, stainless steel is easily deformable and, therefore, the standard material for balloon-expandable stents.

Table 1 | *Overview of materials used in balloon-expandable and self-expandable stents manufacture, different stent forms, stent fabrication, stent geometry and addictions*

Materials		**Balloon expandable stents**		- Stainless steel 316L (vast majority) - Tantalum - Martensitic nitinol - Platinum iridium - Polymers - Niobium alloy - Cobalt alloy
		Self-expanding stents		- Superelsatic nickel-titanium nitinol (majority) - Cobalt alloy - Full hard (stainless steel)
Form		**Wire**		- Wallstent (cobalt alloy) - Bridge, S7, S660, (stainless steel, welded rings) - Angiostent (platinum iridium) - Strecker (tantalum) - Expander (nitinol)
		Tube		- Vast majority
		Sheet		- NIR (steinless steel) - ZR1 (stainless steel) - GRII (stainless steel) - Endotex (nitinol)
		Ribbon		- Horizon prostatic (nitinol) - EndoCoil, esophacoil (nitinol)
Fabrication		**Laser cutting**		- Vast majority
		Photochemical etching		- NIR - Nitinol sheet - Coiled nitinol framework, ePTFE covering
		Braiding		- Wallstent (cobalt alloy)
		Knitting		- Streaker (tantalum)
		Vapor deposition		
		Water jet		- SCS, SCS-Z stent
Geometry	**Slotted Tube / Coil**	**Helical spiral**		- Periodic peak to peak connections - No/minimal connections - Axial spine - Integral with graft
		Woven		- Braided - Knitted
		Individual rings		
		Sequential rings	**Open cells**	- Peak-peak connections - Peak-valley connections - Midstruts connections - Hybrids - Other
			Closed cells	- Regular peak-peak connection - Non-flex connector - Flex connector - Combined connector - Hybrid
		Coil		
Addictions		**Covering**		- WallGraft; coiled nitinol framework, ePTFE covering
		Radiopaque markers		- Tabs: (tantalum end, gold end, platinum within strut) - Sleeve:(gold, platinum) - Welded:(tantalum)
		Radiopaque coating		- Gold, silicone carbide over gold
		Biocompatibility coatings		- Tantalum coating, phosphorylcholine, carbon coating, silicone carbide
		Drug eluting coating		- Rapamicyne, paclitaxel

In its full-hard condition, on the other hand, it exhibits enough elasticity for certain self-expanding stent designs. Alternative materials for balloon-expandable stents are tantalum, platinum alloys, niobium alloys and cobalt alloys. They are used for their better radio-opacity, higher strength, improved corrosion resistance, better MR compatibility or the combination of all these features. Better radio-opacity and higher strength allow the design of stents with smaller delivery profiles. As mentioned above, materials for self-expanding stents should exhibit large elastic strains. The most widely used material is nitinol, a nickel-titanium alloy that can recover elastic deformation of up to 10%. This unusually wide elastic range, commonly known as super-elasticity, is the result of a thermo-elastic martensitic transformation. The limited elastic range of more conventional materials, such as stainless steel or certain cobalt-based alloys, also limits design options.

RAW MATERIAL FORMS

Stents can be made from sheet, wire (round or flat) or tubing *(Table 1)*. A large majority of balloon-expandable and self-expanding stents are made from wire or tubing. A few exceptions are made from sheet metal. Stents made from sheet metal have to be rolled up to a tubular configuration after the pattern has been created.

FABRICATION METHODS

The choice of fabrication method depends mainly on the raw material form used *(Table 1)*. Wires can be formed into stents in various ways using conventional wire-forming techniques, such as coiling, braiding or knitting. The simplest shape for a wire stent is a coil. All coil stents marketed today are made from nitinol and are self-expanding. Welding at specific locations after wire-forming produces closed-cell wire stents or increases longitudinal stability. The most common wire-based self-expanding stent is the WallStent (Boston Scientific), a braided design using multiple elgiloy (cobalt-based alloy) wires. This allows continuous production, *i.e.* the stents can be cut to a specific length from a long wire-mesh "hose". Knitting allows the production of flexible balloon-expandable and self-expanding wire stents. The vast majority of coronary stents, and probably the majority of peripheral vascular stents, are produced by laser cutting from tubing. Typically, Nd: YAG lasers are used, allowing kerf widths of < 20 μm. Intricate patterns can be produced using tube sizes from 0.5 mm diameter. Balloon-expandable stents are cut in the crimped or near-crimped condition, and only require post-cutting deburring and surface treatment, typically electro-polishing. They are marketed as balloon-mounted, or -unmounted for hand-crimping. Self-expanding nitinol stents, on the other hand, can be cut either in the "small" configuration, requiring post-cutting expansion and shape-setting, or in the expanded condition. In either case, they have to be deburred and polished. Self-expanding stents have to be constrained in the delivery system and, therefore, are not available in an "unmounted" configuration. Laser cutting produces a heat-affected zone along the cut edge, which has to be removed for better performance. A cutting method that does not produce a heat-affected zone is water-jet cutting. A focused jet of water with some abrasive additives is used to cut the pattern instead of a laser beam. Another interesting manufacturing method is photochemical etching. Although this method is being used to produce stents from tubing, its real benefit is in sheet processing, when large numbers of parts can be processed in a single run.

GEOMETRY

Early designs were generally classified as either slotted tube geometries, such as the Palmaz stents, or coil geometries, such as the Gianturco-Roubin Flex stent. While slotted-tube type designs had excellent radial strength, they lacked flexibility. The opposite occurred for coil designs. The subsequent evolution of stent design yielded to the development of a rich variety of stent geometries, which can be classified into five main high-level categories: coil, helical spiral, woven, individual rings or sequential rings *(Table 1)*:

Coil

Most common in non-vascular applications, as the coil design allows for retrievability after implantation. These designs are extremely flexible, but their strength is limited and their low expansion ratio results in high profile devices.

Helical spiral

These designs are generally promoted for their flexibility. With no or minimal internal connection points, they are very flexible, but also lack longitudinal support. As such, they can be subject to elongation or compression during delivery and deployment and, consequently, irregular cell size formation. With internal connection points, some flexibility is sacrificed in order to obtain a higher longitudinal stability and additional control over cell size.

Woven

This category includes a variety of designs constructed from one or more strands of wire. Braided designs are often used for self-expanding structures. While these designs offer excellent coverage, they typically shorten substantially during expansion. The radial strength of such a braided structure is also highly dependent on the axial fixation of its ends.

Individual rings

Single "Z"-shaped rings are commonly used to support grafts or similar prostheses; they can be in-

dividually sutured or otherwise attached to the graft material during manufacture. These structures are not typically used alone as vascular stents.

Sequential rings

This category describes stents comprised of a series of expandable Z-shaped structural elements (known as "struts") joined by connecting elements (known as "bridges", "hinges", or "nodes"). This type of construction accounts for the majority of commercially available stents. This category can be further refined according to the manner in which the structural elements are connected, and the nature of the resulting cells:

- *regular connection* describes bridging elements that include connections to every inflection point around the circumference of a structural member;
- *periodic connection* describes bridging elements that include connections to a subset of the inflection points around the circumference of a structural member. Connected inflection points alternate with unconnected inflection points in some defined pattern;
- *peak-peak connection* or *peak-valley connection* are terms used to describe the locations where the bridging elements join adjacent structural members. Peak-peak bridging elements join the outer radii, and peak-valley bridging elements join outer radii to inner radii of the inflection points of adjacent structural members.

Closed cell

This describes sequential ring construction wherein all internal inflection points of the structural members are connected by bridging elements. Such a condition is typically only possible with regular peak-to-peak connections. Early slotted-tube type designs, such as the Palmaz stent, were strong, but inflexible. Later designs, such as the NIR stent, improved upon this concept by adding a flex-connector. These U-, V-, S-, or N-shaped elements plastically deform during bending, allowing adjacent structural members to separate or nest together, to more easily accommodate changes in shape. The primary advantages of closed-cell designs are optimal scaffolding and a uniform surface, regardless of the degree of bending. However, these advantages result in a structure that is typically less flexible than a similar open-cell design.

Open cell

This category describes construction wherein some or all the internal inflection points of the structural members are not connected by bridging elements. This allows periodic peak-to-peak connections, peak-to-valley connections, and mid-strut to mid-strut connections, as well as innumerable hybrid combinations. In open-cell designs, the unconnected structural elements contribute to longitudinal flexibility. Periodically connected peak-to-peak designs are common among self-expanding stents, such as the SMART stent, as well as balloon-expandable stents, such as the AVE S7. The peak-to-valley connection of the ACS Multilink virtually eliminates foreshortening and assures that adjacent structural peaks are aligned peak-to-valley throughout the expansion range of the stent, optimizing scaffolding characteristics. However, the peak-to-valley connectors take up material that could otherwise be used for structural members. Consequently, structures with this type of peak-to-valley connection are generally not as strong as similar structures with peak-to-peak connections. While these peak-to-peak and peak-to-valley connections are the most common, there are also examples of other variations, such as the BeStent, which feature mid-strut to mid-strut connectors.

ADDITIONS

Radio-opacity enhancements

Stents made from stainless steel or nitinol are sometimes hard to see fluoroscopically, particularly if they are small and/or have thin and narrow struts. To improve X-ray visibility, markers are often attached to the stents. These additions are typically made from gold, platinum or tantalum, and can either be sleeves crimped around a strut, rivets coined into tabs at the end of the stent or integrated in a strut, or welded-on tabs (*Table 1*). Electroplating (with gold) is also being used to enhance X-ray visibility.

Coatings

Several active compounds have been used to cover stents in order to increase their biocompatibility and to possibly interact with different cells and molecules present in the blood and in the vessel wall. The rationale was to obtain a significant reduction in the activity of these cells and molecules, enhancing the safety and effectiveness of stents. Among the different compounds tested, *heparin* was one of the first. Its mode of action is to reduce the coagulation cascade (and thus possibly the thrombogenic risk) after the deployment of a stent. Other coatings, such as *phosphorylcoline* and *silicon-carbide* have been used in order to reduce platelet activation and interaction, thus possibly controlling their adhesion to the stent struts during the acute phase of stent re-endothelization.

Passive coverage has been also shown to be useful. Indeed, covered stents have been created, in which a PTFE layer was put between two stents (Jostent graft, Jomed) or one stent was covered by a inner and an outer layer of PTFE (Symbiot, Boston Scientific) In both cases the coverage of the lesion is complete (*i.e.* the stent/artery ratio is 100%), thus the PTFE layer may "entrap" all the material possibly protruding from the stent struts.

Drugs

Optimized drug delivery stents require a combination of refined metal stent designs and drug delivery

technology. The combination of highly refined metallic-stent designs and polymer materials has been the standard approach in several drug-eluting stent (DES) initiatives. Stent-based drug delivery has been accomplished by 3 distinct mechanisms:

- bio-absorbable polymeric stents can be loaded with a drug that is eluted slowly over time;
- metal stents can have a drug bound to their surface or embedded within macroscopic fenestrations or microscopic nano-pores, thus providing more rapid drug delivery;
- metal stents coated with an outer layer of polymer (bio-absorbable or non-bio-absorbable) can be drug-loaded, thus providing more controlled and sustained drug delivery, which might allow more effective drug-tissue interactions.

Recent experimental data [5] suggest that stent-strut configuration directly determines the pattern and degree of drug delivery achieved by the stent. After deployment of even highly soluble and rapidly diffusing drugs, homogeneous drug delivery throughout the vessel with uniform concentration at various depths of the vessel wall is not achieved. Therefore stent designs that maintain regular strut spacing despite expansion in various anatomical circumstances will provide the most regular and predictable drug delivery. For drugs with wide toxic-to-therapeutic window, such as members of the sirolimus family, regularity of strut spacing might be less important and adequate doses can be applied to the stent surface so that, despite broad variability in the location of delivery, an adequate dose is uniformly released. On the other hand, drugs with narrower toxic-to-therapeutic ratios, such as paclitaxel, might suffer from inadequate dosing at sites where stent struts lie far apart and possibly from over-therapeutic or toxic dosing at sites where stent struts bunch together owing to vessel curvature or asymmetric expansion.

Among the different DES currently approved in USA and Europe, the *Cypher*™ (sirolimus-eluting) stent from CordisCorporation, Johnson & Johnson (Miami Lakes, FL, USA) and the *Taxus*™ (paclitaxel-eluting) stent from Boston Scientific (Natick, MA, USA) have a relatively similar platform: both have sequential ring design with inert and non-erodible polymeric coatings. The main difference between the two stents is the drug: sirolimus, along with its analogues, was primarily developed to suppress transplant rejection, whereas paclitaxel is a widely used cancer chemotherapeutic agent, whose window between efficacy and toxicity may be narrower in comparison to sirolimus. Several other "next-generation" DES are currently under investigation. The *Endeavor*™ stent from Medtronic (Medtronic Inc., Minneapolis, MN, USA), which uses the non-erodible polymer phosphorylcholine to release the sirolimus analogue ABT-578, will be the first DES to use a non-stainless steel alloy as the foundation for a polymer-coated DES, *i.e.* the thin-strut cobalt-chromium alloy (Driver). A novel approach is constituted by the *XIENCE V*™ stent from Abbott, Illinois, USA, which uses a highly deliverable metallic stent platform and a bio-stable acrylic coating for drug encapsulation and release, with the potential benefit of the restriction to the abluminal (outer) surface of each strut (so that drug and polymer are not exposed to the flowing blood in the arterial lumen) and the eventual degradation of the polymer to carbon dioxide and water, which are free of any toxic byproducts. Thus, the stent design guarantees the complete elimination of the drug from the stent over a finite period of time without drug retention, potential cause of late adverse events months to years after implantation.

IMPACT OF STENT DESIGN ON CLINICAL OUTCOME

Lesion-related (vessel diameter and length, ostial or bifurcational position, implantation techniques used, IVUS-guidance), and patient-related variables (diabetes, clinical presentation) may be all considered major determinants of acute, subacute and long-term clinical outcomes. Despite the fact that stent design has been shown to be relevant in influencing neointimal hyperplasia in different animal models, in humans the vascular wall response to different stent design does not seem to markedly influence the clinical outcome. On the other hand, in recent years active drug coating (*i.e.* with sirolimus or paclitaxel) has emerged as the new principal determinant of the reduction of angiographic restenosis and repeated revascularization in the target lesion. The choice of a particular type of stent design is mainly affected by the specific knowledge the operator has for one device or another, and by the *a priori* possible performance of that device in a specific lesion. Indeed, as different lesions behave in different ways after stent deployment, each type of lesion may be treated with a different stent.

Acute clinical outcome

Ideally, when a coronary lesion is treated by means of a percutaneous procedure, the endpoint is to dilate the stenosis and gain a lumen equal to the lumen of the non-diseased portion of the coronary artery, without residual dissections or images of haziness or plaque prolapse inside or around the stent deployed. Thus, this primary objective may be achieved after careful evaluation of the specific lesion characteristics and the stent properties. As interventionalists are progressively treating more challenging lesions in more complex situations, stents constructed for specific situations are always more important [6].

Tortuous lesions require particularly conformable and flexible stents, as the modification of the natural conformation of a vessel may alter flow dynamics and possibly increase the risk of events at follow-up.

In case of ostial lesions, stents with strong radial support and good radiological visibility are needed

Table 2 | *Stent versus stent randomized trials*

Trial	Stent type	No. of patients	Early ST rate (%)	RS rate (%)	p-value
RENEWAL [11]	NIR Wallstent	82	2.3 4.8*	26 46§	NS* 0.1§
Lansky *et al.* [12]	GR-II PS	755	3.9 0.3*	47.3 20.6*	< 0.001*
Thuesen *et al.* [13]	NIR Crossflex	223	0.9 0*	17 26*	NS*
ASCENT [14]	ML PS	1040	0.6 1.8*	16 22§	0.04* 0.31§
Miketic *et al* .[16]	NIR Crown	203	0 0	22.0 18.4*	0.4*
Kastrati *et al.* [17]	Inflow ML NIR PS PURA-A	1147	1.8 1.3 1.7 3.0 1.8*	35.0 25.3 28.6 35.9 29.4§	0.724* 0.145§
Kastrati *et al.* [18]	Gold inflow Steel inflow	731	2.5 0.8*	49.7 38.1§	0.08* 0.003§
Park *et al.* [19]	Gold NIR Steel NIR	216	0 0	46.7 26.4*	< 0.05*
Unverdorben *et al.* [20]	NIR Tenax	494	NA NA	26.7 30.0*	0.56*
DISTINCT [21]	DUET BiodivYsio PC	622	0.6 0*	20 20	NS*

** §: p-values for comparison between stent types.*
GR: Gianturco-Roubin stent; ML: Multilink stent; PS: Palmaz-Schatz stent; NIR: NIR Stent; NA: not available; NS: not significant; RS: restenosis. ST: stent thrombosis.

in order to avoid the elastic recoil of the artery and to permit a correct positioning (which is extremely important in this type of lesion) of the stent.

Bifurcational lesions are approached with different stenting techniques, but in all of them, the possibility to rewire the side branch through the stent struts after stent deployment in the main branch is a major factor in determining a good result. Thus stents with large side openings that permit the passage of a balloon or a second stent should be preferred.

Chronic total occlusions constitute a subset of lesions in which good lesion coverage and favorable radial support are important, due to the large amount of plaque present and to the possible formation of a false lumen with re-entry during the reopening of the occlusion with stiff guidewires.

Small vessels require stents with good flexibility and very thin strut structure. Furthermore, as smaller vessels are usually situated in the distal coronary circulation, stent trackability (*i.e.* capacity to reach distal lesions) is of extreme importance in this situation.

PTFE coated stents have been assessed for the treatment of degenerated saphenous vein grafts, in which extensive plaque burden associated with an elevated risk of distal embolization may be "controlled" by these covered self-expandable stents that constrain all the embolic material between the PTFE layer and the vessel wall. Other useful indications for PTFE-covered stents are coronary aneurysm exclusion and coronary perforation.

As the stent is a foreign body not recognized by the blood, the most threatening acute complication of a stenting procedure is stent thrombosis. This event has been reduced to < 1% to 2% (with respect to 5-7% in the first trials), due to the introduction of high-pressure deployment of the device [7] and double anti-platelet therapy (aspirin and a thienopyridine) instead of aspirin and an oral anticoagulant [8, 9]. However, it has been demonstrated that there are substantial differences in haemodynamic and wall rheological characteristics of implanted stents of different designs, and the "hydrodynamic compatibility" of a stent, is now recognized as an important feature of ideal stent design. In this setting, Gurbel *et al.* [10] recently demonstrated that stent design can also affect the degree of platelet activation; stent thrombosis may thus be higher with coil than tubular stents.

Long-term clinical outcome

Stent configuration. Numerous randomized trials [11-21] comparing the mid-term clinical and angiographic outcomes of various stent designs have been published *(Table 2)*. The wire mesh stent (like the self-expanding Wallstent, Boston Scientific) and the coil stent (like the Gianturco-Roubin Flex/GR-II Cook, Bloomington, Ind. USA; and the Wiktor

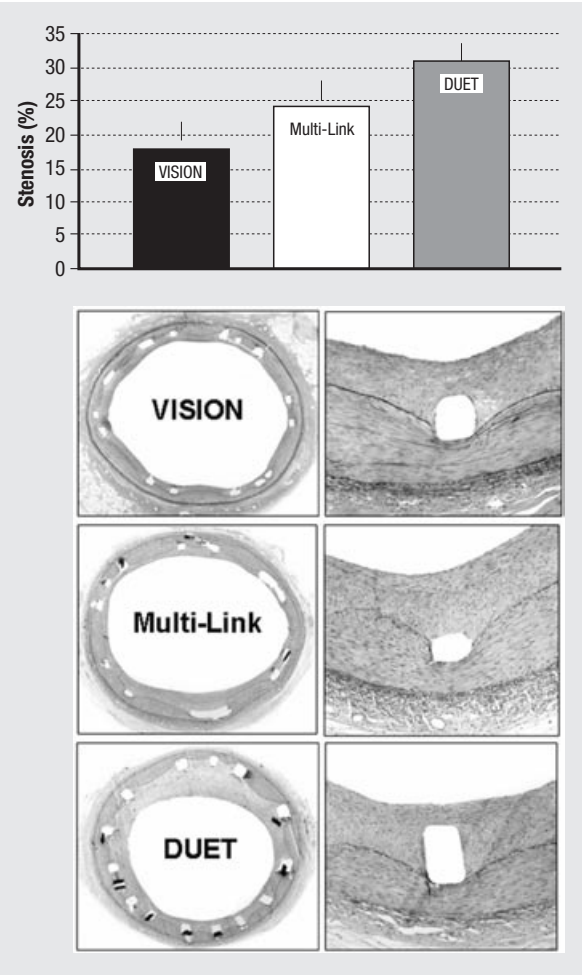

Fig. 2 | *Percentage stenosis due to neointimal formation with different Multi-Link family stents characterized by different strut thickness. Virmani R. et al. (personal communication).*

Medtronic) have been shown to have a high propensity for thrombosis and restenosis, thus leading to a higher major adverse cardiac event rate. These adverse outcomes were mainly determined by the high metal to surface area of the former and by the high degree of elastic recoil (associated with poor radial strength) and tissue prolapse of the latter. In fact, these stents are no longer used by cardiologists for coronary interventions. Other stent designs, such as the tubular stent (like the Palmaz-Schatz, Johnson & Johnson; NIR, Boston Scientific; and Crown, Johnson & Johnson) and the multicellular model (like the Multilink stent, Guidant), have been shown to attain better results than the wire mesh and coil stent. No significant imbalances between tubular and multicellular stents were noted in clinical trials, however multicellular stents, which have the same radial support property as the slotted tube stent type, but with less strut-strut intersections, appear to get the most favorable results. Indeed, in the large ASCENT trial [14], patients who were randomly assigned to receive the Multilink stent showed a trend towards a lower restenosis rate compared with that observed after tubular Palmaz-Schatz stent deployment. In another randomized trial evaluating five different stent models, the Multilink stent was associated with more favorable 6-month angiographic and 1-year clinical outcomes compared with the other four stent designs [17] *(Figure 2)*.

Strut thickness. Although the immediate stent performance may be improved by increasing strut thickness (which increases radiovisibility, radial strength and arterial wall support) excessive strut thickness, on the other hand, may impart more vascular injury, trigger more intimal hyperplasia, and engender a higher risk for restenosis than thinner struts. Clinical studies appear to confirm this direct relationship between strut thickness and arterial wall reaction. In the ISAR-STEREO study [18], in which two stent types of similar design with different strut thickness were randomly implanted in 651 patients with lesions in large coronary arteries (> 2.8 mm RVD), the 6-month binary restenosis rate and 1-year target vessel revascularization were higher following treatment with the ACS Multi-Link RX Duet stent (strut thickness of 0.14 mm) than with the ACS RX Multi-Link stent (strut thickness 0.05 mm); both stents were manufactured by the same company (Guidant, Advanced Cardiovascular Systems). Similar conclusions were demonstrated by the subsequent ISAR-STEREO-2 trial [22], in which two stent types with different design and different strut thickness were randomly implanted in 611 patients: the ACS RX Multi-Link stent (Guidant, Advanced Cardiovascular Systems) with thinner struts (strut thickness 0.05mm) elicited less angiographic and clinical restenosis than the thicker-strut (strut thickness of 0.14 mm) stent BX Velocity (Cordis Corporation, Johnson & Johnson). A similar finding for small vessels (< 3.0 mm RVD) stenting was observed in a retrospective analysis by Briguori *et al* [23] in which strut thickness was observed to be an independent predictor of in-stent restenosis *(Figure 3)*. In an effort to further reduce strut thickness while maintaining adequate radiovisibility and radial strength, novel metallic materials such as cobalt-chromium alloy are being used for the production of stent.

Stent coating. Active coating of stents with *gold*, a highly radiovisible and biocompatible material, has been demonstrated to be inferior to plain stainless steel stents in four randomized trials [19, 24-26].

A higher stent thrombosis and restenosis rate was observed with gold-coated stents compared with bare metal stents in all trials. Coating stents with *silicon carbide*, a potentially less thrombogenic and more compatible material than stainless steel, also did not result in any improvement in angiographic and clinical outcomes compared with bare metal stents in two recent randomized trials [20, 27]. Other randomized trials showed similar results with *phosphorylcholine* [21] and *heparin*-coating [28]. Indeed in all these studies there was no angiographic or clini-

cal benefit compared to bare metal stents. A possible advantage of *heparin*-coated stents, *i.e.* the possible utilization of aspirin alone as the sole acute-phase antiplatelet regimen, was addressed in a non-randomized trial [29]. In this study, patients receiving heparin coated stents were treated with aspirin only and the rate of stent thrombosis was 1% favorably comparing with other historical controls.

Passive coverage of stents with PTFE has been assessed as an appealing solution in the treatment of degenerated saphenous vein grafts containing a considerable amount of friable athero-thrombotic material. Covered stents may prevent distal embolization (and thus periprocedural myocardial infarctions) by entrapping this material against the vessel wall when deployed. These possible benefits were evident in the first registries [30], but two recent randomized trials did not fulfill the initial promise, showing a higher rate of periprocedural myocardial infarctions, compared to a similar restenosis rate [31] .

Drug-elution. The breakthrough appearance of stents eluting *anti-proliferative drugs* with or without a carrier polymer has recently produced unparalleled results with an overall reduction in restenosis rate of between 70% to 85% and in major adverse cardiac events of about 60% compared with bare metal stents and an overall occurrence of restenosis and target lesion revascularization under 10% [32-42]. Sirolimus was used in several trials in the polymer-based system which provides a controlled drug-release over a 4 week period. In the RAVEL trial [32], in which 238 patients were randomized to receive either sirolimus-eluting stent (SES) or bare metal stent, mid-term neointimal hyerplasia was virtually absent in the SES group and correspondingly 6-month in-segment (in-stent and within 5 mm of the stent margins) restenosis was significantly lower in the SES group when compared to the bare metal stent group (0% *versus* 26.6% respectively, p < 0.001). In the SIRIUS trial [33] in which more "real world" patients with more complex lesions than RAVEL trial were enrolled, the superiority of SES was also evident, with a benefit in all patients and lesion subgroups, including those traditionally linked with heightened risk of in-stent restenosis such as small vessel size, long lesions and diabetics. The more recently completed European [34] and Canadian [35] SIRIUS trials and the Italian SES-SMART trial [36] confirmed and extended these findings by clearly demonstrating the efficacy of SES in smaller vessels without an increased risk of stent thrombosis. Paclitaxel has been evaluated in two different delivery systems, either by a carrier polymer or by direct impregnation onto the abluminal stent surface. The former, tested in the TAXUS trials, was shown to offer restenosis rates for paclitaxel-eluting stent (PES) significantly lower than those in the bare metal stent cohort. The results from the TAXUS I [37] , TAXUS II [38] and TAXUS IV [39] trials were impressive and appeared comparable with those obtained with SES. Non-polymer-based PES, tested in two dose-finding trials, ELUTES [40] and ASPECT [41] offered promising results but the efficacy trial DELIVER [42] showed a restenosis rate of around 15%, definitely higher than that seen in the SES and TAXUS trials. Possible explanations for this failure come from to the fact that up to 40% of drug is lost during stent delivery and that non-polymer-based paclitaxel release is relatively rapid and complete within days to weeks, leaving the underlying bare metal stent exposed, while the polymer permits a

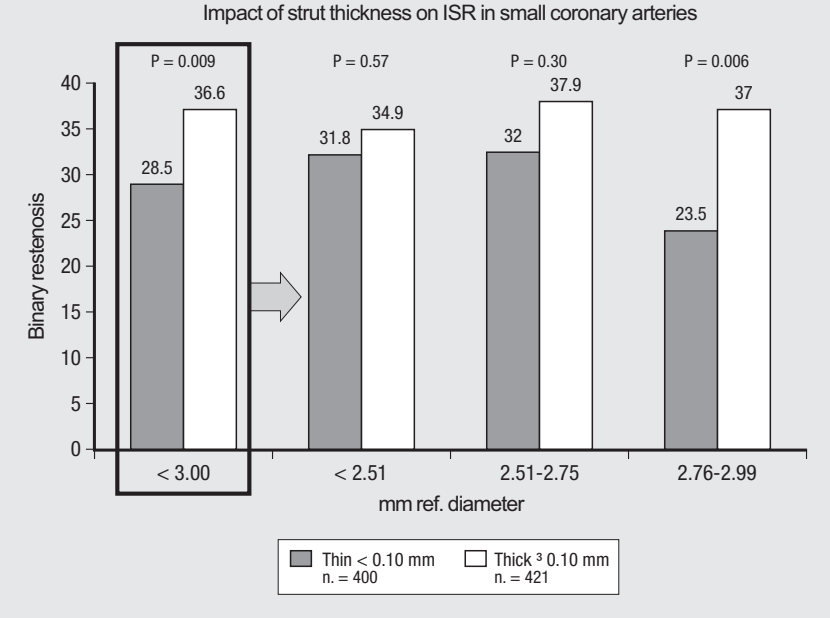

Fig. 3 | *Restenosis rates in lesions treated with a stent with a strut thickness of < 0.10 mm (thin group; grey bars) and stent with a strut thickness ≥ 0.10 mm (thick group; white bars), according to the reference vessel diameter (≤ 2.50, 2,51 to 2,75 and 2.76 to 2.99 mm). Strut thickness significantly influences in-stent binary restenosis between 2.75 and 3.0 vessel size. Modified from Briguori C. et al. J Am Coll Cardiol 2002;40:403-9.*

more gradual and controlled elution of the drug.

Despite the initial enthusiasm, we now realize that while these agents are extremely effective they are not a panacea for restenosis. Indeed, some problems remain still open with DES:

- increased costs for the patients and for the entire healthcare delivery system;
- non completely satisfactory results in some subgroups such as bifurcation lesions [43] and diabetics [44];
- long-term safety, mainly in term of the occurrence of late stent thrombosis [45];
- role of basic design and structure of underlying stent platform.

The ideal DES design may need to have a large surface area of contact with the vascular wall, minimal inter-filament gaps, robust radial support and symmetrical expansion to ensure uniform drug elution. At the same time, it would need to be slim, flexible and conformable to enable successful deployment in complex lesions. For drugs with a narrow toxic-to-therapeutic index (the dosage window between beneficial biological effects – *i.e.* inhibition of smooth muscle cells proliferation – and toxic side effects – *i.e.* endothelial and smooth muscle cells death), customized stent platforms may be required. The potential for long-term adverse effects of the synthetic polymers often used as carriers for anti-mitotic drugs is a major concern. Synthetic polymers may induce an enhanced inflammatory reaction and possibly a pro-thrombotic response [46]. Late stent thrombosis, late stent apposition and coronary aneurysm formation are thus real possibilities [47].

CONCLUSIONS

Albeit stents are currently considered the "gold standard" for the treatment of narrowed coronary arteries, there is experimental and clinical evidence to indicate that a stent is not just a stent. Different stent models have different structural properties, with their own inherent advantages. The design, material composition and surface features of the stent, as well as the stent deployment technique, have an evident impact on its acute performance, risk of thrombosis, degree of vascular response and subsequent risk of in-stent restenosis. Tubular or corrugated stents are better than coil or mesh wire stents, in terms of a better acute and mid-term outcome. Stents with thinner struts and lower metal density yield a lower risk of restenosis than those with thicker struts and should be used for high-risk lesions such as those located in small vessels where the risk of restenosis is often magnified. The availability of new, highly-biocompatible and more radiovisible alloys with the same if not superior tensile strength than stainless steel will enable the production of low metal density stents that may further improve the anatomical and clinical outcomes of current stainless steel stents. Furthermore, stents coated with anti-proliferative agents, in particular sirolimus and paclitaxel, have recently opened a new era in interventional cardiology. They produce restenosis rates that are unrivalled by other bare metal stent models. However, several important questions regarding their cost-effectiveness, long-term safety and durability need to be addressed in order to clearly understand their potential impact in our daily practice. Moreover, as also these devices may be unsuccessful, the progressive understanding of the causes of these failures and of their different performance in various anatomical and biochemical settings becomes of pivotal importance. As scientists and companies are developing new types of stents with different anti-proliferative drugs, it is entirely foreseeable that most interventional procedures in the near future will involve DES, containing sirolimus, paclitaxel or even more effective drugs with both anti-mitotic and anti-thrombotic actions, impregnated onto highly-biocompatible carrier vehicles, and mounted onto a stent design with uniform expansion and with programmable, controllable drug-eluting capability. It is also possible that a co-action of different drugs, *i.e.* paclitaxel eluting stent and oral rapamycine given systemically, may further improve the clinical outcome in term of restenosis. Finally, new stent platforms, such as biodegradable stents or endothelial progenitor cell capturing stents may provide in the near future a more "physiological" answer to stent implantation, reducing vascular injury and accelerating vessel healing with consequent improving in clinical outcome.

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