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Review Article

Drug Eluting Stent: A Promising Drug Delivery System

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ABSTRACT
Drug eluting stent is a topic of current interest in the design of drug delivery systems. Drug-eluting stents deliver potentially high doses of drugs locally for variable time periods in the area of stent implantation, directed at the potential restenosis site. While this is currently achievable, optimal pharmacological therapy is still evolving. Acknowledging the challenge of examining such a dynamic and flourishing field, our goals in this article were to provide a broad perspective of the development of drug-eluting stent technology, to summarize the available clinical data, and to introduce emerging concepts for the understanding and application of this new device in clinical practice.

INTRODUCTION [1]

Since the early 1990s, stents have revolutionized the treatment of vascular disease; they were first reported for use in restoring patency in the coronary artery. [2] Since then, their use has accelerated to the degree that 1.5 million cardiovascular stenting procedures are performed in the United States annually. [3]

They are now also used in peripheral arteries, including the carotid, cerebral, femoral arteries, and in the aorta. Expansion of the stent can be achieved in several ways: by expanding a balloon onto which the stent has been crimped or by releasing a self-expanding stent or a coiled stent from a restraining sheath. In the vast majority of cases, the deployment of a stent restores an unimpeded blood flow in the direct post-intervention period. However, three types of post-stent narrowing of the vessel may occur:

1. The compressive force created by the vessel may cause elastic recoil of the stent and an associated immediate narrowing of the lumen.
2. Injury caused by stent deployment may initiate intimal hyperplasia (IH) whereby smooth muscle cells in the vessel wall proliferate into the lumen (the inner part of the vessel) causing a process of re-stenosis to occur over time.
3. Remodeling of the vessel wall may occur as the stiffness of the vessel wall changes in response to the stresses generated in the tissue and the vessel narrows termed ‘‘negative’’ remodeling.

Renarrowing of a stented vessel is termed in-stent restenosis and it involves the formation of IH though a complex cascade of cellular events post-stenting. [4] Drug-eluting stents have shown superior performance in prevention of instent restenosis one of the key clinical trials shows a reduction from 26.6 % for the bare-metal stents compared with 7.9 % for the drug-eluting stents.

Drug-eluting stents deliver potentially high doses of drugs locally for variable time periods in the area of stent implantation, directed at the potential restenosis site. While this is currently achievable, optimal pharmacological therapy is still evolving. Proliferation, the prime cause of restenosis in the stent error, is the result of a local injury response modulated by platelet and fibrinolytic effects, inflammation as well vascular (endothelial) healing. Choosing the optimal drug(s) and doses for stent delivery will require testing to optimally prevent proliferation while enhancing healing. The time course of drug delivery is also important. Finally, potential complications must be evaluated. These include subacute thrombosis, delayed proliferation with resultant later restenosis than currently seen, aneurysm formation and/or consequences of malapposition of the stent to the vessel wall. [5]

Table 1: Pitfalls and corresponding variables influencing drug-eluting stent performance

Pitfalls	Variables
Bio and blood compatibility	Physicochemical properties of the polymer and drug
Limited surface area (usually < 20 %) of current stents	Drug potency; total amount of drug
Maintain drug properties after coating	Degree of cross-linking
Heterogeneous underlying tissue characteristics	Drug solubility
Sterilization and stent expansion	Polymer and drug elasticity
Inflammation	Porosity of the polymer, molecular weight of the polymer, thickness for the coating, degree and mode of degradation; drug toxicity; local drug concentration (per mm^2); drug solubility

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History of stents

Early 1990: Bare-metal stents were first used
2003: Cypher (sirolimus-eluting) stent introduced in the US
2004: Taxus (paclitaxel) stent introduced

There are currently ~6 million people with drug-eluting stents

Average costs: Drug-eluting stent: >$2000
Bare-metal stent: $800

Regulatory Jurisdictions [6]

Combination Products (21 CFR Part 3)
CDRH lead center with CDER consultation
http://www.fda.gov/oc/combination/updates.html
Divisions involved include…

- Cardiovascular Devices (ODE/CDRH)
- Cardio-Renal Drug Products (OND/CDER)
- New Drug Chemistry I (OPS/CDER)
- Pharmaceutical Evaluation I (OCP/CDER)
- Mechanics & Materials (OST/CDRH)
- Submissions: IDEs & PMAs

Manufacturing and Fabrication methods of drug-eluting stent

a. Steps involved in Manufacturing of drug-eluting 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.

Stents can be wound coils (Cardiocoil), woven mesh designs (Wallstent), or laser-cut designs. Most stents available today are laser-cut stents and the closed-cell types are slotted tubes whereby the stent geometry is machined from a full cylinder such that no welds exist in the structure; examples include the NIR, BeStent, and Inflow stent designs. Modular open-cell stent designs were commonly manufactured from laser-cut rings welded together (S670 and S7); however, most modular-type stents are now also laser cut slotted tube stents to prevent fatigue and corrosion (MultiLink stents).

b. 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. 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".

Step I: The Carrier Stent

Endovascular stents were initially designed as scaffolding structures, not medication-delivery devices. Consequently, stent design has been altered to afford more flexibility, greater radial strength, and minimal metallic coverage. These alterations are unfavorable for housing a drug-eluting vehicle. Efforts are now directed at coating a stent with a sufficient amount of medication that can be delivered uniformly to the underlying tissue. Uniform drug distribution in human, diseased coronary arteries is unrealistic, however. Besides stent design, other factors govern drug diffusion, such as vessel wall morphology, drug physicochemical characteristics, and the multifaceted milieu of the underlying atherosclerotic plaque.

Step II: The Coating Matrix—A Double-Edged Sword?

Several approaches to coating stents with medications exist (Figure 1). Some drugs can be loaded directly onto metallic surfaces (eg, prostacyclin, paclitaxel), but a coating matrix, which contains the medication, is required for most of the biological agents (Figure 1). The coating ensures drug retention during deployment and modulates drug-elution kinetics.

By altering the release kinetics of different drugs in the same coating matrix, distinct phases of the restenotic process may be targeted. In theory, a sustained release of antirestenotic drugs for at least 3 weeks after deployment is required to prevent smooth muscle cell migration and proliferation. Drugs may be held by covalent bonds (eg. C-C bonds, sulfur bridges) or noncovalent bonds (eg. ionic, hydrogen bonds). [9] The blended matrix may then be attached to the stent surface by dipping or spraying the stent. The coating material should act as a biologically inert barrier. This has only been achieved with a few polymers. [9]

The selection of a noninflammatory, inert coating matrix has been a major obstacle to the development of drug-eluting stents. Van der Giessen and coworkers [9] tested 8 different polymers attached longitudinally across 90° of the circumferential surface of coil wire stents (Medtronic, Inc). These coated stents were implanted in porcine coronary arteries, but none of these proved to be physiologically inert. [9] Coating materials must maintain their physicochemical characteristics after sterilization and after stent expansion. The list of candidate substances for stent coatings is long and ever expanding. [9] These substances may be categorized as organic, inorganic, bioerodable, nonbioerodable, synthetic, or naturally occurring substances.

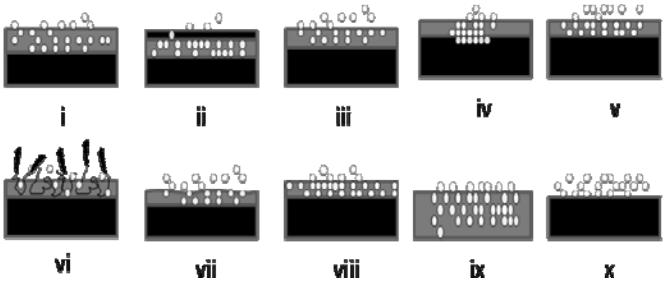

Fig. 1: Schematic representation of different modalities of drug-eluting stent platforms (black - stent strut; gray - coating). i. Drug-polymer blend (diffusion), ii) Drug diffusion through additional polymer coating. iii) Drug release by swelling of coating. iv) Non–polymer-based drug release. v) Drug loaded in stent reservoir. vi) Drug release by coating erosion. vii) Drug loaded in nanoporous coating reservoirs. viii) Drug loaded between coatings (coating sandwich). ix) Polymer-drug conjugate cleaved by hydrolysis or enzymic action. x) Bioerodable, polymeric stent.

Step III: The Biological Agent

The ideal antirestenotic agent for local delivery should have potent antiproliferative effects yet preserve vascular healing. Such a compound should contain hydrophobic elements to

ensure high local concentrations, as well as hydrophilic properties to allow homogeneous drug diffusion. In addition, the drug should have a wide therapeutic to toxic ratio and should not incite thrombosis or inflammation. Other factors such as molecular weight, charge, and degree of protein binding may also affect drug kinetics and ultimately influence the biological success. [10]

Drugs that interfere earlier in the cell cycle (G1 phase) are generally considered cytostatic and potentially elicit less cellular necrosis and inflammation compared with agents that affect the cell cycle in a later stage (beyond the S phase). [11]

On the basis of the mechanism of action of the biological compound and its target in the restenotic process, drug-eluting stents may be generally classified as immunosuppressive, antiproliferative, antiinflammatory, antithrombotic, and prohealing. Some agents, such as sirolimus, may affect multiple targets in the restenotic process but will be discussed under a single category.

Design and Geometry of stent platform [12-14]

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

Materials used for stent construction

Stent materials clearly need to be biologically inert and radiopaque to enable visualization of stent deployment. All stent materials also need to be corrosion-resistant to withstand the highly corrosive environment of the body. The material chosen for a stent depends on the expansion mechanism of the stent, as self-expanding stents must be able to recover considerable elastic deformation and balloon-expanding stents need to plastically deform during deployment. The most common material used for self-expanding.

Stents is the shape memory Nickel-Titanium alloy, Nitinol; examples include the RADIUS (Scimed) stent and the Medtronic AneuRx AAA Stent Graft. Other materials that have been used in self-expanding stents include a platinum core with a cobalt alloy outer layer, which has been used for the mesh of the Wallstent (Boston Scientific).

For balloon-expanding stents, materials that undergo plastic deformation during stent deployment have been used, including medical-grade stainless steel, tantalum, and cobalt chromium. By far, the most widely used material for balloon-expandable stents is 316L stainless steel, a low carbon (0.03 % maximum) steel that has a high chromium content (17–20 %) and molybdenum (2–4 %) to prevent pitting corrosion in saline solutions. [15] Stents made from 316L stainless steel include the first coronary stent, the Palmaz–Schatz stent (Cordis), NIR (Boston Scientific), BeStent, S7 (Medtronic), Jostent (Jomed), Inflow (Inflow Dynamics), and many more (see Table 3). [16-21]

Tantalum has also been used for stents such as the Strecker stent (Medi-Tech) and the Tantalum Crossflex stent (Cordis) because the material is a highly radiopaque material but it has not been used extensively because it is a very brittle material and therefore more prone to fracture than stainless steel. [22]

Cobalt chromium has been used for stents in recent years, including the Multilink Vision (Guidant) and the Driver stents (Medtronic Vascular), to enable stents with thinner struts to be designed, because cobalt chromium alloys have higher strength than stainless steel. [23]

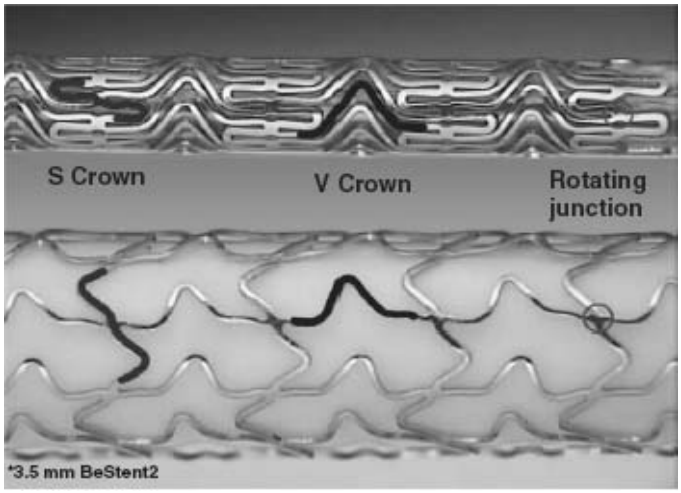

Fig. 2: Crimped BeStent (top) and deployed BeStent (bottom), illustrating the movement of the stent junctions during stent deployment [from www.medtronic.com].

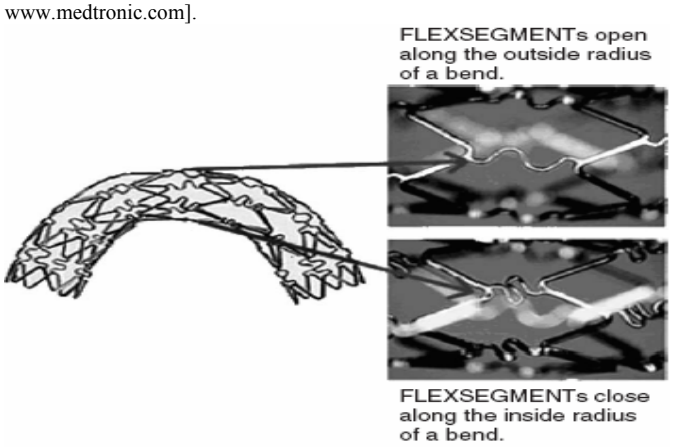

Fig. 3: The deployed BxVelocity stent showing the ability of the stent to conform to a curved vessel using the FLEXSEGMENT technology [from www.cordis.com].

a. Current Metal Options

Most stents are crafted from 316L stainless steel. Current examples include the Cordis Palmaz-Schatz stent, the Cordis Crossflex stent, the Guidant MultiLink stent, and the Medtronic Bestent. Disadvantages of steel stents include the high occurrence of subacute thrombosis and restenosis, bleeding complications, corrosion, and re-dilation of the stented vessel segment. According to the Medtronic website, the "adverse effects" of stents are "death, myocardial infarction, CABG, stent thrombosis, bleeding complications, stroke, vascular complications, stent failures; potential adverse events, e.g., acute myocardial infarction, myocardial ischemia, arrhythmias, dissection, distal emboli, hemorrhage, perforation, restenosis of stented segment, stent embolization, [and] total occlusion of coronary artery." [24]

Gold-plated hybrid stents exhibit good visibility and flexibility, but are also quite expensive. Medtronic's Bestent is a serpentine mesh of stainless steel with no welding point and two radiopaque distal gold markers that allow precise positioning of the stent. [25]

Currently, Conichrome®, Phynox™ and Elgiloy® are trademark names for the cobalt-chromium-nickelmolybdenum-iron alloy, which is specified by

ASTMF1058 and ISO 5832-7. First invented to make watch springs by Batelle Laboratories in 1950, new variations of this "cobalt chromium" alloy can be used for manufacturing stents like the Schneider Wallstent. [26]

Tantalum, element #73, is a shiny, flexible, and highly radio-opaque metal. Though more brittle than stainless steel, tantalum exhibits high ductility and resistance to corrosion.

Current examples of tantalum stents include the Wiktor Stent by Medtronic and the Tantalum Cordis Stent. [27]

The strong intermetallic bond between nickel and titanium has a very low reaction rate, even in patients with increased sensitivity to nickel. This prevents a strong immunological response and decreases corrosion. [28-29]

According to Alan Pelton, PhD and research fellow at Nitinol Devices and Components, a subsidiary of Johnson & Johnson in Fremont, CA, "having shapememory properties and being biocompatible, nickel-titanium probably has the market tied up for quite a while." [29]

b. Polymeric Possibilities

Materials for polymer stents include biodegradable stents coupled with polymeric endoluminal paving, and shape-memory polymers. [30]

Pure plastic biliary stents using polyethylene or polyurethane have also been used in patients. However, polyethylene induces sludge in 20-30 % of patients, encourages protein adherence and biofilm formation, and entraps bile crystals and food particles. In contrast, polyurethane has good tensile and coil strength, and good biodurability, but it is also one of the most reactive materials available. [31]

i. Biodegradable and Bioabsorbable Polymers

Biodegradable and bioabsorbable stents are also viable materials for stenting. Though biodegradation, bioabsorption, and bioerosion are often used incorrectly as synonyms, they have different definitions. By contrast, a bioerodible polymer is a water-insoluble polymer that has been converted under physiological conditions into water-soluble materials. This occurs regardless of the physical mechanism involved in the erosion process. The prefix "bio" in this case refers to erosion occurring in physiological conditions, as opposed to erosion via high temperature, strong acids or bases, or weather. [30]

The Duke Bioabsorbable Stent, designed by Stack and Clark, was the first biodegradable stent. Bier et al. have also tried incorporating natural polymers by forming Type I collagen from purified bovine Achilles' into a tube without slotted sides which was chemically cross-linked for structural stability. The ideal polymer would remain sufficiently strong until the tissue heals, does not invoke a detrimental inflammatory or toxic response, leaves no trace after being metabolized by the body, is easily processed into its final form, has an acceptable shelf life, and is easily sterilized. In "solid" or "structural paving," tin tubes or sheets of biodegradable polymers are transported intraluminally or intravascularly using a catheter, positioned at the deployment site, and locally remolded with catheter-based thermoforming. "Gel paving" uses hydrogels which swell in the presence of water, but eventually form adherent soft structural walls that develop effective drug delivery reservoirs. In liquid paving, flowable polymeric, macromeric, or pre-polymeric solutions are applied to the underlying tissue surface.

ii. Shape Memory Polymers

A final polymeric possibility is the shape-memory polymers, newly developed by Dr. Andreas Lendlein and Dr. Robert Langer. They co-founded nmemoScience in Aachen, Germany to commercialize this new polymer and produce medical devices. Once the polymer is synthesized, it may be heated or cooled into myriad shapes. Upon introducing a suitable stimulus, the polymer will transition from its temporary state to a memorized, permanent shape. Lendlein and Langer have already demonstrated the ability of a polymer fiber to form a corkscrew shape similar to that of a stent. [25] Most of these polymers are created from suitable segments, primarily determined by screening the qualities of existing aliphatic polyesters, especially poly(etherester)s, as well as L,L-dilactide, diglycolid, and p-dioxanone. Macrodiols can be synthesized based on these already-approved monomers. The toxicity of the shape-memory polymer system was measured using the chorioallaptoic membrane test (CAM test).

Types of stent

a. Polymer stents

Stents entirely constructed from Type 1 collagen in a compliant, self-expanding form revealed insignificant resistance to flow *in vitro* [32], but in vivo studies warned of a severe tissue reaction with some polymers. A polyethylene terephthalate braided-mesh stent produced an inflammatory reaction, although the volume of tissue generated did not exceed that seen with metal stents. [33] Stents constructed completely from polyethylene terephthalate led to frequent thrombosis and marked late proliferation [34] with poor support. [35]

b. Polymer-coated stents

Polylactic acid, polycaprolactone and ethylvinylacetate, when presented on a metal backbone, stimulate the growth of an unacceptably thick neointima in porcine coronary arteries.[36]

Yet it appears that not all polymers are detrimental. Polyorganophosphazene coating led to an average 81 % arterial stenosis compared with 32 % for polyurethane and 39 % for bare metal. [37] Polyurethanecoated nitinol stents exhibited no excess reaction over uncoated stents in rabbit carotid arteries [38], and polytetrafluoroethane was associated with a reduction in neointima. [39]

Phosphorylcholine polymer may then be physically adsorbed onto stent steel and exposed to *G* radiation, which both cross-links the polymer and sterilizes the stent. The average thickness of phosphorylcholine polymer on a stent is 50 nm and its weight 20 µg. Elastic and friction studies show that phosphorylcholine adheres well, even after balloon expansion of a stent. In vivo baboon and porcine studies have demonstrated its safety, thromboresistance and long-term biological neutrality. [40-43]

The vascular response reaction to implanting uncoated and phosphorylcholine-coated stainless steel, balloon expandable stents of up-to-date design in the porcine coronary artery at modest oversize showed minimal and equal neointima formation in both groups. [44] In the BiodivYsio registry, with open inclusion criteria, 270 unselected patients had a 30-day rate of major adverse cardiac events of 4·4 %. The equivalent value for the heparincoated Palmaz-Schatz stent (Cordis) in Benestent-II was 3·9 %. [45- 46]

c. Membrane-covered stents

A complete polymer membrane has been applied as a sandwich between two Jostents (JoMed). This system is

designed for repair of vessel rupture and coverage of thrombotic and degenerate plaques in old aortacoronary vein grafts, aneurysms and arterio-venous malformations. Early reports of its use in such a group suggest that it is safe and feasible. [47- 48]

One of the very few studies was in the field of gene therapy. Polylactic acid/polycaprolactone tubes soaked in a solution of recombinant adenovirus and implanted into rabbit carotid arteries produced transgene expression in the media and adventitia at day 5. [49] Paclitaxel- and hirudin-coated biodegradable stents, when placed in a culture of smooth muscle cells obtained from human coronary atherosclerotic plaque, produced severe destruction of cytoskeletal components of the cells, suggesting a possible strategy for in vivo use, assuming the problems of inflammation and radial strength can be overcome. [50]

d. Inorganic coatings

Inorganic strategies may also have potential. Silicon carbide has been investigated for its ability to alter the electro-chemical properties of the stent surface. It has been suggested that the initiation of thrombosis is at least partly due to degeneration of blood proteins by electron transfer to the metal. The ideal surface, from this point of view, is a semi-conductor such as silicon carbide. But, being brittle, silicon carbide can only be applied as a thin layer. Systematic testing of the effect of the silicon-carbide coated Tensum (Biotronik) stent upon cytotoxicity, haemolysis, mutagenicity and haemocompatibility produced favourable results when compared with Palmaz–Schatz (Cordis) and HepaMed (heparin) coated Wiktor (Medtronic) stents. [51] Tantalum stents, coated in the compound, were deployed in rabbit iliac arteries. Complete endothelialization with minimal intimal proliferation was observed. [52] Placement of eight silicon carbide-coated Palmaz–Schatz stents into patients suffering from abrupt closure post-PTCA showed, at coronary angiography the next day, patency of all the stents with no visible thrombus. [53] A series of 165 patients with 215 stents has now been published using the Tensum (Biotronik) tantalum, balloon expandable, silicon carbide-coated stent deployed in a group at high risk of restenosis and thrombosis. There were 2 % stent thromboses. At six months, 32 % of patients (24 % of stents) had had a cardiac event. [54] A 'diamond-like' carbon-coated stent (not, therefore, strictly speaking, inorganic), exposed to flowing, platelet-rich plasma produced less platelet activation and deposition and ion release than uncoated stents. [55-56]

Gold would seem to be the ultimate inert stent coating. A 5 μm thick gold coating was applied to a stainless steel stent and, indeed, showed more than a halving of adherent thrombus mass compared with an uncoated stent. [57] But, disappointingly, a randomized study of 730 patients receiving a gold-coated or bare stent revealed an excess of clinical events in the gold-coated group at one year (24 % vs 13 %). [58]

Drug types used in drug eluting stents [59]

The drugs that may be useful in preventing in-stent restenosis (ISR) fall into four major categories; anti-neoplastics, immunosupressives, migration inhibitors, and enhanced healing factors. ISR is primarily due to natural healing mechanisms including endothelial cell migration and extracellular matrix formation, collectively know as intimal hyperplasia. The damaged tissue attracts platelets and they further the endothelial cell response as well as form thrombosis in the area around the stent. Compounds that can inhibit ISR and intimal hyperplasia are excellent candidates for drug eluting stents.

Table 4: Drug types used in drug eluting stents

Anti-Neoplastics	Anti-Proliferative	Migration Inhibitors	Enhanced Healing Factors
Sirolimus	Taxol (paclitaxel)	Batimistat	BCP671
Tacrolimus	Actinomycin	Prolyl Hydrosylase Inhibitors	VEGF
Everolimus	Methotraxate	Halofunginone	Estradiols
Leflunomide	Angiopeptin	C-preteinase Inhibitors	NO Donor Compounds
M-Prednisolone	Vincristine	Probucol	EPC antibodies
Dexamethasone	Mitmycine		
Cyclosporine	Statins		

- *Anti-neoplastics:* Anti-proliferative compounds include paclitaxel, QP-2, actinomycin, statins and many others. Paclitaxel was originally used to inhibit tumor growth by assembling microtubules that prevent cells from dividing. It has also recently been observed to attenuate neointimal growth.
- *Immunosupressives:* Immunosupressives are generally used to prevent the immune rejection of allogenic organ transplants. The general mechanism of action of most of these drugs is to stop cell cycle progression by inhibiting DNA synthesis. Everolimus, sirolimus, tacrolimus (FK-506), ABT-578, interferon, dexamethasone, and cyclosporine all fall into this category. The sirolimus derived compounds appear especially promising in their ability to reduce intimal thickening.

Biocompatibility of Stent materials [59]

According to Buddy Ratner in *Biomaterials Science: an Introduction to Materials in Medicine*, biocompatibility is "the ability of a material to perform with an appropriate host response in a specific application."

For *in vivo* tests, the medical device is implanted in animals with systems comparable to the device's targeted use in the human body. For example, dogs and sheep provide ideal models for testing devices to be used in bones, whereas guinea pigs are similar to humans in their subcutaneous structures. Porcine models are generally used for modeling cardiovascular disease. The final phase of testing is implanting the device into human beings. Upon surgically inserting the medical device, trauma occurs around the implant region due to tissue injury. The "normal" response is then inflammation, healing of the wound, and a foreign body reaction due to recognition of the new material.

Chemicals in the material itself could also be cytotoxic, inducing cell death. The ideal biocompatible stent material is inert and does not chemically react with human cells. A stent must not evoke an overly prolonged inflammatory reaction, yet must still provide sufficient initial support to oppose the retracting force exerted by the diseased vessel.

Factors affecting distribution Patterns of drug eluting stent

1. Convection

Drives drug radially through the arterial wall, and diffusion is responsible for circumferential distribution and luminal washout. It is instructive to examine drug distribution in terms of Pe, the ratio of convective to diffusive impact on transport. Distribution variability and mean drug concentrations near the intimal are lowest and highest

respectively at low Pe, and these change minimally with increasing Pe while overall concentrations rise. At Pe ~ 10, robust convection coupled with decreased luminal washout maximizes overall drug concentrations without significantly affecting intimal region concentrations. Beyond this value, perivascular washout increases, variation rises, and both infirm region and overall concentrations precipitouslly drop. Intimal and overall concentrations converge at large Pe as overwhelming convection induces a streaming effect, wherein the drug distribution morphs into alternating bands of radial high and low drug zones. Since only solubilized drugs freely diffuse, hydrophilic drugs are far more sensitive to these transport effects than hydrophobic drugs. Indeed, although hydrophobic drugs qualitatively manifest similar variation patterns, they accumulate far more and remain significantly closer to the intima than hydrophilic drugs.

2. Influence of Transport Resistance

Endoluminal transport resistance in areas where the endothelium remains unscathed after stenting can significantly dampen concentration variations in the intimal region of the arterial wall. For an eight-strut stent delivering drug with Pe ~ 1, transport resistance of 100 s/|xm reduces intimal region concentration variation by 83 % and throughout the arterial wall by 35 % compared to arteries with denuded endothelium. However, endoluminal resistance is far less effective at decreasing variations for convection dominated drugs and moreover, increasing resistances beyond 100 s/|xm does not lead to significant additional improvements in distribution, irrespective of Pe. Therefore, optimizing balloon or stent design to minimize endothelial injury may be valuable to a limited extent for drug delivery, especially for small hydrophilic drugs.

3. Influence of Drug Physicochemical Properties

Size and charge

Drug molecular weight and charge impact drug distribution by directly modulating Pe and endoluminal transport resistance. To quantify these effects, transport of anionic, cationic, and neutral dextrans was measured across native and denuded rat carotid arteries. Diffusivity remained constant for neutral compounds at low molecular weights, and only fell significantly above 40 kDa. These data suggest that Pe might increase with negative charge or larger drug size, resulting in lower concentration variability. Since large negative drugs have greater resistances, there may also be lower variability near the intima.

Partitioning

Drugs that partition well into the arterial wall are less prone to washout, resulting in smaller low drug regions and increased risk of local toxicity. Several drugs arterial drug concentrations greatly exceeded applied concentrations, indicating that paclitaxel binds to elements throughout the vessel wall. Drug concentration was greatest in the intima, followed by the adventia and media, likely reflecting different densities of binding sites in these regions Binding sites within the media were also inhomogeneous, with a gradient extending inward from the intima and adventia

Protein-mediated transport.

Interactions of hydrophobic drugs with serum proteins add another layer of complexity Protein-mediated transport of paclitaxel was characterized by determining, in the presence or absence of carrier proteins, drug solubility in aqueous solution, diffusivity in free solution, and diffusivity in arterial tissues. While paclitaxel solubility was raised by glycoproteins, albumin, and calf serum, diffusivity in solution was reduced.

4. Influence of device geometry

Differences between local and mean concentrations become more critical as stent designs I evolve to more complex forms. I Simulations of randomly configured stents Showed that drug distribution uniformity was finely dependent on strut arrangement. This connection was tighter for hydrophilic than for hydrophobic drugs. For hydrophobic drugs, this difference only I increased from 8 % for a 4-strut stent to 21 % for a 12-strut stent. Variations in strut spacing will only amplify this natural variability, increasing areas of overlap toxicity where struts are close together and sub-J therapeutic areas where struts are far apart. Proximity thus does not ensure uniform distribution, particularly for hydrophilic drugs and targets near the intima.

5. Influence of Tissue Ultrastructure and Composition

The cylindrical structure of the arterial wall suggests that the direction of drug movement may influence transport. For hydrophilic drugs, recent data suggest that arterial diffusivity might be highly anisotropic, so that circumferential diffusion takes place significantly faster than radial diffusion. Differential partitioning into different arterial tissue elements, more abundant in some arteries than others, may also influence deposition. Preliminary data for hydrophobic drugs also suggest similar anisotropic transport. The ramifications of the natural dependence of vascular pharmacokinetics on tissue structure have thus been the subject of intense research. It may be that arterial tissue composition must be an important consideration in guiding vascular drug delivery, especially when extrapolating studies from one artery to other vessels of different ultrastructural characteristics.

Products of drug-eluting stents [60-61]

1. Stents Eluting Antiinflammatory Agents

Because of the role of inflammatory cells in restenosis, these cells seemed to be an optimal target in the fight against restenosis. Indeed, corticosteroids have long been shown to reduce the influx of mononuclear cells, to inhibit monocyte and macrophage function, and to influence smooth muscle cell proliferation. Nonetheless, clinical trials have failed to demonstrate any benefit of systemic steroid therapy.

Table 5: Product in Market

Rapamycin Derivatives	Corporation	Clinical Trials
Sirolimus	Cordis	RAVEL/SIRIUS
Tacrolimus	JOMED	--
Everolimus	Guidant	FUTURE I/II/III
ABT-578	Medtronic Abbott	ENDEAVOR
Taxol Derivatives		
Paclitaxel	Boston Scientific	TAXUS I/II/III/IV
Taxane	Quannam	SCORE
Paclitaxel	Guidant	ELUTES/ASPECT/DELIVER
Others		
Batimistat	Bio Compatibles	BRILLIANT
Dexamethosone	BiodivYsio	STRIDE
Actinomycin D	Guidant	ACTION
Resten NG	Medtronic	--
Micophenolic Acid (MPA)	Aventec	--

2. Stents Eluting Immunosuppressive Agents

Encouraged by the early experience with ionizing radiation therapy, researchers have proposed sophisticated pharmacological strategies interfering with cell cycle division. Xenobiotic molecules (rapamycin, FK506,

cyclosporine, and analogues) and antimetabolites (mycophenolate mofetil) have been utilized.

Future Trends

New Solutions for the Next Generation of Drug-eluting Stents

1. New coating (absorbable coating, no coating)
2. New Biological target: (Endothelium, thrombosis, inflammation)
3. New drug (less cytostatic or cytotoxic)
4. New technique of elution (reservoir, dual elution)
5. Pro Healing approach (EPC capture)
6. Pro Healing approach + Sirolimus or Paclitaxel
7. Complete Absorbable metallic or polymeric platform
8. New Stent Design for challenging targets bifurcationstronik, Reva

REFERENCES

1. Sousa E. J., Serruys P.W. and Costa M.A. New Frontiers in Cardiology: Drug-Eluting Stents: Part I. Circulation 2003;107;2274-2279
2. Sigwart U., Puel J., Mirkovitch V., et al., Intravascular stents to prevent occlusion and restenosis in transluminal angioplasty.N. Engl. J. Med. 1987; 316(12):701–706.
3. Arain S. A. And Reilly J. P., Mechanisms of restenosis following percutaneous coronary interventions. In: Drug-Eluting Stents. Advanced Applications for the Management of Coronary Disease. (Ed.: C. J. White), Taylor and Francis, London, pp. 7–17, 2005.
4. Edelman E. R. And Rogers C., Pathobiologic responses to stenting. Am. J. Cardiol. 1998; 81:4E–6E.
5. Vetrovec G.W. Drug-Eluting Stents: Current Outcomes and Potential Impact on Coronary Disease Management. Journal of Invasive Cardiology.
6. http://www.fda.gov/oc/combination/updates.html
7. Whelan DM, van Beusekom HM, van der Giessen WJ. Mechanisms of drug loading and release kinetics. Semin Interv Cardiol. 1998;3:127–131.
8. Costa MA. Drug-coated stents for restenosis. In: Faxon DP, ed. Restenosis: A Therapeutic Guide. London: Martin Dunitz; 2001:113–129.
9. Van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation. 1996;94:1690–1697.
10. Lovich MA, Creel C, Hong K, et al. Carrier proteins determine local pharmacokinetics and arterial distribution of paclitaxel. J Pharm Sci. 2001;90:1324–1335.
11. Braun-Dullaeus RC, Mann MJ, Dzau VJ. Cell cycle progression: new therapeutic target for vascular proliferative disease. Circulation. 1998;98: 82–89.
12. Morton Allison C, Crossman. D, Gunn. J, *The influence of physical stent parameters upon restenosis,* Elsevier SAS, 2004.
13. Rogers, Campbell D.K, MD, *Optimal Stent Design for Drug Delivery,* MedReviews, LLC, 2004.
14. McClean Dougal R, MD, Eigler N, MD, *Stent Design: Implications for Restenosis,* MedReviews, LLC 2002
15. Bronzino J. D., (ed.). The Biomedical Engineering Handbook. 2nd Edition, Volume 1, A CRC Handbook published in cooperation with IEEE Press, 2000.
16. Arain S. A. and Reilly J. P., Mechanisms of restenosis following percutaneous coronary interventions. In: Drug-Eluting Stents. Advanced Applications for the Management of Coronary Disease. (Ed.: C. J. White), Taylor and Francis, London, pp. 7–17, 2005.
17. Serruys P. W., Kutryk M. J. B., Handbook of Coronary Stents. Martin Dunitz: London, 2000.
18. Duerig T., Pelton A., and Sto¨ckel D., An overview of nitinol for medical applications. Mat. Sci. and Eng. 1999; A273-275:149–160.
19. Bronzino J. D., (ed.). The Biomedical Engineering Handbook. 2nd Edition, Volume 1, A CRC Handbook published in cooperation with IEEE Press, 2000.
20. McClean R. And. Eigler N. L, Stent design: implications for restenosis. Rev. in Cardiovascular Med. 2002; 3:S16–S22.
21. Roguin, E.A. Grenadier, S. Linn, W. Markiewicz, and R. Beyar, Continued Expansion of the Nitinol Self-Expanding Coronary Stent: Angiographic Analysis and 1-Year Clinical Follow-Up. Am. Heart J. 1999; 138(2):326–333.
22. Stoeckel D., Bonsignore C., and Duda S., A survey of stent designs. Min. Invas. Ther. & Allied. Technol. 2002; 11(4):137–147.
23. http://www.medtronicave.com/noflash/ physicians/coronary_indepth/s7otw_warnings.shtml
24. Tan, HC, and YT Lim. "What you need to know – Coronary Stenting – What's New in the Horizon?" Singapore Medical Journal. Singapore Med J 1999; Vol 40(06): http://www.sma.org.sg/smj/4006/articles/4006me2.html
25. http://www.fwmetals.com/spec_sheets/ conichrome.htm
26. http://biomed.brown.edu/courses/bi108/BI108_1999_Groups/Stents_Team/balloon.htm
27. http://www.sma-inc.com/biocomp.html
28. Ryhänen, Jorma. "Biocompatibility evaluation of nickel-titanium shape memory metal alloy." University of Oulu. 1999. http://herkules.oulu.fi/ isbn9514252217/
29. Freiherr, Greg. "Untapped Potential." Device Link. http://www.devicelink.com/mddi/archive/98/03/005.html
30. http://www.bostonscientific.com/common_templates/articleDisplayTemplate.jhtml?task=tskMedArticleOverview.jhtml&sectionId=4&relId=8,386,387,388,389,390&deviceId=134&uniqueId=MPAO541
31. Bier JD, Zalesky P, Li ST et al. A new bioabsorbable intravascular stent: in vitro assessment of hemodynamic and morphometric characteristics. J Interven Cardiol 1992; 5: 187–94.
32. Van der Giessen WJ, Slager CJ, Beusekom HMM et al. Development of polymer endovascular prosthesis and its implantation in porcine arteries. J Interven Cardiol 1992; 5: 175–85.
33. Ashby D. T., Dangas G., Mehran R., and Leon M. B., Coronary Artery Stenting Catheterisation and Cardiovascular Interventions 2002; 56:83–102.
34. Wilczek KL, de Scheerder IK, Kai W et al. Comparison of intravascular compatibility of polyethylene terephthalate self-expanding stents with Wallstents (Abstr). Eur Heart J 1995; 16 (Abstr Suppl): 177.
35. Van der Giessen W, van Beusekom HM, Hofma SH et al. Preliminary results with bi-component metal-biodegradable polymer stents in porcine coronary mode (Abstr). Eur Heart J 1996; 17 (Abstr Suppl): 178.
36. De Scheerder IK, Wilczik KL, Verbeken EV et al. Biocompatibility of polymer-coated oversized metallic stents implanted in normal porcine coronary arteries. Atherosclerosis 1995; 114: 105–14.
37. Rechavia E, Fishbein MC, DeFrance T et al. Vascular injury triggered by temporary and permanently implanted polyurethane coated and uncoated stents in rabbit carotid arteries (Abstr). Circulation 1996; 94 (Suppl): I 88.
38. Rogers C, Tseng DY, Gingras PH et al. Expanded polytetra fluoroethylene stent graft encapsulation reduces intimal thickening regardless of stent design (Abstr). J Am Coll Cardiol 1998; 31: (Suppl): 413A.
39. Chronos NAF, Robinson KA, Kelly AB et al. Thromboresistant phosphorylcholine coating for coronary stents (Abstr). Circulation 1995; 92: (Suppl I) 685.
40. Malik N, Gunn J, Shepherd L et al. Phosphorylcholine coated stents in porcine coronary arteries: angiographic and morphometric assessment (Abstr). Eur Heart J 1997; 18 (Abstr Suppl): 152.
41. Kuiper KK, Robinson KA, Chronos NAF et al. Implantation of metal phosphorylcholine coated stents in rabbit iliac and porcine coronary arteries (Abstr). Circulation 1997; 96 (Suppl I): 21.
42. van Beusekom HMM, Whelan DM, Krabbendam SC et al. Biocompatibility of phosphorylcholine coated stents in a porcine coronary artery model (Abstr). Circulation 1997; 96 (Suppl I): 21.
43. Malik N, Gunn J, Newman C et al. Phosphorylcholine-coated stents: angiographic and morphometric assessment in porcine coronary arteries (Abstr). J Am Coll Cardiol 1998; 31: 414A.

44. Cumberland DC, Bonnier H, Colombo A et al. Initial clinical experience with the phosphorylcholine coated divYsio stent. (MS in submission).
45. Serruys PW, van Hout B, Bonnier H et al. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). Lancet 1998; 352: 673–81.
46. Lopez A, Heuser RR, Stoerger H et al. Coronary artery application of an endoluminal polytetrafluoroethylene stent graft: two center experience with the JoMed Jo Stent (Abstr). Circulation 1998; 17 (Suppl I): 855.
47. Morice MC, Louvard Y, Buchard L et al. French registry of coronary stent grafts. Acute and mid-term results (Abstr). Circulation 1998; 17 (Suppl I): 855.
48. Landau C, Willard JE, Clagett GP et al. Biodegradable stents function as vehicles for vascular delivery or recombinant adenovirus vectors (Abstr). Circulation 1995; 92 (Suppl I): 670.
49. Voisard R, Alt E, Baur R et al. Paclitaxel-coated biodegradable stents inhibit proliferative activity and severely damage cytoskeletal components of smooth muscle cells from human coronary plaque material in vitro (Abstr). Eur Heart J 1998; 19 (Abstr Suppl): 376.
50. Toutouzas K, Stefanadis C, Vlachopoulos C et al. Autologous vein graft-coated stent: a comparative experimental study with conventional stenting (Abstr). Eur Heart J 1995; 16 (Abstr Suppl): 178.
51. Unverdorben M, Schywalsky M, Labahn D et al. A new silicon carbide coated stent-experience in the rabbit (Abstr). Eur Heart J 1996; 17 (Abstr Suppl): 178.
52. Unverdorben M, Schywalsky M, Labahn D et al. A new silicon carbide coated stent-experience in the rabbit (Abstr). Eur Heart J 1996; 17 (Abstr Suppl): 178.
53. Heublein B, Pethig K, Elsayed AM. Silicon carbide coating—a semi-conducting hybrid design of coronary stents—feasibility study. J Invas Cardiol 1998; 10: 255–62.
54. Beythien C, Gutensohn K, Kenner T et al. Diamond-like carbon coating of coronary stents: influence on platelet activation, smooth muscle cells and release of metal atoms (Abstr). Eur Heart J 1998; 19 (Abstr Suppl): 497.
55. Beythien C, Gutensohn K, Kuhnl P, et al. Influence of 'diamond-like' and gold coating on platelet activation: a flow cytometry analysis in a pulsed floating model (Abstr). J Am Coll Cardiol 1998; 31: 413A.
56. Herrmann RA, Rybnikar A, Resch A et al. Thrombogenicity of stainless steel coronary stents with a completely gold coated surface. J Am Coll Cardiol 1998; 31: 413A
57. Schomig A, Kastrati A, Neumann FJ et al. Impact of gold plating on the outcome after coronary stent placement: results of randomised trial. Circulation 1998; 17 (Suppl I): 855.
58. Ratner A, Buddy D., et al. Biomaterials Science: An Introduction to Materials in Medicine. Academic Press: San Diego, 1996.
59. http://www.mse.cornell.edu/courses/ engri119/Class_Notes/E119_9p.PDF
60. Berk BC, Gordon JB, Alexander RW. Pharmacologic roles of heparin and glucocorticoids to prevent restenosis after coronary angioplasty. J Am Coll Cardiol. 1991; 17:111B–117B.
61. Pepine CJ, Hirshfeld JW, Macdonald RG, et al. A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. M-HEART Group. Circulation. 1990; 81:1753–1761.