Drug Development and Industrial Pharmacy, 1:59–78, 2005

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1081/DDC-200044002

Taylor & Francis
Taylor & Francis Group

The Intra-Vascular Stent as a Site-Specific Local Drug Delivery System

Imran Ahmad Khan and Vandana B. Patravale
Department of Pharmaceutical Sciences and Technology, University Institute of Chemical Technology (UICT), Matunga, Mumbai, India

ABSTRACT The current review focuses on utilization of a tubular structure (coated or uncoated, balloon expandable or self expanding) known as a "stent" for localized intravascular drug delivery. Emphasis of the review is on technologies currently employed for immobilization and coating for drug onto the stent prior to its placement in various lumen of the body. A brief discussion on stent design, comparison of angioplasty and coronary stenting, and market status complements the review for researchers new to this area.

KEYWORDS Intra-vascular stent, Site-specific local drug delivery system, Restenosis, Stent coating

INTRODUCTION

Vascular disease is a leading cause of death and disability in the developed world. Atherosclerosis is the most common form of vascular disease, characterized by irregularly distributed lipid deposits in the intima of large and medium-sized arteries. Such deposits provoke fibrosis and calcification, leading to insufficient blood supply to the body organs, which may result in heart attack, stroke, or kidney failure. Restenosis is a form of vascular injury in which the vascular smooth muscle cells in the artery wall undergo hyperproliferation and invade and spread into the inner vessel lining. This can make the vessels susceptible to complete blockage when local blood clotting occurs. This can finally lead to death of the tissue served by that artery. In the case of a coronary artery, this blockage can lead to myocardial infarction and death (Zhong & Sheng-P, 2001; Yang et al., 2001).

To prevent vessel blockage due to restenosis, bare metallic/polymeric stents have been in use. Stents are normally tubular structures having either solid walls or latticelike walls and can be either balloon expandable or self-expanding. After angioplasty balloon dilatation, the previously constricted vessel is at least temporarily widened. A stent can be delivered on a catheter and expanded in place or allowed to expand in place against the vessel walls. With the stent in place, restenosis may or may not be inhibited, but the probability and/or degree of blockage is reduced due to the structural

Address correspondence to Vandana B. Patravale, Department of Pharmaceutical Sciences and Technology, University Institute of Chemical Technology (UICT), Matunga, Mumbai, India; Fax: +91-22-24145614; E-mail: vbp_muict@yahoo.co.in

strength of the stent opposing the inward force of vessel due to recoil. Restenosis may occur over the length of the stent and be at least partially opposed by the stent. Restenosis may also occur past the ends of the stent where the inward forces of the stenosis are unopposed (Zhong & Sheng-P, 2001; Yang et al., 2001).

Therapeutic agents to inhibit restenosis are locally administered using stents and are more effective if the drug is delivered over prolonged time periods, at least for the estimated normal reaction time of the body to angioplasty e.g., local prolonged administration of taxol (Drachman et al., 2000).

Coronary stents were first used clinically in 1986 by Sigwart et al. (1987) and Hidio et al. (2000). The wire coil design was approved by the Food and Drug Administration (FDA) in 1993 for stabilizing acute or threatened abrupt closure while the slotted tube design was approved in 1994 for elective treatment of native coronary lesion. In clinical practice, however, both stents are widely used in other circumstances, including restenotic lesion and saphenous vein graft. Earlier reports suggest that metallic implants were prone to either acute (< 24 hr) or subacute (1 to 14 days with peak at 6 days) thrombotic occlusion and that an aggressive anticoagulation regimen (Aspirin, Dipyridamole, low molecular weight Dextran and Warferin) was required to prevent it. This aggressive anticoagulant regimen leads to long-term hospitalization and an increased incidence of local vascular complication at the femoral arterial entry site. More recent data suggests, however, that many of these thrombotic complications were due to incomplete stent expansion (Colombo & Tobis, 2000) and more attention to full initial deployment allows the same stents to be used with antiplatelet drugs (Aspirin and Ticlopidine) with more acceptable thrombosis and vascular complication states (each < 1%). On the basis of overwhelming clinical success of the wire coil and slotted tubular designs, more than a dozen second-generation designs (bare as well as drug eluting) are now emerging from the FDA approval process (Brim & Grossman, 1998).

The use of the stent is not restricted to blood vessels. These are also used in various lumen of the body to provide support to healing tissue and for stricture management, being occluded due to benign and malignant conditions. These lumen include the ureter (Arya et al., 2001; Joshi et al., 2001; Multanen et al., 2000; Ragheb et al., 2001), urethra (Arya et al., 2001; Latal et al., 1994), biliary tract (Arya et al., 2001; Ragheb et al., 2001), colon (Ragheb et al., 2001), esophagus (Ragheb et al., 2001; Roy et al., 1992) and trachea (Ragheb et al., 2001) where local drug delivery is desired for treatment of malignancies.

LOCAL INTRAVASCULAR DRUG DELIVERY OF THERAPEUTIC AGENT

The concept of local intravascular, site-specific drug delivery of pharmacological and biological therapeutics has evolved as a solution to potential limitation of systemic administration of vascular injury associated with percutaneous revascularization. Inhibition of smooth muscle cell proliferation is the primary target for local intravascular drug delivery. However, the local delivery approach is likely to prove useful for treating a variety of cardiovascular diseases as well, e.g., thrombosis, neovascularization of an ischemic focus, and selective alteration of vasomotor tone (Riesen & Isner, 1994).

Three strategies employed for local, intravascular site-specific delivery are:

1. Direct deposition of therapeutic agents or genes into vessel wall through an intravascular system.
2. Systemic administration of inactive agent followed by local activation.
3. Systemic administration of agents that are tagged by specific receptor ligand to proliferating smooth muscle cell at the angioplasty site.

Direct Deposition of Therapeutic Agents into the Vessel Wall

Local therapy of restenosis by means of direct drug delivery should ideally consist of a single-dose application at the time of angioplasty so that subsequent interventions are not required. Symptoms of restenosis in patients, however, occur months after the initial angioplasty, indicating that smooth muscle proliferation or extracellular matrix production or both are ongoing for prolonged periods (Riesen & Isner, 1994). Therefore prolonged maintenance of local drug

concentration at least equivalent to estimated tissue response time is necessary. However, restenosis is a multi factorial event that should be considered in drug treatment.

Systemic Administration of Inactive Agents Followed by Localized Activation

Photodynamic therapy constitutes a form of local therapy in which activity of light excitable photosensitizers is exploited to produce injury of targeted cells. These are relatively nontoxic substances unless activated by appropriate wavelength of light, e.g., use of hematoporphyrin derivatives for treatment of neoplastic disorders (Prout et al., 1987) after activation by red light (635 nm). These substances accumulate in the proliferating tissue such as tumors and have been shown to be present in higher concentrations in atherosclerotic plaques than in normal tissues (Spear et al., 1983). Clinical use of hematoporphyrin, however, is limited by cutaneous photosensitivity that can last for several weeks. To reduce such toxicity, these photosensitizers are now administered in small amounts by using local delivery devices such as porous balloons or stents. Similarly, chloroaluminium-sulfonated phthalocynin has been used to inhibit the neointimal formation after balloon angioplasty (Ortu et al., 1992).

Systemic Administration of Agent with Specific Affinity to Proliferative Smooth Muscle Cells

Proliferating smooth muscle cells compared to quiescent cells often express a higher number of surface receptors for a variety of growth factors. Differential expression of these receptors provides opportunity to use a cytotoxic agent that specifically targets proliferating smooth muscle cells. This is accompanied with recombinant fusion proteins. These chimeric agents combine a potent toxin with peptide linkage on the cell surface receptor leading to internalization of protein and cellular death. For the receptor targeting component, several growth factors including transforming growth factors (TGFs) (Epstin et al., 1991), epidermal growth factors (EGFs) (Pickering et al., 1993), basic fibroblast growth factors (bFGFs) (Biro et al., 1992), and interleukin (Appendix 1) have been used.

Toxins that have been used to complete the hybrid include *pseudomonas* exotoxin (Epstein et al., 1991; Pickering et al., 1993), diphtheria toxin (Biro, et al., 1992), and saporin, a toxin directed on r-RNA. These agents on systemic administration are highly toxic. Preliminary reports show that local administration of fusion protein markedly reduced neointimal formation with clearly reduced systemic side effects (Pastore et al., 1993).

ADVANTAGES OF LOCALIZED DRUG DELIVERY SYSTEMS

Various advantages of localized drug delivery system include:

1. Avoiding excessive exposure of drugs having systemic toxicity.
2. Bypass of first pass metabolism facilitating administration of higher concentration of drug with no significant side effect.

For example, concentration of dexamethasone in arterial tissue targeted with eluting stent was found to be 90,000–3,00,000-fold higher than that of serum during first day after stent implantation and remained 3000-fold higher even after 28 days (Lincoff et al., 1997). It shows that systemic exposure of drug was insignificant, thus minimizing the side effects.

Similar results have been achieved by localized delivery of Paclitaxel. It has been found that 50–60 μ mole/lit peak plasma concentration by systemic delivery resulted in 70% reduction in neointima formation after 11 days of injury in rat carotid artery while application of stent at 0.01 μ mole/lit to 10 μ mole/lit inhibited the growth and migration of smooth muscle cells (Drachman et al., 2000).

DEVICES FOR INTRAVASCULAR DRUG DELIVERY

Devices used for intravascular drug delivery include double balloon catheters, porous balloon catheters,

hydrogel catheters, and iontophoresis catheters. In all these, therapeutic agents in solubilized form are introduced into a sealed evacuated balloon. When this system is introduced into body lumen, the substance is released either by diffusion or by applied hydrostatic pressure, except in the case of iontophoresis catheter wherein the molecules are transported by application of a low electric current (i.e., by applying potential difference between inside of balloon and arterial wall) (Riesen & Isner, 1994). All these are associated with disadvantages such as:

1. Drug is available only for a short period of time until catheter remains inside the lumen. As device is withdrawn, the therapeutic substance is washed out by the circulating blood in short time.
2. As catheter is a completely enclosed system, circulation of fluid is not possible untill the catheter remains (15–30 min) in the lumen.
3. In the case of treatment of stenosis, once the catheter is removed from the blood vessel, elastic recoil occurs, which may lead to closure of blood vessel.
4. Leakage of solutions from balloon.
5. In the case of porous balloon when higher pressure is applied, solution comes out in a jet form, which may lead to vessel injury.

To overcome various disadvantages of the balloon catheter, use of stents is advocated nowadays. Stents have proved their utility as carriers for sustained delivery of anti-inflammatory (Lincoff et al., 1997), antithrombotic (Rox et al., 1995), and/or antiproliferative drugs (Drachman et al., 2000) as well as for genes.

CORONARY STENTING

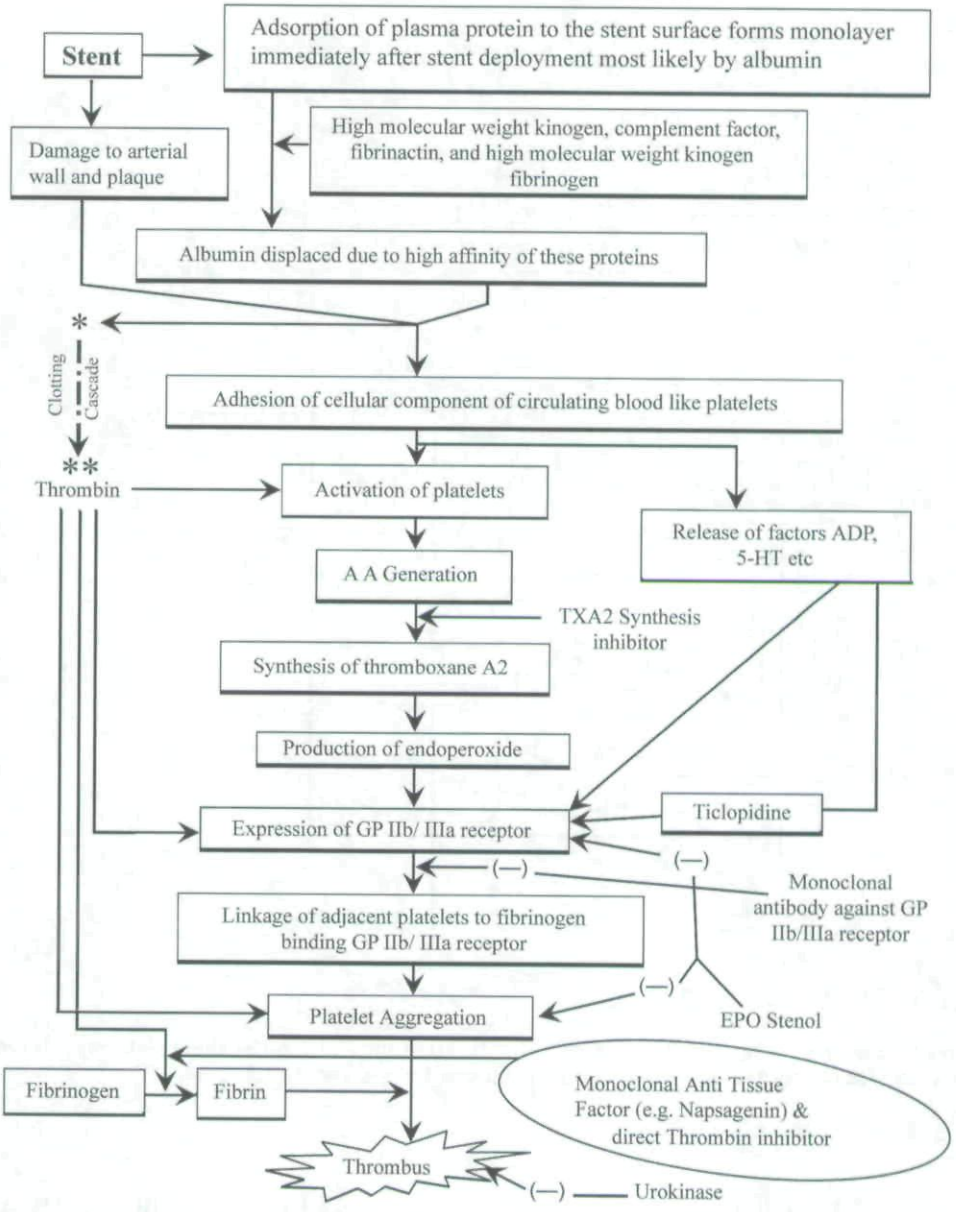
Probably the most common disease causing stenosis of blood vessels is atherosclerosis, affecting the coronary arteries, the aorta, the iliofemoral arteries, and the carotid arteries. Atherosclerotic plaques of lipids, fibroblasts, and fibrin proliferate and cause obstruction of an artery or arteries. As the obstruction increases, a critical level of stenosis is reached to a point where the flow of blood past the obstruction is insufficient to meet the metabolic needs of the tissue distal to the obstruction, resulting in ischemia (Ragheb et al., 2001).

Many medical devices and therapeutic methods are known for the treatment of atherosclerotic disease. One particularly useful therapy for certain atherosclerotic lesions is percutaneous transluminal angioplasty (PCTA). During PCTA, a balloon-tipped catheter is inserted in a patient's artery, the balloon being deflated. The tip of the catheter is advanced to the site of the atherosclerotic plaque to be dilated. The balloon is placed within or across the stenotic segment of the artery and then inflated. Inflation of the balloon "cracks" the atherosclerotic plaque and expands the vessel, thereby relieving the stenosis, at least in part.

PCTA suffers from two major problems:

1. The blood vessel may suffer acute occlusion immediately after or within the initial hours after the dilation procedure. Such occlusion is referred to as "abrupt closure." Abrupt closure occurs in perhaps 5% or so of the cases in which PCTA is employed and can result in myocardial infarction and death if blood flow is not restored promptly. The primary mechanisms of abrupt closures are believed to be elastic recoil, arterial dissection, and/or thrombosis. It has been postulated that the delivery of an appropriate agent (such as an antithrombic) directly into the arterial wall at the time of angioplasty could reduce the incidence of thrombotic acute closure.
2. A second major problem encountered in PCTA is the renarrowing of an artery after an initially successful angioplasty. This renarrowing is referred to as "restenosis" and typically occurs within the first 6 months after angioplasty. Restenosis is believed to arise through the proliferation and migration of cellular components from the arterial wall, as well as through geometric changes in the arterial wall referred to as "remodeling." It has been postulated that the delivery of appropriate agents directly into the arterial wall could interrupt the cellular and/or remodeling events leading to restenosis. Nonatherosclerotic vascular stenosis may also be treated by PCTA.

Proposed mechanism of in-stent thrombosis and restenosis, together with drugs used to interrupt paths



AA-Arachidonic Acid, TX A_2 -Thromboxane A_2; ADP-Adenosine diphosphate; LMWH–Low molecular weight heparin; AT III–Antithrombin III; PL–Negatively charged phospholipids.

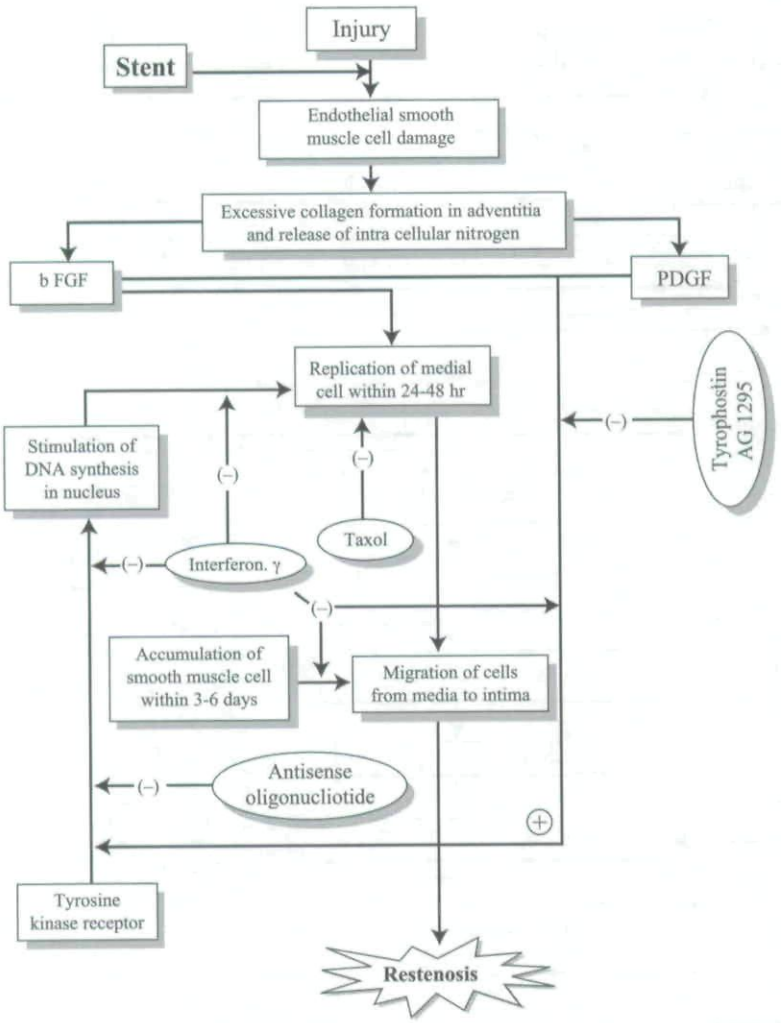
Proposed Mechanism of In-stent Thrombosis Together with Drugs Used to Interrupt Paths of Relevant Pathways. (From Bar, Van der Veen, Benzina, Habets, and Koole, 2000; Hertzog, Thoms, and Sandor, 1999; Fischman et al., 1994; Gunn and Cumberland, 1999; Montalescot, Choussat, and Collet, 2001; Morice et al., 2002; Ross, 1993; Rox, et al., 1995; Serruys et al., 1994; Serruys et al., 1998; Von Langenhore, Kutryk, and Surruys, 2000).

of relevant pathways, are given in Flow Charts 1 and 2.

To overcome the limitations created by the multi-factorial cellular and extracellular response to stent induced injury and adverse as well as exaggerated tissue response to materials bound to the stent, it is required that the drug should be delivered for a prolonged period of time (Drachman et al., 2000).

Several approaches have been investigated to achieve continuous drug delivery from stents (Riesen & Isner, 1994), which include:

1. Coating of metallic stent with drug eluting biocompatible polymer.
2. Seeding of metallic stent with genetically modified endothelial cells to elute agent such as tissue plasminogen activating factor (t-PA).



Proposed Mechanism of Restenosis, Together with Drugs Used to Interrupt Paths of Relevant Pathways. (From Mintz et al., 2003; Montalescot, Choussat, and Collet, 2001; Ross, 1993; Von Langenhore, Kutryk, and Surruys, 2000.)

3. Designing biodegradable polymeric drug eluting stents. Such polymers are listed in Appendix 2.

The stent is placed in the dilated segment of the artery to mechanically prevent abrupt closure and restenosis. Unfortunately, even when the implantation of the stent is accompanied by aggressive and precise antiplatelet and anticoagulation therapy typically by systemic administration, the incidence of thrombotic vessel closure or other thrombotic complication remains significant and the prevention of restenosis is not as successful as desired. Furthermore, an undesirable side effect of the systemic antiplatelet and anticoagulation therapy is an increased incidence of bleeding complications, most often at the percutaneous entry site.

BALLOON ANGIOPLASTY VS. CORONARY STENTS

Various trials have been performed to establish superiority of coronary stents over the balloon angioplasty, such as:

1. Benstent I (Belgium Netherland Stent Trial I) using uncoated stents (Serruys et al., 1994).
2. Stress (Stent Restenosis Study) using uncoated stents (Fischman et al., 1994).
3. Benstent II (Belgium Netherland Stent Trial II) using heparin coated stents (Serruys et al., 1998).

The number of patients and type of therapy in each trial group are given in Table 1 and Results are shown in Table 2.

TABLE 1 Number of Patients According to Type of Therapy

S.N.	Name of trial group	Number of patients		
		Stent group	Balloon angioplasty group	Total
1.	Benstent I (Serruys et al., 1994).	262 (1)[a]	258 (3)[a]	520 (4)[a]
2.	Stress (Fischman et al., 1994).	207 (2)[a]	203 (1)[a]	410 (3)[a]
3.	Benstent II (Serruys et al., 1998).	413	410	823

[a]Excluded.
Source: Fischman et al. (1994); Serruys et al. (1994); Serruys et al. (1998).

Quantitative results in all these trials show higher initial gain immediately after stenting in lumen diameter due to its stricture and the prevention of elastic recoil. However, at later stage, more hyperplasia and late loss have been reported though the net result of lumen gain is still in favor of stented arteries gain is still in favor of stented arteries (Bar et al., 2000). Also, thrombosis and neointimal formation leading to restenosis (Gunn & Cumberland, 1999; Hertzog et al., 1999; Montalescot et al., 2001; Ross, 1993; Von Langenhore et al., 2000) have been reported with bare stents.

Disadvantages of uncoated stents are partially overcome by coated stents as supported by the study of Drachman et al. (2000) as depicted in Fig. 1.

Clinical data also suggest the superiority of drug coated stents over the uncoated stents. Examples include:

Benstent II trial: Results as in Table 1 and Table 2 using heparin-coated stents (Serruys et al., 1998).

RAVEL trial: Performed on 238 patients with discrete nonocclusive coronary stenoses randomized to receive a bare and sirolimus coated Velocity BX stents wherein 0% restenosis in sirolimus coated vs. 26% bare stent was observed (Morice et al., 2002).

ASPECT (Asian Paclitaxel Eluting-Stent Clinical Trial): performed on 177 patients and randomized to low-dose paclitaxel, high-dose paclitaxel, or bare stents. At 6 months, significant reduction in restenosis rate in the coated stent group was observed and results also indicated a clearcut dose-response relationship (Mintz et al., 2003).

TAXUS I trial: It was the first trial evaluating safety and feasibility of the TAXUS NIRx stent system compared with bare NIR stents (control) (Boston Scientific Corp) for treatment of coronary lesions. In this feasibility trial, the TAXUS slow-release stent was well tolerated and showed promise for treatment of coronary lesions, with significant reductions in angiographic and intravascular ultrasound measures of restenosis (Eberhard et al., 2003).

SCORE (Study to compare restenosis rate between QueST and QuaDS-QP2) trial: It was a randomized, multicenter trial comparing 7-hexanoyltaxol (QP2)-eluting stents (qDES) with bare metal stents (BMS) in the treatment of de novo coronary lesions to evaluate the acute expansion property and long-term

TABLE 2 Comparative Results of Trials

S. N.	Variables	Benstent I (Serruys et al., 1994)	Stress (Fischman et al., 1994)	Benstent II (Serruys et al., 1998)
		Angioplasty/stent	Angioplasty/stent	Angioplasty/stent
1.	Restenosis rate	1.45	1.33	1.93
2.	Gain (mm)[a]	0.69	0.72	0.65
3.	Loss (mm)[b]	0.49	0.51	0.57
4.	Net gain (mm)[c]	0.86	0.82	0.72

[a]Gain (minimal lumen diameter after the procedure minus values obtained before the procedure).
[b]Loss (minimal lumen diameter after the procedure minus the follow-up value).
[c]Net gain (minimal lumen diameter at follow-up minus values obtained before the procedure).
Source: Fischman et al. (1994); Serruys et al. (1994); Serruys et al. (1998).

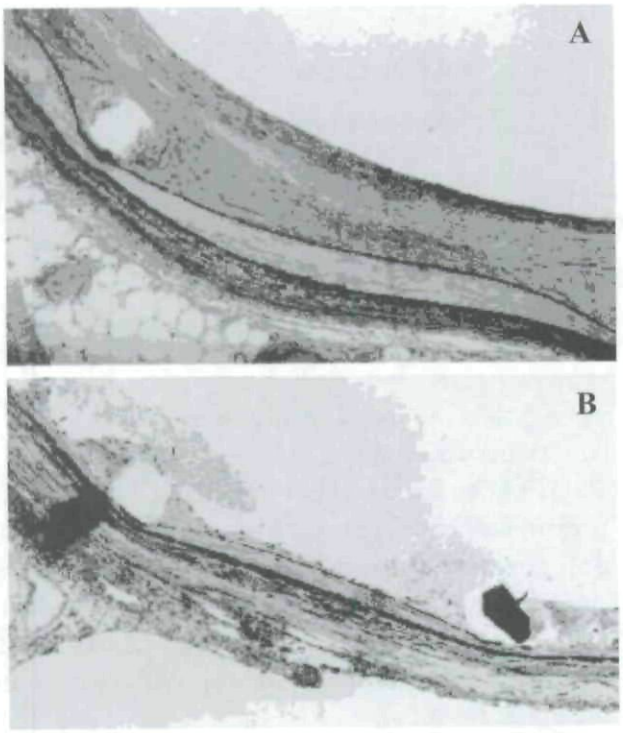


FIGURE 1 Photomicrographs Show Rabbit Iliac Arteries Stained with Verhoeff's Tissue Elastin Stain 6 Months after Balloon Denudation and Stent Implantation. (A) After Uncoated Stent Implantation, a Thick Neointima Separates the Lumen from the Internal Elastic Lamina. (B) After Implantation of a Poly (Lactide-co-S-Caprolactone)-Coated Paclitaxel-Releasing Stent, No Neointima is Present upon the Internal Elastic Lamina with Only a Thin Cap Covering the Stent Struts. Reproduced with Permission from the Journal of the American College of Cardiology 36 (7), © 2000 American College of Cardiology Foundation, in Print and Electronic Format in English Only. Permission Granted Ref: FVandanaDekkarMM4-03.

neointimal responses of qDES compared with BMS as assessed by intravascular ultrasound (IVUS). Results revealed that qDES had comparable acute mechanical and superior long-term biological effects to BMS (Kataoka et al., 2002).

STENT

Stent Design

The underlying structure of the stent can be any stent design, whether of the self-expanding type or of the balloon-expandable type and whether metal or polymeric. The stent could be made of virtually any biocompatible material having physical properties suitable for the design. Although the stent surface should be clean and free from contaminants that may be introduced during manufacturing, it requires no particular surface treatment in order to retain the coating applied. Both the inner and outer surfaces of the stent may be provided with the coating (Barry & Palaqsis, 2001).

Stents are generally designed in one of two configurations such as coil-type stents, i.e., wire stents in the form of coils, spirals, or the like, with or without spines e.g., GR-II® (Cook Inc.) and patterned stents including slotted tube stents, criss-cross tubular stents, braided stents, hexagonal stents, nets, articulated stents, and the like. Patterned stents are generally preferred over coil stents because they provide more radial support for surrounding body lumen.

Stents along with their name, strut design, and name of companies that market them, are given in Table 3.

Dimensions of Stents

Dimension depends on lumen diameter where it is to be placed and is represented in Table 4.

Advantages of Stents

Various advantages of stents are listed below:

1. Prevents elastic recoil.
2. Provides mechanical support to vein, e.g., when used along with veins during grafting as a stent graft.
3. Large initial lumen gain immediately after the procedure and large overall lumen gain.
4. Provides means of localized drug delivery to prevent restenosis.
5. Use of suitable coating, either polymer alone or along with the drug can modify surface properties and performance.

Stent Thrombosis

Acute stent thrombosis occurs within an hour of stenting and is almost always due to incomplete stent expansion and vessel disection (Brim & Grossman, 1998; Von Langenhore et al., 2000). High-pressure balloon expansion can overcome this problem and reduce the incidence to less than 1% of stent procedure (Mak et al., 1996). Subacute thrombosis on the other hand is more common. It can occur 30 days after stenting up to 9 months (Costa et al., 1999). It has been commonly found in hospital discharge patients and ischemic sequelae and death are common (Von Langenhore et al., 2000). Various factors that affect stent thrombosis are device-related factors including

TABLE 3 Details of Marketed Stents

Type of stent and their name	Marketing company	Strut design
Tubular stent		
1. ACS Multi Link Tristar	Guidant vascular International group	Laser cut trans tubular in exact corrugated ring
2. Bestent Bravastent	Medtronic AVE Sonata Rosa, CA, USA	A cylindrical cut in serpentine mesh with no welding point
3. Jostent	Jo Med A.B[a] Helsingborg swiden	Rounded edge
Self-expandable stent		
1. Magic Wall Stent	Boston Scientific SciMed Maple Grove, MN, USA	Rounded wire
2. SciMed Radius Stent	SciMed Live System Maple Grove, MN, USA	Square
Coil stent		
1. Coronary Angio Stent	Angio Dynamics Gen Falls, NY, USA	Continued coil
2. Freedom Coronary Stent	Global Therapeutic Inc. a Cook. Co. Broomfield, USA	Round wire
Ring stent		
AVE, GFX Stent	Arterial Vascular Eng. Inc. Santa Rd., CA, USA	Eliptio-rectangular Electro polished
Multidesign stent		
NIR and NIRoyal Coronary Stent	Medinol/SciMed Life System Maple Grove, MN, USA	Square, transform flexible to rigid
Biodegdrable Stent		
Igaki Tami Stent	Igaki Medical Planning Kyoto, Japan	Zigzag helical coil

[a]Jo Med A.B. Helsingborg swiden has been taken over by Abbott Vascular, Inc.
Source: Serruys and Kutryk, (2000).

surface interactions and rheological factors and patient-related factors including vessel characteristics such as vessel size, anatomic location, and stent placement; hemostatic predictors, and technique related problems.

TABLE 4 Dimensions of Stents Used in Various Body Parts

Type	Length	Diameter
Coronary stents (Regon, 1998)		
Small vessel version	16.0 to 28.0 mm	2.0 to 3.25 mm
Slandered version	16.0 to 28.0 mm	3.0 to 6.0 mm
Urethral stent (Latal et al., 1994)	4.0 mm	8.0 mm[a]
Esophageal stent (Roy et al., 1992)	2.0 cm	1.0 cm

[a]Expanded diameter.

CORONARY STENT COATING

Importance of Stent and Surface Properties

The performance of a stent in its vascular surroundings is determined by a number of parameters (van Beuskeom & Vander Giessen, 2000):

Stent surface properties include longitudinal flexibility, strut geometry and radial strength, chemistry, and charge topography.

Humeral cellular determinants include plasma proteins, inflammatory proliferative mediators, platelets, leukocytes, lesion morphology, compositional vascular geometry, and genetic predisposition.

Stent backbone–various surface properties of a stent that can be modified are given in Table 5.

Different metal and metal alloys used for construction of stents include (Zhong & Sheng-P, 2001; van Beuskeom & Vander Giessen, 2000) stainless steel 316 L, tantalum, platinum-iridium alloy, nickel-titanium

TABLE 5 Surface Properties of Stent that can be Modified

Surface modification	Techniques
Roughness and smoothing	Particle blasting, etching, electro polishing
Chemical modification	Oxidation, plasma treatment
Ion bombardment and implantation	By using Au, Ir, ^{32}P
Coating	Dip coating, spray coating, plasma polymerization

Source: van Beuskeom and Vander Giessen, (2000).

alloy and various synthetic polymers. Various drugs and polymeric coating materials that are incorporated in coating are listed in Appendix 1 and Appendix 2, respectively.

Techniques for Applying Polymeric Coating

Various methods used currently as covered in patents as well as proposed methods for other devices applicable to stents are outlined below.

Dip Coating

On a large scale this coating is done by a method developed by Bio coat Corporation for catheter coating. The process includes:

1. Pretreatment of substrate with isopropyl alcohol (2-propanol).
2. Application of first polymeric coat with solid content 5–20%.
3. Curing to improve the adhesion of coating material to the stent surface by placing the coated stent at a temperature of 45–60°C for 30–60 minutes leading to crosslinking of polymeric material.
4. Application of second coat, usually of drug substance as included in Appendix 1.
5. Curing similar to step 3 to induce binding of the drug to polymeric material.
6. Washing using organic solvent in which coating material and drug is insoluble followed by drying.
7. Sterilization either using ethylene oxide as a chemical means or β-rays or electron beam rather than the γ-rays in case of radiation (Sadat et al., 1993).

Porous Coating

A suitable porous coating (Tuch, 1999) can be provided, e.g., phase inversion precipitation of the polymer in the over layer. According to this technique, a solution of a polymer is prepared in a mixture of two miscible solvents, one being a poorer solvent for this polymer and less volatile than the other solvent. When the solution is allowed to dry, the good solvent evaporates, causing the polymer to slowly precipitate and resulting in an opened, porous structure after complete drying. For example, when using poly (L-lactic acid) as the polymer, a suitable solvent composition can include about 40/60% (w/w) iso-octane/chloroform solution (poorer/good solvent). The nature of the ingredients and their relative concentrations determine the size of pores. Pores in the range of about 0.5 to 10 microns in diameter are suitable. A porous coating may also result under less controlled conditions from application of the over layer at high humidity conditions in which atmospheric moisture condenses on the stent due to localized cooling of the stent as the solvent evaporates.

The coating composition may include other additives like leveling agents, stabilizers, pH adjustment agents, deforming agents, cosolvents, etc., if compatible with the intended use of the coated substrate.

Plasma Polymerization

Monomers in a gas phase that can be activated by radio frequency (RF) waves to yield a polymer on stent surface can be utilized in this technique. Such monomers include silicone-based monomers such as cyclic or acyclic siloxanes, silanes, silylimidazoles; fluorine-based monomers such as hydro fluorocarbons; aliphatic or aromatic hydrocarbons; acrylic monomers, and combinations thereof. The monomer gas may have functional groups that facilitate attachment of drug agents by covalent bonding. Any appropriate polymer for the modifying or modulating layer is selected to have a porosity that provides the modifying or modulating effect as described above, e.g., diamondlike carbon is produced when carbon is deposited under energetic bombardment. The instantaneous local high temperature and pressure induce a proportion of the carbon atoms to bond as diamond. These conditions assist chemical vapor deposition. Components to be coated are placed on an electrode that is capacitively

coupled to a radio frequency source. In a cleaning stage, an inert gas such as argon is introduced. The RF field ionizes the argon and the positive ions bombard and clean the substrates. The cleaning stage is followed by the deposition stage in which a carbon containing gas such as acetylene is introduced to provide the energetic carbon ions [Zhong & Sheng-P, 2001; www.Brunel.ac.uk (accessed May 2002)].

TECHNIQUES FOR IMMOBILIZATION OF DRUG

Drugs can be immobilized on stent surface by using following techniques.

Covalent Immobilization

Covalent immobilization of drugs to a biomaterial consists of activating the material in such a way that coupling between the biomaterial and functional groups on the drugs (–COOH, –OH, $-NH_2$) can be achieved. Thromboresistant surfaces are not necessarily obtained using these processes. The drug, e.g., heparin can be bound too tightly to the surface due to the high abundance of functional groups on the heparin or coupling may result from bonds between the active pentasaccharide sequence on the heparin and the biomaterial, preventing activation of AT-III and thus catalytic deactivation of the proteases. In order to obtain truly antithrombogenic surfaces, proper immobilization of biomolecules is the key.

Reductive Amination

A method has been suggested to activate heparin via a controlled nitrous acid degradation step resulting in degraded heparin molecules of which a part contains a free terminal aldehyde group. Heparin in this form can be covalently bound to an aminated surface in a reductive amination process. Although the molecule is degraded and as a result shows less catalytic activity in solution, the end-point attachment of this type of heparin to a surface results in true antithromogenicity due to the proper presentation of the biomolecule to the surface. In this fashion, the molecule is freely interacting with AT-III and the coagulation enzymes preventing the generation of thrombi and micro emboli (www.Brunel.ac.uk).

Cross-Linking Agent

Particularly preferred polyfunctional cross-linking agents for use are polyfunctional aziridines and polyfunctional carbodimides having more than two functional groups per molecule. Furthermore, it should be noted that a combination of polyfunctional cross-linking agents might be used. The functional groups on the cross-linking agent can serve two purposes (Zhong & Sheng-P, 2001); the first purpose is to cross link the first polymeric coating and the second purpose is to participate in covalent bonding with the organic acid groups present in the second coating. The concentration of cross-linking agent if inadequate, bonding of the second layer is weak as evident by the lack of wear resistance. Such coatings can be easily wiped off the substrate to which they are applied.

By Applying Aminosilanes

On metal or glass surfaces, the binding of the base layer of multilayer coatings can be a problem since there is no organic structure to provide covalent bonds between the metal or glass substrate and the grafted base layer. The problem of binding to metals and glass has been removed by applying aminosilanes to adhere to the surface and then attaching the biomolecule to the aminosilane through the amine functionality of the aminosilane. However, the use of aminosilanes in coatings of this sort has not been very good in producing a surface with a high level of both bioeffectiveness and stability (Barry & Palaqsis, 2001).

TECHNIQUES FOR DRUG COATING

Various techniques used for drug coating are given below.

Application in Multiple Thin Layers

The drug coating may be applied to the surface simply from aqueous solution or dispersion, e.g., heparin can be applied from aqueous solution onto a stent body and allowed to dry. The porous polymeric over layer can then be applied to the heparin-coated stent body such that it controls the release of heparin

from the coating. The total amount of heparin to be included on the stent can be readily controlled by applying multiple thin coats of the solution while allowing it to dry between coats. The overall coating should be thin enough (0.001 inch thick) so that it will not significantly increase the profile of the stent for intravascular delivery by catheter. The adhesion of coating and the rate at which the heparin is delivered can be controlled by selection of an appropriate bioabsorbable or biostable polymer for the porous over layer. This can be accomplished while maintaining the correct therapeutic dosage by applying to a drug-coated device, a thin coating over layer, or several thin over layers of a polymer in a solvent while drying the device between each coating layer (Tuch, 1999).

Bead Coating

The surface concentration of drug on the device can be adjusted by varying the hydrophilicity/hydrophobicity of the base to which the aqueous drug coating is applied. For example, in a tantalum stent, a coating of a hydrophobic polymer can be applied to the stent as an under layer to receive the aqueous heparin solution. When applied to this surface, the aqueous solution of heparin forms beads of heparin on some portions of the stent surface while other portions of the surface are relatively free of the drug. The porous over layer can then be applied over the polymeric under layer to encapsulate the beads of drug and secure them to the stent surface. If a more uniform surface is desired, a hydrophilic polymer can be applied as an under layer or the polymeric under layer can be provided with a plasma treatment to introduce hydrophilic chemical groups onto the polymer surface (Tuch, 1999).

By Using Cross Linking Agent

Cross-linking agent can be used in two ways:

Bifunctional Agent

As per this methodology, the medical device has a coating such as a biocompatible agent, for example, heparin or streptokinase, and a chemical linking moiety. This chemical linking moiety has a structure represented by A-X-B, wherein A is a photochemically reactive group, B is a reactive group that responds to a different stimulus than A and X is a noninterfering skeletal moiety, such as a C_1–C_{10} alkyl. The biocompatible agent is covalently linked to the surface of the medical device via the linking moiety. In particular, the photochemically reactive group (A), when activated, covalently binds to the surface of the medical device. The remaining unreacted reactive group (B), when activated covalently, binds to the biocompatible agent and anchors it to the surface of the medical device. Such devices however, are difficult and inefficient to produce because they require the use of two separate stimuli to activate the A and B groups of the chemical linking moiety, respectively. Furthermore, the UV light used to activate the A group of the chemical linking moiety for covalently binding it to the surface of a medical device can denature bioactive agents. Such denaturization reduces the bioactivity of such agents and can result in undesirable medical outcomes, such as clot formation in the case of an antithrombogenic agent (Zhong, 1999).

Polyfunctional Agent

This technique is a modification of the above technique to improve the bioactivity of the drug by incorporating a polyfunctional cross-linking agent that is reactive with the organic acid groups of the polymer in first coating and drug in second coating. After application of first coating, it is left to dry in order to cross-link and render the first coating substantially water-insoluble. The excess unreacted polyfunctional cross-linking agent remains present in the cross-linked first coating. A continuous bioactive surface coating is then formed on the first coating by contacting the dried first coating layer with a second coating of an aqueous solution or dispersion of a bioactive agent or a derivative thereof, which contain an organic acid functional group or metal salt thereof. The first and second coatings are then dried to covalently bond the organic acid functional groups of the bioactive agent to the polymer through the excess unreacted polyfunctional cross-linking agent (Zhong, 1999).

Coating with Polymeric Blend

In this technique, the active agent is dispersed in at least part or portion of the coating. The coating can include a blend of a first copolymer having high release rate (more hydrophilic) and a second copolymer having

lower release rate relative to the first. The first and second copolymers are preferably erodible or biodegradable, e.g., the first copolymer includes a polylactic acid/polyethylene oxide (PLA-PEO) copolymer and the second copolymer includes a polylactic acid/polycaprolactone (PLA-PCL) copolymer. The relative amounts and dosage rates of active agent delivered over time can be controlled by controlling the relative amounts of the faster releasing polymers relative to the slower releasing polymers. For higher initial release rates, the proportion of faster releasing polymer can be increased relative to the slower releasing polymer. If most of the dosage is desired to be released for a long time period, most of the polymer can be the slower releasing polymer. Spraying the stent with a solution or dispersion of polymer, active agent, and solvent can coat the stent. The solvent can be evaporated, leaving a coating of polymer and active agent. The active agent can be dissolved and/or dispersed in the polymer. In some cases, the copolymers can be extruded over the stent body.

For example, one coating includes 20% by weight PLA-PEO and about 80% by weight PLA-PCL copolymers and another coating includes about 50% by weight PLA-PEO copolymer and about 50% by weight PLA-PCL copolymer. The one having about 20% PLA-PEO and 80% PLA-PCL delivers the active agent over a longer time period, but with a lower initial release, relative to that having the 50%/50% PLA-PEO/PLA-PCL combination. The relative amounts of PLA-PEO and PLA-PCL can be adjusted to achieve the desired combination of high initial dosage rate and subsequent lower but longer lasting dosage rate (Yang et al., 2001).

Endothelial Cell Coating

In this method of medicating stents, the stents are seeded with endothelial cells. Briefly, endothelial cells can be seeded onto stainless steel stents and grown until the stents are covered. The cells can therefore be delivered to the vascular wall to provide therapeutic proteins (Hossainy et al., 2001).

Drug Loading in Depots

This technique is applied for loading a substance into the depots. The method is applicable to any type of porous prosthesis. A first fluid having a substance added therein is applied to a porous prosthesis. During the application, the first fluid containing the substance is capable of penetrating into the pores. The first fluid is removed by evaporation and a second fluid (not capable of significant penetration into the pores) is applied to the prosthesis, having a contact angle greater than about 90° (Rox et al., 1995). A therapeutic substance is added to a first fluid or solvent and dispersed throughout the first solvent so that it is in a true solution–saturated or supersaturated with the solvent or suspended in fine particles in the first solvent. If the therapeutic substance is suspended in particles in the first solvent, the pore size and the diameter of the opening of the pores are to be sufficiently large in comparison to the size of the particles to facilitate loading and unloading of the stent, e.g., suitable pores have a pore size that is more than 10 times the particle size of a suspended therapeutic substance. The first solvent can be virtually any solvent that is compatible with the therapeutic substance and has high capillary permeation, i.e., contact angle less than 90°.

CONTROLLING DRUG RELEASE

To control the release of therapeutic agents, various mechanisms can be utilized.

Diffusion Controlled

Polymeric Over Layer

With an aqueous coating of heparin placed on the stent, the polymer over layer is critical to the control of elution from the implanted stent since heparin is water-soluble and would otherwise elute immediately without providing a desired long-term benefit. For example, spraying a solution or dispersion of heparin onto the stent body can provide an aqueous coating of heparin. When the applied heparin layer is dry, a solution of chloroform and poly (L-lactic acid) can be used to form the over layer by spraying the polymer solution onto the stent (Tuch, 1999).

Matrix

Devices are known having a monolithic layer or coating incorporating a heterogeneous solution and/or dispersion of an active agent in a polymeric

TABLE 6 List of a Few FDA-Approved Stents

Product name	Type	Approval date	Manufacturer
Wallstent TIPS Endoprosthesis	Liver Stent	Sept. 29, 1995	Schneider USA Inc. of Plymouth, MN
UroLume Endoprosthesis	Urinary Stent	May 7, 1996	American Medical Systems of Minnetonka, MN
BiodivYsio™ AS PS (phosphorylcholine) Coated Stent Delivery System	Coronary Stent	September 29, 2000	Abbott Vascular Devices
BeStent™ 2	Coronary Stent	October 16, 2000	Medtronic, Inc. 800 53rd Avenue Northeast, Minneapolis, MN 55421
IntraCoil® Self-Expanding Peripheral Stent	Vascular Stent	January 10, 2001	Sulzer IntraTherapeutics Inc. 651 Campus Drive St. Paul, MN 55113
PALMAZ® Balloon-Expandable Stent for Renal Arteries	Vascular Stent	July 10, 2002	Cordis Corporation 14201 N.W. 60th Avenue, Miami Lakes, FL 22014
Neuroform Microdelivery Stent System SMART Therapeutics	Intravascular Stent	September 11, 2002	Inc. 2551 Merced St. San Leandro, CA 94577 USA
CYPHER™ Sirolimus-Eluting Coronary Stent	Coronary Stent	Apr 24, 2003	Cordis Corporation 14201 N.W. 60th Avenue, Miami Lakes, FL 22014
Absolute 0.035 Self-Expanding Biliary Stent System	Biliary Stent System	Nov 10, 2003	Guidant Corp.
Selfx XPERT Biliary Stent Models ex8l2005 ex8l3	Biliary Stent	Dec 10, 2003	Abbott Laboratories
Express Coronary Stent System	Coronary Stent	Jan 07, 2004	Boston Scientific Scimed Inc.
Oasis Biliary Stent Introduction System	Biliary Stent	Feb 20, 2004	Wilson-Cook Medical Inc.
Taxus Express2 Paclitaxel-Eluting Coronary Stent System	Coronary Stent	Mar 04, 2004	Boston Scientific Corp.
Multi-Link Vision Coronary Stent System	Coronary Stent	Mar 22, 2004	Guidant Corporation Advanced Cardiovascular System
Taxus Express 2 Coronary Stent System	Coronary Stent	May 14, 2004	Boston Scientific Corp.

Source: www.fda.gov (accessed June 15, 2004).

substance, where the diffusion of the agent is rate limiting as the agent diffuses through the polymer to the polymer-fluid interface and is released into the surrounding fluid. In such devices, a soluble substance is also dissolved or dispersed in the polymeric material, such that additional pores or channels are left after the material dissolves. A matrix device is generally diffusion limited with the channels or other internal geometry of the device playing a role in releasing the agent to the fluid. The channels can be

preexisting channels or channels left behind by the released agent or other soluble substances.

Erosion Controlled

Erodible or degradable devices typically have the active agent physically immobilized in the polymer. The active agent can be dissolved and/or dispersed throughout the polymeric material. The polymeric material is often hydrolytically degraded over time through hydrolysis of labile bonds, allowing the polymer to erode into the fluid, releasing the active agent into the fluid. Hydrophilic polymers generally have a faster rate of erosion relative to hydrophobic polymers. Hydrophobic polymers are believed to have almost purely surface diffusion of active agent, having erosion from the surface inwards. Hydrophilic polymers are believed to allow water to penetrate the surface of the polymer, allowing hydrolysis of labile bonds beneath the surface, which can lead to homogeneous or bulk erosion of polymer.

AMOUNT OF THE DRUG TO BE INCORPORATED

The amount of the drug incorporated on the stent surface depends upon the surface area of the stent, therapeutic dose, and also on the amount of polymeric coating. For a cytotoxic drug, total amount is also limited, e.g., heparin is incorporated in amount of 0.5–10% (about 2% by weight of first coat). However, in the case of Taxol, it varies from 0.6–60 mg/mm (Tuch, 1999) of stent surface, but no more than 200 mg/stent.

MARKET STATUS OF STENTS

Uncoated and polymer coated stents are available in the international market. Various companies marketing them are listed in Table 3. The list of FDA-approved stents is exhaustive and a few examples are listed in Table 6 [www.fda.gov (accessed June, 15, 2004)]. The current coronary stent market is $2.3 billion [http://abbott.com/ (accessed August 2004)] and with drug-eluting stents, it is expected to grow to twice its current size [http://www.mindbranch.com/ (accessed August 2004)].

The high incidence of vascular diseases in India has prompted MNCs to invade the Indian market, e.g., coated stents for treatment of in-stent restenosis were expected to be marketed in India by Cordis Corporation [Drug coated stent may prevent clogging of arteries, 2002; http://www.hinduonline.com/ (accessed August 2004)]. The S-7 stent manufactured by Medtronics Inc., one of the world's leading companies engaged in producing these devices, is under a premarketing trial in India and is therefore being supplied free of cost to a number of cardiologists in Pune, Bangalore, New Delhi, and Mumbai [www.news/index.htm (accessed May 2002)]. Indian companies have also realized the potential of stents. Sahajanand Vascular Technovention, Surat, India has begun European trials (SIMPLE-1 and SIMPLE-2). This Indian company's Infinnium, a paclitaxel-eluting stent, uses a Millennium (a slotted tube stainless steel) stent, coated with four layers of biodegradable polymer. The company has filed for a CE Mark based on SIMPLE-1 trial data [http://www.trends-in-medicine.com/ (accessed August 2004)]. Another player from India is Vascular Concepts, Bangalore [http://www.hinduonline.com/ (accessed August 2004)]. The Cardiovascular Technology Institute (CTI) in collaboration with Society of Biomedical Technology (SBMT) India has also developed a stent [http://www.newindiadigest.com (accessed August 2004)].

INDICATIONS

1. To provide physical support to passageways.
2. To carry therapeutic substances for local delivery of the substances to the damaged vasculature as mentioned in Appendix 1, used to prevent thrombosis of the coronary lumen, to inhibit development of restenosis and to reduce post-angioplasty proliferation of the vascular tissue.
3. Localized delivery of an antiproliferative agent is also useful for the treatment of a variety of malignant conditions characterized by highly vascular growth. In such cases, the stent could be placed in the arterial supply of the tumor to provide a means of delivering a relatively high dose of the antiproliferative agent directly to the tumor.
4. Dopamine or a dopamine agonist such as bromocriptine mesylate or pergolide mesylate is useful for

the treatment of neurological disorders such as Parkinson's disease. The stent could be placed in the vascular supply of the thalamic substantia nigra for this purpose, or elsewhere, localizing treatment in the thalamus.

5. By applying proangiogenic/angiogenic agent it can be used for angiogenesis and vessel repair (Riesen & Isner, 1994; Swanson et al., 2003a, 2003b).

CONCLUSION

Stents were first introduced in clinical practice in the early 1990s (Jacob, 1999; Toppl, 1994) as mechanical (Keiser & Uprichard, 1997) means to open stenosed blood vessels. However, disadvantages like thrombosis and late lumen loss were associated with thrombosis. To prevent these events, it was postulated to coat the stents with antirestenotic/antithrombotic therapeutic agents using biodegradable polymers so as to provide smooth and biocompatible, surface-releasing drug for a prolonged period of time. This has met with phenomenal success as evident by statistics. Implantation of the stent covers 60–70% of all percutaneous interventional procedures in comparison to only 15% in 1994 (Jacob, 1999). With improvement in stent design, coating technique, and discovery of potent therapeutic agents, the scope of stent usage is bound to increase beyond cardiovascular intervention (Arya et al., 2001; Joshi et al., 2001; Latal et al., 1994; Multanen et al., 2000; Ragheb et al., 2001; Roy et al., 1992) and the stent may emerge as a device of choice for site-specific, localized drug-delivery systems.

APPENDIX 1

Classes of useful bioactive agents (Chronos et al., 1995; Eriksson et al., 1995; Fleser et al., 1995; Folts et al., 1995; Gunn et al., 1995; Jacob, 1999; Keiser & Uprichard, 1997; Makkar et al., 1995; Ragheb et al., 2001; Riesen & Isner, 1994; Rox et al., 1995; Swanson et al., 2003a, 2003b; Toppl et al., 1994; van Beuskeom et al., 2000; Wu et al., 2001)

Antibiotic agents: Penicillins, Cephalosporins, Vancomycins, Aminoglycosides, Quinolones, Polymyxins, Erythromycins, Tetracyclines, Chloramphenicols, Clindamycins, Lincomycins, Sulfonamides, their homologs and analogs.

Antitumor agents: Paclitaxel (taxol), 2′-succinyl-taxol, 2′-succinyl-taxol triethanolamine, 2′-glutaryl-taxol, 2′-glutaryl-taxol triethanolamine salt, 2′-O-ester with N-(dimethylaminoethyl) glutamide HCl, Docetaxel, Methotrexate, Azathioprine, Vincristine, Vinblastine, Fluorouracil, Doxorubicin hydrochloride, Mitomycin, Cytotoxic fusion proteins, Transforming growth factors (TGFs), Epidermal growth factors (EGFs), Vascular endothelial growth factor (VEGF), Basic fibroblast growth factors (b FGFs), and Interleukin, etc.

Antiviral agents: Amantadines, Rimantadines, Ribavirins, Idoxuridines, Vidarabines, Trifluridines, Acyclovirs, Ganciclovirs, Zidovudines, Foscarnets.

Cytostatic or antiproliferative agents: Angiopeptin.

Angiotensin converting enzyme inhibitors: Captopril, Lisinopril, Antiplatelets, Anticoagulants, Antifibrin, Antithrombin which includes Sodium heparin, Low molecular weight heparins, Heparinoids; Hirudin, Argatroban, Forskolin, Vapiprost, Prostacyclin and prostacyclin analogues, Dextran, D-phe-pro-arg-chloromethylketone(synthetic antithrombin), Dipyridamole, Glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody-m7E3.

Calcium channel blockers: Nifedipine, Nimodipine.

Others: Fibroblast growth factor (FGF) antagonists, Fish oil (omega 3-fatty acid), Histamine antagonists, Lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug), Monoclonal antibodies, Platelet-Derived Growth Factor (PDGF), Nitroprusside, Phosphodiesterase inhibitors, Prostaglandin inhibitors, Suramin, Seratonin blockers, Steroids, Thioprotease inhibitors, Triazolopyrimidine (a PDGF antagonist), Nitric oxide & NO doner like PNSO-BSA (a poly nitrosated albumin NO donor), Alpha-interferon, Interferon-γ, Genetically engineered epithelial cells, Dexamethasone, Radioactive isotope for prosthesis usage in radio therapeutic procedures, Phosphoric acid H_3PO_4, Palladium ^{103}Pd, Cesium ^{131}Cs, Iodine ^{125}I, Antimitotic agents, anti-inflammatory agents, Angiostatin agents, Endostatin agents, Cell cycle regulation agents, Genetic agents including antisence oligionucliotide. c-myc, c-fos, c-myb, including hormones.

APPENDIX 2

List of Coating Materials

Bioabsorbable polymers: Poly (ethylene terephthalate), Polyacetal, Poly (lactic acid), Poly (D, L-lactic acid), Poly (ethylene oxide)/poly (butylene terephthalate) copolymer, Polycaprolactone, Poly (lactide-co-glycolide), Poly (hydroxybutyrate), Poly (hydroxybutyrate-co-valerate), Polydioxanone, Polyorthoester, Polyanhydride, Poly (glycolic acid), Poly (glycolic acid-co-trimethylene carbonate), Polyphosphoester, Polyphosphoester urethane, Poly (amino acids), Cyanoacrylates, Poly (trimethylene carbonate), Poly (iminocarbonate), Copoly (ether-esters) (e.g. PEO/PLA), Polyalkylene oxalates, Polyphosphazenes (Zhong & Sheng-P, 2001; Yang et al., 2001; Ragheb et al., 2001; Rox et al., 1995; Tuch, 1999; Wu et al., 2001; Chronos et al., 1995; Suzuki et al., 2002; Zider et al., 1993)

Biomolecules: Fibrin, Fibrinogen, Cellulose, Starch, Collagen, Hyaluronic acid, Phosphoryl choline.

Biostable polymers: Parylene, Parylast, Polyethylene, Polyethylene teraphthalate, Ethylene vinyl acetate, Silicone, Polyethylene oxide, Polyurethanes,[a] Polyesters.

Other polymers, which can be used by dissolving and curing or polymerizing on the stent: Polyolefins, Polyisobutylene, Ethylene-alphaolefin copolymers, Acrylic polymers and copolymers, Vinyl halide polymers and copolymers (e.g., polyvinyl chloride), Polyvinyl ethers (e.g., polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile, polyvinyl ketones), Polyvinyl aromatics, (e.g., polystyrene), Polyvinyl esters (e.g., polyvinyl acetate), Copolymers of vinyl monomers with each other and olefins, (e.g., ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins and ethylene-vinyl acetate copolymers), Polyamides (e.g., Nylon 66 and polycaprolactam), Alkyd resins, Polycarbonates, Polyoxymethylenes, Polyimides, Polyethers, Epoxy resins, Polyurethanes, Rayon, Rayon-triacetate.

Cellulose: Cellulose acetate, Cellulose butyrate, Cellulose acetate butyrate, Cellophane, Cellulose nitrate, Cellulose propionate, Cellulose ethers, Carboxymethyl cellulose.

APPENDIX 3

Definitions of Few Related Terms

Stent: 1) Originally a compound used in making dental molds (Taber's Cyclopedic Medical Dictionary, 1978); 2) A material used to hold tissue in place to provide support for graft while heeling is taking place (Taber's Cyclopedic Medical Dictionary, 1978).

Stenosis: Constriction or narrowing of passage or orifice (Taber's Cyclopedic Medical Dictionary, 1978).

Angiography: X-Ray film of blood vessel taken in rapid sequence following the (Taber's Cyclopedic Medical Dictionary, 1978) injection of radio opaque substance into vessel. This technique has been used to define the size and shape of various veins, arteries of organ, and tissues.

Angioplasty: Plastic surgery upon blood vessel (Taber's Cyclopedic Medical Dictionary, 1978). Reconstitution or reopening of a blood vessel; may involve balloon dilation, mechanical stripping of the inside of the blood vessel, forceful injection of an elastic filamentous protein, or placement of a stent [www.radiologyinfo.org/glossary/glossary1.cfm (Accessed August 2004)].

Biomaterial: A material substantially insoluble in body fluid designed and constructed to place in the body or into the contact fluid of the body. Ideally, a biomaterial will not induce undesirable reactions in the body such as blood clotting, necrosis, tumerogenesis, allergic reaction, organ rejection or inflammatory reaction; will have the physical properties such as strength, elasticity, permeability, and flexibility required to function for the intended purpose; can be purified, fabricated, and sterilized easily; will substantially maintain its physical properties and function during the time that it remains implanted in or in contact with the body (Tuch, 1999).

Stent grafts: Tube in shaped graft supported by stent used to replace or create an anatomical passageway to provide a new conduit for fluid, e.g., blood. Grafts are

often made from a portion of a vein but can also be constructed from a synthetic material to form a synthetic graft. Like stents, synthetic grafts can be positioned percutaneously at the site of an aneurysm to prevent further dilation and possible rupture of the diseased vessel (Wu et al., 2001).

Bioabsorbable polymer: Bioabsorbable polymer is that which biodegrades or breaks down in the body and is not present sufficiently long after implantation to cause an adverse local response (Wu et al., 2001).

NOTES

[a]In this a class of polymer is also included called "water-borne polyurethanes" among which are the so-called internally emulsified water-borne polyurethane containing carboxylic acid groups and/or sulfonic acid groups, optionally as salts of such groups, as internal emulsifiers are particularly preferred. e.g., NeoRez by Zeneca Resins, for instance NeoRez-940, NeoRez-972, NeoRez-976, and NeoRez-981; under the trade name Sancure by Sancure, for instance Sancure 2026, Sancure 2710, Sancure 1601, and Sancure 899; under the trade names U21 and U21X by B.F. Goodrich; and under the trade names Bayhydrol LS-2033, Bayhydrol LS-2100, Bayhydrol LS-2952, and Bayhydrol LS-2990 by Bayer AG.

REFERENCES

Arya, M., Mostafid, H., Patel, H. R. H., Kellett, J. M., & Philp, T. (2001). The self- expanding metallic ureteric stent in the long-term management of benign ureteric strictures. *BJU International, 88*, 339–342.

Bar, F. W., Van der Veen, F. H., Benzina, A., Habets, J., & Koole, L. H. (2000). New biocompatible polymer surface coating for stents results in a low neointimal response. *Journal of Biomedical Materials Research, 52*, 193–198.

Barry, J. J., & Palaqsis, M. Loading and Release of Water-Insoluble Drugs. US Patent 6,306,166, October 23, 2001.

Biro, S., Sigall, C. B., Fu, Y. M., Speir, E., Pastan, I., & Epstein, S. E. (1992). In vitro effect of recombinant toxin targeted to fibroblast growth factor receptor on rat vascular smooth muscle endothelial cells. *Circulation Research, 71*, 640–645.

Brim, D. S., & Grossman, W. (1998). Fauci, A. S., Wilson, J. D., Martin, J. B., Kasper, D. L., Harssser, S. L., Hango, D. L. (Eds.). *Harrison's Principles of Internal Medicine* (14th ed). Vol. 1. New York: Mc Graw Hill-(Health Professions Division), pp. 1376, 1377.

Chronos, N. A. F., Robinson, K. A., Kelly, A. B., Taylor, A., Yianni, J., King, S. B., III, Harker, L. A., & Hanson, S. R. (1995). Thromboresistant phosporylcholine coating for coronary stents. *Circulation (Suppl. I), 92*(8), I 685.

Colombo, A., & Tobis, J. (2000). Evaluation to our approach to stenting. Colombo, A., & Tobis, J. (Eds.). *Techniques in Coronary Artery Stenting*. London: Martin Dunitz Ltd., pp. 111–127.

Costa, M. A., Sabat, M., & van der Giessen, W. J. (1999). Late coronary occlusion after intra coronary brachytherapy. *Circulation, 100*, 789–792.

Drachman, D. E., Edelman, E. R., Seifert, P., Groothuis, A. R., Bornstein, D. A., Kamath, K. R., Palasis, M., Yang, D., Nott, S. H., & Rogers, C. (2000). Neointimal thickening after stent delivery of paclitaxel: change in composition and arrest of growth over six months. *Journal of the American College of Cardiology, 36*(7), 2325–2332.

Drug coated stent may prevent clogging of arteries. In *Times of India*. 20th March 2002.

Eberhard, G., Sigmund, S., Karl, E. H., Ralf, M., Lutz, B., Ulrich, G., & Mary, E. R. (2003). TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation, 107*, 38–42.

Epstin, S. E., Sigall, C. B., Biro, S., Fu, Y. M., FitzGerald, D., & Pastan, I. (1991). Cytotoxic effect of recombinant chimeric toxin on rapidly proliferating vascular smooth muscle cells. *Circulation, 84*, 778–787.

Eriksson, B. I., Kalebo, P., Ekman, S., Baur, M., Lindbratt, S., & Bach, D. (1995). The most effective and safe profilaxis of thrombo embolic complication in patient undergoing total hip replacement with recombinent hirudin (Revasc CBG 39393 Cibba). *Circulation (Suppl. I), 92*(8), I 868.

Fleser, A., Martel, R., Burchard, M., Voisine, P., & Leclerc, G. (1995). Antisence oligonucleotide transfiction: effect of angioplasty cholesterol linkage and target section on delivery efficiency. *Circulation (Suppl. I), 92*(8), I 670.

Fischman, D. L., Leon, M. B., Baim, D. S., Schatz, R. A., Savage, M. P., Penn, I., Detre, K., Veltri, P. H. L., Ricci, D., Nobuyoshi, M., Cleman, M., Heuser, R., Almonmd, D., Teristein, P. S., Fish, R. D., Colombo, A., Brinker, J., Moses, J., Shaknovich, A., Hirshfeld, J., Bailey, S., Ellis, S., Randel, R. B. S., & Goldberg, S. (1994). A randomized comparison of coronary artery disease. *New England Journal of Medicine, 331*(8), 495–501.

Fishbein, I., Chorney, M., Rabinovich, L., Banai, S., Gati, I., & Golomb, G. (2000). Nanoparticulate delivery system of tryphosin for treatment of restinosis. *Journal of Controlled Release, 65*(1–2), 221–229.

Folts, J. D., Maalej, N., Kaeney, J. F., Jr., & Loscalzo, J. (1995). Coating plmaz-schatz stents with a unique NO donor renders them much less thrombogenic when placed in pig carotid arteries. *Circulation (Suppl. I), 92*(8), I 670.

Gunn, J., & Cumberland, D. (1999). Stent coating and local drug delivery: state of the art. *European Heart Journal, 20*(23), 1693–1700.

Hertzog, B. A., Thoms, C., & Sandor, M (1999). Cardiovascular drug delivery system. Edith, M., (Ed.). *Encyclopedia of Controlled Drug Release*. Vol. 1. New York: Jhon Wiely & Sons Inc., pp. 161–173.

Hidio, T., Kriji, I., Eisho, K., Kunihiko, K., Akiyoshi, K., Shigeo, M., Hidenori, K., Taskafumi, T., Seiichiro, M., & Hiromu, U. (2000). Initial six month result of biodegrable poly-L-lactic acid coronary stents in humans. *Circulation, 102*, 399–404.

Hossainy, Syed, F.A., & Chen, L. Porous Prosthesis and a Method of Depositing Substances Into the Pores. US Patent 6,287,628, September 11, 2001.

Jacob, A. K. (1999). Coronary stents—have they fulfilled their promise. *New England Journal of Medicine, 341*(26), 2005–2006.

Joshi, H. B., Newns, N., Stainthorpe, A., Macdonagh, R. P., Keeley, F. X., Jr. & Timoney, A. G. (2001). The development and validation of patient information booklet on uretric stent. *BJU International, 88*, 329–334.

Kataoka, T., Grube, E., Honda, Y., Morino, Y., Hur, S. H., Bonneau, H. N., Colombo, A., Mario, C. D., Guagliumi, G., Hauptmann, K. E., Pitney, M. R., Lansky, A. J., Stertzer, S. H., Yock, P. G., & Fitzgerald, P. J. (2002). 7-Hexanoyltaxol-eluting stent for prevention of neointimal growth: an intravascular ultrasound

analysis from the study to compare restenosis rate between QueST and QuaDS-QP2 (SCORE). *Circulation, 106*, 1788–1793.

Keiser, J. A., & Uprichard, A. C. G. (1997). Restenosis: is there a pharmacologic fix in the pipe line. August, J. T. (Ed.). *Advances in Pharmacology. 39*, 313–351.

Latal, D., Maraz, J., Zerhu, P., Susani, M., & Merberger, M. (1994). Nitinol urethral stents: long term results in dog. *Urological Research, 22*, 295–300.

Lincoff, A. M., Furst, J. G., Ellis, S. G., Tuch, R. J., & Topol, E. J. (1997). Sustained local drug delivery by a novel intravascular eluting stent to prevent restinosis in the porcine coronary injury model. *Journal of the American College of Cardiology, 29*(4), 808–816.

Mak, K. H., Belli, G., Ellis, S. G., & Moliterno, D. J. (1996). Sub-acute stent thrombosis: evolving issue and current concept. *Journal of the American College of Cardiology, 27*, 494–503.

Makkar, R. R., Eigler, N. L., Nakamura, M., Litvack, F. I., Badimon, L., Jordan, R., Bramfitt, J., & Kaul, S. (1995). Monoclonal antibody to IIb/IIIa receptor (m7E3) is highly effective in inhibiting acute stent thrombosis. *Circulation (Suppl. I), 92*(8), I 685.

Mintz, G. S., Tinana, A., Hong, M. K., Lee, C. W., Kim, J. J., Fearnot, N. E., Park, S. W., Park, S. J., & Weissman, N. J. (2003). Impact of preinterventional arterial remodeling on neointimal hyperplasia after implantation of (non-polymer-encapsulated) paclitaxel-coated stents: a serial volumetric intravascular ultrasound analysis from the asian paclitaxel-eluting stent clinical trial (ASPECT). *Circulation, 108*, 1295.

Montalescot, G., Choussat, R., & Collet, J. P. (2001). Glycoproteins IIb/IIIa receptors and primary stenting in acute myocardial infarction. *European Heart Journal, Suppl 3*(Suppl A), A3–A7.

Morice, M. C., Serruys, P. W., Sousa, J. E., Fajadet, J., Hayashi, E. B., Perin, M., Colombo, A., Schuler, G., Barragan, P., Guagliumi, G., Molinar, F., & Falotico, R. (2002). A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *New England Journal of Medicine, 346*, 1773–1780.

Multanen, M., Talja, M., Hallanvuo, S., Siitonen, A., Valimaa, T., Tammela, T. L., Seppala, J., & Tormala, P. (2000). Bacterial adherence to oflaxacine blend poly lactone coated self- reinforced L- lactic acid polymer urological stent. *BJU International, 86*, 966–969.

Ortu, P., KaMuragila, G. M., Robert, G., Flotte, T. J., & Hasan, T. (1992). Photodynamic therapy of arteries: a novel approach for the treatment of experimental intimal hyperplasia. *Circulation, 85*, 1189–1196.

Pastore, C., Bacha, P., Pickering, J. G., Riessen, R., TakeShita, S., & Inser, J. M. (1993). Local and systemic delivery of DAB389EGF fusion toxin inhibits neointimal thickening in balloon-injured rat carotid. *Circulation, 88*(Supplement I), I 310.

Pickering, J. G., Bacha, P., Weir, L., Jekanowski, J., Nichols, J. C., & Isner, J. M. (1993). Prevention of smooth muscle cell outgrowth from human atherosclerotic plaque by a recombinant cytotoxin specific for epidermal growth factor receptor. *Journal of Clinical Investigation, 91*, 724–729.

Prout, G. R., Lin, C. W., & Benson, R. (1987). Photo therapy with hematoporphyrin derivative in treatment of superficial transitional cell carcinoma of the bladder. *New England Journal of Medicine, 317*, 1251–1255.

Ragheb, Anthony, O., Bates, B. L., Fearnot, N. E., Kozma, T. G., & Voorhees, W. D., III. Coated Implantable Medical Device. US Patent 6,299,604, October 9, 2001.

Range, H. P, Dale, M. M., & Ritter, J. M. (1995). Homeostasis and thrombosis. New York: Chirchill Livingston; pp. 331–350.

Regon, J. W (1998). Biotechnology and drug discovery. In: Delgado, J. N., William, A. R. (Eds.). *Wilson and Gisvold's Textbook of Organic Medicinal Chemistry* (10th ed.) New York: Lippincott, 139–152.

Riesen, R., & Isner, J. M. (1994). Prospects for site specific delivery of pharmacological and molecular therapies. *Journal of the American College of Cardiology, 23*(5), 1234–1244.

Ross, R. (1993). Pathogenesis of atherosclerosis: a prospective for 1990's. *Nature, 362*(29), 801–803.

Rox, S. P., Tschopp, T. B., & Kirchhofer, D. (1995). A monoclonal anti tissue factors antibody and nepsaginin a thrombotic inhibitor are more antithrombotic than heparin in arterial thrombosis. *Circulation (Suppl. I), 92*(8), I 685.

Roy, S., Baijal, S. S., Ishiguchi, T., Hirose, M., Fukatsu, H., Itoh, S., Sakuma, S., & Kasai, K. (1992). Esophageal stenting with a self-expandable metallic device: a preliminary study. *Nagoya Journal of Medical Science, 54*, 59–66.

Sadat, T., Morisseau, D., & Ross, A. (1993). Electron beam sterilization of heterogeneous medical devices. *Radiation Physics and Chemistry, 42*, 491–494.

Scott, N. A., Robinson, K. A., Nunes, G. L., Thomas, C. N., Viel, K., King, S. B., III, Harker, L. A., Rowland, S. M., Juman, I., Cipolla, G. D., & Hanson, S. R. (1995). Comparison of thrombogenicity of stainless steel and tantalum coronary stent. *American Heart Journal, 129*(5), 866–872.

Serruys, P. W., Hout, B. V., Bonnier, H., Legrand, V., Garcia, E., Macaya, C., Sousa, E., Giessen, W. V., Colombo, A., Seasbra-Gomes, R., Kiemenej, F., Ruygrok, P., Ormiston, J., Emanuelsson, H., Fajadet, J., Haude, M., Klugmann, S., & Morel, M. A. (1998). Randomized comparison of implantation of heparin coated stents with balloon angioplasty inspected patients with coronary artery disease (Benstent II). *Lancet, 252*, 495–501.

Serruys, W. P., & Kutryk, M. J. B. (Eds.). (2000). *Handbook of Coronary Stents* (3rd ed). London: Martin Dunitz Ltd.

Serruys, W. P., De Jaegere, P., Kiemeneij, F., Macaya, C., Rutsch, W., Heyndrickx, G., Emanuelsson, H., Marco, J., Legrand, V., Matertne, P., Belardi, J., Sigwart, U., Colombo, A., Goy, J. J., Heuvel, P., Jaun, D., & Morel, M. A. (1994). Compression of balloon expendable stent implantation with coronary angioplasty in patients with coronary artery disease. *New England Journal of Medicine, 331*(8), 495–501.

Sigwart, U., Puel, J., Mirkovitch, V., Joffre, F., & Kappenberger, L. (1987). Intra vascular stent prevent occlusion and retenosis after translumenal angioplasty. *New England Journal of Medicine, 310*(12), 701–706.

Spear, J. R., Serur, J., Shropshire, D., & Paulin, S. (1983). Fluorescence of experimental atheromatous plaques with hematoporphyrin derivative. *Journal of Clinical Investigation, 71*395–399.

Suzuki, T., Hayase, M., Hibi, K., Hosokawa, H., Yokoya, K., Fitzerland, P. J., Yock, P. G., Cooke, J. P., Suzuki, T., & Yeung, A. C. (2002). Effect of local delivery of L–aspargine on in-stent restinosis in humans. *American Journal of Cardiology, 89*, 360–367.

Swanson, N., Hogrefe, K., Javed, Q., & Gershlick, A. H. (2003a). In vitro evaluation of vascular endothelial growth factor (VEGF)-eluting stents. *International Journal of Cardiology, 92*(2–3), 247–251.

Swanson, N., Hogrefe, K., Javed, Q., Malik, N., & Gershlick, A. H. (2003b). Vascular endothelial growth factor (VEGF)-eluting stents: in vivo effects on thrombosis, endothelialization and intimal hyperplasia. *Journal of Invasive Cardiology, 15*(12), 688–692.

Taber's Cyclopedic Medical Dictionary 13th Ed; Thomas, C. L., Ed.; E.A. David Company: Philadelphia, 1978.

Toppl, E. J. (1994). Caveats about elective coronary stenting. *New England Journal of Medicine, 331*(8), 539–541.

Tuch, R. J. Blood Contacting Medical Device and Method. US Patent 5,865,814, February 2, 1999.

van Beuskeom, H. M. M., & Vander Giessen, W. J. (2000). Coronary stent coatings (Appendix E). Serruys, P. W., Kutryk, M. J. B. (Eds.). *Handbook of Coronary Stents* (3rd ed). London: Martin Dunitz Ltd., pp. 403–419.

Von Langenhore, G., Kutryk, M. J. B., & Surruys, P. W. (2000). Pharmacological adjacent to coronary stenting, the case of stent thrombosis (Appendix D). Serruys, P. W., Kutryk, M. J. B. (Eds.). *Handbook of Coronary Stents* (3rd ed.) London: Martin Dunitz Ltd., pp. 155–401.

Wang, A. G., Gunn, A. C., Ku, P., & Kathy, M. (1995). Relative efficay of venous thrombosis. *Circulation (Suppl. I), 92*(8), I 686.

Wu, Steven, Z., Harish, Millare, S., & Guruwiyia, Judy. Implantable Medical Device Having Protruding Surface Structures for Drug Delivery and Cover Attachment. US Patent 6,254,632, July 3, 2001.

Yang, D., Stanslaski, J. L., Wang, L., & Smith, S. R. Stent Coating. US Patent 6,258,121, July 10, 2001.

Zhong, & Sheng-P, P. Stents with Hybrid Coating for Medical Devices. US Patent 6,231,600, May 15, 2001.

Zhong, S. P. Method of Providing a Substrate with a Bio-Active/ Biocompatible Coating. US Patent 5,869,127, February 9, 1999.

Zider, J. P., Mohammad, S. F., Culp, S. C., Brott, B. C., Phillips, H. R., & Stack, R. S. (1993). In vitro thrombogenicity analysis of a new bioabsorbable, balloon expandable endovascular stent. *Journal of the American College of Cardiology, 28*(2), A 483. (Abstracts).