Abstract: Coronary artery disease is characterized by a narrowing (stenosis) of the arteries that supply blood to the tissue of the heart. Continued restriction of blood flow manifests itself as angina and ultimately myocardial infarction (heart attack) for the patient. Heart bypass was once the only treatment for this condition, but over the years percutaneous coronary intervention (PCI) has become an increasingly attractive alternative to medical therapy and surgical revascularization for the treatment of coronary artery disease. A vascular stent is a medical device designed to serve as a temporary or permanent internal scaffold, to maintain or increase the lumen of a blood vessel. Metallic coronary stents were first introduced to prevent arterial dissections and to eliminate vessel recoil and intimal hyperplasia associated with PCI. Further advancement in the treatment of coronary artery disease is the development of drug-eluting stents that dramatically reduce the incidence of in-stent restenosis to less than 5%. Local drug delivery offers the advantages of allowing a relatively high local concentration of drug at the treatment site while minimizing systemic toxic effect. This review describes approaches for prevention of restenosis. It focuses on drugs for prevention of restenosis, bare metal stents, and drug-eluting stents. It also describes recent advances in bioresorbable stents. One of the chapters is dedicated to our novel composite bioresorbable drug-eluting fibers, designed to be used as basic elements in drug-eluting stents. © 2007 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 85B: 583–603, 2008

Keywords: restenosis; stent; drug delivery; bioresorbable polymers; paclitaxel

INTRODUCTION: RESTENOSIS

Restenosis is the narrowing of a blood vessel causing a reduction of the luminal size, consequently restricting blood flow after intravascular procedure. Restenosis is mainly characterized by intimal hyperplasia and vessel remodeling. The intima is the innermost coat of a blood vessel consisting usually of an endothelial layer backed by connective tissue and elastic tissue. The hyperplasia is an abnormal or unusual increase in the cells composing the intima.

Restenosis is a combined result of a biological response and mechanical reaction to percutaneous coronary intervention (PCI). At the early phase of restenosis, elastic recoil takes place due to the mechanical response of the elastic fibers of vascular wall to overstretched by balloon catheter. The recoil occurs within minutes following balloon deflation; the recoil may cause up to a 40% lumen loss. However, this phase may be totally eliminated by introducing a stent. The biological response to the procedure is more complicated to eliminate, and it may consist of the following four phases, as described in Figure 1.

Platelet Aggregation: Immediately after stent placement, endothelial denudation and medial dissection results due to the mechanical injury of PCI. The injury causes platelets aggregation and activation, producing a countless number of various cell-signaling factors initiating an inflammatory cascade and releasing adhesion molecules that cause a thrombus formation.

Inflammatory Phase: Over the next few days to weeks, a variety of white cells will gather at the injury site, secrete their own factors, and exert their own influence on the healing tissue. The inflammatory response can persist for months.

Proliferation Phase: The inflammatory phase stimulates smooth muscle cells (SMCs) migration and proliferation, in an attempt to repair the wound. This process is enabled by leukocytes cells releasing and activating tissue-digesting enzymes, forming a path for the SMCs to move. SMCs migrate to the thrombus that acts as a scaffold, providing the substrate for neoointimal formation. The migrating SMCs form an overgrown, obstructing scar.

Late Remodeling Phase: The final mechanism of restenosis response is the late remodeling of the vessel. This produces a neoointimal layer, which is mainly formed by proliferating SMC and extracellular matrix (ECM). Inflammatory mediators and cellular elements contribute to trigger...
a complex array of events that modulates matrix production and cellular proliferation. As the amount of scar develops (Figure 1(d)), blood flow is gradually reduced. Additionally, there is evidential reendothelialization of partial segments of the injured vessel surface.

A more detailed description of restenosis pathophysiology as well as restenosis-related terminology definition can be found elsewhere.\(^5\) The timeframe of each phase is described in Figure 2.

**In-Stent Restenosis**

Stenting, introduced in 1993, was one of the advances that significantly reduced the procedural complication rates of balloon angioplasty. Stents mitigate the complications of acute and subacute vessel closure, intimal dissection, elastic recoil of the vessel wall, and reduce angioplasty-related restenosis rates.\(^7\) In most of the centers in the United States and Europe, stents are being used in over 70% of PCI.\(^3\) However, despite their advantages, early enthusiasm for stents was somewhat diminished by the complications of stent thrombosis and in-stent restenosis.\(^7\) Stent placement has failed to achieve acceptable restenosis rates, especially in challenging patient groups.\(^5\) Of ~1 million patients who underwent PCI worldwide in 1999, in-stent restenosis has developed in ~250,000.\(^5\) The incidence of ISR may vary from 8% to as high as 80% at 6 months, according to both anatomic and clinical risk factors.\(^6,8\)

In-stent restenosis is most commonly defined as stenosis or lumen loss of over 50% caused following stent placement.\(^6,9\) The rate of lumen loss is the same in value to that of restenosis due to PCI.\(^7\) The problem of in-stent restenosis has been more difficult to overcome and made PCI a less definitive treatment.\(^7\) The process of in-stent restenosis peaks at about the third month and reaches a plateau between the third and sixth months after procedure.\(^10\) Angiographic follow-up studies have shown no further reduction in minimal lumen diameter between 6 months and 1 year.\(^11\)

Studies\(^12,13\) using intravascular ultrasound (IVUS) have demonstrated that stents virtually eliminate vessel recoil and negative remodeling. Moreover, according to these studies, in-stent restenosis is mainly caused by neointimal proliferation. In addition, the stent has a chronic indwelling impact on the vascular biological response causing an inflammatory response thus incurring a greater neointimal growth.\(^5\) The neointimal hyperplasia is more pronounced and exaggerated with stent placement than with balloon angioplasty.\(^9,14\) Several studies evaluated the effect of patients, lesions, and procedure-related predictors of angiography after stent placement on in-stent restenosis. In these studies, diabetes mellitus, lesion length, lesion plaque burden, number of stents, stent design, acute lumen gain, and the final obtained lumen diameter were found to have a significant impact on in-stent restenosis rates.\(^15\)

**STRATEGIES FOR PREVENTION OF RESTENOSIS**

A considerable amount of research was invested in the prevention of in-stent restenosis due to the substantial rate of the phenomenon. This interest prompted various strategies that
have been investigated and employed at the treatment of restenosis. The stent strategy reduced restenosis caused by balloon angioplasty from ~50% to ~15%. Early attempts at the prevention of restenosis focused on the administration of antithrombotic agents, but there was limited success in trials. With technologic advances and greater understanding of vascular pathobiology, novel therapeutic strategies, such as local delivery of ionizing radiation, pharmacological agents, and gene therapy, have been deployed to prevent coronary restenosis. It became clear that although coronary stenting combined with antithrombotic therapies had essentially eliminated the problem of elastic recoil, thrombus formation, and vessel remodeling, in-stent restenosis remained a major problem. Today, it is obvious that vascular SMC (VSMC) growth and migration trigger intimal hyperplasia, which is the main cause of in-stent restenosis.

The following paragraphs briefly describe the strategies for reducing restenosis. These strategies are presented in a chronologic order, while each strategy’s failure to prevent restenosis has prompted the development of the next strategy.

**Stents**

Stents are inserted into the lumen of a vessel to keep a formerly blocked passageway open. The stent provides a radial support to the vascular wall while healing takes place after an invasive procedure. Stents are usually made of metal or polymer filamentous tube. Their diameter may vary from 2.5 to 3.5 mm, and their length is typically in the range of 15–18 mm. In 1993, the FDA approved the balloon-expandable stent to treat acute or threatened closure. One year later, two randomized trials showed an impressive reduction of restenosis in patients treated with stents when compared to patients treated with balloon angioplasty. The acute and long-term benefits of stents over balloon angioplasty have been demonstrated in several studies. Today, stents are used in over 70% of the cases of coronary angioplasty.

**Mechanical Strategy**

Several mechanical techniques were used, including the use of high-pressure stent deployment to achieve larger final luminal diameter, direct stenting without predilatation, and placing an additional stent (stent sandwich). These techniques failed to present benefit over stenting alone.

Another approach to prevent in-stent restenosis was to mechanically reduce plaque volume using an Atherectomy procedure. This catheter-based procedure was originally developed as a potential replacement for balloon angioplasty.

**Figure 2.** Four phases of restenosis that occur poststent implantation: (a) Immediately after stent placement, the injury causes platelets aggregation and activation; (b) A variety of white cells gather at the injury site over the next few days to weeks; (c) SMCs migrate and proliferate to form the neointima and this process decays after a month from the procedure; (d) Late remodeling begins at about the third week. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
plasty, but it was used in conjunction to stenting or balloon angioplasty eventually. The most studied forms of atherec-
tomy are rotational atherecctomy and directional coronary atherecctomy.

Two randomized trials compared angioplasty to rota-
tional atherecctomy plus balloon angioplasty in the treatment of in-stent restenosis. In the multicenter European ARTIST trial,23 angioplasty alone produced a significantly better long-term outcome than atherecctomy followed by adjunctive low-pressure angioplasty. In the smaller single-center US randomized ROSTER24 trial, rotational atherecctomy resulted in less residual intimal hyperplasia, lower repeat stent use, decreased target lesion revascuazation, and similar complications rate compared to angioplasty alone.

The CAVEAT25 randomized trial compared directional coronary atherecctomy with angioplasty and demonstrated a small reduction in angiographic restenosis in the atherecctomy group. However, atherecctomy led to a higher rate of early complications, increased cost, and no apparent clinical benefit after 6 months of follow-up. The BOAT26 trial used an optimal directional coronary atherecctomy method that resulted in significantly lower restenosis rate in the atherecctomy group (32 vs. 40% in angioplasty) with no increase in major complications after 6 months. Yet, the trial failed to reach a statistical significance for clinical events after 1 year.

The AMIGO27 trial was designed to compare the angio-
ographic restenosis rates between stenting with or without prior directional coronary atherecctomy. The study failed to demonstrate the superiority of the combined approach compared to stenting alone in regard to restenosis rate. Conversely, a recently published meta-analysis28 reveals that directional coronary atherecctomy before stenting is advantageous over stenting alone with regard to angiographic results. Nonetheless, the study demonstrated higher rates of major adverse cardiac events mainly due to higher peripro-
cedural myocardial infarction.

These trials caused interventional cardiologists to ques-
tion the value of directional atherecctomy. Accordingly, atherecctomy treatment shifted from routine to discretionary, primarily for problematic lesions.29

### Systemic Drugs

When stents alone failed to eliminate restenosis, systemic drugs were administrated in conjunction.2 The majority of the drugs used and studied were antiplatelets and were antithrombogenic.30 The principal systemic administrated drugs and their effects are presented in Table I. Although there is some evidence that controlling thrombus formation may decrease neointimal hyperplasia, systemic administration of a variety of agents has not had a significant impact on post-PCI restenosis rates in clinical trials.31 Similarly, the systemic administration of drugs that inhibit inflammatory process31 and proliferation and migration of SMC have failed on tri-

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
</table>
| Aspirin       | Aspirin inhibits platelet activation and reduces atherothrombotic compro
in patients at risk of myocardial infarction and stroke.5          |
| Clopidogrel   | Clopidogrel is an inhibitor of platelet aggregation.6                         |
| Ticlopidin    | Ticlopidine is a platelet-inhibiting drug.6                                   |
| Troglitazone  | Successfully inhibited neointima proliferation in human study.9              |
| Tanilast      | Reduced in-stent restenosis in the porcine model, failed in human studies.7  |
| Cilostazol    | Cilostazol is an antiplatelet drug that has been used after implantation o
of coronary stents. It was found that a combination of Aspirin and Ci
lostazol might be an effective regimen for prevention of not only sten
thrombosis but also Restenosis. Results are inconsistent.9          |
| Abciximab     | The drug inhibits platelet aggregation. It prevents fibrinogen from bindin
and stroke.6                                                         |

Table I: Summary of Relevant Systemic Administrated Drugs

Temporary Local Delivery

Trials using the concept of a temporary local delivery administration of an antiproliferative agents, such as with use of microperforated balloons, produced vascular damage and were associated with fast washout and a delayed effect of the drug.6,8,32

Radioactive Stents

The first approved form for local delivery used to prevent in-stent restenosis was Brachytherapy. This is a form of radiation treatment in which radioactive material is implanted directly into the tumor-containing organ. By using this concept, high dose of radiation is delivered to a specific organ while limiting the exposure to the adjacent organs. The energy emitted from an active isotope is believed to block the cell division by causing a double-stranded break in the cell’s DNA, therefore inhibiting the hyperplasia process.33

The first randomized clinical trials to show significant reduction of restenosis, the SCRIPPS trial and the GAMMA I trial, used a γ-emitter, 192Ir, as the radioisotope. The 3-year angiographic follow-up of the SCRIPPS trial showed that the restenosis rate reduction observed during
the first year persisted in the long-term follow-up in the treated group (33 vs. 66%, $p = 0.05$); however, delayed restenosis was suspected. More recent studies were performed with \( \beta \)-emitters, which are considered to be more safety than \( \gamma \)-emitters. The START trial used a \(^{90}\text{Sr}/^{90}\text{Y}\) \( \beta \)-emitters. The target vessel revascularization rate at 9-month follow-up was reduced from 24% in the placebo patients to 16% in the treated patients.

The radioactive approach has shown its capability of effectively suppressing tissue growth within the stent, but in long-term follow-ups, edge restenosis and late thrombosis were evident. In addition, it has been postulated that the combination of vessel wall injury with suboptimal radiation dosage may promote excessive intimal hyperplasia.

**Passive Coating**

Evidence shows that restenosis following stent placement entails a series of interrelated host responses: thrombosis, inflammation, and SMC proliferation. The adhesion of cells to surfaces is believed to be mediated in the first instance by the adsorption of a protein layer onto the surface, altering their conformation and encourage further adhesion of blood components. It is known that the thrombogenic potential of bare metal stent prompting protein to rapidly cover the high energy surface eventually results in restenosis. Therefore, less thrombogenic and inflammatory stent coatings have been developed for reducing neointimal hyperplasia. These passive methods alter selected properties of the stent surface without delivery of drugs or other agents. These techniques are expected to remove surface initiators of the host response, although less intense cellular responses to the surface may continue. The coating materials, both organic and inorganic compounds, have generally caused slight decreases in thrombosis without substantially decreasing in-stent restenosis. Comparing to the systemic drug approach, the advantage of passive coating was questionable. Moreover, results of animal trials...
with polymer-coated stents have been diverse, with many of the so-called biocompatible polymer coatings (both resorbable and nonresorbable) invoking severe inflammatory reactions coupled with abnormally high neointimal proliferation that can be directly attributable to the presence of the coating.\textsuperscript{3,37} Table II presents the biocompatibility properties of stents coated with various materials.

### Active Stent Coating

The goal of drug-eluting stents is to place the right amount of drug at the site of injury in the time of injury. Also, it is difficult to achieve desired drug levels in the artery without undesired side effects when releasing drugs with a narrow therapeutic window.\textsuperscript{2} Two of the most important active coating methods currently available are as follows:

- **Drug-Eluting Stents:** Stents coupled with local delivery of drugs demonstrated a tremendous effect on reducing restenosis rates. Drug-eluting stents will be further discussed in this review.
- **Gene Therapy:** Stents may serve as carriers for gene therapy. Three known gene therapy approaches are as follows: stents seeded with cells that are transfected with the desired gene, stents loaded with recombinant adenovirus gene transfer vectors,\textsuperscript{6} and stents loaded with naked DNA impregnated in various matrices.\textsuperscript{37} Gene therapy directly released from stents in animal studies shows a dramatic improvement in neointima proliferation.\textsuperscript{9} Yet, human trials present unsuccessful results. Moreover, gene therapy potential side effects are of concern.\textsuperscript{37,42}

### DRUGS FOR PREVENTION OF RESTENOSIS

The ideal biological agent should have potent antiproliferative effects but also to 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 provoke thrombosis or inflammation.\textsuperscript{8} Other factors such as molecular weight, charge, and degree of protein binding may also affect drug kinetics and ultimately influence the biological success.\textsuperscript{8} On the basis of the mechanism of action of the biological compound and its target in the restenotic process, drugs loaded in stents may be generally classified as follows: anticoagulants, antiplatelet drugs, antiproliferative drugs, and immunosuppressive drugs (Table III).\textsuperscript{1,8} To date, the immunosuppressant drug rapamycin and the antiproliferation drug paclitaxel have achieved significant efficacy in preventing stent restenosis in clinical trials and have been approved for clinical use as stent coating. These drugs are described in detail in the following sections. There is a long list of agents that have failed to prevent in-stent restenosis or

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**TABLE III. Classification of Drugs for Prevention of Restenosis**

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug Name</th>
<th>Way of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti Coagulants</strong></td>
<td>Heparin</td>
<td>Antithrombotic and possibly direct inhibition of SMC proliferation</td>
</tr>
<tr>
<td></td>
<td>Hirudin</td>
<td>Antithrombotic and potentially antiproliferative</td>
</tr>
<tr>
<td></td>
<td>Iloprost</td>
<td>Prostacyclin analog that is antithrombotic and potentially antiproliferative</td>
</tr>
<tr>
<td><strong>Anti Platelet</strong></td>
<td>Sodium nitroprusside</td>
<td>NO donor</td>
</tr>
<tr>
<td></td>
<td>Abciximab</td>
<td>GP IIb/IIIa inhibitor</td>
</tr>
<tr>
<td></td>
<td>AZ1</td>
<td>GP IIb/IIIa receptor antibody</td>
</tr>
<tr>
<td></td>
<td>Eptifibatide</td>
<td>GP IIb/IIIa inhibitor</td>
</tr>
<tr>
<td></td>
<td>L-703081</td>
<td>GP IIb/IIIa antagonist</td>
</tr>
<tr>
<td></td>
<td>Argatroban</td>
<td>Inhibitor of thrombin-induced platelet activation</td>
</tr>
<tr>
<td><strong>Anti-proliferation</strong></td>
<td>ST638</td>
<td>Tyrosine kinase inhibitor</td>
</tr>
<tr>
<td></td>
<td>Angiopeptin</td>
<td>Inhibitor of SMC proliferation</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>Microtubular inhibitor</td>
</tr>
<tr>
<td></td>
<td>Taxane (QP2)</td>
<td>Microtubular inhibitor</td>
</tr>
<tr>
<td></td>
<td>Antiomycin D</td>
<td>Inhibits RNA synthesis</td>
</tr>
<tr>
<td><strong>Immunosuppressant</strong></td>
<td>Methylprednisolone</td>
<td>Anti-inflammation</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>Anti-inflammation</td>
</tr>
<tr>
<td></td>
<td>Sirolimus (Rapamycin)</td>
<td>Immunosuppressant and antiproliferative</td>
</tr>
<tr>
<td></td>
<td>Everolimus</td>
<td>Immunosuppressant and antiproliferative</td>
</tr>
<tr>
<td></td>
<td>ABT 578</td>
<td>Inhibitor of SMC proliferation</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus (FK 506)</td>
<td>Immunosuppressant</td>
</tr>
<tr>
<td></td>
<td>Mycophenolic Acid</td>
<td>An antibiotic derived from Penicillium species</td>
</tr>
</tbody>
</table>

Refs. 1, 4, 8, 37, 43.
shown only limited efficacy compared to rapamycin and paclitaxel.\(^\text{44}\)

### Antiproliferation Drugs

These drugs directly inhibit vessel SMC proliferation and migration. Stents coated with such drugs proved to reduce neointimal growth in both animal and clinical studies. Paclitaxel is the most popular drug in this group. Other drugs include Texane, Isotaxel 2, and Tyrophostin.

**Paclitaxel.** Paclitaxel is a potent inhibitor of cell proliferation and therefore is known to be very effective in treatment of cancer as well as neointimal hyperplasia, which is known as the main cause of restenosis. Paclitaxel was originally isolated from a trace compound found in the bark of the Pacific Yew (Taxus brevifolia).\(^\text{44}\) Paclitaxel’s antitumor activity was detected in 1967 in the US National Cancer Institute (NCI), and later it was found to be a novel, promising antineoplastic drug. It was approved by FDA for ovarian cancer in 1992, for advanced breast cancer in 1994, and for early stage breast cancer in October 1999. Today, it is synthetically produced as Taxol\(^\text{50}\) and became a standard medication in oncology.\(^\text{44,45}\)

Paclitaxel acts to inhibit mitosis in dividing cells by binding to microtubules and cause the formation of extremely stable and nonfunctional microtubules. Since microtubule disassembly is essential for the transition from the G2 to the M phase in the mitotic cycle, stabilization arrests mitosis and cell proliferation.\(^\text{44}\) G2-M is the transition in the cell division cycle from the state G2, where the cell produces enough proteins to divide, to the state, mitosis (M), where the cell is divided into two daughter cells. Therefore, it inhibits VSMC proliferation, migration, secretion of extracellular matrix, and angiogenesis, eventually reducing restenosis.\(^\text{44}\)

Slow release of paclitaxel applied perivascularly totally inhibits intimal hyperplasia and prevents luminal narrowing following balloon angioplasty. Paclitaxel is very potent at low concentrations and can be loaded in high doses into polymers.\(^\text{8}\) The drug interacts with arterial tissue elements as it moves under the forces of diffusion and convection and can establish substantial partitioning and spatial gradients across the tissue.\(^\text{45-47}\) Studies indicate

![Paclitaxel's chemical structure.](image)

**TABLE IV. Paclitaxel's Properties**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Solubility</td>
<td>5 µg/mL(^\text{50})</td>
</tr>
<tr>
<td>Solvents</td>
<td>DMSO, methanol, ethanol, acetonitrile, methylene chloride</td>
</tr>
<tr>
<td>Melting temperature</td>
<td>216–217°C</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>853.93 g/mol</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C(<em>{47})H(</em>{51})NO(_{14})</td>
</tr>
</tbody>
</table>

There are several limitations in clinical application of paclitaxel. The first limitation is related to its limited occurrence in nature and high production costs.\(^\text{44}\) Second, endothelialization is delayed within 90 days after treatment; therefore, antiplatelet therapy with aspirin and ticlopidine/clopidogrel is necessary.\(^\text{50}\) Third, paclitaxel is susceptible to solvolysis of its ester linkage leading to loss of its cytotoxic activity with maximum stability in the range of pH 3–5 at 37°C.\(^\text{53}\) Finally, paclitaxel is highly hydrophobic, causing a limited drug delivery; therefore, it must be delivered in conjunction to supplementary materials (such as Cremophor for treatment of cancer). This additive is believed to cause serious side effects.\(^\text{50}\) The hydrophobic nature of paclitaxel is a serious obstacle for *in-vitro* studies, since it adsorbs to glass and plastic vials.

Paclitaxel release mechanism using several biomaterials was studied extensively. The conclusions can be summarized as follows:\(^\text{50}\):

- **When surface-eroding polymers were used, erosion was found to be the main mechanism by which paclitaxel was released.** However, diffusion is the main mechanism of release through slow bulk degrading polymers.
- **The release profile is mainly affected by the molecular weight and relative hydrophilicity of the polymers.** Since
paclitaxel is extremely hydrophobic, hydrophilic biomaterials are required to shorten the release rate. Moreover, hydrophobic polymers will sustain paclitaxel’s diffusion and therefore will decrease the release rate.

- The presence of additives with appropriate hydrophilic–lipophilic balance (HLB) can help in achieving the desired paclitaxel release rate.

**Taxane (QP2 or 7-Hexanoyltaxol).** The structure of this drug is similar to paclitaxel.\(^5\) Results of the SCORE trail using stent coated with this drug were discouraging because of an unacceptable rate of subacute thrombosis and a high rate of acute myocardial infarction.\(^5\)

**Isotaxel 2.** This compound is a synthesized water-soluble paclitaxel prodrug.\(^5\) This prodrug has no additional functional auxiliaries released during conversion to paclitaxel. This is a great advantage in toxicity and medical economics, since the potential side effects caused by reported auxiliaries and the use of detergent for solubilization can be omitted.

**Tyrophostin (AGL-2043).** Tyrophostin is a potent, synthetic, inhibitor of several intracellular protein tyrosine kinases. A series of experiments show selective inhibition of SMC proliferation in culture and attenuation of the outgrowth of SCMs from porcine and human arterial explant tissue.\(^5\) This drug was found to reduce SMC proliferation and migration in vitro and in balloon-injured porcine femoral arteries, and reduce restenosis in stented porcine coronaries administrated within biodegradable particles. Also, stents coated with PLGA-encapsulated Tyrophostin reduced neointimal hyperplasia in porcine coronary arteries by 50% after 28 days.\(^5\)

**Salirasib (S-trans, trans-farnesylthiosalicylic Acid, FTS).** Salirasib (FTS) is a potent Ras inhibitor acting selectively on the active GTP-bound form of Ras. Salirasib is a nontoxic Ras inhibitor with no adverse side effects in animal models.\(^5\) Ras proteins are critically involved in the control of cell proliferation and migration through the activation of signaling pathways including the Raf/MEK/ERK MAP kinase and the PI3K/Akt/mTOR cascades.\(^5\) Therefore, Ras inhibitors could be expected to ameliorate restenosis to the extent of targeting mTOR by rapamycin and possible even more. Salirasib (FTS) was found to inhibit intimal thickening in rat carotid artery injury model.\(^5\) FTS inhibited VSMC and splenocytes proliferation, reduced the levels of active Ras and active ERK in balloon injured rat arteries, and reduced the number of NFkB- and iNOS-positive cells in sections of the injured arteries.\(^5\) Salirasib went through phase I clinical trials with no reported adverse side effects. The hydrophobic nature of FTS, which also contains a hydrophilic carboxyl group, may suggest that it could be an appropriate drug for stents.

**Immunosuppressive and Anti-Inflammatory Drugs**

The immunosuppressive agents attack neointimal growth by possessing both anti-inflammatory effects as well as immunosuppresive effects. The inflammatory cells seem to be an optimal target in the fight against restenosis, due to their role in restenosis.\(^9\) Anti-inflammation agents have long been shown to reduce the influx of mononuclear cells, to inhibit monocyte and macrophage function, and to influence SMC proliferation. However, clinical trials have failed to demonstrate any benefit of systemic steroid therapy.\(^8\)

**Sirolimus.** This drug was originally known as Rapamycin, which was discovered in 1977, and found to have potent cell cycle inhibitory activity, which inhibits VSMC proliferation.\(^7\) It was approved by the FDA in 1999 as Rapamune (Wyeth, NJ) as immunosuppressive drug for transplant rejection.\(^8\) The properties are presented in Table V. From a therapeutic point of view, Sirolimus is a natural macrocyclic, lipophilic lactone with immunosuppressive antibiotic activity.\(^6\) Sirolimus blocks cell cycle progression at the G1-S transition and inhibits VSMC proliferation.\(^6\) G1-S is the transition in the cell division cycle between the phase G1, where the cell increase with size producing proteins and RNA, to the phase S in which the DNA replication occurs. Studies show that Sirolimus is capable of abolishing T-cell proliferation as well as SMC proliferation and migration, which are the main sources of restenosis.\(^6\) Trials show that the drug should be present in the vessel wall for at least the first 7–14 days to be efficacious.\(^6\)

**Everolimus (40-O-(2-Hydroxyethyl)-Rapamycin).** This drug is an immunosuppressive drug that has been shown to inhibit cell proliferation. Animal studies have shown a potent antirestenotic effect of Everolimus given orally or via a drug-eluting stent. However, its immunosuppressive activity is 2- to 3-fold lower than Sirolimus in vitro.\(^8\) The S-Stent (Biosensor) has been impregnated with a blend of Everolimus and slowly biodegradable Hydroxyacid Polylactic acid polymer. Low (180 µg/stent) and high-dose (360 µg/stent) Everolimus-eluting stents were implanted in pig coronary arteries. Percent area stenosis by histomorphometric analysis was 62% in bare stents, 70% in polymer-coated stents, 39% in low-dose Everolimus-eluting S-stents, and 38% in high-dose Everolimus-eluting S-stents.\(^8\)

**ABT-578 (Methyl Rapamycin).** This drug is a synthetic analog of Sirolimus. Preliminary animal studies have shown significant inhibition of intimal proliferation after stenting.\(^8\) The clinical ENDEAVOR I trial, N = 100, using a cobalt alloy stent platform presented in-stent late lumen loss of 0.33 mm at 4 months. One-year follow-up results, however, showed an increase in in-stent late lumen loss to 0.58 mm.\(^7\) The ENDEAVOR II Pivotal Clinical Trial completed enrollment of 1200 patients and presented impressive results. The Endeavor stent is produced by
<table>
<thead>
<tr>
<th>Stent/Platform</th>
<th>Coating</th>
<th>Manufacturer</th>
<th>Drug</th>
<th>Clinical Trials</th>
<th>Follow-up</th>
<th>Binary Restenosis Rate</th>
<th>Measured at Follow-up (MACE are not included)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cypher™/BX Velocity©</td>
<td>Nondegradable Poly(n-butyl methacrylate/Poly (ethylene vinyl acetate) [PEVA/PBMA] (50/50) coated stainless steel stent</td>
<td>Cordis, Johnson &amp; Johnson</td>
<td>Sirolimus (Rapamycin)</td>
<td>FIM (N = 45)</td>
<td>24 m</td>
<td>0% (SR DES), 0% (FR DES)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RAVEL (N = 238)</td>
<td>6 m</td>
<td>0% (DES) vs. 26.6% (BS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SIRIUS (N = 1,100)</td>
<td>9 m</td>
<td>2% (DES) vs. 31.1% (BS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E-SIRIUS (N = 352)</td>
<td>9 m</td>
<td>5.9% (DES) vs. 42.3% (BS)</td>
<td></td>
</tr>
<tr>
<td>QuaDDS-QP ©</td>
<td>Nonbiodegradable polyacrylate sleeves</td>
<td>Quanam</td>
<td>7-hexanoytaxol (QP2)</td>
<td>SCORE (N = 266)</td>
<td>6 m</td>
<td>Trail halted prematurely due to high incidence of stent thrombosis 6.4% (DES) vs. 36.9% (BS) at 6 months</td>
<td></td>
</tr>
<tr>
<td>Taxus™/NIRx Conformer©</td>
<td>Poly(Lactide-co-Σ-caprolactone)</td>
<td>Boston Scientific</td>
<td>Paclitaxel</td>
<td>TAXUS I (N = 61)</td>
<td>6 m</td>
<td>0% (DES) vs. 10.3% (BS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TAXUS II (N = 536)</td>
<td>6 m</td>
<td>2.3% (DES) vs. 17.9% (BS) in (SR) 4.7% (DES) vs. 20.2% (BS) in (MR)</td>
<td></td>
</tr>
<tr>
<td>Taxus™/Express 2</td>
<td>Poly(Lactide-co-Σ-caprolactone)</td>
<td>Boston Scientific</td>
<td>Paclitaxel</td>
<td>TAXUS III (N = 28)</td>
<td>6 m</td>
<td>16% (DES) 16</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TAXUS IV (N = 1,326)</td>
<td>9 m</td>
<td>5.5% (DES) vs. 24.4% (BS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TAXUS V (N = 1,172)</td>
<td>12 m</td>
<td>Overall TLR: 11.2% (DES) vs. 19.0% (BS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TAXUS VI (N = 448)</td>
<td>9 m</td>
<td>Overall TLR: 6.8% (DES) vs. 18.9% (BS)</td>
<td></td>
</tr>
<tr>
<td>Endeavor/Driver Medtronic</td>
<td>Phosphorylcholine</td>
<td>Medtronic Inc</td>
<td>ABT-578</td>
<td>ENDEAVOR I (N = 100)</td>
<td>48 m</td>
<td>TLR: 3.1% (DES)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ENDEAVOR II (N = 1,197)</td>
<td>36 m</td>
<td>TLR: 7.3% (DES) vs. 14.7% (BS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ENDEAVOR III (N = 436)</td>
<td>9 m</td>
<td>TLR: 6.3% (Endeavor) vs. 3.5% (Cypher)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ENDEAVOR IV (N = 1,548)</td>
<td>9 m</td>
<td>Enrolling</td>
<td></td>
</tr>
<tr>
<td>Supra G ©</td>
<td>Directly impregnated</td>
<td>Cook, Inc</td>
<td>Paclitaxel</td>
<td>ASPECT (N = 177)</td>
<td>6 m</td>
<td>4% (high dose DES), 12% (low dose DES) vs. 27% (BS)</td>
<td></td>
</tr>
<tr>
<td>V-Flex Plus PTX™</td>
<td>Directly impregnated</td>
<td>Cook, Inc</td>
<td>Paclitaxel</td>
<td>ELUTES (N = 192)</td>
<td>6 m</td>
<td>3.1% (2.7 µg/mm² DES), 13.5% (1.4 µg/mm² DES), 11.8% (0.7 µg/mm² DES), 20% (0.2 µg/mm² DES) vs. 20.6% (BS)</td>
<td></td>
</tr>
<tr>
<td>Logic PTX™</td>
<td>Directly impregnated</td>
<td>Cook, Inc</td>
<td>Paclitaxel</td>
<td>PATENCY (N = 50)</td>
<td>9 m</td>
<td>38.1% (DES) vs. 35.3% (BS)</td>
<td></td>
</tr>
<tr>
<td>Multi-Link Tetra</td>
<td>Proprietary</td>
<td>Guidant</td>
<td>Actinomycin D</td>
<td>ACTION (350)</td>
<td>6 m</td>
<td>Trial halted due to high MACE, TLR rates at 30 days</td>
<td></td>
</tr>
<tr>
<td>Multi-Link Penta</td>
<td>Directly impregnated</td>
<td>Guidant</td>
<td>Paclitaxel</td>
<td>DELIVER (N = 1,043)</td>
<td>9 m</td>
<td>14.9% (DES) vs. 20.6% (BS)</td>
<td></td>
</tr>
<tr>
<td>ACHIEVE™</td>
<td>Directly impregnated</td>
<td>Guidant – Cook</td>
<td>Paclitaxel</td>
<td>DELIVER II (N = 50)</td>
<td>6 m</td>
<td>In lesion: 20% (DES) vs. 16% intracoronary radiation</td>
<td></td>
</tr>
</tbody>
</table>
Medtronic™ is coated with a Phosphorylcholine (PC) polymer, and received CE Mark approval in July 2005.

**Tacrolimus (FK506).** This drug is a potent immunosuppressive drug with proven inhibitory activity on human VSMC by leading to G1 cell cycle arrest. The drug exerts inhibitory effect in T-lymphocyte activation by binding specifically to FK506-binding protein 12 (FKBP12) in the cytoplasm. The tacrolimus-FKBP12 complex inhibits calcineurin, which interrupts signal transduction pathways in T-cells as well as SMC growth. The drug has been used clinically to prevent renal transplant rejection. One trial had shown a significant reduction (around 50%) in neointima thickness using ceramic-coated stents loaded with tacrolimus compared to bare stents.

**Dexamethasone.** Dexamethasone is a glucocorticoid that interferes with macrophages and reduces growth factors and cytokines, thus producing potent anti-inflammatory properties. BiodivYsio Dexamethasone-eluting stent was studied on the STRIDE trial. The stents were immersed on site in a solution of Dexamethasone. At 6-month follow-up, angiographic binary restenosis was 13.3%, and late loss was 0.45 mm. The stent have been approved for clinical use in Europe.

**Tranilast (N-[3,4-dimethoxycinnamoyl]anthranilic Acid).** This drug has been shown to inhibit proliferation and migration of VSMC in experimental models. This drug is an antiallergic drug that also inhibits the migration and proliferation of VSMCs induced by platelet-derived growth factor and transforming growth factor $\beta_1$. Tranilast was found to significantly suppress vascular intimal hyperplasia in rabbit artery after balloon injury and in pig coronary arteries after balloon angioplasty and stent implantation.

**Anticoagulants**

Early studies of drug-eluting stents examined stents coated with anticoagulants or thrombin inhibitors such as heparin and hirudin. These studies indicated reduced thrombosis. However, these stents do not seem to have a significant long-term impact on restenosis rates during clinical trials, when compared to uncoated stents used in conjunction with systemically administrated antiplatelet drugs. Animal studies have revealed that heparin is the inherent modulator of vascular repair after injury due to its anti-proliferative and anti-inflammatory properties. However, human trials using Heparin after PCI have proven ineffectiveness in preventing restenosis. Hirudin-coated stents are believed to reduce neointima formation in the same way as Heparin. Alt et al. implanted stents coated with a layer of poly(lactic acid), which contained the drugs hirudin and iloprost in pigs and sheep. They demonstrated a significant restenosis reduction after 4 weeks without inflammatory reactions.
Antiplatelet Drugs

Nitric oxide donors, glycoprotein IIb/IIIa receptor antagonist/antibodies, and Angiopeptin V significantly reduce platelet deposition in animal studies. The platelet glycoprotein IIb/IIIa receptor is involved in the final common pathway of platelet aggregation, and antibodies against this receptor have recently proven their efficacy in the treatment of unstable angina. Unfortunately, no indication has revealed that the reduction of thrombosis by these means resulted in the inhibition of intimal growth. Research of antithrombotic therapies led to great excitement over the possibility that blocking platelet aggregation would eliminate in-stent restenosis. One such agent, the antibody Abciximab, which targets glycoprotein IIb/IIIa on platelets, seems to have the potential to reduce in-stent restenosis to insignificant levels.

VASCULAR STENTS

Metal Stents

Since their introduction, in 1993, vascular stents significantly reduced restenosis as well as other balloon procedural related complication rates. It has been shown to reduce late restenosis relative to conventional balloon angioplasty. Early designs, including the Wallstent (Schneider), Palmaz-Schatz (Johnson and Johnson), Wiktor (Medtronic), and Gianturco-Roubin (Cook) stents, have been replaced by the Micro (AVE), Multilink (ACS), and other designs. The metals used to prepare these stents are selected for strength, elasticity, and malleability or shape memory. Stainless steel, tantalum, and nitinol alloys are among the most commonly used materials. Nitinol offers superelastic and thermal shape memory properties, which allow self-expansion of the stent during deployment and thermally-induced collapse for theoretical removal procedures. Several metal stent designs are presented in Figure 4.

Stent design (i.e., struts thickness, number of struts per cross-section, and strut design), stent material, and surface smoothness have been shown in histological restenosis studies to have an important impact on the amount of intimal hyperplasia. A thin strut thickness with a corrugated-ring stent design was found to induce the smallest intimal hyperplasia thickness between tested metal stents. Studies show that surface irregularities could serve as sites for thrombus attachment and growth. Smooth surfaces tend to be less thrombogenic than textures in irregular device. Monocytes and macrophages attracted to the implant site are known to form foreign body giant cells to isolate the prostheses from the surrounding tissue. The substantial rate of in-stent restenosis led to redesigning stents to improve their antithrombotic properties.

Metal stents are available as either balloon-expandable or self-expandable. The balloon-expandable stents expand by the balloon catheter, while the self-expandable stents employ a shape memory alloy that acts over a mild temperature range. The metal stent expansion principle is based on the plastic deformation of metal beyond its elastic limit. The metals currently used in stents demonstrated several

Figure 4. Examples for Metal stent designs: (a) TAXUS Express 2, Paclitaxel eluting stent (Boston Scientific); (b) Cypher – sirolimus eluting stent (Johnson and Johnson); (c) Cordis minicrown – slotted tube design (Cordis Corporation); (d) ChromoFlex – thin struts design (DISA Vascular).
disadvantages. First, their electropositivity results in thrombogenicity, since blood elements that are mostly negatively charged, and also proteins, will rapidly cover the high energy surface. This may also be an advantage, since endothelial cells are able to migrate and cover the exposed metal surface within a number of days after implantation, encasing the stent in a cellular sheath. Second, the presence of the metallic material is permanent and irritates the immunological response occurring at the injury site. Third, sensitization is a concern to those who are hypersensitive to metals. And finally, metal stents are considered to hold limited capacity for local drug delivery. Therefore, the current tendency is to coat stents with less thrombogenic materials such as polymer or biodegradable polymer coating.

**Bioresorbable Polymeric Stents**

The rationale for bioresorbable stents is to support the vascular wall during the vessel healing process alone; while gradually transferring the mechanical load to the vessel wall as stent mass and strength decreases over time. Restenosis commonly occurs within 3–6 months after coronary intervention, and it rarely occurs thereafter. Therefore, the clinical need for stents is limited after this period. These stents can present longer term of drug delivery from an internal reservoir. In addition, there is no need for a second surgery to remove the device.

Several early designs of expandable bioresorbable stents have been developed as alternatives to metallic vascular stents. The first biodegradable stent was developed by Stack and Clark of Duke University in the early 1980s. They investigated several biodegradable polymers and chose PLLA as the stent material. This Duke University stent was constructed of a specialized PLLA polymer woven into a diamond-braided pattern from eight polymeric strands. It was designed to withstand compression pressures of up to 1000 mmHg (the Palmaz-Schatz stent can withstand pressures of 300–500 mmHg and maintain its radial strength for 1 month). In vivo studies demonstrated minimal thrombosis and inflammatory responses, and moderate neointimal growth. Gao et al. reported the Tianjin/Beijing stent, a PDLLA/PCL stent with an inner heparin layer, deployed with a balloon catheter and employing heating and pressurization. This stent produced mild neointimal proliferation in swine carotid artery models at 2 months. Yamawaki et al. reported a Kyoto University PGA coil stent, which exhibited thrombus deposition in canine implant studies, but no subacute closure. Nuutinen et al. developed knitted PLLA and 80/20 PDLGA stents with mechanical properties similar to those of commercially available metallic stents. They found that the knitting geometry has a marked effect on the stents’ mechanical properties. Such knitted bioresorbable stents are more suitable for urological, gastrointestinal, and tracheo-bronchial indications, where the size of the delivery device is not critical, as opposed to peripheral vascular or even coronary indications, for which a small-diameter delivery device is critical.

Tamai et al. described the Igaki/Tamai stent, a bioresorbable balloon-expandable zigzag coil design, based on a PLLA monofilament. The thickness of the stent strut is 0.007 inches (0.17 mm) and the stent surface area is 24% at an arterial diameter of 3.0 mm. The stent has a self-expanding capacity, with an expansion range of up to 4.5 mm. This bioresorbable stent combines the features of a thermal self-expandable and a balloon-expandable stent. The stent initially autoexpands in response to the heat transmitted by a delivery balloon inflated with a 70°C contrast-water mixture (50°C at the balloon site). Subsequent expansion is obtained by inflation at a moderate to high pressure (6–14 atm). This stent will continue to expand to its nominal size within the following 20–30 min at 37°C. The most important and unique innovation made by these authors, compared with prior investigators, is the change in stent design from a knitted pattern to a zigzag helical coil design.

Vessel wall injury causes neointimal proliferation, and the severity of vessel injury is strongly correlated with neointimal thickness and the percentage of stenosis after balloon angioplasty or stenting. The stent design may reduce the extent of vessel wall injury caused by the stent implantation and may influence the neointimal proliferation and the inflammatory response. Animal studies of the Igaki/Tamai stents have demonstrated that the PLLA coil stent reduced the percentage of stenosis in porcine coronary arteries at 2 weeks from 64% to 19%, compared with the PLLA-knitted type stent. Minimal neointimal hyperplasia was found within the PLLA coil stents, whereas moderate to severe neointimal hyperplasia was observed in knitted PLLA stents. The PLLA coil stents also exhibited long-term biocompatibility with a minimal inflammatory response in porcine coronary arteries after 16 weeks. Unlike stents used in previous studies, the Igaki/Tamai stent was made from a high molecular weight PLLA that resulted experimentally in a minimal inflammatory response, compared with that observed in previous reports. In this study, 25 stents were deployed successfully in 15 patients. No stent thrombosis or major cardiovascular adverse events occurred within 30 days. After 6 months, restenosis occurred in 10.5% of the patients and target lesion revascularization occurred in 6.7%. This study actually provided the first report on immediate and 6-month results following implantation of a bioresorbable PLLA stent in humans. The Igaki-Tamai and the double-spiral helical stent designs are presented in Figure 5.

The multiple-lobe vascular stent (Figure 6) was developed and studied by us. This fiber was prepared using a linear, continuous coil array principle, by which four furled lobes convert to a single large lobe upon balloon expansion. Melt-extruded PLLA fibers with a 0.15 mm diameter were woven continuously around a four-man- drel array (one central, three peripheral) into a four-lobe configuration. Three longitudinal fibers were interwoven and glued to the coil for mechanical support. The fully
expanded stent has a helical coil structure with three longitudinal reinforcing fibers. The stents’ initial and final diameters in this stent design are adjustable.

Stents of 15 mm length, 3 mm final (dilated) diameter, and 1.8 mm predilated diameter were fabricated. The initial radial compression strength of the stent in its dilated form was higher than 200 kPa. The stents were immersed in PBS at 37°C to investigate the effect of their in vitro degradation on mechanical properties. The mode of failure observed was rupture of binding points, between the coils and the longitudinal support fibers. The stents did not undergo any failure after applying 200 kPa throughout the first 8 weeks. Then, the radial compression pressure required to create a rupture at binding points showed a linear decrease with time and the number of ruptures was increased with time. We demonstrated that these stents generally exhibited good radial compression endurance. They resisted at least 150 kPa (≈75% of the initial strength) and exhibited only few rupture points, while most of the binding points remained intact. The combination of the suggested design and the relatively high molecular weight PLLA may thus be applicable for supporting blood vessels for at least 20 weeks and was chosen for further studies.

Figure 5. Examples for biodegradable fiber-based stents: (a) The double helical PDLLA stent; (b) The Igaki-Tamai PLLA stent; (c) The knitted 96L/4D PLA stent, the arrows indicate the loop height.

**DRUG-ELUTING VASCULAR STENTS**

**Drug-Eluting Metal Stents**

A drug-eluting stent is a device releasing single or multiple bioactive agents into bloodstream. The agent can deposit in or affect tissue adjacent to the stent eventually eliminating in-stent restenosis. Drug-eluting stents offer relatively high drug concentration at the site of stent deployment and minimal systemic side effects. Using this method, drugs are gradually and locally released from the coating matrix and taken up by the surrounding tissue. Most of the released drugs are via a polymer matrix such as silicone, cellulose esters, polyurethane, polyethylene vinyl alcohol, and copolymers of polylethylene glycol. The matrices control the drug released over a certain period of time. Unfortunately, many of these synthetic polymers induce exaggerated inflammatory response and neointimal hyperplasia in animal models. The drug should interfere with SMC proliferation, the main source of restenosis, thus a sufficient drug amount should be released by the appropriate kinetics. This effect must be maintained throughout the first 3–4 weeks after procedure. Also, a confluent endothelial coverage of the stent must be achieved. A reduction of neointimal hyperplasia is expected during the period that the drug actions remain in effect and beyond (Figure 7). The drug is usually incorporated in a polymeric coat, but sometimes it is bound directly to the metal stent. When using the first method, the agent is usually loaded in the polymeric coat by physical entrapment or sometimes by chemical bonding to the polymer chain. A schematic representation of various types of drug-loaded coatings is presented in Figure 8. By altering the physiochemical properties of the polymer matrix, one can control the kinetics of the drug elution so that the drug is released in a sustained fashion over a period of weeks after implantation. An optimal combination of drug and coating polymer, and the kinetics of release determines the safety and optimizes the local therapeutic benefit, and therefore enables patency of the stented vessel. Various important drug-eluting metal stent developments and their clinical trials results are summarized in Table V. We will focus below on paclitaxel-eluting stents and on sirolimus-eluting stents.

**Paclitaxel-Eluting Stents.** Paclitaxel-coated stents received CE approval on September 2002 and FDA approval on April 2004 under the name TAXUSTM following extensive successful clinical trials [49]. TAXUS is a 15 mm NIRx™ stent (316L stainless steel, Boston Scientific coated with poly(lactide-co-e-carpolactone) copolymer loaded with either ‘‘low’’ dose of 85 μg or a ‘‘moderate’’ dose of 171 μg of paclitaxel. The release profile is characterized by an initial release over the first 48 h followed by slow release over the next 10 days. Clinical trials of paclitaxel-eluting stents have been encouraging. Early studies were performed using a variety of stent platforms, drug concentrations, polymer matrix, or without a matrix. Although the early human and animal trials of...
paclitaxel-coated stents had mixed results, more recent results using TAXUS-eluting stents are very promising.7

Recently, Boston Scientific developed its next generation paclitaxel-eluting coronary stent, the TAXUS Liberte’, which is based on the TAXUSTM Express 2.

**Animal Studies.** Various animal studies using paclitaxel-eluting stents reported that inhibition of restenosis is associated with delayed or incomplete intimal healing characterized by increased local arterial inflammation and fibrin deposition. The coating polymers and their degree of sterilization may be the cause of these reactions.2,49,77

Paclitaxel-eluting Palmaz-Schatz coronary stent trial in pigs49 has shown to significantly reduce restenosis in a dose-dependent manner with the largest reduction in neointima at the high dose group. This stent was coated with a range of paclitaxel doses by dipping the stent into Ethanolic paclitaxel and evaporating the solvent. No hyperplastic edge effects were found in any of the groups; however, the trial did raise concerns regarding vascular complication (aneurysm, wall rapture).

Stents coated with a crosslinked biodegradable polymer, Chondroitin Sulfate A and Gelatin (CSG) containing paclitaxel, were examined on rabbits.94 The results have shown a suppressed neointimal formation at 28 days in a dose-dependent manner (42.0, 20.2, 8.6, or 1.5 μg of paclitaxel per stent) without systemic toxicity. Higher dose produced higher reduction in restenosis rates. However, findings suggested that paclitaxel delayed neointimal growth, and the healing was incomplete. Studies of Conor Med stent implanted in porcine coronary for 30 days exhibited inhibition of restenosis and delayed healing.95

**Clinical Studies.** Paclitaxel-eluting stents presented very promising preclinical and clinical results. A graded dose response is observed, where restenosis rates are lower in the higher dose groups. TAXUS, which is a paclitaxel-coated stent, was found effective and safe in a wide range of complex patients and lesions, including small vessels, long lesions, and diabetic patients.8 More details can be found in Table V.

**Sirolimus (Rapamycin)-Eluting Stent.** Cypher (Cordis, Miami, FL, a Johnson and Johnson Company) was approved in April 2002 for use in Europe and FDA approved it in April 2003. The Cordis Cypher is a tubular stainless steel stent coated with a 5-μm-thick layer of non-erodable polymer (50:50 mixture of polyethylene-vinyl-ace-tate and poly-n-butyl methacrylate) containing 140 μg/cm² Sirolimus (Rapamycin). The drug is released slowly over 4–6 weeks; approximately 80% is released after 4 weeks and 100% after 6 weeks.2

**Bioresorbable Drug-Eluting Stents**

Several drug-eluting fiber-based and film-based vascular stents have been reported lately. In these stent designs, the drug molecules were located within the fibers or films, or in a coating.

**Fiber-Based Stents.** Drugixed polymer stents can be loaded with larger amounts of drug than drug-coated stents can, because the polymer stent struts can contain the drug. The tranilast-eluting Igaki-Tamai stent was made of a PLLA monofilament mixed with tranilast, and its shape was similar to that of the regular Igaki-Tamai stent without the drug. The radial compression strength of the drug-loaded stent was ~10% lower than that of the neat stent.
Tsuji et al.\textsuperscript{96} compared the tranilast content in the tranilast-eluting Igaki-Tamai stent with that in a tranilast-coated Palmaz-Schatz stent that was coated with a 20–40 $\mu$m layer of tranilast-mixed PCL. The tranilast content of the former was found to be at least four times higher than that of the latter. The authors developed three types of tranilast-eluting stents: a noncoated stent, which can release tranilast rapidly, a PCL-coated stent for relatively slow release of tranilast through the PCL barrier layer, and a stent with a tranilast-loaded PCL coating designed to rapidly release the drug from the PCL coating followed by a slower release through the PCL layer. The authors stated that clinical experiments are necessary to elucidate these stents’ safety and efficacy.

\textbf{Figure 7.} The response to PCI and methods for restenosis prevention. Beginning with a coronary artery that has already stenosed owing to plaque formation, PCI is performed either with or without stent implantation. With PCI alone, the artery is subject to elastic recoil, thrombus formation, neointimal growth, and late vessel remodeling. If a stent is implanted, the effects of elastic recoil and late vessel remodeling are limited, but the artery is still at risk of neointimal hyperplasia. If a drug-eluting stent is implanted, neointimal hyperplasia can be nearly abolished by blocking cell-cycle progression.\textsuperscript{2} [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
Uurto et al.\textsuperscript{97} evaluated in-vivo a new fiber-based drug-eluting bioresorbable vascular stent, with respect to biocompatibility, neointimal hyperplasia formation, and reliability. Monofilaments made of a polymer consisting 96% \( \varepsilon \)-lactic acid and 4% \( \delta \)-lactic acid were manufactured by melt-spinning. The stents were formed from a mesh design consisting of 16 monofilaments braided over a mandrel. These stents were coated with 50/50 two bioactive agents: dexamethasone or simvastatin. Both, PCL and a polymer containing 50% \( \varepsilon \)-lactic acid and 50% \( \delta \)-lactic acid, were used as coating materials. The in-vivo results (pig experiments) indicated that all stented arteries were angiographically patent. The dexamethasone-loaded stents decreased the mean luminal diameter compared to other stents, and they induced minimal intimal hyperplasia. The vascular injury scores demonstrated only mild vascular trauma for all studied stents. Hence, the authors concluded that biodegradable stents appear to be biocompatible and reliable, and can be used as local drug delivery vehicle. The findings showed a need for further investigation to prove the efficacy and safety of this new biodegradable drug-eluting stent.

The two fiber-based drug-eluting bioresorbable vascular stents described above demonstrated promising results. Other fiber-based vascular stents were developed by companies, and their studies are in progress. The growing number of such stents includes for example the paclitaxel-loaded REVA stent (developed by REVA company) and a stent developed by TissueGen and Endovasc companies. PLLA stents coated with drug-loaded microspheres were developed and studied by us.\textsuperscript{92} Drug-loaded bioresorbable microspheres were developed and bound to the PLLA fibers and to our multiple-lobe stents.\textsuperscript{92,98} These microsphere reservoirs, which were prepared by the double emulsion technique, can be loaded with biologically active aqueous or nonaqueous molecules. Since mild materials and processing steps are used, these microspheres can be loaded with all drugs, proteins, and gene transfer vectors. The processing conditions can be controlled to yield single-reservoir or multiple-reservoir microspheres. The initial radial compression strength of all types of microsphere-loaded stents exceeded 200 kPa. This indicates that the partial dissolution of the surface layers that was performed to enable microsphere attachment to the fiber had practically no effect on the strength of the stent. It has been demonstrated that the microsphere structure strongly affects the release profile of the agent from the microspheres and from the microsphere-loaded stents.\textsuperscript{92,96} In fact, the release profile from the microsphere-loaded fibers and stents is determined by the chemical structure of the microsphere’s polymer, and its initial molecular weight and the processing conditions.

**Film-Based Stents.** Vogt et al.\textsuperscript{90} reported a novel PDLLA double-helical stent designed according to the material’s properties, based on a finite element method.
This stent was manufactured using the controlled expansion of saturated polymers (CESP) for molding the PDLLA. This method is characterized by a low process temperature that enables the processing of thermally sensitive polymers and the incorporation of biologically active substances. This stent exhibited sufficient mechanical stability and a significant potential to reduce restenosis after vascular intervention was observed following the incorporation of paclitaxel. Paclitaxel was shown to effectively inhibit proliferation and coronary stenosis in a pig model after vascular injury in a long-term course. The authors suggest that invitro pharmacokinetics with a very slow release pattern of paclitaxel over a time span of more than 2 months might contribute to this favorable outcome. The authors also reported that paclitaxel loading did not increase toxicity, as reflected by media necrosis or delayed healing of endothelial cells.

Alexis et al. studied the in vitro release kinetics of paclitaxel and rapamycin from solution-cast PDLLA and PDLGA films and from nonexpandable helical stents prepared from strips cut from the films. The results demonstrated that the release mechanism for both drugs combined diffusion and degradation. The films and stents exhibited the same release profiles, indicating homogenous degradation kinetics. No burst effect was observed for either drug. This is especially important during paclitaxel administration, where cardiotoxicity is sometimes a concern. The authors also demonstrated that the release period can vary from 1 month to several months, depending on the matrix polymer.

Ye et al. demonstrated the successful transfer and expression of a nuclear-localizing β-Gal reporter gene in cells in the arterial wall of rabbits after the implantation of biodegradable stents made of bioresorbable PLLA/PCL films creating a porous tubular structure impregnated with a recombinant adenovirus carrying that gene. Although they used a nonexpandable stent design, they demonstrated the exciting possibility of transferring genes that encode for key proteins in the central regulatory pathways of cell proliferation inside arterial wall cells, using bioresorbable stents as vehicles.

**Novel Composite Fiber Structures Used as Basic Stent Elements.** As have already stated, bioresorbable stents can simultaneously support blood vessels and serve as drug/protein delivery platforms. Certain drugs, such as steroids, can be incorporated into the PLLA fiber during melt processing. However, only small drug quantities can be incorporated in dense polymeric structures such as fibers without having an adverse effect on the mechanical properties of the fiber and the stent. Furthermore, most drugs and all proteins are destroyed when exposed to the high melt processing temperature. To solve these problems, we developed and studied novel drug-loaded composite fibers that can be used as basic elements of stents such as the multiple-lobe stent (described above). These unique fibers, which resemble sutures, actually contain two sections: (a) a dense core fiber with good tensile mechanical properties (high strength and good flexibility) and (b) a porous shell, i.e. a bioresorbable “coating” that contains the drug molecules. This section is prepared via freeze drying of inverted emulsions using mild processing conditions, and can therefore include any bioactive agent, while preserving its activity. This new concept of composite fiber structures is schematically presented in Figure 9(a), and a SEM fractograph of a fiber’s cross section is presented in Figure 9(b). We prepared fiber structures with porous shell loaded with the antiproliferative agent paclitaxel. Investigation of these composite fibers focused on the effects of the emulsion’s composition (formulation) and processing conditions on the drug release profile from the fibers and on the fibers’ tensile mechanical properties.

In general, extremely porous “shell” structures (mean porosity of ~85% and mean pore size 6 μm) were obtained with good adhesion to the core fiber [Figure 9(c)]. These new fibers demonstrated good mechanical properties with a

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**Figure 9.** The structure of the core/shell composite fibers: (a) A schematic representation showing the concept; (b, c) SEM fractograph of a specimen; (d) The effect of paclitaxel content on its release profile from core/shell fiber structures. Red square, 0.7% w/w; Pink circle, 1.4% w/w; Blue triangle, 2.9% w/w; Turquoise square, 7.1% w/w. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
versatile drug release profile. The porous PDLGA shell contained 1.6–6 μg of paclitaxel per 1 cm of fiber (16–60 μg/cm²). The fibers released a maximum of 40% of the paclitaxel, and most of the release occurred during the first 30 days. Paclitaxel release from the porous shell was relatively slow due to its extremely hydrophobic nature, and the main release mechanism during the tested period was diffusion rather than polymer degradation.

The release rate and quantity increased with the increase in drug content or the decrease in polymer content, while other emulsion’s formulation parameters and processing conditions showed a minor effect on the release profile. The effect of drug content on the paclitaxel’s release profile from the fibers is presented as an example in Figure 9(d). Incorporation of surfactants in the organic phase of the emulsion increased the rate of drug release through a microstructure with a larger surface area for diffusion. Although our new fibers exhibited versatile drug release profiles, the paclitaxel release profile obtained for most studied structures during the test period demonstrated a very low initial burst effect, accompanied by a decrease in release rate with time. It is clear that a second release phase should occur after more than 4 months. This means that during the first release phase, most of the drug is released within the first month and a second release phase should occur later as the polymer undergoes degradation into very small fragments. Such a release profile can be advantageous for our application, especially since it is known that restenosis may occur within 6 months after the procedure. It should be mentioned that the specimens maintained their mechanical integrity throughout the entire test period, without visible cracking or discharge of degradation products to the medium. Our results indicate also that the new composite fibers are strong and flexible enough to be used as basic elements for stents. We have demonstrated that proper selection of processing conditions, based on kinetic and thermodynamic considerations, can yield polymer/drug systems with desired drug release behaviors and good mechanical properties. Our novel coating technique can be used on biodegradable core fibers to get totally biodegradable stents, and it can also be used for bare metal stents, where only the drug-loaded coat degrades with time.

CONCLUSION

This review presents an extensive overview of approaches for prevention of restenosis. It focuses on drugs for prevention of restenosis, metal stents, and drug-eluting stents. It also describes published studies of new biodegradable stents with drug delivery. These stents are actually used as drug delivery platforms in addition to their support function, releasing drugs for prevention of restenosis from the stent in a desired controlled manner. Basic elements, such as our new composite core/shell fiber structures, can be used to build new biodegradable drug-eluting stents. New drugs and stent designs may thus advance the therapeutic field of restenosis prevention.

REFERENCES


