

Stents as Carriers for Applying a Local Active Agent: The Concept of the "Drug-Eluting Stent"

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Summary

Coronary intervention using stents started with the purpose of reducing the stent's surface-tissue response. Such stents avoid a local negative remodeling effect; however, neointimal proliferation could not be positively influenced. Altogether, in daily practice the in-stent(re-)stenosis (ISR) rate is about 20 – 25%. Passive coatings are apparently insufficient for a convincing reduction of ISR, however, just in the actual beginning era of active drug coatings, such coatings have now an expanded application with respect to the permanently antithrombotically active base (e.g. silicon carbide) or as a biocompatible drug reservoir (e.g. phosphorylcholine, aluminiumhydroxide). An effectively influence of antiproliferative drugs locally and temporarily administered by stents should be expected – the era of active coatings currently dominates experimental and clinical research. The paper describes some important advantages and drawbacks of local drug elution using direct application and polymer based release of different drugs. With respect to such initial clinical studies as RAVEL and SIRIUS, an ISR-rate of 10% can be expected under routine conditions. Because of various differences in mechanisms, no general conclusions applicable to all agent groups can be expected. It will be the task of further experimental and clinical research to gradually define the real indication areas and to develop different systems for applications (multistaged and multitargeted systems) and drugs (e.g. from cell killing to smooth muscle cell phenotype modulators). In addition, the preconditions for optimizing stent therapy will be further improved by the use of completely degradable stent systems (basic carrier and coating). Thus, by borrowing from nature, a more physiological healing of the lesion will be the final goal of the interventional efforts at the way from "reduce the surface tissue response" to "induce an adequate local host response".

Key Words

Stent coating, drug-eluting stents, polymers, biocompatibility, local host response

Introduction

Coronary stenting undoubtedly constitutes a breakthrough technology in interventional cardiology. However, its long-term success has led to the development of an iatrogenic form of a new localized disease, in-stent (re)stenosis formation (ISR). The increasing number of implanted coronary stents also means an increase in the number of stent (re)stenoses that require treatment. This increase can also be attributed to an expansion of indications (diabetes, small

vessels, recanalization of acutely and chronically occluded vessels, etc.). Trying to solve a localized problem with a localized solution seemed like the obvious approach. Aside from the (local) administration of radioactivity, there has been no shortage of attempts to reduce the excessive neointimal reaction within the stent (in-stent) and on its proximal and distal ends (in-segment) following implantation. Examples include: tailored changes of the stent design

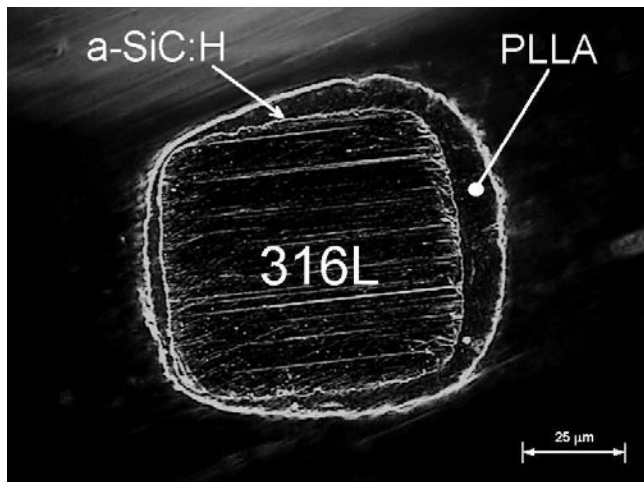


Figure 1. Example of a hybrid coating consisting of 316L, basis coated with a-SiC:H, topcoat with a high-molecular polylactide.

(better scaffolding, smaller strut thicknesses, "assimilated stenting" by adapting the mechanical properties to the local requirements, etc.), optimizing the physico-chemical surface characteristics of the implanted material (e.g., electro-polishing), and the use of passive stent coating (for examples of passive coatings, see [1-3]). This improves the biocompatibility of the surfaces, reduces local cellular and plasmatic

Stent design

- Strut (in)conformity along the stent
- Strut penetration depth(s) (injury)
- Used cell sizes
- Max./min. distance between the struts in tortuous vascular passages (inner and outer radius)
- Max./min. diffusion distance

Active agent(s)

- Retaining pharmacologic activity after sterilization
- Hydrophilic or hydrophobic
- Mechanism(s) of the biologic action (e.g., Does the medication reach the target location?)
- Toxicity/concentration – therapeutic window
- Type and kinetics of the releasing agent
- Specific diffusion and convection properties (molecular size and charge, binding to proteins, etc.)

Lesion to be treated

- Excentricity
- Calcification
- Endothelization
- Matrix composition
- Cellular uptake/activation (e.g., for gene-therapeutic concepts)

Table 1. Additional requirements/influence factors for a local vascular active agent application by stent application.

reactions, and inhibits allergen-caused inflammatory reactions (nickel, molybdenum) [4]. Significant partial successes (Braunwald IIIb) could thus be achieved in clinical subgroups (e.g., unstable angina pectoris), but there is an increased risk for an ISR (TRUST Study – see [5]). However, passive coatings are apparently not sufficient for a convincing reduction of ISR that also includes broader indications (even when heparin bindings are included – see [6]). But in the age of active coatings, passive coatings are now gaining new, expanded application as a permanently antithrombotically active base (e.g., silicon carbide) or as a biocompatible reservoir (e.g., phosphorylcholine) (Figure 1).

All previous attempts to effectively influence the ISR by systemic active agent applications have so far been unsuccessful [7]. Apparently, the concentration of the necessary agent is not reached locally in the vascular wall. Therefore, the use of the stent itself as a carrier for the active agent(s) was an obvious approach in this case. With the help of the stent, the essential concentrated local agent reached the site without having to worry about negative systemic effects. This approach is also favored because the agent can be applied directly to the site (within limits – see below) and at the same time as the application. The active coating principle, that of "drug-eluting" stents, currently dominates experimental and clinical research – another breakthrough through technology enriching interventional cardiology, even though a well-grounded description is not yet available.

Principle

The basic principle combines mechanical coverage of the lesion (at the moment still permanent) with local pharmacologic modulation of the subsequent biologic processes; the stent serves as the carrier for the (more or less controlled) application of an active agent. Principally, active agents can be attached at/in the non-degradable stent in three forms:

- by direct (adsorptive or covalent) binding of the agent to the strut surface;
- by putting them into specially created cavities in the struts (with or without additional covering by a resorbable polymer); and
- by polymer coating (of the struts-coating, or of the entire stent as a polymer sheath-covering).

Polymer types for stent coating according to their degradability

- Non-degradable polymers (e.g., polyvinyl-pyrrolidone, polyurethane, polyethylene vinylacetate, polybutyl methacrylate);
- Degradable polymers (e.g., polyhydroxy butyl acid, poly-(l)-lactide)

Polymer types for stent coating according to their synthesis

- Synthetic polymers (e.g., polybutyl methacrylate, poly-(l)-lactide, phosphorylcholine)
- Biologic polymers (e.g., hyaluronic acid, chondroitin sulfate, fibrin)

Polymer types for stent coating according to their biological effect

- Polymers with mostly lacking local effects on cellular and humoral elements (passivation) (e.g., poly-(l)-lactide, phosphorylcholine)
- Bioactive polymers (e.g., hyaluronic acid, polymerized glucosamino-glycane)

Table 2. Polymers for stent coatings. Note, this is not a complete list.

The disadvantage of the first form is its low concentration of active agent. However, the possibility of including a selective abluminal stent coating could be advantageous, by reducing the negative effects on luminal neo-endothelialization when using anti-proliferatively active substances (e.g., in the paclitaxel-eluting stent by Cook Inc., USA). The second form complicates the distribution of the controlled local agent (and the connected spatial distribution in the tissue). Therefore, the efforts of developers are currently concentrated on a polymer coating. Table 1 contains the principal significant factors for a local vascular active agent application.

Carrier Substances

The functional basic types of carrier substances are listed in Table 2. Aside from the necessity of meeting certain mechanical requirements (breaking elongation, recoil behavior, mechanical strength during the crimping process and balloon application, and sufficient adherence to the stent struts even in areas with the highest mechanical stress, see Figure 2), it is not a trivial technology to concentrate a sufficient amount of the active agent in the polymer and to release it to the surrounding tissue under in-vivo conditions with controlled (known) release kinetics just with respect to the lack of thrombogenicity, and the requirement to retain

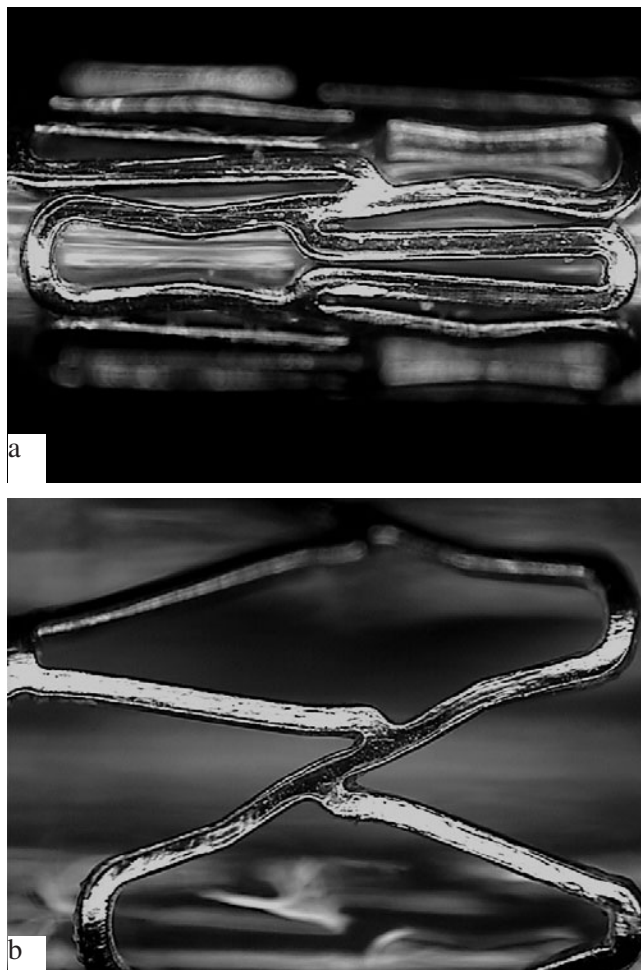


Figure 2. Example demonstrating the quality of a stent coating. Lekton, diameter = 3.5 mm, burst pressure = 10 bar (Biotronik, Germany) with high-molecular polylactide; Panel a) prior to stent opening; Panel b) after balloon dilatation.

all these characteristics even after the necessary sterilization process. Finally, the polymers themselves may not cause a local (unspecific) inflammatory reaction which, in turn, would have to be treated with the used active agent. Principally it has to be assumed that all foreign non-resorbable and resorbable polymers induce at least an initial tissue reaction. In the case of resorbable polymers, further reactions are to be expected in the final stage of degradation (release of soluble components, fragmentations). After negative experiences with some polymers (non-degradable ones as well as degradable ones – the so-called pro-proliferative effect) [8], some polymers (usually a polymer mix) have been successfully developed that show no relevant additional deleterious effects under in-vivo conditions,

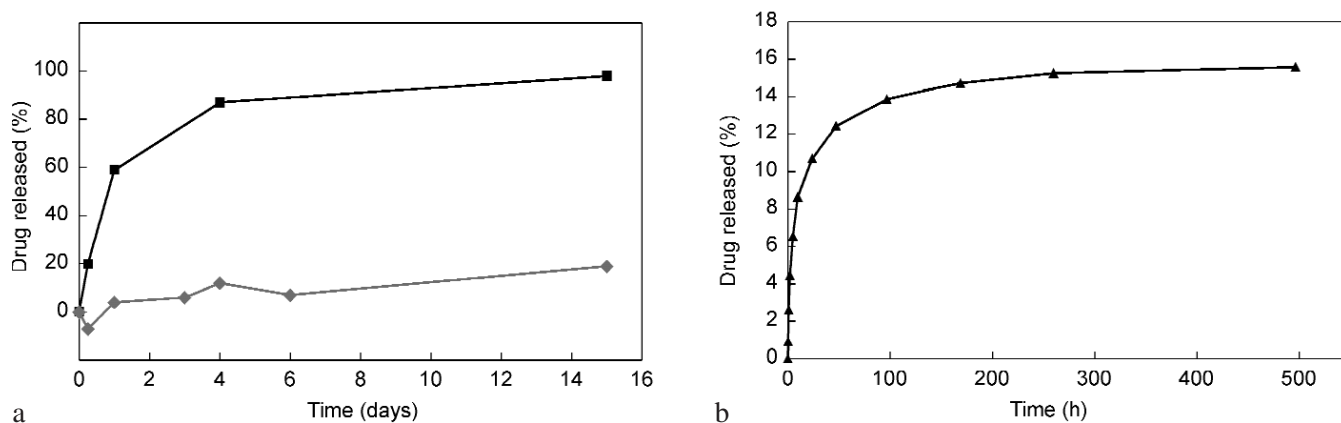


Figure 3. Panel a) *in-vivo* active agent release (here sirolimus) from a stent without (fast release ■) or with (slow release ♦) top-coat (BX Velocity, Cordis, USA) modified according to Wilensky. Panel b) example for agent release of a peroxisome-proliferator-activated receptor (PPAR) agonist (40 weight %) from a high-molar poly-L-lactide (PLLA) stent coating (60 weight %).

at least in the early phase. Along with degradation kinetics and the decomposition products formed during degradation, the molecular weight is also important for the biologic effect [9]. An observed correlation between the primary molecular weight and the degradation kinetics may provide the explanation [10]. Layer thickness, electrochemical properties, pore sizes, and the squeezing phenomena during the stent application determine, in combination with the specific characteristics of the drug, the amount and kind of agent release for the currently experimental and clinically used non-degradable polymers. Diffusion and convection follow their respective laws, and their release (and thus effect) kinetics can only be controlled by additional mechanisms (so-called "top-coating"). Here the basis layer serves as the active agent's reservoir; the additional outer layer (topcoat) constitutes a diffusion barrier, which helps to delay the release of the agent (slow drug release – for example, the sirolimus-eluting BX velocity stent system, Cordis/Warren, USA) (Figure 3). The total amount of releasable active agent is limited by the total amount of the attached polymer. The physico-chemical properties (e.g., crystallization) additionally limit the agent's uptake capability for a given polymer, or they in turn influence the mechanical properties of the layer itself [10]. The requirements for local "passivity" are undoubtedly higher for degradable polymers; however, they have potential advantages for a prolonged controlled-release of the active agent. Poly-L-lactide (PLLA) must be regarded currently as the most suitable resorbable polymer for coronary stents. In accordance with its chemical structure, the partially crystalline polyester PLLA is decomposed by hydroly-

sis (in an aqueous milieu) to lactic acid (L-lactate), the monomer starting material. The known long degradation time of PLLA is caused by the hydrophobic character of the polymer, which guarantees a relatively low water uptake, leading to a diminished hydrolysis rate. Decomposition comprises four phases:

- loosening and dissolution of secondary and tertiary polymer structures by water uptake (hydration);
- hydrolytic cleavage of ester bindings – causing shortening of the polymer chains and reduction in mol mass (loss of solidity);
- further cleavage of ester bindings until falling below a critical mol mass (10 000 – 20 000 g/mol) necessary for mass coherence (loss of mass coherence); and
- complete decomposition – fragmentation and dissolution of the low-molecular compounds.

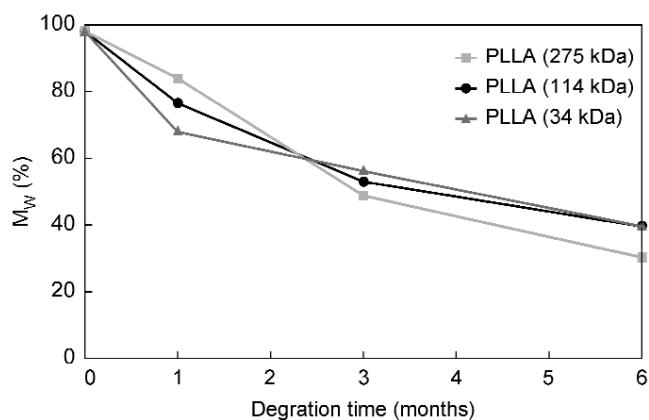


Figure 4. Dependency of poly-L-lactide (PLLA) degradation from the primary mol mass (in kDa = $\mu\text{g/mol}$) according to Gogolewski [10]. M_w = mass/mol.

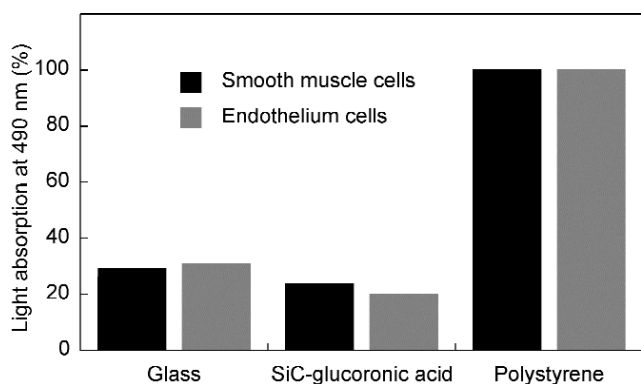


Figure 5. Vitality behavior of human endothelium cells and smooth muscle cells in a cell culture. Comparison between glass, cross-linked hyaluronic acid, and polystyrene via the membrane touch switch test.

During degradation, a rise in crystallinity can be observed, caused by the crystallization of chain fragments in the hydrolyzed, amorphous regions of the polymer. The degree of crystallinity and mol mass are important for degradation kinetics ([10] and Figure 4). Other important factors are the implant size (surface – volume ratio), the implantation location, and additions (in the form of amorphous or hydrophilic blend partners). One must also consider that water-soluble additions (even water-soluble active agents) lead to a larger inner surface due to the wash-out of the addition from the polymer matrix, which may cause acceleration of the degradation. Resulting from the chemical structure

of PLLA, an accelerated degradation can also be expected from acidic and alkaline additions (including respective active agents), because the cleavage of the ester bindings is catalyzed by acids as well as bases. Furthermore, the influence of intrinsic enzymes must be taken into account under in-vivo conditions [11]. For PLLA this means that a degradation time between 1 and 2 years can be assumed with direct blood contact, and of more than 2 years in the tissue. A marked acceleration of the polymer degradation can be achieved by combination with other polymers (e.g., poly-3-hydroxy butyric acid) [12]. With a well-designed active agent binding and release from the polymer or its components, agent release systems can be imagined that are in the end determined by the degradation kinetics themselves.

Another improvement can be expected from the use of so-called bioactive polymers (of synthetic or biologic origin) [13,14]. Based on a ligand-receptor binding, they allow combining so-called passivation effects (absent or minimally developed local cellular reactions) with tailored active elements (controlled cellular reaction). One example for such a development is the stent coating with polymerized hyaluronic acid. Aside from the excellent local compatibility (passivation) of this water-insoluble, but degradable bio-polymer, receptor-mediated active effects on the proliferation properties of the smooth muscle cells (RHAMM and CD44) are expected (inherent intrinsic effect of the active agent carrier) [15,16] (Figures 5 and 6). Further

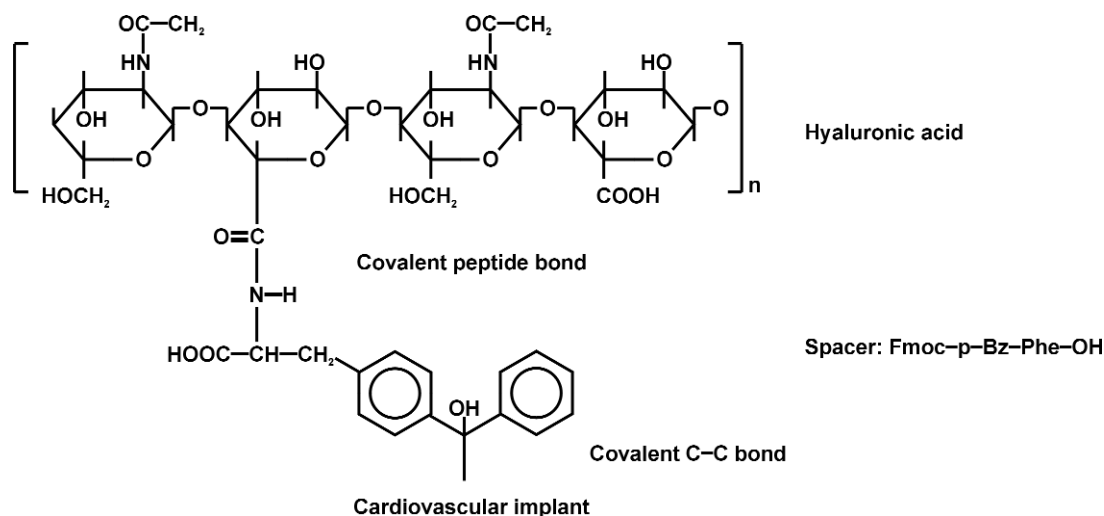


Figure 6. Covalent binding of cross-linked hyaluronic acid to a-SiC:H – an example of an inorganic-organic stent coating (Biotronik, Germany).

advances can be anticipated especially in the field of carrier substances, particularly in the field of degradable carriers.

The Role of the Stent Design

Table 1 describes some important aspects for a suitable stent design, whereby it is impossible to separate the intended biologic action mechanism of the applied active agent from the design itself. It cannot be expected that one stent design will be sufficient for all potential active agents. If a potential agent (e.g., c-myc antisense) is to reach the smooth muscle cells quickly and directly, a controlled intramural application is advantageous, if not completely necessary [17]. Currently, existing conventional stents can achieve this only if the struts puncture the lamina elastica interna (and thus cause themselves a relevant undesired "injury response" in return [18]). At the moment, rather impractical (costs, additional risks, access to lesion) additional systems (e.g., infiltrator, IVT, USA) are necessary. For the currently existing or experimentally and clinically tested drug-eluting stent systems, the mechanical contact between coated (and therefore agent-loaded) strut and the endothelium or the sub-endothelial tissue (depending on the strut penetration depth) is crucial. Because of the differing strut density (e.g., in tortuous vascular passages), a spatial concentration difference of the applied active agent has to be assumed [19,20]. Zones with agents that are too low or too highly concentrated are to be expected in the same stented vascular segment. To reduce this influence of the stent geometry on the concentrated agent in the tissue – an important influence for local tissue reaction – a stent design with strut distances that are as evenly spaced as possible along the entire course of the stent in its dilated or implanted state is preferred. This especially applies to systems that use hydrophobic active agents

- Inhibition of cell division at as early a phase as possible
- Induction of apoptosis, not of cell necrosis
- Primarily selective inhibition on smooth muscle fibers (no or only slight impairment of the neo-endothelialization)
- Inhibition of cell migration and excessive collagen expression by the cells
- Inhibition of the local inflammatory reaction (if exceeding the normal wound healing process)
- Avoidance of (short- and longer-term) counter-regulation

Table 3. Strategies for selecting suitable active agents.

(e.g., paclitaxel) or active agents with a narrow therapeutic window. If it is necessary to implant multiple stents in one lesion, the uneven agent distribution gains additional significance. On the one hand, a "gap" between the stents must be avoided, in order not to generate zones where the agent concentration is too low (at the site of the space between the stents). On the other hand, an overlapping stent implantation can lead to a local overdose with negative consequences, e.g., for the subsequent neo-endothelialization at the site of the overlapping agent-carrying stent struts. There are already primary clinical indications that phenomena similar to those known from brachytherapy (where they are referred to as the "candy wrapper effect," while they are restenosis formations at the site of the stent ends, so-called in-segment obstructions, in these cases) occur at the stent ends, possibly caused by a drop in the concentration of the active agent [21]. Further studies are needed to decide whether "cold ends" or "hot ends" (analogous to brachytherapy) might be the solution, whether other phenomena (e.g., high pressure after-dilatation at SIRIUS) might be responsible, and whether these phenomena are of a general nature at all or perhaps are restricted to specific active agents.

Active Agents

The ISR is apparently a multifactor process, with proliferation and expression of the smooth muscle cells in the vascular wall, and differently activated hematogenous cell types playing the dominant role. It is hard to imagine that such a multifactor and "multi-staged" process, combined with very different individual initial conditions, can be completely brought under control by one active agent administered at a single time. Theoretically, the principles listed in Table 3 should be promising for the selection of suitable agents. A number of potential candidates for a promising approach were experimentally derived from these principles, and some have also been clinically studied (though only under selective initial conditions; see Table 4). This list of candidates is incomplete since new interesting and theoretically promising active agents are constantly added. However, the current approach in the search for suitable agents is mostly one of trial and error ("find a drug, don't search for the drug"). Positive as well as negative surprises can be expected. The properties of the agent are important for the release kinetics of incorporated active agents from the polymer matrix, as well

Mostly anti-proliferative effect*

- Paclitaxel or taxol derivatives
- Methotrexat
- Actinomycin
- Vincristin
- c-myc antisense
- Angiostatin

Mostly anti-inflammatory effect including immunosuppression**

- Sirolimus/rapamycin
- Tacrolimus/FK 506
- Cyclosporin
- Dexamethason/methylprednisolon
- HMG CoA reductase inhibitors

Combination of (*) and ()**

- Proteasomic inhibition
- Peroxisomic receptor activation (PPAR agonists)
- Ubiquitin-proteasomic inhibition

Mostly coagulation inhibition or inhibition of the coagulation activation

- Heparin
- Hirudin
- Iluprost
- Abciximab
- Clopidogrel

Mostly inhibition of the cell migration/modulators of the extracellular matrix

- Batimastat
- Halofuginone
- Hyaluronan
- Tyrphostin
- PPAR agonists

Mostly effect on an early restoration of the endothelial function

- VEGF
- HMG CoA reductase inhibitors
- iNOS gene transfer
- 17- β -estradiol

Table 4. Active agent candidates (selection) for a "drug-eluting" stent modified according to [17].

- Lacking relevant thrombogenicity (for ongoing thrombocyte-inhibitory therapy with clopidogrel or ticlopidine)
- Dose-dependent reduction of the neointimal formation
- Mostly absent or in comparison to non-coated stent with analogous design reduced local inflammatory reaction
- Proof of a neo-endothelialization
- Absent or only very slightly developed fibrin deposition in the immediate vicinity of the strut
- Lacking epicardiac reaction
- Lacking intramural necrosis or hemorrhages

Table 5. Evaluation criteria for the suitability of the active agent. Porcine animal experiment, minimum duration 4 weeks at coronary implantation, compared to non-coated stent with an analogous design.

as the chemical structure of the polymer and the resulting physico-chemical properties. For instance, given the same polymer matrix, agents that dissolve well in water (hydrophilic) are eluted faster from the polymer than substances that dissolve poorly in water (hydrophobic). The lipophilic response is also of great importance for tissue distribution. Without a polymer basis (e.g., direct binding of the active agent on the metal), only lipophilic substances can be used. During the clinical application (with the respective different local initial conditions), it is expected that only different concentrations of agents with different release kinetics will bring the desired optimal success. Experts agree that an active agent should show positive effects under the conditions of an animal experiment, porcine if possible, before it is clinically tested (for evaluation criteria, see Table 5). However, there are increasing indications that (aside from the known principal problems with applying data from animal experiments to the human situation) negative long-term effects cannot be excluded using the preferred test duration of 28 days. This is equivalent to a follow-up of 6 months under human conditions. These effects are well-known from the use of paclitaxel (in animal experiments and clinical experience) [22,23]. It is precisely this objective inability to apply animal data to humans that calls for caution in evaluating early clinical successes and in applying the therapy concept to a broad clinical population (too early). Thus, the first euphoric zero-percent restenosis reports from selected patients [24,25] are now being followed by reports of considerable restenosis rates when high-risk patients are analyzed (e.g., diabetics with 17.6% in-segment stenoses and 18.9% in-segment stenoses for smaller vessels [26]. On the one hand, a lack of alternatives makes clinical tests based on well-founded concepts and carefully gathered in-vitro and in-vivo data necessary. On the other hand, it should not be overlooked that about 70% of all stented patients apparently do not need a "drug-eluting system" because they do not develop an ISR in the first two years after implantation. Non-coated and passively coated stents (as well as the "conventional balloon dilatation" itself) have not lost their importance in clinical therapy [27]. It should also be studied whether drug-eluting systems based on (permanent) hypothrombogenic stent coatings, with anti-proliferatively active substances and negative effects on the neo-endothelialization, might have desirable effects (e.g., avoidance of long-term medication with platelet aggre-

gation inhibitors – see also [28]). In the author's opinion, the exciting field of active agent-carrying stents has to generally be put on a more solid scientific foundation with the necessary critical perspective to allow its entrance into a wider therapeutic spectrum for patients with coronary vascular disease.

The Complete System (Balloon Catheter with Stent)

It was previously mentioned that sterilization must be possible without any negative consequences for the carrier substance and the active agent. The agent load creates new requirements on the durability of the entire system. "Loading" shortly before the intervention is possible but not very practical. The approval requirements will change (and become more expensive), because we are mostly dealing with combinations of systems. Uncontrolled damage to the layer and agent losses during the balloon dilatation (e.g., due to friction) should be excluded by suitable in-vitro tests. In case of a partial or complete "covering," the mechanical properties of the stent are changed (crossability, flexibility, etc.). To reduce possible consequences, a pre-dilatation is currently recommended prior to stent implantation; this also makes the entire process more expensive. Based on the existing pathophysiologic knowledge, it is difficult to ask for or justify certain defined release forms (duration, initial and final concentration, etc.). Nevertheless, validated and thus standardized release mechanisms must be requested if only to gather the necessary experiences for further development in a targeted clinical application.

Current Limitations

This therapeutic attempt has several variables including unknown biological correcting variables. The necessary local active agent concentrations and distributions in the vascular wall under different local preconditions (lesion types) and genetic variants (e.g., polymorphisms), and the corresponding optimal timing are not known and cannot be directly measured under in-vivo conditions. With certain substances and preferred methods of action (diffusion with the existing or absent endothelium cell barrier), local overdosages (local toxicity) or underdosages may therefore occur. According to the RAVEL study (sirolimus-LDD), stent malappositions occurred 20% of the time (by IVUS examination). They could be undesirable, induced, regional

remodeling phenomena, as they are also found in brachytherapy. This has also led to an extension of several months of the accompanying drug therapy with thrombocyte aggregation inhibitors in patients after the implantation of a drug-eluting stent, in order to prevent late complications. The reactive biological effects in the vascular wall in cases of decreasing active agent concentration (stent ends, but also after conclusion of the agent's active phase) are not well understood. Because of the differing mechanisms, no general conclusions applicable to all agent groups can be expected. In the long term, we must determine how the vascular wall adapts to a variable active agent concentration, as well as (if carrier substances are used) to the remaining or degrading polymer.

Outlook

This paper is intentionally technology-oriented with the intention of focusing on "unfinished subjects" and to underscore how probability and therapeutic potency are associated with local "drug elution" (see the respective references for current clinical data). It will be the task of experimental and clinical research, as well as organized, practical experiences, to gradually define the actual indication areas and develop different systems for various applications (e.g., intramural application, "multi-staged and multi-targeted" systems) in order to meet the problem of ISR with the necessary breadth and required critical depth. It can be expected that the preconditions for optimizing stent therapy will be further improved by the use of completely degradable implants (on a polymer basis – [29] or based on metallic alloys [30]), since this potentially achieves better (and more diverse) preconditions for a "multi-staged/multi-targeted system," and also prevents the permanent mitogenic irritation in a constantly moving

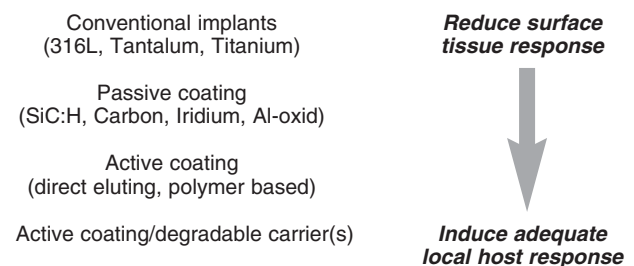


Figure 7. Paradigm change in the development of cardiovascular implants.

system, which apparently exists after all [31,32]. In the end, a "borrow-from-nature" concept, the introduction of a "more physiologic" healing of the lesion, is the final goal of the interventional efforts (Figure 7).

References

- [1] Heublein B, Pethig K, Elsayed AM. Silicon carbide coating: a semiconducting hybrid design of coronary stents: a feasibility study. *J Invasive Cardiol*. 1998; 10: 255-262.
- [2] Windecker S, Mayer I, De Pasquale G, et al. Stent coating with titanium-nitrite oxide for reduction of neointimal hyperplasia. *Circulation*. 2001; 104: 928-933.
- [3] Whelan DM, van der Giessen WJ, Krabbendam SC, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. *Heart*. 2000; 83: 338-345.
- [4] Rzany A, Schaldach M. Smart material silicon carbide: reduced activation of cells and proteins on a-SiC:H coated stainless steel. *Prog Biomed Res*. 2001; 6: 182-194.
- [5] Hamm C. TRUST - study. Late breaking clinical trial presentation at the XXIII Congress of the European Society of Cardiology. 2001 Sep 1-5; Stockholm, Sweden.
- [6] van der Giessen WJ, van Beusekom HM, Eijgelshoven MH, et al. Heparin-coating of coronary stents. *Semin Interv Cardiol*. 1998; 3: 173-176.
- [7] Lefkovits J, Topol E. Pharmacological approaches for the prevention of restenosis after percutaneous coronary intervention. *Prog Cardiovasc Dis*. 1997; 40: 141-158.
- [8] van der Giessen WJ, Lincoff AM, et al. Marked inflammation sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation*. 1996; 94: 1690-1697.
- [9] Lincoff AM, Furst JG, Ellis SG, et al. Sustained local delivery of dexamethason by a novel intravascular eluting stent to prevent restenosis in the porcine coronary injury model. *J Am Coll Cardiol*. 1997; 29: 808-816.
- [10] Gogolewski S, Jovanovic M, Perren SM, et al. Tissue response and in vitro degradation of selected polyhydroxyacids: polylactides (PLA), poly(3-hydroxybutyrate) (PHB), and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHB/VA). *J Biomed Mat Res*. 1993; 27: 1135-1148.
- [11] Reed A. In vivo and in vitro studies of biodegradable polymers for use in medicine. Thesis, Liverpool 1978. In: Pistner H. Osteosynthese mit bioresorbierbaren Materialien, Entwicklung einer Schraube vom Werkstoff bis zur klinischen Anwendung. Reibek: Einhorn Presse Verlag. 1999.
- [12] Freier T, Kunze C, Nischan C, et al. In vitro and in vivo degradation studies for development of a biodegradable patch based on poly (3-hydroxybutyrate). *Biomaterials*. 2002; 23: 2649-2657.
- [13] Cook AD, Hrkach JS, Gao NN, et al. Characterization and development of RGD-peptide-modified poly(lactic acid-co-llysine) as an interactive, resorbable biomaterial. *J Biomed Mater Res*. 1997; 35: 513-523.
- [14] Chupa JM, Foster AM, Sumner SR, et al. Vascular cell response to polysaccharide materials: in vitro and in vivo evaluations. *Biomaterials*. 2000; 21: 2315-2322.
- [15] Rohde R, Heublein B, Ohse S, et al. Stent covering using insolubilized degradable biopolymers based on cross-linked hyaluronan or chitosan - response to stent injury in coronary arteries of pigs (abstract). *Circulation*. 2001; 104 (Suppl): 666-667.
- [16] Heublein B, Evagorou EG, Rohde R, et al. Stent-Based Delivery of Hyaluronan as Carrier with Inherent Inhibitory Effects to Reduce Neointimal Formation in a Porcine Coronary Model. *International J Artificial Organs*. In press 2002.
- [17] Kipshidze NN, Kim H-S, Iversen P, et al. Intramural coronary delivery of advanced antisense oligonucleotides reduces neointimal formation in the porcine stent restenosis model. *J Am Coll Cardiol*. 2002; 39: 1686-1691.
- [18] Kornowski R, Hong MK, Tio FO, et al. In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. *J Am Coll Cardiol*. 1998; 31: 224-230.
- [19] Hwang CW, Wu D, Edelman ER. Physiological transport forces govern drug distribution for stent-based delivery. *Circulation*. 2001;104: 600-605.
- [20] Regar E, Degertekin M, Tanabe K, et al. Drug eluting stent. Proceedings of the Paris Course on Revascularization; 2002 May 21-24; Paris, France. 2002: 233-237.
- [21] Moses J for the SIRIUS study investigators. The SIRIUS - in between report. Late breaking clinical trial presentation at the Paris Course on Revascularization; 2002 May 21-24; Paris, France.
- [22] Farb A, Heller PF, Shroff S, et al. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. *Circulation*. 2001; 104: 473-479.
- [23] Heldman AW, Cheng L, Jenkins M, et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. *Circulation*. 2001; 10: 2289-2295.
- [24] Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neo-intimal proliferation by sirolimus-eluting stents. One-year angiographic and intravascular ultrasound follow-up. *Circulation*. 2001; 104: 2007-2011.
- [25] Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. The RAVEL trial. *N Engl J Med*. 2002; 346: 1773-1780.
- [26] Results from the SIRIUS trial, presented at the 14th annual Transcatheter Cardiovascular Therapeutics (TCT) symposium. 2002 Sep 24-28; Washington DC, USA.
Available from:
URL: http://www.clinicaltrialresults.org/shows/sirius%20tct%202002_files/frame.htm
- [27] Sousa JE, Costa MA, Sousa AGMR. What is "the matter" with restenosis in 2002? *Circulation*. 2002; 105: 2932-2933.
- [28] Bayer G, Hartwig S, Nagel M, et al. Future strategies for anti-proliferative stent coatings. *Prog Biomed Res*. 2001; 6: 222-225.
- [29] Tamai H, Igaki K, Kosuga K, et al. Initial and 6-month results of biodegradable poly-L-lactic acid coronary stents in humans. *Circulation*. 2000; 102: 399-404.
- [30] Heublein B, Rohde R, Hausdorf G, et al. Bio-corrosion - a new principle for temporary cardiovascular implants? (abstract) *Eur Heart J*. 2000; 21: 286.

- [31] Kimura T, Abe K, Shizuta S, et al. Long-term clinical and angiographic follow-up after coronary stent placement in native coronary arteries. *Circulation*. 2002; 105: 2986-2991.
- [32] Yutani C, Ishibashi-Ueda H, Suzuki T, et al. Histologic evidence of foreign body granulation tissue and de novo lesions in patients with coronary stent restenosis. *Cardiology* 1999; 92: 171-177.

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