The future of drug-eluting stents

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Introduction:
In-stent restenosis (ISR) is the major drawback of percutaneous coronary interventions, occurring in 10–40% of the patients [1]. Drug-eluting stents (DES) are successful in a large majority of cases in preventing restenosis for the first year following implantation. Recently, new stents have emerged which are loaded with anti-inflammatory, anti-migratory, anti-proliferative or pro-healing drugs. These drugs are supposed to inhibit inflammation and neointimal growth and subsequently ISR. One problem with current DES is that, as many as 40% of patients receiving DES require very long stented segments in order to provide adequate coverage. Further when the coronary tree is excessively tortuous or heavily calcified delivery of long DES is technically difficult.

Newer stent designs and innovative ideas of drug delivery, as well as newer drugs are likely to emerge to prevent ISR, however results with new DES are available in only limited number of cases. The future of DES lies in innovation of better (1) stents with new stent design, (2) polymers with emerging of biological polymers and biological biodisolvable stent coating and (3) new drugs.

[A]. Current status of DES:
Some DES are effective in preventing ISR, although long-term results from large studies are missing. The longest follow-up period of the clinical studies is 2 years in the case of the RAVEL, SIRIUS and TAXUS-I studies. Of interest there is no major increase in target lesion revascularisation rates between 1 and 2 years of follow-up [2]. In some animal models a delayed healing between 90 and 180 days after implantation has been observed [3]. At present, the long-term pathobiology of the interference of locally delivered drugs with the complex process that ensues vascular injury associated with stent implantation is uncertain, thus long-term clinical and angiographic follow-up is therefore mandatory.
[B]. The future prospectives of DES:
The future of DES lies in the advances and new technology of
(1) New stent design.
(2) Polymer (coating) with emerging of biological polymers and biological biodisolvable stent coating.
(3) New drugs including stent-based gene delivery using antibody-tethered viruses.

[1]. The stent
The ideal DES is flexible, has a good radial strength and a large surface area to load one or more drugs. The gaps between the struts have to be small to get optimal and equal distribution of the drug over the target lesion. Stent material, electrophysiological properties and biocompatibility of the stent surface also influence neointimal proliferation [4].
Theoretically, a drug-eluting biodegradable stent may be the ideal solution to prevent ISR. Early response to injury of the vessel wall can be suppressed by the drug, whereas elastic recoil and negative remodelling can be prevented by the stent. Eventually, the stent will be degraded over time and chronic vessel wall injury will be prevented. The future of DES will lie in delivery of multiple drugs at timed intervals through newer stent designs.

[1].A. Conor stent
Conor's stent design [5] incorporates hundreds of small holes, each acting as a reservoir into which drug-polymer compositions can be loaded and has the potential to deliver multiple drugs, enhance control of the rate and direction of drug delivery, enable a wider range of drug therapies and potentially increase the range of clinical applications of drug eluting stents.
The design allows for greater control of release kinetics or control over the rate of drug release over time. Since drug release kinetics are controllable by selecting the
pattern in which polymers and drugs are loaded into the holes, a wide range of release kinetics can be achieved. Because of Conor's ability to vary the structure of the drug inlay within the reservoirs, it is capable of delivering a broad range of compounds, including fat-soluble drugs, water-soluble drugs, proteins, peptides and oligonucleotides. The deep reservoirs provide greater dose capacity than thin surface coatings, allowing deliver more drug for an extended period of time.

[1].B. Janus Sorin stent:

Another design [6] directly blasts the drug onto the stent. It has multiple grooves (reservoirs) on its medial side into which the drug is loaded inside sculptures on the stent external surface, so there is no need for a polymeric coating. Moreover, the drug load is delivered to the vessel wall without drug loss in the blood stream. The sculpture design reduces the early and late thrombosis risk and plays an important role in the early endothelialization of the stent, also this design protects the drug during the implantation procedure.

The tacrolimus-eluting Janus Stent underwent pharmacokinetic in-vivo evaluation, the short and long-term pharmacokinetic studies were performed and tissue drug concentration was measured, tacrolimus concentration in the artery wall peaked few days after implantation and then declined to steady values over the following weeks, about 50% of the drug was released from the stent one month after implantation with no drug was released into the blood stream. In a porcine model, neointimal proliferation was significantly reduced with Janus stent.

In JUPITER I study, two different phases of the study were designed. In phase I, 30 patients with native de novo coronary lesions were enrolled [7], event-free survival at 1-month follow-up was 100%. Phase II of the JUPITER I study is designed to complete phase I ("safety" evaluation). JUPITER II is a double blind randomised clinical trial investigation for the treatment of stenosis of coronary lesions with Janus Sorin stent, it involves 331 patients in 16 European centres.
[2] Polymer:
Polymer coatings are needed for most drugs because they do not adhere to the metallic stent surface. The polymer coating also modifies drug-elution kinetics, which can be varied by using multiple polymer layers to achieve optimal drug release over time. Initially, all biodegradable or non-biodegradable polymers induced an increased inflammatory reaction and enhance neointimal proliferation [8]. Later some polymers were found to be biologically inert and stable for at least 6 months [9,10]. New developments are biocompatible and inorganic coatings. Biocompatible coatings mimic the surface of normal tissue or cells. Phosphorylcholine-coating does not interfere with re-endothelization and the degree of neointimal formation and thus is one of the platforms particularly suited for stent-based drug delivery [11]. The purpose of inorganic substances as stent coating is to improve the electromechanical properties. This has to result in reduced platelet activation and inflammatory response. Ceramic stents with nanocavities containing tacrolimus are among the promising new devices under investigation.

[2].A. Drug-eluting poly(ε-caprolactone) stent:
A perivascular cuff to reduce ISR is constructed of a poly(ε-caprolactone) (PCL) formulation suitable for the controlled delivery of drugs [12]. Placing the PCL cuff around the femoral artery, in vivo, resulted restenosis-like lesions containing predominantly smooth muscle-actin positive cells. Loading the cuff with the anti-restenotic compounds paclitaxel and rapamycin resulted, in vitro, in a sustained and dose-dependent release for at least 3 weeks. Paclitaxel- and rapamycin-eluting PCL cuffs placed around the femoral artery of mice resulted in intimal thickening reduction at 21 days. Perivascular sustained release of both anti-restenotic agents is restricted to the cuffed vessel segment with no systemic adverse effects.
[2].B. Phosphorylcholine-coated stents:
Phosphorylcholine-coated (PC) stents have been approved for the treatment of native coronary arterial lesions [13,14], several studies have demonstrated the durability and stability of the PC stent surface coating [15,16]. In experimental models, PC coating of the strut surface has been shown to reduce thrombus formation on metallic stents [17]. The PC coating has been employed as a drug delivery matrix for stent-based delivery of the potent antiproliferative compound “ABT-578” which inhibits SMC proliferation by blocking cell cycle regulatory protein, mTOR.

Experimental studies have shown that at 28 days the mean injury score for the control, PC and PC with ABT-578 coated stents was similar, the mean neointimal area was significantly reduced for ABT-578-eluting stents. Further studies are necessary to determine the dose-response and long-term effects. The ENDEAVOR I, II, and III clinical trials evaluate a PC-coated ABT-578-eluting stent for the prevention of ISR. Angiographic analysis at 4 months in 100-patient with focal de novo lesion (ENDEAVOR I) demonstrated a mean in-stent diameter stenosis of approximately 14% and a late lumen loss of 0.3 mm with a low frequency of target lesion revascularization (1%) [18]. The clinical outcomes from the ENDEAVOR II (1,500 patients randomized to ABT-578 or BMS) and the ENDEAVOR III (436 patients randomized to ABT-578 or sirolimus DES) trials will determine efficacy of the PC-coated ABT-578-eluting stent [19].

[2].C. Biodegradable Polymer:
Biodegradable polymers are increasingly being used for the design of drug delivery system. As these polymers hydrolyse in the body into low molecular degradation products which are metabolized. Biodegradable delivery systems do not have to be removed after completion of release. In-vitro studies showed that Biodegradable polymer behaved highly biocompatible in a porcine coronary artery model and the
histopathological evaluation showed only a mild inflammatory response. The extent of ISR of polymer-only coated stents was comparable with that of bare metal stents. EuroSTAR Trial is designed to evaluate the safety, performance and efficacy of a different stent in *de novo* native coronary artery lesions using paclitaxel and a biodegradable polymer matrix Poly (DL-lactide-co-glycolide) (PLGA), it is prospective, multi-center and is designed to enrol up to 320 patients, it demonstrates promising results [6] for the use of this stent in the treatment of *de novo* lesions in native coronary arteries.

**[2].D. Amorphous oxide DES:**
Amorphous oxide has its unique chemical and physical properties, this oxide film could be an ideal substitute for the polymer coating for the drug-loading purpose. Amorphous oxide coating on 316LVM stainless steel wires, and heparin-loaded on amorphous oxide of 316LVM stainless steel wire surfaces have been studied [20] and evidence shows that amorphous oxide can be an ideal substitute for the polymer coating of drug-loaded stents to minimize metallic corrosion, inflammation, late-thrombosis, and restenosis. The feasibility of heparin loaded onto an amorphous oxide layer and the efficacy of a heparinized 316LVM stainless steel wire were confirmed by various experimental studies [20].

**[2].E. Plasmid DNA-eluting biodegradable polymer-coated metallic stent:**
The plasmid DNA in the stent coating mixture is dispersed within micro-emulsion droplets, this preparation forms a uniform film [21] over the outer surface of the Crown stent with a thin polymeric web between the struts. Upon balloon expansion, deployment of the stent results in stretching of the polymer without fragmentation. Sustained release of DNA from coated stents in vitro is characterized by an early burst of DNA with more than 50% eluted during the first hour of incubation. Seven days later neotimal formation was found to be comparable in arteries stented with and without a DNA polymer stent coating. Polylactic-polyglycolic acid (PLGA)-coated stents, whether DNA is present or not, demonstrate no early (seven days) evidence of
inflammatory activity in response to the polymer coating. Further long term studies will be of great importance for future implementation of plasmid DNA eluting stents.

[3]. Drug

The drug is the biologically active agent that has to inhibit the formation of neointimal hyperplasia by suppression of platelet activation, suppression of inflammatory response, inhibition of smooth muscle cell migration and proliferation. Ideally, the drug should have an outstanding overall safety profile and a broad therapeutic window. Besides the biological effects, the drug has its own chemical properties, which influence achieving optimal tissue levels and the possibilities for loading on a stent. Tissue levels depend on lipophilic or lipophobic characteristics, molecular weight and the degree of protein binding of the used drug [22,23]. Some drugs can be loaded directly onto the metallic surface of the stent, but most drugs need a polymer coating, which forms a reservoir for the drug.

[3]. A. Tyrphostin AGL-2043 eluting stent:

Tyrphostin AGL-2043 is a potent tricyclic quinoxaline inhibitor of PDGF β-receptor tyrosine kinase (PTK). Selective inhibition of PDGF β-receptor PTK by tyrphostins reduces SMC proliferation, migration and reduces neointimal formation. A study was designed to determine the effect of AGL-2043 delivered from a stent-based, biodegradable polymeric coating on neointima formation in the porcine coronary artery model [24]. Stents coated with biodegradable, polylactic/glycolic acid (PLGA) polymer, with or without AGL-2043 have been implanted into the LAD of porcine coronary model, after 28 days, histomorphometric analysis showed that ISR in animals treated with AGL-2043 was reduced by 50%, the absolute neointimal area was reduced by 44%, and the absolute luminal area was increased by 57%. Long-term studies should be the next step in testing applicability to the human interventional setting.
[3]. B. Stent-Based Delivery of Adenovirus TIMP-3

A recent study at Bristol Heart Institute has demonstrated that stent-based antiproliferative therapies appear to decrease ISR using Adenovirus [25], express the tissue inhibitor of metalloproteinase-3 (RAdTIMP-3) which inhibits neointima formation, decrease smooth muscle cell migration, stabilize the extracellular matrix and uniquely promote apoptosis.

[C]. The future has started:

DES have shown to be beneficial in treatment of atherosclerotic coronary artery disease, however biocompatibility of current used synthetic polymer stent coatings that serve as a vehicle for local stent mediated drug delivery remains a concern. Biological coatings based upon biological substances like fibrin, collagen, hyaluronic acid and biological oils can serve as a valid alternative as stent coatings. Gene-eluting stent, biological biodissolvable stent coating and bioabsorbable magnesium stent all have been studied with promising results while more long term and in vivo studies are needed.

[C].1. Gene-Eluting Stents

The hypothesis of local delivery via gene-eluting stent of naked plasmid DNA encoding for human vascular endothelial growth factor (VEGF)-2 has been tested to reduce neointima formation. PhVEGF-2 plasmid coated BiodivYsio phosphorylcholine polymer stents versus uncoated stents have been deployed in a randomized, blinded fashion [26] in iliac arteries of normocholesterolemic and hypercholesterolemic rabbits. Re-endothelialization was nearly complete in the VEGF stent group after 10 days and was significantly greater than in control stents. At 3 months, intravascular ultrasound analysis revealed that lumen cross-sectional area was significantly greater and percent cross-sectional narrowing was significantly lower in
VEGF stents compared with control stents. Acceleration of re-endothelialization via VEGF-2 gene–eluting stents provides an alternative treatment strategy for the prevention of restenosis. VEGF-2 gene–eluting stents may be considered as a stand-alone or combination therapy with more extensive studies with long term follow-up are essential.

[C].2. Biological Biodissolvable Stent Coating (ZISCOAT):

NV Ziscoat and Lubbeek [27] have studied the biocompatibility of biological oil based stent coatings in a porcine coronary model. At 5 days mural thrombus formation and inflammatory response were similar compared to bare stents. At 4 weeks follow-up, complete healing of the stented arterial segments has been found, inflammation score is even slightly lower in the coated stent group compared to the bare stent group. Neointimal hyperplasia at that time is similar in the coated stent group compared to the bare stent group. Results suggest a very good short term outcome of these totally biosoluble biological oil based stent coating with long term follow-up is needed. These coatings are very interesting to use for stent mediated local drug delivery.

[C].3. Bioabsorbable magnesium stent:

Stenting technology has moved toward the development of temporary implants composed of biocompatible materials which mechanically supports the vessel during the period of high risk of recoil and then completely biodegrades later. Degradable implants offer better physiological repair and reconstitution of local vascular compliance. It has better radial straightening effect and higher possibility for late positive remodelling. Experimental data have shown promising results with magnesium in ischaemia reperfusion injury, both in reducing infarct size as well as reversing myocardial stunning. Preliminary data after 3 months after bioabsorbable magnesium stent implantation [28] yield a primary clinical patency of nearly 90%. 
Pre-clinical work has demonstrated that absorbable metal stents based on magnesium offer a real possibility to improve both the acute and long term results of percutaneous coronary revascularisation.

**Conclusion:**

With several drugs have been tested in animal models and human trials, the recent advances of DES have concerned with reduction and prevention of ISR. As efficacy and safety of DES differ depending on the drug and stent delivery system, recent studies have focused on the various constituents of DES, including stent backbone, polymers used for drug delivery and the pharmacokinetic properties of the pharmacological agents themselves. Although altered stent surface may be able to carry drugs, the most difficult question is, how much drug, how uniformly distributed and over what period should the drug be delivered. While the mid-term clinical results with sirolimus- and paclitaxel eluting stents are promising, post-DES restenosis, remains a concern, in case of sirolimus-eluting stent up to 5% of patients require repeated revascularization. Sub-acute thrombosis, hypersensitivity reactions to sirolimus-eluting stents, drug resistance to sirolimus & paclitaxel and aneurismal dilatation of the stented segment were reported. With more understanding of restenosis mechanisms, new therapeutics with high potency and less toxic effects are under evaluation to overcome these remaining problems.

The future lies in delivery of multiple drugs at timed intervals through new stent designs (Conor stent which has the potential to deliver multiple drugs and Janus Sorin stent which has reservoirs for drug delivery with no polymer). Advantages of biodegradable polymers include high drug loading capacity, controlled long term drug release and full degradation of the polymer over a certain time period resulting in a full release of the drug during a well controlled time interval. Gene-eluting stents are currently under experimental and clinical trials and we expect that Gene-eluting stents alone or in conjunction with other DES will be the near coming future with less ISR rate. In the future, DES may be used for prevention of acute coronary syndrome
(plaque sealing concept). It is believed that acute coronary syndrome is caused by unstable plaques of mild to moderate stenosis (< 50%) that do not result in angina symptoms [29]. Given the high event-free survival rate achieved with drug-eluting stents, one could argue for treating these lesions with stent therapy. The effect of DES on other difficult lesions such as left main coronary artery disease, bifurcation disease and chronic total occlusions is currently under investigation. However, it is important to keep in mind that the efficacy of the DES is based on avoiding recurrent angina and additional revascularization procedures. With the recent development of the DES an even more spectacular evolution is taking place that will forever change the landscape of interventional cardiology.

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