Expert Opinion

informa
healthcare

Progressive stent technologies: new approaches for the treatment of cardiovascular diseases

Sophia Vaina & Patrick W Serruys†
† *Thoraxcentre, Ba 583, Erasmus Medical Centre, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands*

The CYPHER® (Cordis, Johnson & Johnson) sirolimus-eluting stent and the TAXUS® (Boston Scientific) paclitaxel-eluting stent have been extensively evaluated and have been proven to be significant novel tools for the treatment of coronary artery disease. Several sirolimus derivatives have already emerged, receiving CE Mark approval. However, in the future, it is likely that drugs presently under investigation will address additional mechanisms associated with neointimal formation, either as single agents or in combination with antiproliferative compounds. Concurrently, alterations on stent platform design (helicoidal, open-closed cell), coatings (biodegradable, bioabsorbable, nanoporous) and polymers are being explored.

Keywords: bioabsorbable stent, drug-eluting stent, polymer coating, stent design

Expert Opin. Drug Deliv. (2006) 3(6):783-797

1. Introduction

Large-scale, randomised trials have shown that the currently commercially available drug-eluting stents significantly reduce restenosis when compared with bare metal stents [1,2]. However, there are still limitations in the unrestricted use of drug-eluting stents, which hinder their absolute superiority over bare-metal stents. One of the main growing concerns is subacute and late stent thrombosis, a potentially lethal complication [3] that is a hot issue and is being thoroughly investigated. A prospective observational study of 2229 real-world patients treated with drug-eluting stents demonstrated a 9-month incidence of stent thrombosis of 1.3% [4]. These results were in accordance with the data reported by Ong *et al.*, who showed 1.0% angiographic incidence of early stent thrombosis [5] and 0.35% angiographically proven late stent thrombosis during the 1-year follow-up in 2006 patients who received either a sirolimus- or a paclitaxel-eluting stent [6]. In view of the risk of stent thrombosis, which has been shown to rise up to 4.3% in complex bifurcation lesions [7], the duration of dual antiplatelet therapy has become a matter of debate. Although the current indication for dual antiplatelet therapy is 3 months for sirolimus-eluting stents and 6 months for paclitaxel-eluting stents [8], in higher-risk patients and lesions, aspirin and clopidogrel 75 mg/day is often being recommended for 1 year or even indefinitely. However, this practice may increase the risk of bleeding complications and add to the cost of treatment for both the patient and the social security system. In addition, even though drug-eluting stents constitute the most effective tool available to deal with the problem of restenosis, their efficacy has not been uniform across different patient populations [9]. Recent studies have shown increased risk of restenosis after sirolimus- or paclitaxel-eluting stent placement in patients with complex lesions [10], small vessels [11], bifurcations [7] or chronic total occlusions [12,13]. Therefore, continuing research for new therapeutic agents and novel stent designs is mandatory, in order to most efficiently abolish restenosis and simultaneously maximise the immediate and long-term safety of

the implanted device. This review discusses the next generation of drug-eluting stents that are either already commercially distributed or are under investigation.

2. New pharmaceutical compounds on durable stents and polymers

Table 1 provides a summary of the new compounds on durable or absorbable stents and polymers.

2.1 Sirolimus analogues

Figure 1 provides an overview of the pathway of activation of the -limus drugs. Zotarolimus is a tetrazole-containing macrocyclic immunosuppressant and potent antiproliferative agent that inhibits the protein phosphorylation events associated with translation of mRNA and cell-cycle control. Zotarolimus has been used for the Endeavor™ (Medtronic Inc) zotarolimus-eluting stent system (zotarolimus 10 μg per mm stent length), which consists of Medtronic's Driver™ cobalt alloy coronary stent and a phosphorylcholine carrier that is a polymeric replica of the outer surface of a red blood cell, which acts as a biologically inert coating. The ENDEAVOR I was the first clinical trial to evaluate the safety and the feasibility of the Endeavor zotarolimus-eluting stent system (**Table 2**). The study included 100 patients treated in 8 centres in Australia and New Zealand. The primary end points were the major adverse cardiac event (MACE) rate at 30 days and angiographic late lumen loss at 4 months. At 4 months, the MACE rate was 2% with one myocardial infarction and one target lesion revascularisation (TLR). The in-segment/in-stent late lumen loss was 0.20 ± 0.40 and 0.33 ± 0.35 mm, respectively [14].

The ENDEAVOR II clinical trial, was a randomised, double-blind, pivotal trial designed to evaluate the safety and efficacy of the Endeavor zotarolimus-eluting coronary stent compared with the Driver cobalt alloy coronary stent (**Table 2**). The study enrolled 1197 patients from 17 countries. The primary end point of the trial was target vessel failure (TVF), which includes death, myocardial infarction and target vessel revascularisation at 9 months. The study successfully met its primary and secondary end points (TVF of the Endeavor stent versus the Driver stent: 8.0 versus 15.1%; $p < 0.0005$). The study also demonstrated a 61% reduction in TLR between the Endeavor arm (4.6%) and the control group (11.8%) [15]. However, even though in-stent neointimal hyperplasia was significantly reduced with the Endeavor stent compared with the Driver cobalt alloy coronary stent (0.62 ± 0.47 versus 1.03 ± 0.59 mm, $p < 0.0001$), neointimal proliferation was not as low as observed with other drug-eluting stents [15]. The ENDEAVOR III study (Endeavor zotarolimus-eluting stent versus the CYPHER® Sirolimus-eluting stent) was conducted in US, and randomised a total of 436 patients (**Table 2**). At 8-month follow-up, the zotarolimus-eluting Endeavor stent had significantly greater in-segment late loss than the sirolimus-eluting stent (0.34 versus 0.13 mm; $p < 0.001$), as well as in-stent late loss (0.60 versus 0.15 mm; $p < 0.001$), and did not achieve the non-inferiority end point [16]. However, no significant differences were observed between the two stents in the secondary clinical end points of major adverse coronary events, TLR, target vessel revascularisation and TVF at 9 months. In addition, the Endeavor stent had a superior device success rate versus CYPHER® (98.8 versus 94.7%), and superior procedure success [17]. ENDEAVOR IV will be a comparison with the TAXUS® stent, and will involve ~ 1000 patients (**Table 2**).

The ZoMaxx™ (Abbott) drug-eluting stent consists of the TriMaxx™ stent (Abbott), a phosphorylcholine polymer coating and zotarolimus. The TriMaxx stent has a trilayer composite of 316L stainless steel and tantalum (middle layer). The phosphorylcholine polymer of the ZoMaxx stent is identical to the Endeavor stent, but contains an additional cap layer of coating that differentiates the drug-elution rate. The Endeavor stent elutes ~ 75% of the drug from the stent in the first 48 h and 100% at 10 days, whereas the ZoMaxx stent elutes ~ 75% of the drug from the stent in the first 10 days, and 100% at 30 days. The ZoMaxx intravascular ultrasound (IVUS) trial included 40 patients with singe-vessel coronary disease and evaluated the efficacy of the TriMaxx stent to reduce intimal hyperplasia (**Table 2**) [18]. Angiographic follow-up at 4 months revealed an in-stent late loss of 0.20 ± 0.35 mm. IVUS measurements demonstrated low neointimal volume (9.1 ± 10.2 mm) and minimal neointimal volume obstruction (6.5 ± 6.2%) with no late malapposition (incomplete apposition of the stent struts to the intimal surface of the arterial wall, not present after implantation [19]). During the follow-up period no major adverse cardiovascular events (MACE) were reported [18]. ZOMAXX I conducted in Europe, Australia and New Zealand and ZOMAXX II in North America are prospective and randomised clinical trials designed to evaluate the safety and efficacy of the ZoMaxx drug-eluting stent system in comparison with the TAXUS® Express2™ (Boston Scientific) drug-eluting stent (**Table 2**) [20].

Everolimus is also a sirolimus derivative, which blocks growth factor derived cell proliferation, arresting the cell cycle at the G1 to S phase (**Figure 1**). This agent has been used for the XIENCE V™, the Champion™ and the BVS (Bioabsorbable Vascular Solutions) stents (Guidant Corporation). The Champion and the BVS stents will be discussed in the particular section regarding the bioabsorbable materials. The XIENCE V coronary stent system consists of the MULTI-LINK VISION™ stent (Guidant Corporation), a serpentine configured, thin strut cobalt chromium stent and a non-erodable polymer, which elutes everolimus. This stent is designed to release ~ 70% of the drug within 30 days after implantation. The SPIRIT I multi-centre randomised trial investigated the safety and effectiveness of the everolimus-eluting XIENCE V coronary stent system (Guidant Corporation) (**Table 3**) [21,22]. At 12 months follow-up, the everolimus-eluting stent compared with the

Table 1. Drug-eluting stents.

Name of stent	Stent platform	Coating	Drug	Manufacturer	Status
CYPHER®	Stainless steel	Durable polymer	Sirolimus	Cordis	CE Mark
TAXUS®	Stainless steel	Durable polyner	Paclitaxel	Boston Scientific	CE Mark
Endeavor™	Cobalt alloy	Durable polymer	Zotarolimus	Medronic	CE Mark
Zomaxx™	Stainless steel – tantalum	Durable polymer	Zotarolimus	Abbott Vascular	CE Mark
Xience™	Cobalt chromium	Durable polymer	Everolimus	Guidant Corporation	CE Mark
Dexamet™	Stainless steel	Durable	Dexamethasone	Abbott Vascular	CE Mark
BVS	Biodegradable	Bioabsorbable	Everolimus	BVS, Guidant	–
Biomatrix™	Stainless steel	Bioabsorbable	Biolimus A9	Biosensorss	CE Filed
Nobori™	Stainless steel	Bioabsorbable	Biolimus A9	Terumo	–
Champion™	Stainless steel	Bioabsorbable	Everolimus	Guidant Corporation	–
Infinnium™	Stainless steel	Bioabsorbable	Paclitaxel	Sahajanand	CE Mark
Supralimus™	Stainless steel	Bioabsorbable	Sirolimus	Sahajanand	CE Mark
CoStar™	Cobalt chromium	Bioabsorbable	Paclitaxel	Conor Medsystems	CE Mark
Nanoporous stent	Stainless steel	Alumina/aluminium oxide/Al_2O_3	Tacrolimus	Jomed	–
Yukon DES™ microporous stent	Stainless steel	Aluminium oxide	Sirolimus	Translumina	CE Mark
Janus™	Stainless steel	–	Tacrolimus	Sorin	CE Mark

Information from [38].

MULTI-LINK VISION bare metal stent had significantly lower in-stent late loss (0.24 ± 0.27 versus 0.84 ± 0.45 mm; $p < 0.001$) and diameter stenosis (18 ± 13% versus 37 ± 17 mm; $p < 0.001$) [22]. The overall MACE rate was 15.4% in the everolimus-eluting stent group and 21.4% in the bare metal stent group [22]. This was the first study to show that everolimus released from a durable polymer on a cobalt chromium stent can effectively inhibit neointimal proliferation compared with the conventional bare metal stent [21,22]. The SPIRIT II clinical trial will evaluate the XIENCE V stent compared with the TAXUS Express 2 paclitaxel-eluting stent. The SPIRIT III, a large-scale pivotal clinical trial conducted in US, will also compare the XIENCE V with the TAXUS stent (**Table 3**). Recently, the company received CE Mark approval for the XIENCE V Everolimus Eluting Coronary Stent System.

Other sirolimus analogues that have been used as pharmaceutical compounds for drug elution are biolimus, tacrolimus and pimecrolimus (**Figure 1**). Biolimus A9 inhibits growth factor-driven cell proliferation, such as T cells and vascular smooth muscle cells. Biolimus A9 is used in the BioMATRIX™ (Biosensors International) and the Nobori™ (Terumo Corporation) stents, which are coated with a biodegradable polymer. Tacrolimus (FK506) is a water-insoluble macrolide immunosuppressant [23]. It has been widely used to reduce the incidence and severity of allograft rejection after organ transplantation and to treat other inflammatory conditions, such as atopic dermatitis. Tacrolimus is loaded on the Janus™ stent (Sorin Group), which has a reservoir design. Pimecrolimus is also an anti-inflammatory and immunosuppressive agent that belongs to the macrolide family and inhibits the production and release of pro-inflammatory cytokines. This agent has been incorporated in the Conor CoStar™ stent (Conor Medsystems) and will be soon evaluated in clinical trials. The abovementioned stents do not use a durable polymer coating for local drug delivery and will be discussed in the appropriate sections.

2.2 Endothelial protective agents

It has been shown that a functionally intact endothelium is a prerequisite for the inhibition of neointimal growth after percutaneous coronary intervention [24] and endothelial progenitor cells (EPC) have been identified as a key factor for re-endothelialisation [25]. The Genous™ Bio-engineered R stent™ (OrbusNeich) is developed to enhance accumulation of EPC at the site of arterial injury after stent implantation, in order to rapidly create a functional endothelial layer, and thus reduce potential thrombosis and restenosis. EPC recruitment is achieved through surface immobilised antibodies directed toward EPC surface antigens. The HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth – First In Man) registry was the first clinical investigation using the particular technology. The

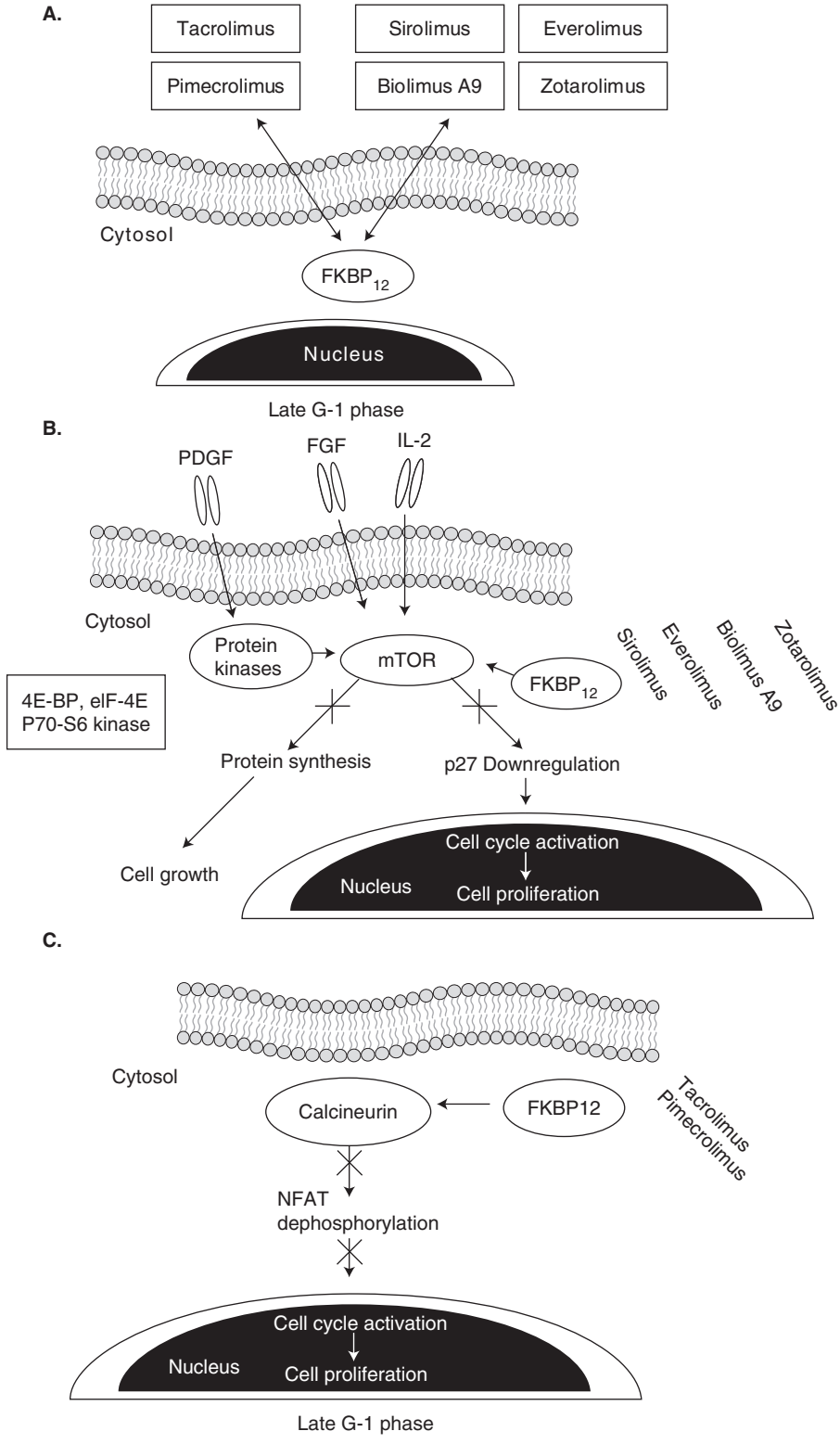

Figure 1. Schematic representation of the -limus family pathway of activation. A. All of the -limus drugs originally form a complex with the cytoplasmic ptotein FKBP12. **B.** Thereafter the complex FKBP12-sirolimus, zotarolimus, biolimus A9 or everolimus inhibits mTOR, resulting into inhibition of smooth muscle and T-cell proliferation respectively. **C.** The complex FKBP12-tacrolimus or pimecrolimus binds to calcineurin and blocks the activation of NFAT, thus preventing its entrance into the nucleus and inhibiting T cell activation.

mTOR: Mammaliam target of rapamycin; NFAT: Nuclear factor of activated T cells.

Table 2. ENDEAVOR AND ZOMAXX clinical programmes.

Study	Study design	Inclusion criteria	Study groups	End points	Primary end point results
ENDEAVOR I [14]	Safety and performance	Single *de novo* native coronary lesions RVD: 3.0 – 3.5 mm Lesion length: < 15 mm	Endeavor™ drug-eluting stent (n = 100)	Primary: MACE at 30 days, late loss at 4 months. Secondary: TVF and TLR at 9 months, late loss at 12 months.	MACE: 1% In-segment late loss: 0.20 ± 0.40 mm In-stent late loss: 0.33 ± 0.35 mm
ENDEAVOR II [15]	Pivotal, double-blind, randomised	Single *de novo* native coronary lesions Stent diameter: 2.25 – 3.5 mm Lesion length < 14 – 27 mm	Endeavor™ drug-eluting stent (n = 600) Driver™ bare-metal stent (n = 600)	Primary: TVF at 9 months. Secondary: acute success, MACE at 30 days, 6, 9, 12 months and annually to 5 years, in-stent and in-segment BR and MLD, neointimal hyperplastic volume and late lumen loss at 8 months, TLR and TVR at 9 months.	TVF of the Endeavor versus the Driver stent: 8 versus 15.1%; $p < 0.0005$
ENDEAVOR III [16]	Randomised, single-blind, multi-centre	Single *de novo* native coronary lesions Stent diameter: 2.5 – 3.5 mm Lesion length < 14 – 27 mm	Endeavor™ drug-eluting stent (n = 327) CYPHER® stent (n = 109)	Primary: in-segment late loss at 8 months. Secondary: MACE at 30 days, 6, 9, 12 months and annually, BR and in-stent late lumen loss at 8 months, TLR, TVR and TVF at 9 months.	In-segment late loss of the Endeavor versus the CYPHER stent: 0.34 ± 0.44 versus 0.13 ± 0.32 mm; $p < 0.001$
ENDEAVOR IV [16]	Randomised, single-blind, multi-centre	Single *de novo* native coronary lesions RVD: 2.5 – 3.5 mm Lesion length < 27 mm	Endeavor™ drug-eluting stent (n = 529) TAXUS® stent (n = 529)	Primary: TVF at 9 months. Seconadary: in-stent % diameter stenosis, MACE at 30 days, 6, 9, and 12 months, TLR and TVR at 9 months, QCA and IVUS subset at 8 months.	
ZOMAXX IVUS [18]	FIM, single-centre trial	Single *de novo* native coronary lesions RVD: 2.75 – 3.25 mm Lesion Length: 10 – 15 mm	ZoMaxx™ stent (n = 40)	Primary: percentage in-stent net volume obstruction at 4 months (IVUS). Secondary: MACE, TVF, TLR, TVR, binary restenosis, in-stent late loss, neointimal volume, device, lesion and procedure success.	% In-stent volume obstruction: 6.5 ± 6.26%
ZOMAXX I [20]	Randomised, multi-centre, non-inferiority trial	Single *de novo* native coronary lesions RVD: 2.5 – 3.5 mm Lesion length: 10 – 30 mm	ZoMaxx™ stent (n = 200) TAXUS® stent (n = 200)	Primary: in-segment late loss at 9 months. Secondary: MACE at 30 days, 6, 9, 12 months and annually to 5 years, TVF, TLR, TVF at 9 months, in-stent and in-segment binary restenosis and proximal and distal MLD at 9 months, in-stent late loss and neointimal volume obstruction at 9 months.	
ZOMAXX II [20]	Randomised, multi-centre, non-inferiority trial	Single *de novo* native coronary lesions Stent diameter: 2.5 – 3.75 mm Lesion length: 10 – 28 mm	ZoMaxx™ stent (n = 835) TAXUS® stent (n = 835)	Primary: TVR at 9 months. Secondary: MACE at 30 days, 6, 9, 12 months and annually to 5 years, in-stent late lumen loss at 9 months, in-stent and in-segment BR and proximal and distal MLD at 9 months, neointimal hyperplastic volume at 9 months, TLR and TVF at 9 months, device, lesion and procedural success.	

BR: Binary restenosis; FIM: First-time-in-man-study; MACE: Major adverse cardiovascular events; MLD: Minimum lumen diameter; RVD: Reference vessel diameter; TLR: Target lesion revascularisation; TVF: Target vessel failure; TVR: Target vessel revascularisation.

Table 3. Everolimus and biolimus-eluting stent trials.

	Study design	Inclusion criteria	Study groups	Key end points
FUTURE I [43,44]	Safety and performance study, prospective and randomised	Single *de novo* native coronary lesions Stent diameter: 2.5 – 4.0 mm Stent length: 14 – 18 mm	Everolimus-eluting stent (n = 27) Bare-metal stent (n = 15)	Primary: MACE, including death, CABG to the target vessel, Q-wave and non-Q-wave myocardial infarction, and TLR at 30 days Secondary: quantitative angiographic and IVUS observation within the vessel, device success, MACE and restenosis rate at 6-month follow-up
FUTURE II [45]	Safety and performance study, prospective and randomised	Single *de novo* native coronary lesions Stent diameter: 2.5 – 4.0 mm Stent length: 14 – 18 mm	Everolimus-eluting stent (n = 21) Bare-metal stent (n = 43)	Primary: late loss at 6 months Secondary: MACE at 1 and 6 months and BR at 6 months
SPIRIT I [21]	Prospective, randomised, single-blind, multi-centre trial	Single *de novo* native coronary lesions Stent diameter: 3.0 mm Stent length: 18 mm	XIENCE™ V everolimus-eluting stent (n = 28) Bare-metal Multi-Link Vision™ stent (n = 32)	Primary: in-stent luminal late loss Secondary: in-stent and in-segment late loss, BR, percentage diameter stenosis and in-stent percentage volume obstruction at 6 and 12 months, MACE or TVF at 30 days, 6, 9, 12 months and annually to 5 years
SPIRIT II	Randomised, single-blind, multi-centre trial	A maximum of two *de novo* native coronary lesions	XIENCE™ V everolimus-eluting stent (n = 150) TAXUS® Express 2™ paclitaxel-eluting stent (n = 150)	Primary: in-stent late loss at 6 months
SPIRIT III	Randomised, single-blind trial	A maximum of two *de novo* native coronary lesions RVD: 2.5 – 3.5 mm	XIENCE™ V everolimus-eluting stent (n = 668pts) TAXUS® Express 2™ paclitaxel-eluting stent (n = 334)	Primary: in-segment late loss at 240 days Secondary: TVF at 270 days
STEALTH [42]	Safety and efficacy study, prospective and randomised	Single *de novo* native coronary lesion RVD: 2.75 – 4.0 mm Lesion Length: < 24 mm	BioMATRIX™ biolimus-eluting stent (n = 80) Bare-metal S-stent™ (n = 40)	Primary: in-segment luminal late loss Secondary: event-free survival at 6 months
NOBORI I	Prospective, randomised, multi-centre trial	Single *de novo* native coronary lesion RVD: 2.5 – 3.5 mm Lesion Length: 5 – 25 mm	Nobori™ Stent bioloimus-eluting stent (n = 240) TAXUS® Express 2™ paclitaxel-eluting stent (n = 120)	Primary: in-stent late lumen loss at nine months Secondary: in-stent and in-segment BR rate at 9 months, MACE at 30 days, 4, 9, 12 months and annually to 5 years, TLR and TVR at 9 months, in-stent, in-segment, proximal and distal MLD at 9 months, stent thrombosis at 30 days and 9 months, neointimal hyperplastic volume at 9 months, device, lesion and procedural success

BR: Binary restenosis; MACE: Major adverse cardiovascular events; MLD: Minimum lumen diameter; RVD: Reference Vessel Diameter; TLR: Target lesion revascularisation; TVF: Target vessel failure; TVR: Target vessel revascularisation.

primary end point of the study was the absence of stent thrombosis up to 6 months. In the first month after implantation, there was no subacute thrombosis or major adverse cardiac and cerebrovascular events. At 6-months follow-up, one patient presented with non-Q myocardial infarction, but without angiographic evidence of stent thrombosis [26]. However, regarding the efficacy end point, in-segment late loss (0.63 ± 0.52 mm) in the EPC capture coating stents was not significantly reduced when compared with the late loss observed after conventional bare metal stent implantation [26,27]. This has been attributed to the fact that EPC capture coating exclusively covers the stent struts and not the inter-strut space, where the formation of a functional endothelial layer may be delayed. The HEALING II trial was a multi-centre, prospective, registry, which aimed to evaluate the safety and the effectiveness of the Genous Bio-engineered R stent in single *de novo* native coronary lesions. In total, 63 patients from 10 European centres were included. The study showed that the EPC titer directly correlated with the angiographic and IVUS outcomes. TLR and TVR were restricted to the low EPC group. Moreover, it was observed that patients without statin therapy at the time of stent implantation had low EPCs with significant late loss [28].

2.3 Other antirestenotic agents

Dexamethasone causes modification of protein synthesis and inhibition of inflammatory responses. Glucocorticoids also exert an effect on the prostaglandin synthesis pathway, which is responsible for the production of the lipid-inflammatory mediators. In the clinical setting, the STRIDE (Study of Anti-Restenosis with the BiodivYsio Dexamethasone-Eluting Stent) trial evaluated the safety and the efficacy of the BiodivYsio Matrix LO stent loaded with dexamethasone (0.5 μg/mm^2 of stent) [29]. The study demonstrated a low MACE (5.6%) and revascularisation rate (2.8%) at 6-months follow-up. Repeat angiography showed an in-lesion late loss of 0.47 ± 0.47 mm and an in-stent late loss of 0.57 ± 0.48 mm. When the patients were stratified according to the clinical syndrome, late loss was significantly lower in the unstable angina arm compared with the stable angina arm (0.32 ± 0.39 mm versus 0.60 ± 0.55 mm; $p < 0.03$) [29]. This pronounced difference between the two groups may be explained by the more extensive inflammatory process found in the unstable patients, who are, thus, most likely to benefit from an anti-inflammatory agent. Based on these results, the Dexamet™ stent (Abbott Vascular Devices) received CE Mark approval. However, this study was performed in a small number of patients, without a control group, and the treated lesions were short, with reference vessel diameters of 2.75 – 4.0 mm. The SAFE registry was performed in Europe, the Middle East, Africa and the Asia-Pacific Region and included 1000 real world patients. Preliminary results presented at the Transcatheter Therapeutics Scientific Sessions in 2003 showed a 0.68% in-hospital MACE for 735 patients [30]. The long-term results of the registry are pending.

Preliminary experiments have shown that statins have a potent antiproliferative effect on smooth muscle cells [31]. In addition, simvastatin seems to reduce neointimal hyperplasia, and enhances re-endothelialisation [32]. Animal studies explore the utilisation of the Tsumani™ stent (Terumo Corporation) as the platform for local simvastatin delivery [33].

3. Bioabsorbable – biodegradable materials

3.1 Bioabsorbable stents

Even though stenting has significantly improved outcomes in patients undergoing percutaneous coronary interventions, permanent metallic implants still have some limitations. These include thrombogenicity, mismatch in mechanical behaviour between stented and non-stented vessel areas, long-term endothelial dysfunction, chronic inflammatory local reactions [34], increasing neo-intima formation with time, malapposion and fracture. With regard to the aforementioned limitations, degradable implants may offer some advantages (**Box 1**). At present, their major disadvantage is the induced marked inflammatory response during degradation [34,35].

Experimental studies on magnesium alloys, which contain small amounts of aluminium, manganese, zinc, lithium and rare earth elements, have been reported [34]. In humans, a magnesium alloy biodegradable stent has been implanted in peripheral vessels (**Table 4**). A total of 20 patients with critical limb ischaemia were treated. No adverse effects were reported, and at 1-month follow-up, a 90% patency was observed by Doppler imaging [36]. The PROGRESS study is a prospective, non-randomised, multi-centre trial designed to evaluate the safety and efficacy of the magnesium alloy stents in patients with coronary artery disease. At 4-months follow-up, the study reached its primary end point (MACE < 30%), with an ischaemically driven TLR of 23.8%. During this follow-up period no deaths, stent thrombosis or acute myocardial infarction were observed [37].

Polylactide polymers are widely used as suture and osteosynthesis materials, where they are hydrolytically degraded to lactic acid (**Table 4**) [38,39]. A poly (D,L)-lactic acid double helical paclitaxel-loaded stent that can release the drug over a period of at least 4 weeks, has been evaluated in a porcine restenosis model [40]. A significant reduction in restenosis was observed in animals that received paclitaxel-eluting stents. However, as expected, a local inflammatory response due to the polymer absorption process was detected.

The Igaki-Tamai stent (Igaki Medical Planning Co. Ltd) is a coil stent also made of a polylactide polymer (poly-L-lactic acid) with a zigzag helical design [41]. A total of 25 stents were successfully implanted in 15 patients, and the angiographic success was achieved in all procedures. No stent thrombosis and no major cardiac events occurred within 30 days. The stents used in this study seemed to maintain their scaffolding properties at 6 months, with low revascularisation rates. One of the major limitations stated in the report was the impossibility to identify signs of biodegradation. Although polylactide

Box 1. Potential characteristics of biodegradable stents.

- Increased drug-loading and chronic drug-release capabilities
- Prevention of negative remodelling for the first 3 – 6 months
- Elimination of mechanical stent deformity and strut fractures
- Compatibility with MRI and CT imaging
- After absorption:
  - the vessel can undergo positive remodeling
  - reintervention is easier
  - chronic inflammatory effects are eliminated
  - long-term dual antiplatelet therapy is not required

biodegradable stent implantation is feasible, safe and effective in humans, long-term follow-up with more patients will be required to validate their long-term efficacy.

The BVS everolimus-eluting stent consists of a bioabsorbable polymer-containing drug (everolimus 98 μg/cm^2 of surface area) on a bioabsorbable stent (**Table 1**). The ABSORB trial is a prospective, open-labelled, first-time-in-man clinical study that will evaluate the safety and the efficacy of the single 3.0 × 12 mm BVS everolimus eluting stent.

3.2 Bioabsorbable coating polymers

The BioMATRIX stent comprises a stainless steel, corrugated ring, quadrature-link design S-stent and a bioabsorbable polylactic polymer/Biolimus A9 coating. The stent delivers 15.6 μg of drug/mm of stent and its coating is asymmetric to allow greater localised drug delivery, simultaneously reducing systemic release. The STEALTH trial (Stent Eluting A9 Biolimus Trial in Humans) was the first-time-in-man study to investigate the safety and efficacy of the BioMATRIX stent (**Table 3**) [42]. The STEALTH study randomised 80 patients to the BioMATRIX stent and 40 patients to the bare metal S-stent. The 6-month in-lesion and in-stent late loss was significantly reduced in the drug-eluting stent compared with the control, whereas event-free survival was similar in both groups [42]. These results suggest that the BioMATRIX stent is superior in reducing late loss compared with the respective bare metal stent, with similar clinical safety.

The Nobori drug-eluting stent system also uses Biosensors' bare-metal S-Stent as its platform and is coated with a polylactic acid biodegradable polymer and Biolimus A9. The NOBORI I clinical trial will compare the Nobori Biolimus A9-eluting coronary stent system with the TAXUS stent, and plans to prospectively randomise ~ 400 patients in up to 30 centres in Europe, Australia and Asia (**Table 3**). The study was originally initiated in 2005, but it was temporarily halted due to three reported stent dislodgements during placement. In order to recommence the clinical trial, the company changed the balloon material (from Biosensors' to Terumo's) and slightly modified the stent design with the intension to substantially increase the retention force, however, without changing the drug, the polymer and the drug release pattern.

The Champion drug-eluting stent incorporates everolimus into a bioabsorbable polymer matrix coating on a stainless steel multi-link vision delivery system. The FUTURE (First Use to Underscore Restenosis Reduction with Everolimus) I trial evaluated both safety and feasibility of the everolimus-eluting stent that utilises a bioabsorbable polymer. The binary in-segment restenosis rate at 6 months follow-up was 4.3% in the everolimus-eluting stent group versus 36.4% in the controls ($p = 0.01$) [43]. Furthermore, MACE rate was 7.7%, with no late thrombosis and no late malapposition [43]. The 12-month results demonstrated sustained safety and efficacy, with no additional MACE [44]. The FUTURE II trial confirmed the encouraging results of the FUTURE I trial, demonstrating an acceptable safety profile without evidence of stent thrombosis or late stent malapposition. Moreover, a remarkable reduction of neointimal proliferation with everolimus-eluting stent implantation versus bare-metal stents was observed [45].

The Infinnium™ stent (Sahajanand Medical Technologies) uses the Millennium Matrix™ stent as the platform for paclitaxel release. The binding agent in the Infinnium stent is a biocompatible and biodegradable polymer (paclitaxel concentration of 2.0 μg/mm^2, cumulative release of the drug from the polymer at 38 days). The stent is coated with three different layers of polymers. The outermost protective layer does not contain any drug and dissolves immediately after the deployment of the stent. The middle layer is a moderate drug-release layer and the final basal layer is a slow drug-release layer. The safety and the efficacy of the Infinnium stent was investigated in the SIMPLE (A Study with the Infinnium Paclitaxel Eluting Stent in the Treatment of Patients with Single *de novo* Coronary Artery Lesions) I trial [46]. SIMPLE II was a multi-centre, prospective study, conducted at eight centres in India, South America and Europe. The study's preliminary results are encouraging, suggesting that the Infinnium stent is safe, with efficacy comparable to that of other drug-eluting stents. The company recently introduced a new stent that has been evaluated in the experimental setting [47]. The stent consists of the Millennium Matrix stent and a biodegradable polymer derived from lactic and glycolic acid, and delivers simultaneously sirolimus (1.19 μg/mm^2) and heparin (0.28 μg/mm^2) [47]. A new study will be launched soon and will compare sirolimus-eluting stent with this new dual drug-eluting stent.

A Japanese company (Kaneka, Osaka) has recently presented a new tacrolimus-eluting stent coated with a biodegradable polymer. Preliminary animal studies assessed the safety and the efficacy of the particular stent and determined the optimum dose [38]. The first-time-in-man study is expected to start in 2006.

The Conor MedStent™ (Conor Medsystems) differs significantly from the first generation of drug-eluting stents. The first Conor stents were made of 316L stainless steel,

Table 4. Materials for biodegradable stents.

Materials	Melting point (°C)	Degradation time (months)
Poly-L-lactic acid	173 – 178	> 24
Polyplycolic acid	225 – 230	6 – 12
Poly-D,L-lactide/glycolide	Amorphous	12 – 16
Polycaprolactone	58 – 63	> 24
Magnesium alloy	–	1 – 3

Information from [39].

whereas the current generation is made of Cobalt-Chrome alloy and offers lower profiles and greater flexibility. The Conor MedStent has a characteristic stent design with several hundred laser-cut holes along its struts and connecting bridges. These wells can be individually filled with a combination of polymer and drug. The Conor MedStent uses an erodable polymer, which releases drug by a combination of diffusion and erosion. The use of slowly eroding barrier layers at the lumen surface enables elution of the drug towards the vessel wall. The addition of a cap polymer slows the initial 24-h burst release. The PISCES (Paclitaxel In-Stent Controlled Elution Study) was a multi-centre dose optimisation registry (**Table 5**) [48]. The registry evaluated high and low paclitaxel dose delivery in mural and bidirectional profiles with slow and fast release kinetics. At 4-months follow-up, the best efficacy was observed in the long-release groups [48]. In the two long release formulations, the TLR and MACE rates remained low at 12 months [49]. These results indicate that the most important predictor of efficacy is the release rate rather that the dose.

The COSTAR (Cobalt Chromium Stent with Antiproliferative for Restenosis) trial applied the cobalt-chrome metal platform. The study was designed to evaluate three different release formulations of Paclitaxel (bidirectional release of 30 µg in 10 days, mural release of 10 µg in 30 days and mural release of 3 µg in 30 days), in order to define the dose-response curve for paclitaxel (**Table 5**) [50,51]. The most favourable results in terms of late loss and binary restenosis were observed in the long release formulation arms [52]. The COSTAR II pivotal trial will include ~ 1700 patients at up to 70 US sites and 15 international sites and will compare the CoStar stent with the TAXUS Express2 drug-eluting stent (Boston Scientific).

Finally, the EUROSTAR (European Cobalt Chromium Stent with Antiproliferative for Restenosis) trial was looking at the 10 and 30 µg, long-release formulations of the CoStar™ cobalt chromium stent, with 6-months angiographic and IVUS follow-up, and 6-month and 1-year clinical follow-up (**Table 5**) [53]. A total of 145 patients were treated with the paclitaxel 10 µg long-release formulation, and 125 patients were treated with the 30 µg formulation. The angiographic follow-up at 6 months in the 10 µg group showed an in-stent late loss of 0.26 ± 0.39 mm. At 12-months follow-up, the TLR rate was 2.9%, and the rate of MACE was 7.6%. There were no reported cases of stent thrombosis between the cessation of antiplatelet therapy at 6- and 12-months follow-up [53]. The CoStar cobalt chromium paclitaxel-eluting stent recently received CE Mark approval.

4. Non-polymer coated stents

4.1 Polymer-free stents

The safety and efficacy of the non-polymer paclitaxel-eluting V-Flex plus™ stent (Cook Inc.) was evaluated in the ELUTES (European Evaluation of Paclitaxel Eluting Stent) trial. A 6-months angiographic follow-up demonstrated a benefit in the highest dose group (range of paclitaxel dose: 0.2, 0.7, 1.4 and 2.7 µg/mm^2 stent surface area), in which the binary restenosis and late-loss were significantly reduced [54]. Thereafter, the three-centre randomised ASPECT (Asian Paclitaxel-Eluting Stent Clinical Trial) (n = 177) confirmed these positive results by comparing patients treated with either a drug-eluting Supra-G™ stent (Cook Inc.) loaded with two different drug doses or a bare metal Supra-G stent [55]. The first large trial evaluating the efficacy of this paclitaxel-eluting stent was the randomised, multi-centre DELIVER (the RX Achieve Drug-Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Lesions) trial (n = 1043), evaluating a non-polymer-based paclitaxel-coated ACHIEVE™ stent (Cook Inc.) compared with a stainless steel MULTI-LINK PENTA™ stent (Cook Inc.) [56]. However, the study failed to meet its end point of a 40% reduction of TVF, and the stent was not commercialised.

4.2 Non-polymer coatings

Biodegradable polymers that allow gradual and controlled release of the drug seem to be an appealing solution. However, induced inflammatory response during the process of degradation remains an issue. Thus, the ongoing research has been focused on exploring biodegradable materials that are completely biocompatible. Two new bioabsorbable coatings, one with bioabsorbable oil (Atrium Medical) [57] and one with hydroxyapatite (MIV Therapeutics) have been investigated in the experimental setting. The bioabsorbable oil coating consists of a very lipophilic, omega-3 fatty acid blend that is applied after the stent has been crimped on the balloon [57]. Hydroxyapatite is a bioactive porous material that is normally

Table 5. Conor stent trials.

Study	Study groups	n
DepoStent	Bare stainless steel	53
PISCES [48,49]	Stainless steel with paclitaxel	237
	10 µg/5 days – bidirectional release	30
	10 µg/10 days – mural release	30
	10 µg/10 days – bidirectional release	29
	10 µg/30 days – mural release	39
	30 µg/30 days – mural release	29
	30 µg/10 days – bidirectional release	30
	Bare metal stent	50
SCEPTER	Stainless steel with paclitaxel	271
	10 µg/5 days	138
	10 µg/10 days	133
COSTAR I [50,51]	Cobalt chromium with paclitaxel	87
	30 µg/10 days – bidirectional release	10
	10 µg/30 days – mural release	40
	3 µg/30 days – mural release	37
EUROSTAR [53]	Cobalt chromium with paclitaxel	320
	10 µg/30 days – mural release	145
	30 µg/30 days – mural release	175
COSTAR II	Cobalt chromium with paclitaxel	~ 1700

found in the bones and the matrix of teeth. It is widely used as a bone substitute material and for coating implantable devices in orthopaedic and dental applications.

Titanium is a material used for biomedical implants. Animal studies demonstrated that titanium-nitride-oxide coating significantly reduces neointimal hyperplasia in stainless steel stents [58]. The safety and efficacy of titanium-nitride-oxide for stent coating has been investigated in a prospective randomised trial, which used a commercially available stainless steel stent with a tubular slotted design (OMEGA, Qualimed Inc) [59]. The titanium-nitride-oxide coating was achieved by physical vapour deposition of titanium in a gas mixture of nitrogen and oxygen in a vacuum chamber. The study met its primary end point, demonstrating at 6-months follow-up a significantly lower late loss in lesions treated with a titanium-nitride-oxide-coated stent compared with those treated with a control stent (0.55 ± 0.63 versus 0.90 ± 0.76 mm; p = 0.03). In addition, during the 6-month clinical follow-up period, a significantly higher incidence of MACE was observed in patients assigned to control compared with titanium-nitride-oxide-coated stents (27 versus 7%; p = 0.02) [59]. Although the angiographic results of the titanium-nitride-oxide-coated stents are favourable, they are still inferior to those reported with sirolomus- or paclitaxel-eluting stents. Modification of stent design may further reduce restenosis and improve the long-term angiographic outcome.

4.3 Porous stents

Porosity allows drug deposition and retards drug release without obligating the application of a polymer. A new inorganic ceramic nanoporous aluminum oxide stent (Jomed, Rangendingen) has been introduced as a carrier for immunosuppressive drugs, such as tacrolimus. A two-step process is required for the coating of the stent. First, a thin layer of aluminum is used to coat inside and outside the stent. Thereafter, the metallic layer is electrochemically converted into a nanoporous ceramic using a bath of 2% oxalic acid in 0°C water. The pore size is adjusted by this process. Drug loading is achieved by dipping the stents into a defined solution of tacrolimus 3 mg. In the experimental setting, this ceramic nanolayer loaded with tacrolimus was implanted in the common carotid artery of New Zealand rabbits. Ceramic coating of coronary stents with a nanoporous layer of aluminum oxide in combination with tacrolimus resulted in a significant reduction in neointima formation and inflammatory response [60]. However, subsequent studies showed that major particle debris from a nanoporous stent coating counteract the inhibitory effect of tacrolimus [61]. The PRESENT I (Preliminary Safety Evaluation of Nanoporous Tacrolimus Eluting Stents) study was a safety trial that utilised 60 µg of tacrolimus adhered to the nanoporous aluminum oxide stent. After repeat revascularisations occurred in three patients, the study was halted. This lack of efficiency was also observed in the PRESENT II, where a higher dose of tacrolimus (230 µg) was adhered to the stent surface [62].

Another drug-eluting stent system that consists of two components, the mobile coating device and the sandblasted 316L stainless steel microporous stent (Yukon DES; Translumina) has been recently investigated. The loading process is performed on-site by a positionable ring containing three jet units, which allow for uniform delivery of the drug onto the stent surface. The microporous stent has been evaluated in a clinical study involving a high proportion of patients with acute coronary syndromes, multi-vessel disease and complex lesions [63]. A total of 602 patients were randomised to four groups, to the microporous bare metal stent and to the microporous stent loaded with different concentrations of sirolimus solution (0.5, 1.0 and 2.0%, respectively). Compared with the microporous bare metal, in-segment restenosis and 1-year target lesion revascularisation were significantly reduced in the sirolimus-eluting stents.

4.4 Depo-drug reservoirs

The Janus stent (tacrolimus-eluting carbostent) utilises a drug-release system with reservoirs on the stent's outer surface and requires no polymer matrix to carry the drug (tacrolimus 2.3 µg). The JUPITER II trial investigated the safety and the efficacy of the Janus stent compared with the bare metal Tecnic™ carbostent (Sorin Group). A total of 332 patients

were enrolled in 16 European centres and randomised to either the Janus tacrolimus-eluting carbostent (166 patients) or the bare metal Tecnic carbostent (166 patients). The study failed to show significant difference in late loss between the two groups at 6-month angiographic follow-up (Janus stent versus bare metal Tecnic carbostent, in-segment late loss: 0.42 ± 0.46 mm versus 0.48 ± 0.52 mm, in-stent late loss: 0.65 ± 0.47 mm versus 0.66 ± 0.53 mm). The overall, cumulative MACE rates at 12 months were similarly low in both groups (total MACE in the Janus stent and the Tecnic carbostent group was 16.1 and 19.5%, respectively, p = nonsignificant; and TLR was 10.3 and 16.4%, respectively, p = nonsignificant) [64].

5. Conclusions

Conventional drug-eluting stents have shown remarkable effectiveness in reducing both angiographically and clinically defined restenosis. Following the first generation of sirolimus- and paclitaxel-eluting stents, a variety of new stent designs, coatings and locally delivered agents are emerging. Some of them are already commercially available. Most likely, several more will become available in a few years time.

The development of more biocompatible and bioabsorbable materials that will promote rapid endothelialisation and will concurrently inhibit the potentially induced inflammatory process is an appealing therapeutic approach to optimally abolish restenosis.

6. Expert opinion

Although the available drug-eluting stents have significantly contributed to the reduction of restenosis, they are far from being the ideal device. Therefore, there are still some concerns that restrain their widespread use in all patient and lesion subsets and necessitate further research.

First, delayed endothelialisation [5], premature antiplatelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, and low ejection fraction may lead to increased rates of late thrombosis [4,65]. In addition, it has been recently reported that drug-eluting stents may cause systemic or local hypersensitivity, associated with late stent thrombosis and death [66]. This generates the need for long-term dual antiplatelet therapy, which is associated with increased risk of bleeding and imposes a large economical burden on the national health systems.

Second, the treatment of in-stent restenosis remains a therapeutic dilemma, as many pharmacological and mechanical approaches have shown conflicting results. In a subgroup of 44 patients with complex in-stent restenosis included in the RESEARCH registry, the data showed at 1 year that the incidence of repeat intervention due to re-restenosis was 11.6%, with no stent thromboses or deaths [67]. In addition, the TROPICAL (Treatment of Patients with an In-Stent Restenotic Native Coronary Artery Lesion) study, a prospective multi-centre registry, assessed the effectiveness and safety of sirolimus-eluting stents in the treatment of patients with in-stent restenosis, and confirmed the efficacy of sirolimus-eluting stents in the treatment of in-stent restenosis [68]. However, the ISAR DESIRE (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-stent Restenosis) randomised trial (balloon angioplasty versus sirolimus or paclitaxel eluting stent implantation for in-stent restenosis) showed that drug-eluting stents are superior to balloon angioplasty [69], but the results were less remarkable than those for *de novo* lesions.

Third, even if angiographic restenosis after drug-eluting stent implantation is an infrequent event, it is still observed in complex lesions, such as bifurcations, total occlusions, left main disease or ostial stenoses and in patients with diabetes mellitus [13,70-74].

On the other hand, the role of drug-eluting stents in the treatment of multi-vessel disease is not yet clarified. The ARTS II study (The Arterial Revascularization Therapy Study II) compared sirolimus-eluting stents in multi-vessel disease with the outcomes in ARTS I. The results clearly showed that use of drug-eluting stents in this study was better than the bare metal stent arm results in ARTS I, and although overall events were similar to the coronary artery bypass graft arm of ARTS I, the need for repeat revascularisation remained lower with surgery [75]. The CARDia (Coronary Artery Revascularisation in Diabetes) is a UK and Ireland based trial currently in progress and will randomise 600 diabetic patients with either complex one-vessel disease or multi-vessel disease to coronary artery bypass graft or PCI [76]. The outcome of SYNTAX (Synergy Between PCI with TAXUS and Cardiac Surgery) [77], FREEDOM (Future Revascularisation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) and COMBAT (Comparison of Bypass Surgery and Angioplasty using Sirolimus Eluting Stents in patients with left main coronary disease), three randomised, large-scale trials that are comparing percutaneous coronary intervention with coronary artery bypass grafting for three-vessel disease or left main disease are expected with great interest.

Next-generation drug-eluting stents under investigation are focused on addressing the aforementioned unresolved issues of stent thrombosis and restenosis. Emerging novel stent designs that do not use polymers or biodegradable polymers to bond to the drug may eliminate the inflammatory process that potentially leads to stent thrombosis. Pharmaceutical agents may provide the most favourable balance between rapid endothelialisation, and prohibition of neo-intima formation, in order to completely abolish thrombosis and restenosis, respectively. The currently explored pharmaceutical agents that belong to the -limus family, such as zotarolimus, have been shown to allow rapid endothelialisation, even though they have demonstrated significantly greater in-stent late loss than the sirolimus-eluting stent [17]. Alternatively, endothelial progenitor cell recruitment seems to be an appealing approach to rapidly create a functional endothelial layer.

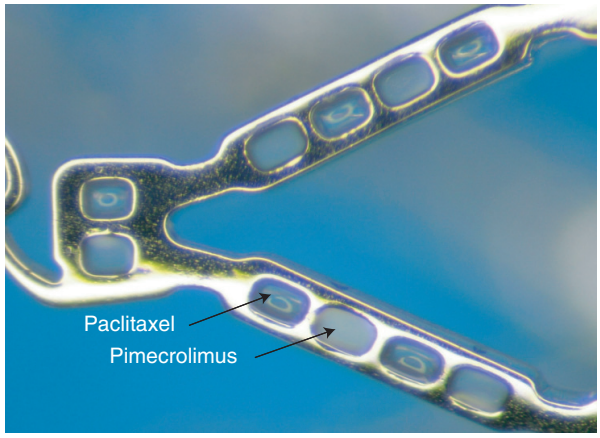

Figure 2. Conor CoStar™ stent. The reservoir design allows the individual filling of each well with a different therapeutic agent.

In the future, it will be possible to combine the delivery of two different pharmaceutical agents, one targeting cell proliferation and the other targeting the inflammatory process within the vulnerable plaque. In addition, it will be feasible to control elution toward both sides of the stent, delivering one agent to the vessel wall to prevent local restenosis and another agent into the lumen to treat diffuse disease. Stents that have a reservoir design provide the possibility to load each individual hole with a different compound. Dual drug-elution of pimecrolimus and paclitaxel has been recently investigated with the Conor Costar stent (**Figure 2**) in a porcine experimental model with good results [78]. Based on these results, the company will shortly launch the Genesis trial, in which both the pimecrolimus-eluting stent and the dual paclitaxel–pimecrolimus-eluting stent will be evaluated.

So far, the commercially released drug-eluting stents are permanent implants that, in case of restenosis, may render a second intervention more difficult and complicated. It has been suggested that fully bioabsorbable stents that will disappear during drug delivery, leaving behind a healthy artery, may overcome this limitation. The safety and the efficacy of fully bioabsorbable stents has been already investigated in animals [40]. However, there are concerns that surface coatings may interfere with the absorption process and that the migration of stent degradation bioproducts through a coating may harm the drug. Thus, a biodegradable metal stent that combines the reservoir design with the capability of drug-elution is a novel concept that might address these possible disadvantages of polymer-coated biodegradable stents, and warrants further investigation. Presently, a 'Conorised' reservoir absorbable metal stent (AMS-1) is under development by Biotronik and will soon be evaluated in the experimental setting [78].

Concurrently, several drug-eluting stent systems that are dedicated to the treatment of specific complex lesions, such as the Devax Axxess™ (Devoa Inc.) self-expanding stent system for bifurcations and the Xtent™ (Xtent) modular system for long lesions, are under evaluation, and may be proven more effective in the management of the particular high-risk subsets.

It is safe to conclude that drug-eluting stents indeed represent advances in the field of interventional cardiology. The elution of antiproliferative or anti-inflammatory pharmaceutical agents delivered locally by innovative bioabsorbable stents holds a great promise for the future against restenosis. Several first-time-in-man studies with a fully bioabsorbable stent to test this hypothesis are ongoing and others are on the way. Of course, large-scale trials in real world patients will finally show whether we are on the right track or not.

Bibliography

1. STONE GW, ELLIS SG, COX DA *et al.*: One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* (2004) **109**(16):1942-1947.
2. MORICE MC, SERRUYS PW, SOUSA JE *et al.*: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N. Engl. J. Med.* (2002) **346**(23):1773-1780.
3. KUCHULAKANTI PK, CHU WW, TORGUSON R *et al.*: Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. *Circulation* (2006) **113**(8):1108-1113.
4. IAKOVOU I, SCHMIDT T, BONIZZONI E *et al.*: Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* (2005) **293**(17):2126-2130.
5. ONG AT, HOYE A, AOKI J *et al.*: Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J. Am. Coll. Cardiol.* (2005) **45**(6):947-953.
6. ONG AT, MCFADDEN EP, REGAR E *et al.*: Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J. Am. Coll. Cardiol.* (2005) **45**(12):2088-2092.
7. HOYE A, IAKOVOU I, GE L *et al.*: Long-term outcomes after stenting of bifurcation lesions with the 'crush' technique: predictors of an adverse outcome. *J. Am. Coll. Cardiol.* (2006) **47**(10):1949-1958.
8. SMITH SC Jr, FELDMAN TE, HIRSHFELD JW Jr *et al.*: ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous

Coronary Intervention). *Circulation* (2006) **113**(7):e166-e286.

9. KASTRATI A, DIBRA A, MEHILLI J *et al.*: Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. *Circulation* (2006) **113**(19):2293-2300.
10. KIM YH, PARK SW, HONG MK *et al.*: Comparison of simple and complex stenting techniques in the treatment of unprotected left main coronary artery bifurcation stenosis. *Am. J. Cardiol.* (2006) **97**(11):1597-1601.
11. MEHILLI J, DIBRA A, KASTRATI A *et al.*: Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels. *Eur Heart J.* (2006) **27**(3):260-266.
12. HOYE A, TANABE K, LEMOS PA *et al.*: Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions. *J. Am. Coll. Cardiol.* (2004) **43**(11):1954-1958.
13. GE L, IAKOVOU I, COSGRAVE J *et al.*: Immediate and mid-term outcomes of sirolimus-eluting stent implantation for chronic total occlusions. *Eur. Heart J.* (2005) **26**(11):1056-1062.
14. MEREDITH I, ORMISTON J, WHITBOURN R *et al.*: First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in *de novo* native coronary artery lesions: Endeavor I Trial. *EuroIntervention* (2005) **1**:157-164.
15. MEREDITH I, WIJNS W: ENDEAVOR I and II clinical program. Long term follow-up. *European Society of Cardiology Congress.* Stockholm, Sweden (4 September 2005).
16. KANDZARI DE: Overview of ABT-578/PC/Cobalt technology and clinical trial program. *55th Annual Scientific Session of the American College of Cardiology.* Atlanta, GA, USA (11 – 16 March 2006).
17. KANDZARI DE, LEON MB: ENDEAVOR III. A randomized trial to confirm the safety and efficacy of the medtronic zotarolimus eluting stent in *de novo* native coronary artery lesions. *17th Transcatheter Cardiovascular Therapeutics Scientific Symposium.* Washington, DC, USA (16 – 21 October 2005).
18. ABIZAID A, LANSKY A, FITZGERALD P *et al.*: Percutaneous coronary revascularization using a trilayer phosphorylocholine-coated zotarolimus-eluting stent: the ZoMaxx IVUS trial. *55th Annual Scientific Session of the American College of Cardiology.* Atlanta, GA, USA (11 – 16 March 2006).
19. HONG MK, MINTZ GS, LEE CW *et al.*: Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. *Circulation* (2006) **113**(3):414-419.
20. YEUNG AC: The Zomaxx Trials. *55th Annual Scientific Session of the American College of Cardiology.* Atlanta, GA, USA (11 – 16 March 2006).
21. SERRUYS PW, ONG ATL, PIEK JJ *et al.*: A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: the SPIRIT first trial. *EuroIntervention* (2005) **1**(1):58-69.
22. TSUCHIDA K, PIEK JJ, NEUMANN FJ *et al.*: One-year results of a durable polymer everolimus-eluting stent in *de novo* coronary narrowings (The SPIRIT FIRST Trial). *EuroIntervention* (2005) **1**:266-272.
23. STEPKOWSKI SM: Molecular targets for existing and novel immunosuppressive drugs. *Expert Rev. Mol. Med.* (2000) **2000**:1-23.
24. KIPSHIDZE N, DANGAS G, TSAPENKO M *et al.*: Role of the endothelium in modulating neointimal formation: vasculoprotective approaches to attenuate restenosis after percutaneous coronary interventions. *J. Am. Coll. Cardiol.* (2004) **44**(4):733-739.
25. WERNER N, JUNK S, LAUFS U *et al.*: Intravenous transfusion of endothelial progenitor cells reduces neointima formation after vascular injury. *Circ. Res.* (2003) **93**(2):e17-e24.
26. AOKI J, SERRUYS PW, VAN BEUSEKOM H *et al.*: Endothelial progenitor cell capture by stents coated with antibody against CD34: the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) registry. *J. Am. Coll. Cardiol.* (2005) **45**(10):1574-1579.
27. SKETCH MH Jr, BALL M, RUTHERFORD B *et al.*: Evaluation of the Medtronic (Driver) cobalt-chromium alloy coronary stent system. *Am. J. Cardiol.* (2005) **95**(1):8-12.
28. DUCKERS E: Endothelial progenitor cell capture (EPC): update and perspectives. *EuroPCR.* Paris, France (24 – 27 May 2005).
29. LIU X, HUANG Y, HANET C *et al.*: Study of antirestenosis with the BiodivYsio dexamethasone-eluting stent (STRIDE): a first-in-human multicenter pilot trial. *Catheter Cardiovasc. Interv.* (2003) **60**(2):172-178; discussion 179.
30. DE SCHEERDER I: The Abbott vascular devices dexamethasone eluting stent: from STRIDE to the 'real-world' SAFE registry. *Transcatheter Therapeutics Scientific Sessions, Washington, DC, USA* (2003).
31. LEFER AM, SCALIA R, LEFER DJ: Vascular effects of HMG CoA-reductase inhibitors (statins) unrelated to cholesterol lowering: new concepts for cardiovascular disease. *Cardiovasc. Res.* (2001) **49**(2):281-287.
32. INDOLFI C, CIOPPA A, STABILE E *et al.*: Effects of hydroxymethylglutaryl coenzyme A reductase inhibitor simvastatin on smooth muscle cell proliferation in vitro and neointimal formation in vivo after vascular injury. *J. Am. Coll. Cardiol.* (2000) **35**(1):214-221.
33. TANABE K, ISHIYAMA H, VAN DER GIESSEN W, SERRUYS PW: Terumo statin releasing stent (preclinical results). In: Drug-Eluting Stents. Gershlick A (Ed.), Taylor and Francis Group, London, UK (2005):313-321.
34. HEUBLEIN B, ROHDE R, KAESE V *et al.*: Biocorrosion of magnesium alloys: a new principle in cardiovascular implant technology? *Heart* (2003) **89**(6):651-656.
35. VAN DER GIESSEN WJ, LINCOFF AM, SCHWARTZ RS *et al.*: Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation* (1996) **94**(7):1690-1697.
36. DI MARIO C, GRIFFITHS H, GOKTEKIN O *et al.*: Drug-eluting bioabsorbable magnesium stent. *J. Interv. Cardiol.* (2004) **17**(6):391-395.
37. ERBEL R: Coronary results of the first absorbable metal stent: The Progress-I trial. *55th Annual Scientific Session of the American College of Cardiology.* Atlanta, GA, USA (11 – 16 March 2006).
38. SERRUYS PW: Emerging technology 1. Stents – new drugs. *55th Annual Scientific Session of ACC, Atlanta, GA, USA, 11 – 14 March* (2006).

39. MIDDLETON J, TIPTON A: Synthetic biodegradable polymers as orthopedic devices. *Biomaterials* (2000) **21**(23):2335-2346.
40. VOGT F, STEIN A, RETTEMEIER G *et al.*: Long-term assessment of a novel biodegradable paclitaxel-eluting coronary polylactide stent. *Eur. Heart J.* (2004) **25**(15):1330-1340.
41. TAMAI H, IGAKI K, KYO E *et al.*: Initial and 6-month results of biodegradable poly-l-lactic acid coronary stents in humans. *Circulation* (2000) **102**(4):399-404.
42. GRUBE E, HAUPTMANN KE, BUELLESFELD L, LIM V, ABIZAID A: Six-month results of a randomized study to evaluate safety and efficacy of a Biolimus A9™ eluting stent with a biodegradable polymer coating. *EuroIntervention* (2005) **1**:53-57.
43. COSTA RA, LANSKY AJ, MINTZ GS *et al.*: Angiographic results of the first human experience with everolimus-eluting stents for the treatment of coronary lesions (the FUTURE I trial). *Am. J. Cardiol.* (2005) **95**(1):113-116.
44. GRUBE E, SONODA S, IKENO F *et al.*: Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. *Circulation* (2004) **109**(18):2168-2171.
45. GRUBE E: FUTURE II: Multicenter evaluation of the bioabsorbable polymer-based everolimus-eluting stent. *15th Annual Transcatheter Cardiovascular Therapeutics.* Washington, DC, USA (15 – 19 September 2003).
46. GAMBHIR DS: The Infinnium polymer-based paclitaxel drug-eluting stent: Results from real world clinical trials SIMPLE 1 and SIMPLE 2. *Transcatheter Cardiovascular Therapeutics 2004.* Washington, DC, USA (22 October 2004).
47. LELE S: Heparin sirolimus stent. *EuroPCR 2006.* Paris, France (16 – 19 May 2006).
48. SERRUYS PW, SIANOS G, ABIZAID A *et al.*: The effect of variable dose and release kinetics on neointimal hyperplasia using a novel paclitaxel-eluting stent platform: the Paclitaxel In-Stent Controlled Elution Study (PISCES). *J. Am. Coll. Cardiol.* (2005) **46**(2):253-260.
49. AOKI J, ONG AT, ABIZAID A *et al.*: One-year clinical outcome of various doses and pharmacokinetic release formulations of paclitaxel eluted from an erodable polymer. Insight in the Paclitaxel In-Stent Controlled Elution Study (PISCES). *EuroIntervention* (2005) **2**:165-172.
50. KAUL U: Erodablepolymer-reservoir paclitaxel drug eluting stents II: cobalt chromium platforms in complex lesions *Transcatheter Cardiovascular Therapeutics 2004.* Washington, DC, USA (22 October 2004).
51. SERRUYS PW: The new CoStar™ stent: 12 month results with the new DES technology. *EuroPCR.* Paris, France (24 – 27 May 2005).
52. WIJNS W: CoStar™ Paclitaxel-eluting stent: relevance in drug-eluting stent clinical data landscape. *EuroPCR 2006.* Paris, France (16 – 19 May 2006).
53. DAWKINS K: The Eurostar trial. *EuroPCR.* Paris, France (24 – 27 May 2005).
54. GERSHLICK A, DE SCHEERDER I, CHEVALIER B *et al.*: Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaLUation of pacliTaxel Eluting Stent (ELUTES) trial. *Circulation* (2004) **109**(4):487-493.
55. PARK SJ, SHIM WH, HO DS *et al.*: A paclitaxel-eluting stent for the prevention of coronary restenosis. *N. Engl. J. Med.* (2003) **348**(16):1537-1545.
56. LANSKY AJ, COSTA RA, MINTZ GS *et al.*: Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with *de novo* coronary lesions: angiographic follow-up of the DELIVER clinical trial. *Circulation* (2004) **109**(16):1948-1954.
57. VIRMANI R: Atrium medical bioabsorbable oil based delivery of a sirolimus analogue from a stent and balloon. *Transcatheter Cardiovascular Therapeutics 2005.* Washington, DC, USA (17 – 21 October 2005).
58. WINDECKER S, MAYER I, DE PASQUALE G *et al.*: Stent coating with titanium-nitride-oxide for reduction of neointimal hyperplasia. *Circulation* (2001) **104**(8):928-933.
59. WINDECKER S, SIMON R, LINS M *et al.*: Randomized comparison of a titanium-nitride-oxide-coated stent with a stainless steel stent for coronary revascularization: the TiNOX trial. *Circulation* (2005) **111**(20):2617-2622.
60. WIENEKE H, DIRSCH O, SAWITOWSKI T *et al.*: Synergistic effects of a novel nanoporous stent coating and tacrolimus on intima proliferation in rabbits. *Catheter Cardiovasc. Interv.* (2003) **60**(3):399-407.
61. KOLLUM M, FARB A, SCHREIBER R *et al.*: Particle debris from a nanoporous stent coating obscures potential antiproliferative effects of tacrolimus-eluting stents in a porcine model of restenosis. *Catheter Cardiovasc. Interv.* (2005) **64**(1):85-90.
62. GERCKENS U, BUELLESFELD L, HORSKOTTE D *et al.*: Evaluation of a tacrolimus-eluting coronary stent with nanoporous ceramic coating in treatment of native coronary artery lesions: Phase I and II of the PRESENT study. *J. Am. Coll. Cardiol.* (2003) **41**(Suppl. A):7A.
63. HAUSLEITER J, KASTRATI A, WESSELY R *et al.*: Prevention of restenosis by a novel drug-eluting stent system with a dose-adjustable, polymer-free, on-site stent coating. *Eur. Heart J.* (2005) **26**(15):1475-1481.
64. MORICE MC, BESTEHORN HP, CARRIE D *et al.*: Direct stenting of the *de novo* coronary stenoses with tacrolimus-eluting versus carbon-coated carbostents. The randomized JUPITER II trial. *EuroIntervention* (2006) **2**:45-52.
65. MCFADDEN EP, STABILE E, REGAR E *et al.*: Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* (2004) **364**(9444):1519-1521.
66. NEBEKER JR, VIRMANI R, BENNETT CL *et al.*: Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J. Am. Coll. Cardiol.* (2006) **47**(1):175-181.
67. SAIA F, LEMOS PA, ARAMPATZIS CA *et al.*: Routine sirolimus eluting stent implantation for unselected in-stent restenosis: insights from the rapamycin eluting stent evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. *Heart* (2004) **90**(10):1183-1188.
68. NEUMANN FJ, DESMET W, GRUBE E *et al.*: Effectiveness and safety of sirolimus-eluting stents in the treatment of restenosis after coronary stent placement. *Circulation* (2005) **111**(16):2107-2111.
69. KASTRATI A, MEHILLI J, VON BECKERATH N *et al.*: ISAR-DESIRE: drug-eluting stents for in-stent restenosis. *European Society of Cardiology Congress.* Munich, Germany (28 August – 1 September 2004).

70. LEMOS PA, HOYE A, GOEDHART D *et al.*: Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. *Circulation* (2004) **109**(11):1366-1370.

71. COLOMBO A, MOSES JW, MORICE MC *et al.*: Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation* (2004) **109**(10):1244-1249.

72. SHARMA SK: Simultaneous kissing drug-eluting stent technique for percutaneous treatment of bifurcation lesions in large-size vessels. *Catheter Cardiovasc. Interv.* (2005) **65**(1):10-16.

73. NAKAMURA S, MUTHUSAMY TS, BAE JH *et al.*: Impact of sirolimus-eluting stent on the outcome of patients with chronic total occlusions. *Am. J. Cardiol.* (2005) **95**(2):161-166.

74. WERNER GS, KRACK A, SCHWARZ G *et al.*: Prevention of lesion recurrence in chronic total coronary occlusions by paclitaxel-eluting stents. *J. Am. Coll. Cardiol.* (2004) **44**(12):2301-2306.

75. SERRUYS PW, ONG AT, COLOMBO A *et al.*: Arterial revascularization therapies study part II: sirolimus-eluting stents for the treatment of patients with multivessel *de novo* coronary artery lesions. *54th American College of Cardiology Annual Scientific Session.* Orlando, FL, USA (6 March 2005).

76. KAPUR A, MALIK IS, BAGGER JP *et al.*: The Coronary Artery Revascularisation in Diabetes (CARDia) trial: background, aims, and design. *Am. Heart J.* (2005) **149**(1):13-19.

77. ONG AT, SERRUYS PW, MOHR FW *et al.*: The Synergy Between Percutaneous Coronary Intervention with TAXus™ and Cardiac Surgery (SYNTAX) Study: design, rationale and run-in phase. *Am. Heart J.* (2006). **151**(6):1194-1204.

78. SERRUYS PW: Drug-eluting stents: results from clinical trials. The PISCES trials. *55th Annual Scientific Session of the American College of Cardiology.* Atlanta, GA, USA (11 – 16 March 2006).

Affiliation

Sophia Vaina[1] MD, PhD & Patrick W Serruys[†2] MD, PhD, FESC, FACC
[†]Author for correspondence
[1]Interventional Cardiologist, Department of Interventional Cardiology, Thorax centre, Erasmus Medical Centre, Rotterdam, The Netherlands
[2]Professor of Interventional Cardiology, Thoraxcentre, Ba 583, Erasmus Medical Centre, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands
Tel: +(31) 10 4635260; Fax: +(31) 10 4369154; E-mail: p.w.j.c.serruys@erasmusmc.nl