Preclinical evaluation of anti-restenotic therapies and drug-eluting stents : efficacy and safety considerations

Pires, Nuno Miguel Marques

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DRUG-ELUTING STENTS: RESULTS, PROMISES AND PROBLEMS

BL van der Hoeven
NMM Pires
HM Warda
PV Oemrawsing
BJM van Vlijmen
PHA Quax
MJ Schalij
EE van der Wall
JW Jukema

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Abstract

In-stent restenosis is the major drawback of percutaneous coronary interventions, occuring in 10-40% of the patients. 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 in-stent restenosis. In this review article the results of human clinical studies investigating drug-eluting stents are discussed from a clinical point-of-view, focussing on the efficacy in the prevention of restenosis and their potential side effects. Both success and failure in the field of drug-eluting stents have been described. Successful devices are the sirolimus- and the polymer-based paclitaxel-eluting stent. Potentially dangerous side effects of drug-eluting stents are adverse drug interactions, incomplete stent apposition and increased in-stent thrombosis rates. Demonstration of long-term efficacy is mandatory since in some animal studies a delayed healing has been observed. Currently, the successful drug-eluting stents are under investigation in all types of lesions. We conclude that the results with some drug-eluting stents are promising, but further evidence on long-term efficacy and safety, also in high-risk subgroups, is needed.

Introduction

The major limiting factor of balloon angioplasty is the occurrence of restenosis in about 30-60% of patients, depending on clinical risk factors, lesion characteristics and technical aspects of the intervention.[1] Restenosis is characterized by a three-stage response of the vessel wall to balloon dilatation-induced injury: acute elastic recoil, negative remodeling, and neointimal proliferation.[2] The first, partly effective, strategy to lower the restenosis rate has been intracoronary stenting.[3,4] Intracoronary stenting has resulted in a decline of the restenosis rate to 10-40% by the virtual elimination of elastic recoil and negative remodeling.[5,6] However in-stent restenosis, mainly due to neointimal proliferation, remains the major limiting factor of percutaneous interventions for coronary artery disease.

The pathological process of in-stent restenosis is characterized by an inflammatory healing response after damage of the vessel wall.[7-10] Initially, platelets are activated and attach around the stent struts followed by adhesion of inflammatory cells. Cytokines and growth factors are released, leading to smooth muscle cell (SMC) migration and proliferation. The peak in neointimal volume is present at three to six

months after stent implantation followed by a 25% reduction in neointimal volume due to replacement of SMC by extracellular matrix.[11-14] Based on observations that in-stent restenosis is a consequence of inflammation and SMC proliferation, several immunosuppressive and anti-proliferative therapies have been investigated to inhibit these processes. The results of intracoronary brachytherapy to prevent in-stent restenosis have been disappointing, although brachytherapy may be an effective treatment of diffuse in-stent restenosis.[15] Systemic drug therapies generally failed in humans and have been hampered by systemic side effects.[16] Recently, dexamethasone and sarpogrelate were shown to be effective in selected patients.[17,18] Until recently, locally delivered drugs have been unsuccessful in humans due to rapid washout of the drug.[19] Heparin coating was one of the first attempts to use stent-based drug delivery, but this approach failed to reduce restenosis rates.[20]
Here, we first outline the concept of drug-eluting stents. Secondly, we review the current clinical drug-eluting stent studies. Finally, we discuss some topics as long-term efficacy, side effects and implantation techniques from a clinical point-of-view.

The drug-eluting stent

In recent years, the combination of stent properties to inhibit recoil and negative remodeling with drugs that inhibit neointimal proliferation, utilizing the stent as a local delivery platform, have emerged as a highly promising alternative to reduce in-stent restenosis. Generally, the drug-eluting stent consists of three major components: I) the drug, II) the polymer coating, and III) the stent.

I) The 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 SMC migration or proliferation, or promotion of healing. Ideally, this drug also has an outstanding overall safety profile and a broad therapeutic window. Figure 1 shows an overview of the main targets of drugs used on current drug-eluting stents. Most of these drugs have been originally used as chemotherapeutic agents, drugs for anti-transplant rejection, or immunosuppressive drugs. Besides the biological effects the drugs have their 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.[21,22] 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.

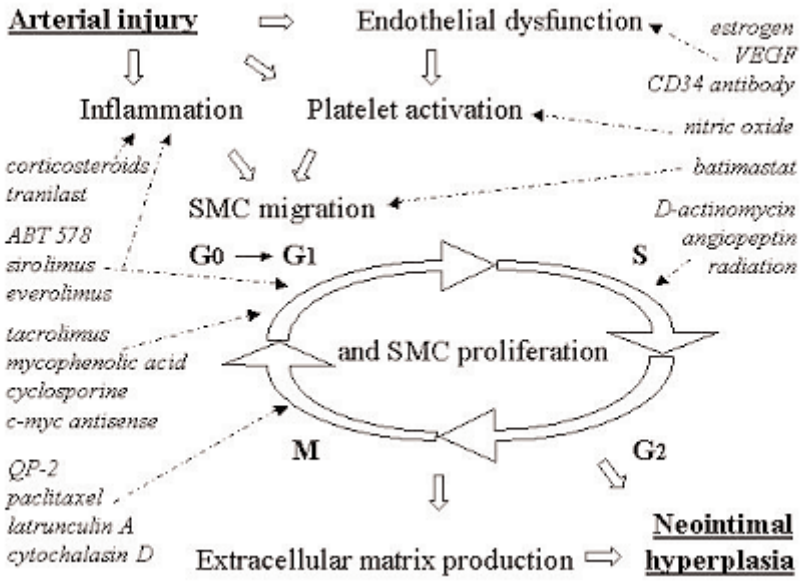

Figure 1. Main targets of drugs in relation to the cell cycle.

II) The polymer coating

Polymer coatings are needed for most drugs because they do not adhere to the metallic stent surface per se. The polymer coating also dictates drug-elution kinetics, which can be varied by using multiple polymer layers to achieve optimal drug release over time. Until recently, the polymer coating was the major limiting factor in the development of drug-eluting stents. Initially, all biodegradable or non-biodegradable polymers induced an increased inflammatory reaction and enhanced neointimal proliferation.[23] Later, some polymers were found to be biologically inert and stable for at least six months or biodegradable without increased proliferative response.[24,25]

New developments are biocompatible and inorganic coatings. Biocompatible coatings mimic the surface of normal tissue or cells. Phosphorylcholine-coating does not interfere with reendothelization and the degree of neointimal formation and thus is one of the platforms particularly suited for stent-based drug delivery.[26] 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.

III) The stent

The ideal drug-eluting stent 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 area. Stent material, electrophysiological properties and biocompatibility of the stent surface also influence neointimal proliferation.[27]

Theoretically, a drug-eluting biodegradable stent may be the ideal solution to prevent in-stent restenosis. The early response to vessel wall damage can be suppressed by the drug, whereas elastic recoil and negative remodeling can be prevented by the stent. Eventually, the stent will be degraded over time and chronic vessel wall injury will be prevented. In the past, biodegradable stents induced increased neointimal proliferation due to an enhanced inflammatory reaction except for the poly-l-lactate biodegradable stent.[28] A biodegradable stent eluting tranilast, an immunosuppressive drug, is currently under investigation.

Currently, all stents used as a drug delivery vehicle are conventional stents, not specially designed for this purpose. Although unknown, the design of these stents could be non-optimal to be used as a drug-eluting stent. The Conor™ drug-eluting stent is under investigation as a specially designed drug vehicle.[29] This stent has laser-cut pockets in which different drugs at different doses with different types of polymers can be combined to get optimal drug elution over time and at different locations of the target lesion. For the future, a further adaptation of stent designs to get optimal properties for drug loading can be expected. In conclusion, the ideal drug-eluting stent is a harmonized composition of a drug, a stent and a polymer.

Results of drug-eluting stent studies

In Table 1, the findings of drug-eluting stent studies are listed with regard to lesion and stent characteristics, angiographic (in-stent restenosis rate, late loss) and clinical endpoints (MACE rate, target lesion revascularisation rate, myocardial infarction and death rate). Some of these studies are presented at major congresses and in the process of being published.

Sirolimus

The target of sirolimus is mTOR (mammalian target of rapamycin) that regulates protein translation, resulting in a G_1 arrest of the cell cycle and inhibition of vascular SMC migration, proliferation and growth.[30] Sirolimus is also a strong inhibitor of inflammation without cellular toxicity in low doses. Clinical studies that have addressed sirolimus-eluting stents are: RAVEL,[31] SIRIUS,[32] E-SIRIUS[33] and

Table 1. Results of clinical studies with drug-eluting stents.

Study	Lesion type, length, diameter	Stent	Drug	Polymer	N	CAG fup (M)	ISR (%)	*P* value	In-stent LL (mm)	Clinical fup (M)	MACE	MI/ death	TLR	*P* value
RAVEL	*de novo*, <15 mm	Bx-Velocity	sirolimus 140 μg/cm²	yes	120	6	0.0%	<0.001	-0.01	12	5.8%	5.0%	0.0%	<0.001
	2.5-3.5 mm		bare stent		118		26.6%		0.80		28.8%	5.9%	22.9%	
SIRIUS	*de novo*, 15-30 mm	Bx-Velocity	sirolimus 140 μg/cm²	yes	533	8	3.2%	<0.001	0.17	9	7.1%	3.8%	4.1%	<0.001
	2.5-3.5 mm		bare stent		525		35.4%		1.00		18.9%	3.8%	16.6%	
E-SIRIUS	*de novo*, 15-32 mm	Bx-Velocity	sirolimus 140 μg/cm²	yes	175	8	3.9%	<0.001	0.20	9	8.1%	4.6%	4.0%	<0.001
	2.5-3.0 mm		bare stent		175		42.3%		1.05		22.8%	2.8%	20.9%	
C-SIRIUS	*de novo*, 15-32 mm	Bx-Velocity	sirolimus 140 μg/cm²	yes	50	8	0.0%	<0.001	0.09	9	4.0%	2.0%	6.0%	<0.001
	2.5-3.0 mm		bare stent		50		41.9%		1.01		18.0%	4.0%	18.0%	
FUTURE-I	*de novo*, <18 mm	S-Stent	everolimus	yes	25	6	0.0%	NS	0.11	6	7.7%	3.8%	3.8%	NS
	2.75-4.0 mm; no DM		bare stent		12		9.1%		0.85		8.3%	0.0%	8.3%	
ELUTES	*de novo*, <16 mm	V-flex Plus	paclitaxel 2.7 μg/mm²	no	37	6	3.0%	0.055	0.10	12	14.0%	5.4%	5.4%	NR
	3.0-3.5 mm		bare stent		38		21.0%		0.73		18.0%	0.0%	15.8%	
ASPECT	*de novo*, <15 mm	Supra-G	paclitaxel 3.1 μg/mm²	no	60	6	4%	<0.001	0.29	12	18.3%	3.3%	10.0%	NS
	2.25-3.5 mm		paclitaxel 1.28 μg/mm²	no	58		12%		0.57		13.8%	3.4%	8.6%	
			bare stent		58		27%		1.04		10.3%	1.7%	8.6%	
TAXUS I	*de novo*, <12 mm	NIRx	paclitaxel SR 1 μg/mm²	yes	31	6	0.0%	NS	0.36	12	3.2%	0.0%	0.0%	NS
	3.0-3.5 mm		bare stent		30		10.0%		0.71		10.0%	0.0%	10.0%	
TAXUS-II	*de novo*, <12 mm	NIRx	paclitaxel SR 1 μg/mm²	yes	131	6	2.3%	<0.001	0.31	12	10.9%	3.1%	4.7%	0.008
	3.0-3.5 mm		paclitaxel MR 1 μg/mm²	yes	136		4.7%		0.30		9.9%	4.4%	3.1%	0.001
			bare stent		270		19.0%		0.78		21.7%	5.9%	13.3%	
TAXUS-IV	*de novo*, 10-28 mm	Express	paclitaxel SR 1 μg/mm²	yes	638	9	5.5%	<0.001	0.39	9	8.5%	4.9%	3.0%	<0.001
	2.5-3.75 mm		bare stent		632		24.4%		0.92		15.0%	4.8%	11.3%	
DELIVER	*de novo*, <25 mm	ML RX Penta	paclitaxel 3.0 μg/mm²	no	517	8	14.9%	NS	0.81	9	10.3%	2.1%	8.1%	NS
	2.5-4.0 mm		bare stent		512		20.6%		0.98		13.3%	2.0%	11.3%	
SCORE	*de novo*, <21 mm	QuaDDS	QP-2 800 μg/sleeve	sleeves	138	6	10.1%	<0.001	0.35	12	49.2%	25.0%	25.0%	NS
	3.0-3.5 mm		bare stent		128		36.9%		0.65		30.4%	3.0%	21.1%	
ACTION	*de novo*, <18 mm	Tetra	D-actinomycin 10 μg/mm²	yes	121	6	17.0%	<0.05	0.93	12	28.1%	3.3%	23.1%	<0.05
	3.0-4.0 mm		D-actinomycin 2.5 μg/mm²	yes	120		25.0%		1.02		18.3%	0.8%	17.5%	
			bare stent		88		11.0%		0.76		10.2%	1.1%	9.1%	

CAG: coronary angiography; DM: diabetes mellitus; ISR: in-stent restenosis; LL: late loss; MACE: major adverse cardiac event; MI: myocardial infarction; MR: moderate release; SR: slow release; TLR: target lesion revascularization; NR: not reported; NS: not significant.

C-SIRIUS. Currently, the sirolimus-eluting stent is being investigated in all types of lesions and patients in clinical studies and registries, such as restenotic lesions, bifurcation lesions, acute coronary syndromes, diabetics and multi-vessel disease. Especially important will be the FREEDOM trial which will randomize diabetics with multi-vessel disease to CABG or sirolimus-eluting stent placement in conjunction with abciximab. The primary endpoint will be five year mortality.

Everolimus

Everolimus is an analogue of sirolimus with essentially the same mode-of-action. Everolimus is a strong anti-proliferative drug. In the first pilot study, a significant reduction in neointimal volume has been observed. Further clinical investigations with this drug are currently ongoing.

Paclitaxel

Paclitaxel belongs to the group of taxanes which are potent anti-proliferatives used to treat cancer. The mode-of-action is polymerisation of the α- and β-units of tubulin, thereby stabilizing microtubules which are needed for G_2 transition into M phase.[34] In low doses this results in a nearly complete inhibition of growth, proliferation and migration of SMC for a long period because of the structural changes in the cytoskeleton.

The studies investigating paclitaxel-eluting stents can be divided into two groups: non-polymer-based (ELUTES,[35] ASPECT,[36] DELIVER) and polymer-based paclitaxel delivery (TAXUS-I,[37] II[38] and IV). The polymer-based paclitaxel-eluting stents have been effective in reducing restenosis. The non-polymer-based paclitaxel-eluting stent studies showed different results. There was a dose-dependent reduction in in-stent restenosis rates in ELUTES. In ASPECT there was a reduction in in-stent restenosis rate, but also an increase in subacute thrombosis rate in the drug-eluting stent groups associated with the use of Cilostazol. The DELIVER-I study failed to show a significant reduction in target lesion revascularisation.

QP-2 (or 7-hexanoyltaxol)

The QuaDDS-QP2 stent contains a high dose of taxol-derivate released from polymer sleeves. The mode-of-action of QP-2 is essentially the same as for paclitaxel. The first pilot study showed promising results, but the results of the SCORE trial have been disappointing.[39-41] Although a significant reduction in neointimal volume at six months was observed, an increase in myocardial infarction and cardiac death rates occurred in the drug-eluting stent group due to late in-stent thrombosis.[41,42]

Actinomycin-D

Actinomycin-D is a chemotherapeutic drug, which blocks the cell cycle in the S phase by blocking the transcription of DNA. In animal studies, actinomycin-D inhibits SMC proliferation in a dose-dependent manner. The ACTION trial was prematurely stopped due to increased restenosis rates in the actinomycin-D groups.

Other drugs

Several drugs are currently under investigation in animals and humans. A pilot study using the batimastat-eluting Bx-Velocity stent showed a six month restenosis rate of 25%. Batimastat inhibits SMC migration. Seen this restenosis rate, a large trial with this drug will not be started. The dexamethasone-eluting BiodivYsio stent showed a 13% restenosis rate after six months. The EASTER trial investigated 30 patients with the 17β-estradiol-eluting BiodivYsio stent. 17β-estradiol is a vascular healing promoting drug, mainly targeting the endothelium. The restenosis rate at six months was 6.6%.[43] The ENDEAVOR-I study investigated ABT-578 (a sirolimus analogue). The four months target lesion revascularisation was 2.5%. Some of the other drugs under investigation in humans and animals are tacrolimus, mycophenolic acid, cyclosporin, tranilast, angiopeptin, latrunculin-A, cytochalasin-D, c-myc antisense, vascular endothelium growth factor (VEGF) and nitric oxide (NO). Other developments are the CD34 antibody-coated stent and endothelial progenitor cell-seeded stent.[44,45] The aim of these devices is fast reendothelization and repair of endothelial function. This should limit the inflammatory reaction and consequently neointimal proliferation.

Specific subgroups

In Table 2, findings with regard to target lesion revascularisation rates for specific subgroups are listed. According to current evidence, drug-eluting stents are effective in long lesions and small vessels. In the case of diabetics, both the sirolimus- and the paclitaxel-eluting stents are effective to prevent restenosis. However for both devices there was no significant reduction in target lesion revascularisation rates for insulin-dependent diabetics. This could be due to small patient numbers and low statistical power. However, the amount of reduction in late loss was less compared with non-insulin dependent diabetics and non-diabetics, especially in sirolimus-eluting stents. The clinical benefit of drug-eluting stents in patients with insulin-dependent diabetes remains therefore uncertain but seems to be promising. Further research is needed to clarify the pathophysiological mechanisms contributing to the decreased drug response in this important subgroup of patients. Some small

Table 2. Results with drug-eluting stents in specific subgroups.

Study	Drug	Polymer	N	Fup(M)	TLR(%)
Diabetic patients					
SIRIUS subgroup analysis					
Non-insulin dependent	paclitaxel	yes	93	9	4.4%
	bare stent		104		23.8%
Insulin dependent	paclitaxel	yes	38		13.9%
	bare stent		44		20.8%
TAXUS-IV subgroup analysis					
Non-insulin dependent	paclitaxel	yes	104	9	4.8%
	bare stent		109		17.4%
Insulin dependent	paclitaxel	yes	51		5.9%
	bare stent		54		13.0%
Bifurcation lesions					
*SIRIUS-bifurcation study**					
Stent MB + Stent SB	sirolimus	yes	63	6	9.5%
Stent MB + PTCA SB	sirolimus	yes	22		4.5%
Small vessels					
SIRIUS subgroup analysis					
vessel diameter <2.75 mm	sirolimus	yes	523	9	6.3%
	bare stent				18.7%
TAXUS-IV subgroup analysis					
vessel diameter <2.5 mm	paclitaxel	yes	206	9	3.4%
	bare stent		214		15.4%
E- and C-SIRIUS (Table 1)					
Long lesions					
SIRIUS subgroup analysis					
lesion length >13.5 mm	sirolimus	yes	519	9	5.2%
	bare stent				17.4%
TAXUS-IV subgroup analysis					
lesion length >20 mm	paclitaxel	yes	91	9	3.3%
	bare stent		97		18.6%
Restenotic lesions					
Liistro et al.	QP-2	sleeves	15	6	20.0%
				12	60.0%
TAXUS III	paclitaxel	yes	28	6	17.9%
				12	17.9%
Degertekin et al.	sirolimus	yes	16	4	0.0%
				9	0.0%
Sousa et al.	sirolimus	yes	25	4	0.0%
				12	0.0%
Complex lesions					
DELIVER-II study**	paclitaxel	no	1531	6	10.5%

MB: main branch; SB: side branch; TLR: target lesion revascularization.
*Per protocol analysis.
**Including: multivessel disease, restenotic lesions, bifurcation lesions, chronic (sub)total occlusions, small vessels and long lesions.

registries investigated drug-eluting stents in restenotic lesions.[46-49] The short-term results of the sirolimus-eluting stent in this subgroup of patients are promising but needs further investigation. The additional value of drug-eluting stents in chronic total occlusions, acute myocardial infarctions and degenerated vein grafts needs to be assessed.

Discussion

Long-term outcome

Some drug-eluting stents are effective in preventing in-stent restenosis, although long-term results from large studies are missing. The longest follow-up period of the clinical studies is two years in the case of the RAVEL, SIRIUS and TAXUS-I studies. There was no major increase in target lesion revascularisation rates between one and two years of follow-up. Theoretically, we could expect a delayed healing due to inhibitory effects of sirolimus and paclitaxel on the inflammatory and hyperplastic response to vascular trauma.[50] In some animal models a delayed healing between 90 and 180 days after implantation has been observed, while there was evidence of complete reendothelization after 90 days.[51] At present, the long-term pathobiology of the interference of locally delivered drugs with the complex process that ensues vascular trauma associated with stent implantation is uncertain. Long-term clinical and angiographic follow-up is therefore mandatory. In general, it could be argued to be reluctant with liberal drug-eluting stenting and deploying "full metal jackets" in multivessel disease at this moment in absence of clear evidence of long-term efficacy.

Side effects

The occurrence of late stent malapposition, especially in the sirolimus-eluting stent studies, is a side effect which is still of unknown clinical relevance. In RAVEL, a 21% rate of incomplete stent apposition after six months has been observed compared with 4% in the control group. In SIRIUS, 9% late acquired incomplete stent apposition has been observed compared with 0% in the bare-metal stents group. Late incomplete stent apposition was not related to events within 12 months. Most likely, the pathophysiological background is inhibition of normal vessel repair after injury. This results in positive remodeling and incomplete strut apposition. This is confirmed by the observation that diabetes mellitus, which shows a more proliferative healing response, has been a protective factor for occurrence of late incomplete

stent apposition. An other explanation could be that sirolimus or the polymer induces apotosis or necrosis. The major concern of incomplete stent apposition is the occurrence of late in-stent thrombosis and myocardial infarction. Invasive follow-up is needed to evaluate the natural course of this finding. Whether incomplete stent apposition disappears over time as seen in brachytherapy is still uncertain. To prevent complications of incomplete stent apposition, besides the long-term use of combined anti-platelet medication, no additional intervention is advocated based on the absence of related adverse events at present.

In the DELIVER study, using multivariate analysis, an increased rate of in-stent restenosis has been observed when glycoprotein IIb/IIIa inhibitors had been used. Most likely this is due to more frequent use of abciximab in complex lesions, which also have higher risk of in-stent restenosis. However an adverse drug interaction between paclitaxel and glycoprotein IIb/IIIa inhibitors should be taken into acount. In the several TAXUS studies, which also used paclitaxel, this has not been observed. The pathophysiolgical background and clinical relevance of this finding remains uncertain.

A potentially important adverse effect of sirolimus is increased platelet aggregation.[52] In combination with delayed re-endothelialisation this could result in higher in-stent thrombosis rates, especially in high-risk subgroups such as patients with unstable angina or acute myocardial infarction. The first results of sirolimus-eluting stent implantation in combination with adequate anti-thrombotic therapy in patients with acute coronary syndromes did not reveal increased thrombosis rates during 30 days following the acute event.[53,54] Increased thrombosis rates are thus far not reported in the clincal studies with the sirolimus-eluting stent. However, use of this stent in the real world for indications not tested in clinical studies might result in a higher risk of subacute thrombosis. The U.S. Food and Drug Administration (FDA) published a web notification on this, because they received numerous reports of subacute thrombosis.[55] Therefore, randomized clinical studies in complex lesions are needed to establish the extent and clinical relevance of subacute thrombosis after implantation of the sirolimus-eluting stent.

Polymer-related risks

An important factor of uncertainty about the efficacy of drug-eluting stents is the use of polymers. It is not certain whether the used polymers are stable over a long period of time and if they are completely inert. In a recent study poly-methacrylate induced SMC apoptosis in vitro.[56] Poly-methylacrylate is the major component of the polymer used in the sirolimus-eluting stent. Furthermore, the polymer could also be

damaged due to calcifications or overlapping stenting, which could result in inadequate drug release and restenosis. This should be taken into account in the evaluation of long-term effects.

Technical factors

Complete lesion coverage seems an important issue when drug-eluting stents are used. In the TAXUS-III study, restenosis was probably caused by insufficient stent coverage of the treated lesion resulting in restenosis between two stents.[49] In the SIRIUS trial the 8.6% target vessel failure rate was mainly based on proximal edge restenosis. The rate of geographic miss at the proximal and distal edge of the stent was 22.9% and 14.7%, respectively. This could be the reason why proximal edge restenosis occurred relatively often in this study. Later, in E- and C-SIRIUS this problem was circumvented by coverage of the whole dilated lesion with a drug-eluting stent. Data of the SIRIUS bifurcation trial showed increased restenosis at the side branches due to incomplete coverage of the lesion by the stent placed in the side branch (see also Table 2). All these studies show that the implantation technique, especially whole coverage of the predilated lesion by the drug-eluting stent, is very important. Direct stenting may prevent geographical miss and thereby edge restenosis in selected lesions if the delivery device does not cause edge trauma outside of the stent. Further evidence is needed about the efficacy of drug-eluting stents in lesions in which unequal strut distribution is common (e.g. very angulated or heavy calcified lesions). There is also very little known about the local effects of overlapping stenting. Does the double dose cause delayed re-endothelialization or toxic side effects?

In-stent restenosis in drug-eluting stents

The in-lesion restenosis rate after sirolimus-eluting stent implantation in single *de novo* lesions is less than 7% at six months in current clinical studies with sirolimus- and polymer-based paclitaxel-eluting stents. The first study about in-stent restenosis in "real world" complex lesions reports a rate of about 15%.[57] The pattern of restenosis after sirolimus-eluting stent implantation thus far reported is mainly focal. Local conditions as geographic miss or discontinuity in stent coverage as a consequence of stent fracture or gaps between two stents seem to play a major role.[57,58] Further study is needed to determine the backgrounds and treatment strategy of in-stent restenosis after drug-eluting stent implantation.

Study design

In the drug-eluting stent studies, IVUS and angiography have given important insights in the amount and distribution of neointimal hyperplasia in relation to implantation techniques. These invasive techniques are therefore mandatory in the evaluation of drug-eluting stents. In all these studies the angiographic and IVUS secondary endpoints have been assessed before the primary clinical endpoints. For three reasons this approach is problematic. First, evaluating the efficacy of drug-eluting stents by measuring neointimal volume or late loss has limited value. These parameters are important for evaluation of the biological effect, but less neointimal volume does not always mean a better result. If less neointimal volume leads to incomplete stent apposition than potential dangerous side effects occur. Second, there is a discrepancy in time between peak in-stent restenosis rate as assessed by coronary angiography and clinical-driven target lesion revascularisation rate. Peak in-stent restenosis rate is present at three to six months while target lesion revascularisation rate significantly increases after six months, indicating that functional assessment of restenotic lesions is more important than anatomical findings by angiography.[14,59] Third, measuring angiographic endpoints before clinical endpoints results in increased target lesion revascularization rates.[59] About 50% of the angiographic restenotic lesions are asymptomatic and should probably not be treated, especially since there is evidence for late regression of neointimal hyperplasia beyond six months. In the RAVEL trial, the in-stent restenosis rate and target lesion revascularisation rate in the bare-metal stent group were 26.6% and 22.9%, respectively, indicating that nearly all angiographic restenotic lesions have been treated. This overestimates the significance level of the findings in this study. Randomized studies comparing drug-eluting stents and bare-metal stents with long-term clinical and functional endpoints are therefore needed to establish the true clinical benefit of drug-eluting stents.

Indications for drug-eluting stents

The sirolimus- and polymer-based paclitaxel-eluting stents are generally better performing than bare-metal stents although some studies investigating bare-metal stents report similar in-stent restenosis rates.[60,61] Improved stent design and implantation techniques have resulted in a significant decline in in-stent restenosis rates over the last years. The costs are a major limiting factor of drug-eluting stents. Currently, the cost of drug-eluting stents is about five-fold of the expense of bare-metal stents. In most centres this resulted in selective implantation in high-risk groups such as those with long lesions, small vessels, restenosis and diabetes, being

subgroups in which hardly any evidence exists. It could be argued to be cautious with drug-eluting stents since they only reduce target lesion revascularization rates but do not reduce myocardial infarction and death rates. The side effects of drug-eluting stents are potentially dangerous, while additional revascularization procedures are generally safe.

Conclusion

There is success and failure in the new field of drug-eluting stents. The sirolimus- and polymer-based paclitaxel-eluting stents appear very promising at least in single *de novo* lesions. Longer follow-up of current clinical studies is mandatory with regard to long-term efficacy, polymer-related risks and side effects. Further randomized controlled studies are needed to assess optimal implantation techniques and efficacy and safety in high-risk lesions. For general wide-spread application of drug-eluting stents many questions need to be answered.

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Reference List

1. Landau C, Lange RA, Hillis LD. Percutaneous transluminal coronary angioplasty. N Engl J Med 1994;330:981-993.
2. Mintz GS, Popma JJ, Pichard AD, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. Circulation 1996;94:35-43.
3. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994;331:496-501.
4. Kiemeneij F, Serruys PW, Macaya C, et al. Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of Benestent-I trial. J Am Coll Cardiol 2001;37:1598-1603.
5. Lowe HC, Oesterle SN, Khachigian LM. Coronary in-stent restenosis: current status and future strategies. J Am Coll Cardiol 2002;39:183-193.
6. Hoffmann R, Mintz GS, Dussaillant GR, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. Circulation 1996;94:1247-1254.
7. Grewe PH, Deneke T, Machraoui A, et al. Acute and chronic tissue response to coronary stent implantation: patho-

logic findings in human specimen. J Am Coll Cardiol 2000;35:157-163.
8. Farb A, Sangiorgi G, Carter AJ, et al. Pathology of acute and chronic coronary stenting in humans. Circulation 1999;99:44-52.
9. 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.
10. Brasen JH, Kivela A, Roser K, et al. Angiogenesis, vascular endothelial growth factor and platelet-derived growth factor-BB expression, iron deposition, and oxidation-specific epitopes in stented human coronary arteries. Arterioscler Thromb Vasc Biol 2001;21:1720-1726.
11. 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.
12. Glover C, Ma X, Chen YX, et al. Human in-stent restenosis tissue obtained by means of coronary atherectomy consists of an abundant proteoglycan matrix with a paucity of cell proliferation. Am Heart J 2002;144:702-709.
13. Chung IM, Gold HK, Schwartz SM, et al. Enhanced extracellular matrix accumulation in restenosis of coronary arteries after stent deployment. J Am Coll Cardiol 2002;40:2072-2081.
14. Kuroda N, Kobayashi Y, Nameki M, et al. Intimal hyperplasia regression from 6 to 12 months after stenting. Am J Cardiol 2002;89:869-872.
15. Salame MY, Verheye S, Crocker IR, et al. Intracoronary radiation therapy. Eur Heart J 2001;22:629-647.
16. Faxon DP. Systemic drug therapy for restenosis: "deja vu all over again". Circulation 2002;106:2296-2298.
17. Versaci F, Gaspardone A, Tomai F, et al. Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation (IMPRESS Study). J Am Coll Cardiol 2002;40:1935-1942.
18. Fujita M, Mizuno K, Ho M, et al. Sarpogrelate treatment reduces restenosis after coronary stenting. Am Heart J 2003;145:E16.
19. Lincoff AM, Topol EJ, Ellis SG. Local drug delivery for the prevention of restenosis. Fact, fancy, and future. Circulation 1994;90:2070-2084.
20. Wohrle J, Al Khayer E, Grotzinger U, et al. Comparison of the heparin coated vs the uncoated Jostent - no influence on restenosis or clinical outcome. Eur Heart J 2001;22:1808-1816.
21. Lovich MA, Creel C, Hong K, et al. Carrier proteins determine local pharmacokinetics and arterial distribution of paclitaxel. J Pharm Sci 2001;90:1324-1335.
22. Hwang CW, Wu D, Edelman ER. Physiological transport forces govern drug distribution for stent-based delivery. Circulation 2001; 104:600-605.
23. 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;94:1690-1697.
24. Drachman DE, Edelman ER, Seifert P, et al. Neointimal thickening after stent delivery of paclitaxel: change in composition and arrest of growth over six months. J Am Coll Cardiol 2000;36:2325-2332.
25. Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. Circulation 2001;104:1188-1193.
26. Lewis AL, Stratford PW. Phosphorylcholine-coated stents. J Long Term Eff Med Implants 2002;12:231-250.
27. Palmaz JC, Bailey S, Marton D, et al. Influence of stent design and material composition on procedure outcome. J Vasc Surg 2002;36:1031-1039.
28. 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;102:399-404.
29. Finkelstein A, McClean D, Kar S, et al. Local drug delivery via a coronary stent with programmable release pharmacokinetics. Circulation 2003;107:777-784.
30. Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. Circulation 2001;104:852-855.
31. 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;346:1773-1780.
32. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315-1323.
33. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362:1093-1099.
34. Rowinsky EK, Donehower RC. Paclitaxel (taxol). N Engl J Med 1995;332:1004-1014.
35. Gershlick AH. European evaLUation of pacliTaxel eluting Stent (ELUTES). Circulation 2002;105:E39.
36. Park SJ, Shim WH, Ho DS, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. N Engl J Med

2003;348:1537-1545.
37. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107:38-42.
38. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108:788-794.
39. de La Fuente LM, Miano J, Mrad J, et al. Initial results of the Quanam drug eluting stent (QuaDS-QP-2) Registry (BARDDS) in human subjects. Catheter Cardiovasc Interv 2001;53:480-488.
40. Honda Y, Grube E, de La Fuente LM, et al. Novel drug-delivery stent: intravascular ultrasound observations from the first human experience with the QP2-eluting polymer stent system. Circulation 2001;104:380-383.
41. Kataoka T, Grube E, Hauptmann KE, et al. Prevention of restenosis by a new drug eluting stent: An intravascular ultrasound substudy of the SCORE trial. Circulation 2001; 104:3307.
42. Liistro F, Colombo A. Late acute thrombosis after paclitaxel eluting stent implantation. Heart 2001;86:262-264.
43. Abizaid AA, New G, Abizaid AS, et al. First clinical experience with 17-estradiol-eluting BiodivYsio matrix LO Stent to prevent restenosis in de-novo native coronary arteries: Six-month clinical outcomes and angiographic follow-up from the EASTER trial. J Am Coll Cardiol 2003;41:56A.
44. Shirota T, Yasui H, Shimokawa H, et al. Fabrication of endothelial progenitor cell (EPC)-seeded intravascular stent devices and in vitro endothelialization on hybrid vascular tissue. Biomaterials 2003;24:2295-2302.
45. Kutryk MJB, Kuliszewski MA. Progenitor cell capture for the accelerated endothelialization of endovascular devices. Am J Cardiol 2002;90:TCT180.
46. Degertekin M, Regar E, Tanabe K, et al. Sirolimus-eluting stent for treatment of complex in-stent restenosis. The first clinical experience. J Am Coll Cardiol 2003;41:184-189.
47. Liistro F, Stankovic G, Di Mario C, et al. First clinical experience with a paclitaxel derivate-eluting polymer stent system implantation for in-stent restenosis: immediate and long-term clinical and angiographic outcome. Circulation 2002;105:1883-1886.
48. Sousa JE, Costa MA, Abizaid A, et al. Sirolimus-eluting stent for the treatment of in-stent restenosis: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation 2003;107:24-27.
49. Tanabe K, Serruys PW, Grube E, et al. TAXUS III Trial: in-stent restenosis treated with stent-based delivery of paclitaxel incorporated in a slow-release polymer formulation. Circulation 2003;107:559-564.
50. Virmani R, Kolodgie FD, Farb A, et al. Drug eluting stents: are human and animal studies comparable? Heart 2003;89:133-138.
51. Long-term effects of stent-based delivery of sirolimus in the porcine model. Am J Cardiol 2002;90:199.
52. Babinska A, Markell MS, Salifu MO, et al. Enhancement of human platelet aggregation and secretion induced by rapamycin. Nephrol Dial Transplant 1998;13:3153-3159.
53. Lemos PA, Lee CH, Degertekin M, et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. J Am Coll Cardiol 2003;41:2093-2099.
54. Lee CH, Lemos PA, Van Domburg RT, et al. Safety and efficacy of sirolimus-eluting stent (cypher) in acute myocardial infarction: A substudy of the rapamycin-eluting stent evaluation at Rotterdam cardiology hospital (RESEARCH) study. J Am Coll Cardiol 2003;41:21A.
55. FDA Public Health Web Notification: Information for Physicians on Sub-acute Thromboses (SAT) and Hypersensitivity Reactions with Use of the Cordis CYPHER™ Coronary Stent. 29-10-2003.
56. Curcio A, Torella D, Cuda G, et al. Effect Of Stent Coating Alone On In Vitro Vascular Smooth Muscle Cell Proliferation and Apoptosis. Am J Physiol Heart Circ Physiol 2004;286:H902-908.
57. Lemos PA, Saia F, Ligthart JM, et al. Coronary Restenosis After Sirolimus-Eluting Stent Implantation. Morphological Description and Mechanistic Analysis From a Consecutive Series of Cases. Circulation 2003:108:257-260.
58. Colombo A, Orlic D, Stankovic G, et al. Preliminary observations regarding angiographic pattern of restenosis after rapamycin-eluting stent implantation. Circulation 2003;107:2178-2180.
59. Cutlip DE, Chauhan MS, Baim DS, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. J Am Coll Cardiol 2002;40:2082-2089.
60. Morice MC, Aubry P, Benveniste E, et al. The MUST Trial: Acute Results and Six-Month Clinical Follow-up. J Invasive Cardiol 1998;10:457-463.
61. de Jaegere P, Mudra H, Figulla H, et al. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC Study). Eur Heart J 1998;19:1214-1223.