Which Parameter Should Be Chosen as Primary Endpoint for Randomized Drug-Eluting Stent Studies?

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In Europe, 1,108 percutaneous coronary interventions (PCIs) per one Mio inhabitants are currently annually performed, most of them with stent implantation. Drug-eluting stents have been the focus of attention of interventional coronary therapy since the RAVEL study was first presented in September 2001 at the European Society of Cardiology Meeting. Ever since, numerous studies have assessed the effects of various antiproliferative and anti-inflammatory substances and a variety of different stents was used as platform, either covered with polymer carriers of different chemical and physical properties or without a polymer carrier. CE- or FDA-certified drug-eluting stents are increasingly replacing the use of bare metal stents to reduce in-stent restenosis. Today, physicians have a choice of several approved drug-eluting stents and, therefore, need some evidence-based guidance through the "jungle of information" to make the right decisions. Even when focusing on randomized trials, differences between the studies regarding primary endpoints and sample sizes exist, making it difficult to compare the various drug-eluting stent studies. Randomized studies use either nonclinical (i.e., angiographic diameter stenosis, in-stent MLD, or in-stent late lumen loss) or clinical (i.e., TVF, TVR, and MACE) parameters as primary endpoints. Choosing an angiographic parameter as primary endpoint results in two major limitations: first, a significant improvement of an angiographic "surrogate" parameter does not necessarily translate into a better clinical outcome (DELIVER-I); second, conclusions regarding possible improvements of clinical outcome are underpowered, because the sample size calculation is based on the primary endpoint. Usually the number of patients needed is lower for angiographic than for clinical endpoints. Until today, only three trials with a primary clinical endpoint have shown a significantly positive impact on patients' outcome: the SIRIUS trial (Cypher stent) with its reduction of primary endpoint TVF (21.0% vs 8.6%), the TAXUS-IV trial (Taxus stent) with its reduction of primary endpoint TVR (12.0% vs 4.7%) and TAXUS-VI in long lesions with its reduction of primary endpoint TVR (19.4% vs 9.1%). Although the angiographic results of other drug-eluting stents are encouraging, they will have to prove their clinical impact based on adequately powered randomized trials with a primary clinical endpoint at an adequate time interval.
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Introduction

Nearly 8 million catheterizations are now annually performed worldwide to either diagnose or treat vascular diseases. With an annual increase between 15% and 25%, in the year 2001 577,767 PCIs, i.e., 1,108 percutaneous coronary interventions (PCIs) per one Mio inhabitants were performed, most of them with stent implantation.[1,2]

Restenosis after stent implantation is an old and still annoying problem, the "risk factors" for the occurrence of in-stent restenosis are well delineated.[3–8] Drug-eluting stents have been the focus of attention of interventional coronary therapy since the RAVEL study was first presented in September 2001 at the European Society of Cardiology Meeting in Stockholm.[9] Ever since, numerous studies have assessed the effects of various antiproliferative and anti-inflammatory substances, like sirolimus and its derivatives (tacrolimus, everolimus, ABT-578, biolimus), paclitaxel and one of its derivatives (QP2), as well as other drugs, like dexamethasone, 17-β-estradiol, batimastat, actinomycin-D, methotrexat, angiopeptin, tyrosinkinase inhibitors, vincristin, mitomycin, cyclosporin, as well as the C-myc antisense technology (Resten-NG, AVI-4126).[10–22] Statins, carvedilol, abciximab, and trapidil were also

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suggested as drugs to be released from stents.[23–27] A variety of different stents was used as platform either covered with polymer carriers of different chemical and physical properties or without a polymer carrier. Recently, nitinol stents,[28] carbofilm stents,[29] and other stents with special "microcontainers" have been developed for storing the drugs.[30] Progress is being made in the development of biodegradable stents and biodegradable polymers for drug-eluting stents.[31,32]

CE or FDA-certified drug-eluting stents are increasingly replacing the use of bare metal stents to reduce in-stent restenosis. Today, physicians have a choice of several approved drug-eluting stents and, therefore, need some evidence-based guidance through the "jungle of information" to make the right decisions. Even when focusing on randomized trials, differences between the studies regarding primary endpoints and sample sizes exist, making it difficult to compare the various drug-eluting stent studies.

The following article discusses the presently available randomized drug-eluting stent studies with special emphasis on the primary endpoints used.

Methods

A literature review was performed using Medline (PubMed).[33] Peer-reviewed published literature was preferably considered. In general, the use of abstracts should be avoided.[34] However, since the field of interventional cardiology is so rapidly evolving and many important pivotal studies have recently been orally presented at major meetings, these presentations were also included if considered as pivotal. The primary endpoints were classified as nonclinical (angiographic, IVUS) or clinical.

Nonclinical Endpoints.

Quantitative Coronary Analysis. Quantitative coronary analysis (QCA) usually determines the following parameters of coronary angiograms: reference vessel diameter (RVD in mm), lesion or stenosis length (LL in mm), the degree of stenosis as a percentage of diameter stenosis (DS in percent), the minimal lumen diameter (MLD in mm), the restenosis rate (RR in percent), the late lumen loss (LLL in mm) and the late lumen loss index (LLLI in percent). Due to potentially different effects within the stent and at the stent edges, the angiographic parameters DS, MLD, RR, LLL, and LLLI should be listed separately as results for the stented segment (e.g., in-stent restenosis) and for the entire analyzed segment (e.g., in-segment restenosis). Unfortunately, the acronym "ISR" is sometimes used for "in-stent restenosis"—and sometimes for "in-segment restenosis," leading to confusion, like the term "in the stented segment." Nowadays, an analysis of the stent and the stent edges for a length of ± 5 mm ("peristent area") is a general practice.

The restenosis rate (RR) is based on the arbitrarily defined limit of $\geq 50\%$ diameter stenosis and is, therefore, expressed as "yes" or "no" (thus also called "binary" or "dichotomous" restenosis rate). Even when restenosis rates are provided, a clear differentiation between in-stent RR and in-segment RR must be made.

Restenosis rate is a purely angiographic parameter—conclusions regarding its clinical relevance may not be drawn: for a paradoxical example, a high restenosis rate of 70% could be more clinically beneficial than a restenosis rate of 40% when the first restenosis rate is based on a diameter stenosis of 55% and the latter on a diameter stenosis of 80%. For this reason, another partially confusing parameter was introduced: the "clinical restenosis rate," which usually represents a clinically indicated (clinically driven) revascularization of the target vessel.

Late lumen loss has recently become more important within the context of drug-eluting stents: since the inside of the stent has negligible recoil, late (lumen) loss within the stent (in-stent LLL or in-stent LL) can be considered an indirect measure of neointimal proliferation—and thus as an indirect "IVUS-like" parameter. Low late lumen loss at the time of angiographic follow-up reflects a lower intimal hyperplasia within the previously implanted stent. It is, however, unclear which LLL represents the optimal level. Of course, a certain degree of intimal proliferation (LLL reduction) is desired for sufficient coverage of the stent struts. A negative LLL could even induce a stent malapposition.

Intravascular Ultrasound. Intravascular ultrasound (IVUS) is usually performed with an automated pullback at 0.5 mm/s to examine the stented vessel segments. The lumen, stent and external elastic membrane (EEM) contours are detected with special analysis software, applying three-dimensional reconstruction. If the EEM could not be detected (because of extensive calcification with acoustic shadowing), that patients are excluded from analysis. In the stented segment and in each subsegment, mean total vessel area (VA), mean stent area (SA), and mean lumen area (LA) are measured. Mean neointimal hyperplasia area (NIHA) and

peristent area (PSA) are derived by SA, LA and VA, SA, respectively. Percentage of NIHA and PSA are calculated as NIHA/SA 100 and PSA/VA 100, respectively. In TAXUS-II, the primary endpoint was the percentage of the stent volume obstructed by neointimal proliferation measured by IVUS at 6 months.

Additionally, IVUS is the only method to reliably detect and measure incomplete stent apposition, defined as separation of one or more stent struts from the vessel wall with evidence of blood flow behind the strut.

Clinical Endpoints. The classic clinical parameter is MACE (major adverse cardiac events), the sum of various clinical single parameters: the hard endpoints are death (coronary death, cardiac death, or death from any cause) or myocardial infarction (MI, with or without Q wave or STEMI or NSTEMI).

In some studies, the angiographic analysis (QCA) did not precisely differentiate between the SA and PSA; therefore, the clinical parameter TLR (target lesion revascularization) underestimated the clinical impact of restenosis. The description of TVR (target vessel revascularization) becomes increasingly important, because TVR is independent of angiographic definitions of the stent edges. TVR clarifies the dispute whether a re-PCI was caused by a stenosis at the stent edge or by a more distally, newly developed stenosis. Therefore, both parameters (TLR and TVR) should always be provided. In addition, publications should also report the type of TLR or TVR, such as re-PCI of the target lesion or target vessel, or bypass surgery including the target vessel.

TLR and TVR require the patient to undergo another cardiac catheterization. If a study investigates a new procedure and after treatment of, e.g., the LAD, an anterior wall infarction occurs but no further catheterization, PCI, or surgery are performed, this severe event will not be reflected by TLR or TVR; another parameter becomes extremely important: TVF (target vessel failure) comprises all hard events and target-vessel-related parameters, such as target-vessel-related MI and stent thromboses (even without further cardiac catheterization). Therefore, each TVR is also a TVF, but not each TVF is a TVR. The advantage of TVF is that it also reflects coronary events in patients not undergoing another angiography or revascularization procedure, such as a new onset of angina pectoris with conservative treatment, which is not reflected by RR and TVR. The definitions of TVF are not consistent—this is also true for MACE, which has been differently defined in various studies (e.g., death by any cause or only coronary death, Q wave infarction or NSTEMI are included or excluded in MACE, any bypass surgery or only bypass surgery on the target vessel, etc.).

The need for repeat revascularization during long-term follow-up, beyond the timing of repeat angiography, should not be reported as TLR or TVR at 2 or 3 years, but rather as "repeat reintervention." It is indeed likely that an additional number of patients would receive re-PCI or CABG if angiography was available in all of them. The figures on late revascularization are indeed critical but cannot be compared to TLR or TVR rates obtained at the time of systematic follow-up angiography.

Results

Despite initially encouraging experimental and clinical results,[35] the intracoronary application of many antiproliferative and anti-inflammatory drugs via drug-eluting stents was abandoned because the clinical results were either harmful (e.g., QP2 in the SCORE study,[36–40] actinomycin-D in the ACTION study[19]) or too weak (e.g., dexamethasone in the STRIDE study[41] or the metalloproteinase-inhibitor batimastat BB-94 in the BRILLIANT-I study[42]). For this reason, some already planned, randomized consecutive studies were terminated or not even initiated, like EMPEROR for dexamethasone and BRILLIANT-II for Batimastat. Also, antisense technology[14,21] is not yet clinically mature (AVAIL study). But whole series of new, promising drugs have emerged, like Biolimus (STEALTH-I, first use of Biolimus A9 on biosensors' challenge stent platform) and ABT-578, another sirolimus derivative (methyl-rapamycin) in ENDEAVOR-I.[43,44] The results of the ongoing, controlled ENDEAVOR-II study (ca. 1,200 patients) are expected soon. SPIRIT will evaluate Everolimus on the Vision stent.

Presently, only three drugs have shown significantly positive effects in prospective randomized studies: Paclitaxel, sirolimus and its derivative, and everolimus. Their pharmacological properties will not be discussed here.

A total of 3,815 patients have been investigated in randomized Paclitaxel studies, 1,748 patients in sirolimus studies, and 106 patients in everolimus studies. Table 1 characterizes the studies that have been performed with Paclitaxel-eluting stents in relation to the stent technology, dose density, and primary endpoint. The underdosed (and hence less or not effective) Paclitaxel groups are not listed in

Table 1. Key Characteristics of Prospective, Randomized Studies with Paclitaxel-Eluting Stents in Patients with De Novo Lesions

	ASPECT	ELUTES	DELIVER-I	TAXUS-I	TAXUS-II	TAXUS-IV	TAXUS-VI
Company	Cook	Cook	Guidant/Cook	Boston Scientific	Boston Scientific	Boston Scientific	Boston Scientific
Stent platform	Supra G™	VflexPlus™	Multi-Link Penta™	NIR™	NIR™	Express™	Express™
Polymer carrier	No	No	No	Yes	Yes	Yes	Yes
Coating	Proprietary	Proprietary	Achieve™	Translute™	Translute™	Translute™	Translute™
Dose density (μg/mm^2)	1.3/3.1	0.2/0.7 1.4/2.7	3.0	1.0 (SR)	1.0 (SR / MR)	1.0 (SR)	1.0 (MR)
Primary endpoint	Angiographic	Angiographic	Clinical	Clinical	IVUS	Clinical	Clinical
At time	4–6 months	6 months	9 months	1 month	6 months	9 months	9 months
Parameter	% diameter stenosis	% diameter stenosis	TVF	MACE	% stent obstruction volume	TVR	TVR

For abbreviations see text.

Table 1, such as the 1.3 μg/mm^2 group in the ASPECT study[45] and the 0.2 μg/mm^2, the 0.7 μg/mm^2, and the 1.4 μg/mm^2 groups in the ELUTES study[46] as well as the PATENCY study[47] (2.0 μg/mm^2, no polymer, 50 patients, Cook-Logic PTX Stent). The Conor drug-release technology offers a potential alternative concept with its bio-resorbable polymer, delivering 100% of the drug at substantially lower total doses: the PISCES registry determined in 191 patients with single de novo lesions the optimal dose and kinetic release formulation for Paclitaxel. In some subgroups, late loss was 0.30–0.38 mm and restenosis rates were 0–3.7%.[48] More data will be obtained from the EuroSTAR trial.

The characteristics of the sirolimus and everolimus studies are listed in Table 2. Results of controlled randomized studies regarding tacrolimus[49] are not presently available. The relevant results of randomized, controlled studies with angiographic or IVUS parameters or 30-day MACE as primary endpoint are listed in Table 3: four studies with Paclitaxel (ASPECT,[45,50] ELUTES,[46] TAXUS-I,[51,52] TAXUS-II[53–55]), three studies with sirolimus (RAVEL,[9] E-SIRIUS,[56] C-SIRIUS[57]), and two studies with everolimus (FUTURE-I[58] and FUTURE-II[59]). TAXUS-I, -II, and -III have been conducted with the NIR-conformer stent, TAXUS-IV, and TAXUS-VI with the Express stent as platform.[60,61]

Table 4 describes the relevant results of the four controlled studies with a clinical primary endpoint at an adequate time interval: paclitaxel without a polymer carrier did not reach the primary endpoint in spite of a positive trend in DELIVER-I.[62,63] In DELIVER-I, angiographic follow-up was performed in the angiographic substudy with 214 control (ML Penta) and 228 DES (Achieve) patients. In contrast, when released

Table 2. Key Characteristics of Prospective, Randomized Studies with Sirolimus- and Everolimus-Eluting Stents in Patients with De Novo Lesions

	RAVEL	SIRIUS	E- SIRIUS	C- SIRIUS	FUTURE-I	FUTURE-II
Company	Cordis/J&J	Cordis/J&J	Cordis/J&J	Cordis/J&J	Guidant/ Biosensors	Guidant/ Biosensors
Drug	Sirolimus	Sirolimus	Sirolimus	Sirolimus	Everolimus	Everolimus
Stent platform	Bx-Velocity	Bx-Velocity	Bx-Velocity	Bx-Velocity	S-Stent	S-Stent
Polymer carrier	Yes	Yes	Yes	Yes	Yes	Yes
Coating	Basecoat+ Topcoat	Basecoat+ Topcoat	Basecoat+ Topcoat	Basecoat+ Topcoat	PLA (biodegradable, no topcoat)	PLA (biodegradable, no topcoat)
Dose density (μg/mm^2)	1.4	1.4	1.4	1.4	197	197
Primary endpoint	Angiograph.	Clinical	Angiograph.	Angiograph.	clinical	Angiograph.
At time	6 months	9 months	8 months	8 months	1 month	6 months
Parameter	In-stent LLL	TVF	In-stent MLD	In-stent MLD	MACE	LLL

For abbreviations see text.

Table 3. Prospective, Randomized Trials with Angiographic, IVUS, or 1-Month Clinical Endpoints in Patients with De Novo Lesions and Their Inclusion Criteria Depending on Coronary Anatomy and Key Results

	ASPECT		ELUTES		TAXUS-I		TAXUS-II		RAVEL		E-SIRIUS/C-SIRIUS		FUTURE-I		FUTURE-II	
Drug	Paclitaxel		Paclitaxel		Paclitaxel		Paclitaxel		Sirolimus		Sirolimus		Everolimus		Everolimus	
Polymer carrier	No		No		Yes		Yes		Yes		Yes		Yes		Yes	
Inclusion criteria: Ref. Diameter (mm)	2.25–3.5		3.0–3.5		3.0–3.5		3.0–3.5		2.5–3.5		2.5–3.0		2.75– 4.0		2.75–4.0	
Inclusion criteria: Lesion length (mm)	<15		<15		<12		<12		<15		15–32		≤ 18		≤ 18	
Group randomized	Control	DES	Control	DES	Control	DES (SR)	Control (SR/MR)	DES (SR/MR)	Control	DES	Control	DES	Control	DES	Control	DES
Patients	59	60	38	37	30	31	270	266 (131+135)	118	120	177/50	175/50	15	27	43	21
Ref. vessel diameter (mm)	2.88	2.94	2.99	2.95	2.94	2.99	2.8 2.7	2.8 2.7	2.64	2.60	2.51/2.62	2.60/2.65	2.96	3.10	2.97	2.91
Lesion length (mm)	10.5	10.9	10.9	11.1	11.9	10.7	10.5 10.7	10.6 10.7	9.61	9.56	15.1/12.6	14.9/14.5	8.32	9.17	11.62	11.07
RR (%) in-segment	27	4*	20.6	3.2*	10	0	20.1 23.8	5.5* 8.6*	26.6	0*	42.3/52.3	5.9*/2.3*	9.1	4.0	30.6	4.8*
LLL (mm) in-stent	1.04	0.29*	0.73	0.11*	0.71	0.36*	0.79 0.77	0.31* 0.30*	0.8	-0.01*	1.05/1.02	0.20* /0.12*	0.85	0.11*	0.85	0.12*
TLR (%)	3.4	3.4	7.9	2.7	7	0	12.0 14.6	4.6* 3.1*	22.9	0*	20.9/18.0	4.0*/4.0*	7.1	3.8	15.0	4.8
TVR (%)	k.A.	k.A.	k.A	k.A.	7	0	14.3 17.7	7.7* 6.2*	n. a.	n. a.	n. a.	n. a.	–	–	–	–
MACE (%) 6–9 months	4/10	4/33	11	11	7	0	19.5 20.0	8.5* 7.8*	–	–	22.6/18.0	8.0*/4.0*	7.1	7.7	17.5	4.8
MACE (%) 12 months	10/12	10/42	18	14	10	3	22.0 21.4	10.9* 9.9*	18.6	5.8*	–	–	–	–	–	–
Primary endpoint reached?	Yes (DS from 39% to 14%)		Yes (DS from 34% to 14%)		n/a, because MACE after 1 month in both groups = 0%		Yes in SR: from 23.2% to 7.9%; in MR from 20.5% to 7.8%		Yes (in-stent LLL)		Yes in-stent MLD (mm) E-SIRIUS: 1.33 vs 2.22* C-SIRIUS: 1.49 vs 2.46*		n/a, because MACE after 1 month in both groups = 0%		yes (LLL)	

For ASPECT and ELUTES, only the highest of the tested dosages are listed (for dosages see Table 1). In ASPECT, the first number represents the MACE for ASS + clopidogrel/ticlodipine, the second for ASS + cilostazol. In TAXUS-II, the first number reflects the result for SR (slow release), the second for MR (moderate release). TVF results are not published. For further abbreviations please see text.
*$P < 0.05$ compared with the bare stent.

from a polymer carrier, Paclitaxel significantly improved clinical outcome, like in the TAXUS-IV[64] and TAXUS-VI[65,66] trials (Table 4). Thus, not all Paclitaxel-eluting stents are equal.[67] In TAXUS-I, -II, and -IV, Paclitaxel was released from the slow-release formulation (SR, 12 μg in vivo release from a 3.0 $\times$ 24 mm stent over 30 days). In TAXUS-II and TAXUS-VI, Paclitaxel was released from the moderate release (MR, 33 μg in vivo release from a 3.0 $\times$ 24 mm stent over 30 days).[65]

Sirolimus has been clinically tested only by being eluted from a polymer carrier, like in the SIRIUS trial[68] (Table 4).

Long-term (>1 year)[69] results from randomized trials with Cypher and Taxus stents are available for RAVEL (3 years),[70] SIRIUS (2 years)[71] and TAXUS-IV (1 year):[72] in RAVEL, the 3-year freedom from TLR was even significantly improved by SES (85.6% vs 95.0%)—but the event-free survival was no longer significant with 77.1% for the bare versus 85.0% for SES with uneven distribution of noncardiac deaths.[70] There were four late (beyond 1 year) TLR in the SES group with 0 late TLR in the bare stent group (n.s.). This might be the first hint that the stellar outcomes after DES implantation may not be maintained over the long term, but one must be cautioned that this was a small study of fairly low-risk patients and that more long-term data are needed. In SIRIUS, the MACE rate after 2 years was still significantly reduced from 24.3% to 10.9% and in TAXUS-IV after 1 year significantly from 20.0% to 10.8%.

Discussion

As the results show, the fact that a drug-eluting stent shows a significant improvement in an angiographic parameter does not necessarily mean that this stent will also lead to a clinical benefit: a statistically significant reduction of late lumen loss in DELIVER-I did not translate into an improved clinical outcome. Therefore, despite encouraging angiographic results in ELUTES, FUTURE-I, and FUTURE-II the stents used in these studies have to prove their positive impact on clinical outcome in randomized trials with a clinical primary endpoint at an adequate time interval.

Nonclinical versus Clinical Endpoints. A special challenge in interventional cardiology is that in many studies angiographic endpoints were defined as the primary endpoint and clinical outcome as a secondary endpoint. However, sample size calculations—and hence the power of the study—are based on the primary endpoint. If, for example, a randomized trial is conducted to test intervention A versus intervention B and the primary endpoint is an angiographic one (e.g., in-stent late lumen loss), the power calculation is based on the

Table 4. Prospective, Randomized Controlled Studies with a Clinical Parameter (TVF or TVR) as Primary Endpoint at an Adequate Time Interval (9 Months)

	DELIVER-I		TAXUS-IV		SIRIUS		TAXUS-VI	
Drug	Paclitaxel		Paclitaxel		Sirolimus		Paclitaxel	
Polymer carrier	No		Yes		Yes		Yes	
Inclusion criteria Ref. diameter (mm)	2.5–4.0		2.5–3.75		2.5–3.5		2.5–3.75	
Inclusion criteria Lesion length (mm)	<25		10–28		15–30		18–40	
Randomized group	Control	DES	Control	DES	Control	DES	Control	DES
Patients	519	522	652	662	525	533	227	219
Ref. diameter (mm)	2.77	2.85	2.75	2.75	2.81	2.78	2.77	2.81
Lesion length (mm)	11.1	11.7	13.4	13.4	14.4	14.4	20.3	20.9
RR (%) in-segment	22.4	16.7	26.6	7.9*	36.3	8.9*	35.7	12.4*
LLL (mm) in-stent	0.98	0.81*	0.92	0.39*	1.0	0.17*	0.99	0.39*
TLR (%)	11.3	8.1	11.3	3.0*	16.6	4.1*	18.9	6.8*
TVR (%)	–	–	12.0	4.7*	19.2	6.4*	19.4	9.1*
TVF (%)	14.5	11.9	14.4	7.6*	21.0	8.6*	22.0	16.0
Death (%)	1.0	1.0	1.1	1.4	0.6	0.9	0.9	0.0
Infarction (%)	1.0	1.2	3.7	3.5	3.2	2.8	1.3	1.4
MACE 9 mo (%)	13.3	10.3	15.0	8.5*	18.9	7.1*	22.5	16.4
Primary endpoint reached?	No (TVF)		Yes (TVR)		Yes (TVF)		Yes (TVR)	

For further abbreviations, please see text.
*$P < 0.05$ compared with the bare stent.

Table 5. Recommendations for the Use of Drug-Eluting Stents According to the ESC Guidelines (Ref. 75)

Drug-Eluting Stent	Indication	Level of Recommendation	Studies for Levels A or B
Cypher stent	De novo lesions in native vessels according to the inclusion criteria	I B	SIRIUS
Taxus stent	De novo lesions in native vessels according to the inclusion criteria	I B	TAXUS-IV
Taxus stent	De novo long lesions in native vessels according to the inclusion criteria	I B	TAXUS-VI

There are only three positive controlled, randomized, adequately powered trials with a primary clinical endpoint at an appropriate time interval.

expected reduction in late lumen loss. If the result of this study is positive (i.e., statistically significant reduction in late lumen loss), the secondary endpoint of patient outcome (e.g., target vessel revascularization) may also be significantly improved. Although the evidence of this improvement of clinical outcome might be "statistically significant" ($P < 0.05$), it is still underpowered. Therefore, many studies make "underpowered conclusions." Medical history is full of "underpowered conclusions" of smaller sample sizes, which were misleading and had to be corrected later by larger, adequately powered trials.

In general, a power calculation for a primary *clinical* endpoint requires considerably more patients than for a surrogate endpoint, like a primary *angiographic* endpoint. The primary goal of interventional procedures and medical treatments is to improve patient outcome and not solely to improve angiographic or other surrogate parameters. Another weakness of angiographic parameters as primary endpoint is their time dependence with a trend for increased MLD over the years—at least for bare stents.[73,74]

For these reasons, the PCI guidelines of the European Society of Cardiology (ESC)[75] graded as level A (or B) only that evidence for which at least two (or one) randomized studies (study) showed a significant improvement of patients' outcome as a primary endpoint at an adequately powered sample size. The time interval between "index procedure" and the clinical primary endpoint should have been adequately chosen to meet the specific requirements of the hypothesis: for example, if a study testing a new drug-eluting stent had a primary clinical endpoint of 4 weeks, then this time interval would be too short to observe a reduction of an even clinically driven repeat revascularization. An interval of 6–9 months would be more appropriate for this objective. Overall, the hurdle to level A should be more difficult to reach—last but not least to encourage investigators to conduct more PCI studies with clinical primary end points.

Main inclusion criteria for SIRIUS, TAXUS-IV, and TAXUS-VI were similar: stable or unstable angina or documented ischemia. The stenoses had to be in native vessels >50% and <100%. In SIRIUS, reference diameter and lesion length for inclusion were 2.5–3.5 mm and 15–30 mm, respectively. The reference diameter in TAXUS-IV and TAXUS-VI was 2.5–3.75 mm. In TAXUS-IV, the lesion length was 10–28 mm and in TAXUS-VI 18–40 mm. The main common exclusion criteria were acute MI or s/p MI with elevated CK/CK-MB, bifurcational, or ostial lesions, unprotected left main, visible thrombus, severe tortuosity, and/or calcification.

Indications for Drug-Eluting Stents. Fears of medicolegal repercussions for either using or failing to use DES are unfounded and unlikely to materialize.[76] DES should never be implanted solely to avoid potential litigation.[76]

There are two alternative approaches for making recommendations for the use of drug-eluting stents: one is based on cost-effectiveness calculations, the other is purely recommending the use according to the inclusion/exclusion criteria of the pivotal randomized trials. Today, drug-eluting stents may already be cost effective.[77–82] Based on a thorough cost-effectiveness analysis, the UK NHS NICE Institute recommended the use of drug-eluting stents as follows:[83] "The use of either a Cypher (Sirolimus-eluting) or Taxus (Paclitaxel-eluting) stent is recommended in PCI for patients with symptomatic coronary artery disease (CAD), in whom the target artery is less than 3 mm in calibre (internal diameter) or the lesion is longer than 15 mm. This guidance for the use of DES does not apply to people who have had an MI in the preceding 24 hours, or for whom there is angiographic evidence of thrombus in the target artery." [83]

According to the initially given definitions, the level of recommendation I B may only be valid for the Cypher and Taxus stents—and only for the inclusion

and exclusion criteria applied in these studies (see Table 4 and Table 5). All of the following applications, especially in situations with increased risk of restenosis, must wait for further evidence-based recommendations and are thus presently only at evidence level C:

- long lesions
- small vessels
- chronic total occlusions
- bifurcational/ostial lesions
- bypass stenoses
- insulin-dependent diabetes mellitus
- multivessel disease
- unprotected left main stenoses
- in-stent restenoses

Preliminary experience in patients with very long lesions (>36-mm long stented segments) revealed a binary restenosis rate of 11.9% and an in-stent late loss of 0.13 ± 0.47 mm.[84] The results for bifurcation stenoses are still problematic and seem to depend on the implantation technique: although the results with the Cypher stent in coronary bifurcation lesions are an improvement compared with historical controls using bare metal stents, restenoses at side branches remain a problem.[85] At this time, no statement can be made regarding the most appropriate technique to use while treating bifurcations with the Cypher stent.[85] Perhaps combining drug-eluting stents with the support of a cutting balloon may be helpful in optimizing the treatment of bifurcations.[86]

For chronic total occlusions (CTO), the preliminary results from the PACTO study, having matched 34 patients receiving the TAXUS stent after successful reopening with 68 controls, are encouraging with a significant reduction of reocclusion from 21% to 3%.[87] The same was reported for the Cypher stent in the SICTO registry of 25 patients with CTO of a mean vessel size of 2.6 mm with a 6 month in-stent late loss of –0.1 mm, a TLR of 0% and a TVR of 8%.[88] In the RESEARCH registry, 56 patients with CTO and Cypher stenting were compared with a similar group of patients (n = 28) treated in the preceding 6-month period with bare metal stents (BMS): at 1 year, the cumulative survival-free MACE was 96.4% in the SES group versus 82.8% in the BMS group ($P < 0.05$).[89]

Treatment of multivessel disease resulted in a 6-month MACE of 22.3%; a lesion-related TVR was required in 16.1%.[90] SES postdilatation with largely oversized balloons (generally not recommended) appeared a safe and effective strategy for selected patients, including stenting of saphenous vein grafts.[91] Although randomized trials have yet to be performed, direct stenting appears to be safe and effective with the Cypher[92,93] and the Taxus[94] stents.

A convincing reduction of costs in medical care will be additionally achieved if drug-eluting stents considerably reduce the number of CABG-surgeries, especially in patients with diabetes and multivessel disease.[95–99] Although the first results for unprotected left main stenoses are encouraging,[100] it cannot be generally recommended at the present time.

Although the dream of "no restenosis"[101] is beyond realisation,[102,103] drug-eluting stents provide a fair single-digit number for angiographic and clinical restenosis at 9 months with a TVR of 4.7% for Paclitaxel in TAXUS-IV and of 6.4% for sirolimus in SIRIUS (VI-5). In "real life" (RESEARCH-registry)[104] the 1-year risk of clinically driven TVR in the sirolimus-eluting stent (SES) group was even lower with 3.7%. MACE after 9 months in the DES groups was 7.1% in SIRIUS, 8.5% in TAXUS-IV, and 9.7% after 1 year in the RESEARCH registry. In a Swiss registy, MACE-free survival at 6–9 months was 95.6%.[105]

The objective of the ARTS-II registry was to compare the effectiveness of coronary Cypher stent implantation with that of surgery as observed in ARTS-I, measured as MACE-free survival at 1 year. A total of 606 patients with stable, unstable, or silent ischemia and at least 2 lesions in different vessels and different territories were stratified to reach a population with at least 2.7 lesions/patient. Mean total stent length per patient was 73 mm (12–253 mm). The 1-month results have been presented with a total MACE of 2.8% compared with 4.1% in the historical surgery control group.[106]

The two trials randomizing bypass surgery versus stenting with Cypher (FREEDOM trial in diabetics) or Taxus (SYNTAX in patients with left main stenoses and/or multivessel disease) will help in making the choice between drug-eluting stents and coronary bypass surgery.

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