Cypher Versus Taxus: Are There Differences?

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Today, drug-eluting stents (DES) are the standard stenting procedure in the USA and in Switzerland. The objective of this analysis is to answer the two questions: what clinically relevant data regarding DES have been published, and is there a clinically relevant difference between the Cypher and the Taxus stents? Twenty-two randomized, controlled studies with a total of 11,118 patients were identified: 18 randomized studies compared a DES to a bare metal stent of identical design in 8,301 patients, and 4 randomized studies compared the Cypher and the Taxus stents in 2,817 patients. Three studies regarding Paclitaxel-releasing stents without polymer (1,235 pats) and five studies regarding Paclitaxel released from a polymer (3,513 pats) were analyzed. Sirolimus released from a polymer was investigated in five studies (2,070 pats). Everolimus released from a polymer was investigated in three studies (166 pats), Biolimus A9 released from a polymer in one (120 pats), and Zotarolimus (ABT-578) released from a polymer in also one (1,197 pats) trial. Thirteen studies chose either a surrogate primary endpoint (angiographic or IVUS) or a clinical endpoint insufficient for a power calculation. A primary clinical endpoint with an adequate sample size for a power calculation was chosen in three trials for the Taxus stent (TAXUS-IV, TAXUS-V, TAXUS-VI; 2,916 patients), in one trial for the Cypher stent (SIRIUS; 1,058 patients), and in one trial for the Endeavor stent (ENDEAVOR-II; 1,197 patients). In all these trials, the primary clinical endpoint was reached. Of the four studies comparing Cypher stents to Taxus stents, one did not define the primary endpoint (TAXi), two assumed superiority of the Cypher stent (REALITY with a surrogate endpoint and SIRTAX, a single-center study), and one was designed as a non-inferiority trial (ISAR-Diabetes, single-center study with a surrogate endpoint). Based on the European Society of Cardiology established strict criteria with a clinical primary endpoint as a prerequisite to recommend a DES, only three DES have thus far had proven positive effects on clinical outcome: the Cypher-stents, Taxus-stents, and Endeavor-stents. A trial proving the superiority of one DES over another would require a multicenter study with a clinical primary endpoint at an adequate power. As long as such a trial does not exist, Cypher and Taxus are regarded as being equivalent. (J Interven Cardiol 2005;18:441–446)

Introduction

Today, drug-eluting stents (DES) are the standard stenting procedure in the USA and in Switzerland. In the USA and in Europe, the Sirolimus-eluting Cypher stents and the Paclitaxel-eluting Taxus stents are commercially available. In addition, Europe has the Tacrolimus-eluting Janus stent, and will soon have several other stents commercially available based on their CE-certification. Physicians and their administration will thus have the choice between several DES.

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The objective of this article is to answer the following questions:

1. What clinically relevant data regarding DES have been published?
2. Is there a clinically relevant difference between the Cypher and the Taxus stents?

Methods

Studies included in this analysis need to meet the following requirements.

Study design: randomized, controlled study, comparing the DES to a bare metal stent (BMS) of identical design or comparing two different DES in patients with

de novo coronary lesions. The studies had to have been published in a peer-reviewed journal or at least presented at one of the major scientific meetings in the USA (AHA, ACC, TCT) or in Europe (Euro-PCR). Studies were analyzed according to their primary endpoint (clinical or surrogate), their power calculation, and whether they reached the primary endpoint. Subgroup analyses of randomized trials and registries were not considered.

Results

A total of 22 randomized, controlled studies with a total of 11,118 patients were identified: 18 randomized studies compared a DES to a BMS of identical design in 8,301 patients, and 4 randomized studies compared the Cypher and the Taxus stents in 2,817 patients.

Three studies regarding Paclitaxel-releasing stents without polymer (ASPECT,[1] ELUTES,[2] and DELIVER-I[3]) and five studies regarding Paclitaxel released from a polymer (TAXUS-I,[4] TAXUS-II,[5] TAXUS-IV,[6] TAXUS-V,[7] and TAXUS-VI[8]) were analyzed. Sirolimus released from a polymer was investigated in five studies (RAVEL,[9] SIRIUS,[10] E-SIRIUS,[11] C-SIRIUS,[12] and SCANDSTENT[13]). Everolimus released from a polymer was investigated in three studies (FUTURE-I,[14] FUTURE-II,[15] and SPIRIT FIRST[16]), Biolimus A9 released from a polymer in one (STEALTH-I[17]), and Zotarolimus (ABT-578) released from a polymer in one trial (ENDEAVOR-II[18]) (Tables 1 and 2).

Thirteen studies chose either a surrogate primary endpoint (angiographic or IVUS) or a clinical endpoint insufficient for a power calculation (e.g., MACE after 4 weeks) (Table 2). A primary clinical endpoint with an adequate sample size for a power calculation was chosen in three trials for the Taxus stent (TAXUS-IV, TAXUS-V, and TAXUS-VI; 2,916 patients), one trial for the Cypher stent (SIRIUS; 1,058 patients), and one trial for the Endeavor stent (ENDEAVOR-II; 1,197 patients). In all these trials (Table 3), the primary clinical endpoint was reached (TVR in TAXUS-IV, TAXUS-V, and TAXUS-VI; TVF in SIRIUS and in ENDEAVOR-II; Table 4).

Of the four studies comparing Cypher stents to Taxus stents, one did not define the primary endpoint (TAXi[19]), two assumed superiority of the Cypher stent (REALITY[20] and SIRTAX[21]), and one was designed as a non-inferiority trial (ISAR-Diabetes[22]) (Table 5). The multicenter REALITY trial did not reach the primary endpoint, whereas the single-center SIRTAX trial did (Table 5). No randomized, controlled multicenter trial with a primary clinical endpoint and adequate power calculation exists, showing that one DES is superior to another.

Table 1. Drugs and Number of Patients Enrolled in Randomized, Controlled Studies Comparing a DES to a BMS of Identical Design in Patients with De Novo Coronary Lesions

Paclitaxel:	8 Studies,	4748 Patients
Without polymer:	3 Studies,	1235 Patients
With polymer:	5 Studies,	3513 Patients
Sirolimus:	5 Studies,	2070 Patients
Everolimus:	3 Studies,	166 Patients
Biolimus A9:	1 Studies,	120 Patients
Zotarolimus(ABT 578):	1 study,	1197 Patients

Discussion

The Importance of the Clinical Primary Endpoint. The European Society of Cardiology has established strict criteria, with a clinical primary endpoint as a prerequisite, to recommend a DES based on its effectiveness in improving patients' outcome.[23]

However, many DES studies chose a surrogate primary endpoint, like angiographic (DS, RR, MLD, LLL) or IVUS (e.g., percent volume obstruction) parameters as primary endpoints (Table 2). A surrogate endpoint, e.g., late lumen loss, is not, however, sufficient to document an improvement in clinical outcome: in DELIVER-I, although late lumen loss was statistically significantly reduced, there was no significant benefit for the clinical outcome.

If a clinical parameter (e.g., TLR, TVR, TVF, MACE; Table 2) is chosen as a secondary endpoint and significantly reduced, a $P < 0.05$ does not necessarily mean that the statistical proof is sufficient: in clinical trials, the needed sample size is calculated based on the "type 1 error" (alpha error) and the "type 2 error" (beta error). Usually, the alpha error is set to 5% ($P < 5\%$, i.e., $P < 0.05$) and the beta error to $<20\%$ (i.e., power $\geq 80\%$). A $P < 0.05$ means that the likelihood of a coincidental result is less than 5%. In contrast, the power describes the likelihood that if somebody else would repeat the trial, the chance of

Table 2. Randomized, Controlled Studies Comparing a DES to a BMS of Identical Design in Patients with De Novo Coronary Lesions, According to the Drug, Type of Coating, the Parameter Chosen for Primary Endpoint, and the Result of the Primary Endpoint

Study	Drug/Coating	Primary Endpoint Parameter	Primary Endpoint Reached
ASPECT	Paclitaxel—no polymer	Surrogate endpoint: diameter stenosis	Yes
ELUTES	Paclitaxel—no polymer	Surrogate endpoint: diameter stenosis	Yes
DELIVER-I	Paclitaxel—no polymer	Clinical endpoint: TVF	No
TAXUS-I	Paclitaxel—with polymer	Clinical endpoint: MACE	n/a
TAXUS-II	Paclitaxel—with polymer	Surrogate endpoint: IVUS	Yes
TAXUS-IV	Paclitaxel—with polymer	Clinical endpoint: TVR	Yes
TAXUS-V	Paclitaxel—with polymer	Clinical endpoint: TVR	Yes
TAXUS-VI	Paclitaxel—with polymer	Clinical endpoint: TVR	Yes
RAVEL	Sirolimus—with polymer	Surrogate endpoint: in-stent LLL	Yes
SIRIUS	Sirolimus—with polymer	Clinical endpoint: TVF	Yes
E-SIRIUS	Sirolimus—with polymer	Surrogate endpoint: in-stent MLD	Yes
C-SIRIUS	Sirolimus—with polymer	Surrogate endpoint: in-stent MLD	Yes
SCANDSTENT	Sirolimus—with polymer	Surrogate endpoint: in-stent MLD	Yes
FUTURE-I	Everolimus—with polymer	Clinical endpoint: MACE	n/a
FUTURE-I	Everolimus—with polymer	Surrogate endpoint: in-stent LLL	Yes
SPIRIT	Everolimus—with polymer	Surrogate endpoint: in-stent LLL	Yes
STEALTH-I	Biolimus A9—with polymer	Surrogate endpoint: in-stent LLL	Yes
ENDEAVOR-II	Zotarolimus (ABT-578)—with polymer	Clinical endpoint: TVF	Yes

LLL = late lumen loss; MLD = minimal lumen diameter; TVR = target vessel revascularization; TVF = target vessel failure; MACE = major cardiac events.

attaining the same result is >80%. Therefore, a P-value alone should not be taken as proof without knowing the power.

Since the needed sample size and therefore the power are calculated only for the primary endpoint, the results of the secondary endpoints are usually "underpowered." Often, angiographic endpoints are chosen as the primary endpoint, because restenosis rates or late lumen loss require less patient numbers. Therefore, studies with surrogate endpoints are smaller studies than studies with a clinical primary endpoint. The decision for the primary endpoint is often driven by financial considerations (surrogate endpoints for lower budgets). A clinical secondary endpoint should be only used to generate a hypothesis, which must be tested in a follow-up study with the former secondary endpoint as a primary endpoint. In analogy, the results of subgroup analyses of randomized trials are usually totally

Table 3. Randomized, Controlled Studies with a Primary Clinical Endpoint and an Adequate Power Comparing a DES to a BMS of Identical Design

	TAXUS-IV	TAXUS-V	TAXUS-VI	SIRIUS	ENDEAVOR-II
Drug	Paclitaxel	Paclitaxel	Paclitaxel	Sirolimus(Rapaymycin)	Zotarolimus(ABT 578)
Company	Boston Scientific	Boston Scientific	Boston Scientific	Cordis/ J&J	Medtronic
Stent Platform	Express™	Express™	Express™	Bx-Velocity	Driver (Cobalt-Chrome)
Polymer Carrier	Yes	Yes	Yes	Yes	Yes
Coating	Translute™	Translute™	Translute™	Basecoat+Topcoat	PC
Dose Density(μg/mm^2)	1.0(SR)	1.0(SR)	1.0(MR)	1.4	10 μg/mm
Patients	652/662	579/577	227/219	525/533	599/598
Primary endpoint	TVR	TVR	TVR	TVF	TVF
Time of primary endpoint	9 months	9 months	9 months	9 months	9 months
Restenosis in Segment	26.6/7. 9*	33.9/18.9*	35.7/ 12.4*	36.3/8.9*	34.2/13.3*
Late Lumen Loss in Stent	0.92/0.39*	0.90/0.49*	0.99/0.39*	1.0/0.17*	1.03 /0.62*

Details of the stent design and the angiographic results are presented.
SR = slow release; MR = moderate release; TVR = target vessel revascularization; TVF = target vessel failure.

Table 4. Clinical Results of the Randomized, Controlled Studies with a Primary Clinical Endpoint and an Adequate Power Comparing a DES to a BMS of Identical Design

	TAXUS-IV (Paclitaxel, Polymer)		TAXUS-V (Paclitaxel, Polymer)		TAXUS-VI (Paclitaxel, Polymer)		SIRIUS (Sirolimus, Polymer)		ENDEAVOR-II (Zotarolimus, Polymer)	
Lesions	"Standard"		Long		Very long		"Standard"		"Standard"	
Lesion length	10–28 (13.4/13.4)		16–46 (17.2/17.3)		18–40(20.3/20.9)		15–30(14.4/14.4)		14–27(14.4/14.1)	
Vessel diameter	2.5–3.75(2.8/2.8)		2.25–4.0(2.7/2.7)		2.5–3.5(2.8/2.8)		2.5–3.5(2.8/2.8)		2.25–3.5(2.8/2.7)	
Group	Control	DES	Control	DES	Control	DES	Control	DES	Control	DES
TLR(%)	11.3	3.0*	15.7	8.6*	18.9	6.8*	16.6	4.1*	12.1	4.6*
TVR(%)	12.0	4.7*	17.3	12.1*	19.4	9.1*	19.2	6.4*	12.8	5.7*
TVF(%)	14.4	7.6*	20.3	14.6*	22.0	16.0	21.0	8.6	15.4	8.1*
Death(%)	1.1	1.4	0.9	0.5	0.9	0.0	0.6	0.9	0.5	1.2
MI(%)	3.7	3.5	4.6	5.3	1.3	1.4	3.2	2.8	0.9	0.3
MACE (%) (9 months)	15.0	8.5*	21.2	15.0*	22.5	16.4	18.9	7.1*	14.7	7.4*
Primary Endpoint reached?	Yes(TVR)		Yes(TVR)		Yes(TVR)		Yes(TVF)		Yes(TVF)	

TLR, target lesion revascularization; TVR = target vessel revascularization; TVF = target vessel failure; MI = myocardial infarction; MACE = major cardiac events.

underpowered, and therefore a matter of chance—at least unless they all go in the same direction. Comparing two randomized trials based on their subgroup analyses might be leading to wrong conclusions. The history of medicine is replete with errors made by misleading underpowered "significant" findings (Magnesium in AMI, reduction of PVCs, hormone replacement therapy, etc.).

For a convincing randomized, controlled trial, the following questions need to be answered:

1. Was it a multicenter trial?
2. Which primary endpoint: clinical or surrogate (coronary) parameter?
3. Was a power-calculation performed? (Was the assumed power obtained?)
4. Was the required number of patients enrolled and followed?
5. In case of a premature study termination: due to safety? or other reasons?
6. Was the primary endpoint reached, yes or no?

Table 5. Randomized, Controlled Studies Comparing Cypher Stents to Taxus Stents

	TAXi	REALITY	SIRTAX	ISAR-Diabetes
Study design	not defined	Cypher superior	Cypher superior	non-inferior
Multicenter	no	yes	no	no
Clininical primary endpoint	n/a	no	yes	no
Primary endpoint	n/a	angiographic	clinical	angiographic
Time of PE	(6 months)	8 months	9 months	6 months
Parameter	n/a	in lesion RR	MACE	in-segment LLL
Patients	102/100	684/669	503/509	125/125
Lesion length	not mentioned	>15;>10(17.0/17.3)	"all"(12.4/13.4)	13.8/12.4
Vessel diameter	(3.2/3.2)	2.25–3.0(2.4/2.4)	2.25–4.0(2.8/2.8)	2.7/2.8
Restenosis in Segment	n/a	9.6/11.1	6.7/11.9*	6.9/16.5*
Late lumen Loss in Stent	n/a	0.09/0.31*	0.13/0.25*	0.43/0.67*
TVR	2.0/1.0	1.6/1.2	6.0/9.2*	6.4/12.2(TLR)
MACE	6.0/4.0	9.2/10.8	6.2/10.8*	
Primary Endpoint reached	n/a	no	yes	(no) in Seg LL(0.19/0.46*)
Major limitation	no primary endpoint	no clinical primary endpoint	no multicenter trial	no clinical primary endpoint

The only study reaching the primary endpoint was SIRTAX, but it was not a multicenter study. There is no randomized, controlled multicenter trial with a primary clinical endpoint and adequate power showing that one DES is superior to another.
TVR = target vessel revascularization; MACE = major cardiac events.

According to these criteria, only three DES have thus far had proven positive effects on clinical outcome: the Cypher-stents, Taxus-stents, and Endeavor-stents (Table 4).

Proving the Superiority of One DES Over Another. For a randomized trial comparing two different DES, the situation is even more complex: the comparison can be based on a superiority assumption (e.g., REALITY, SIRTAX; Table 5) or on a non-inferiority design (ISAR-Diabetes; Table 5). In contrast to superiority trials with a pre-specified treatment effect, equivalency trials define an "acceptable difference" to the reference treatment effect ("delta"). This "delta" can be freely chosen. To save money, studies can be conducted with a less number of patients, showing "statistically significant equivalency" of a new DES as compared to a standard DES. After several "non-inferiority trials," there is a substantial risk of an "outcome drift," i.e., an extremely weak DES would be considered "non-inferior" to Cypher or Taxus.

A trial proving the superiority of one DES over another would require a multicenter study with a clinical primary endpoint at an adequate power. Decisions about reinterventions should be made by an independent board—blinded to the type of implanted DES. As long as such a trial does not exist, Cypher and Taxus are regarded as being equivalent.

Are Registries Helpful in Comparing Different DES?. In contrast to randomized trials, which enroll a selected group of patients according to their inclusion/exclusion criteria for the proof of concept, registries better reflect the "real world." However, in contrast to randomized trials, registries have no "primary endpoint" (no treatment effect, no power calculation). Therefore, their goal should rather be called "primary objective"—not to be confused with randomized trials. Since registries have no power calculation, they cannot be used to demonstrate the superiority of one DES over another. One has to be cautious not to compare "apples and oranges," like different definitions in different studies and registries. As in subgroup analyses, registries can serve to generate a hypothesis, which must be confirmed by a randomized trial with adequate power.

Nevertheless, registries can be of high quality: the ideal registry enrolls a large number of patients, preferably "all comers." Therefore, registries are better suited to assess safety rather than efficacy. A good registry provides high quality monitoring (over 10% of data entries); and the follow-up rate should not be lower than that of randomized trials. For the assessment of late DES thrombosis, the follow-up rate ideally needs to be 100%.

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