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Innovative therapies for optimizing outcomes of coronary artery disease

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Chapter 4

Clinical performance of drug eluting stents with Biodegradable polymeric coating, a meta-analysis and systematic review

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ABSTRACT

Aim Different biodegradable-polymer drug eluting stents have not yet been systematically analysed. We sought to; 1) evaluate the risk of target lesion revascularisation (TLR) and definite stent thrombosis (DST) among different groups of biodegradable-polymer (BioPol) DES, and 2) to compare them with permanent polymer (PermPol) DES.

Methods and results We searched PubMed and relevant sources from January 2005 until October 2010. Inclusion criteria were (a) Implantation of a drug eluting stent with biodegradable polymer; (b) available follow-up data for at least one of the clinical endpoints (TLR/DST) at short term (30 days) and/or mid-term (one year). A total of 22 studies, including randomised and observational studies, with 8264 patients met the selection criteria; 9 studies (2042 patients) in whom biodegradable-polymer sirolimus eluting stents (BioPol-SES) were implanted, 8 studies (1731 patients) in whom biodegradable-polymer paclitaxel eluting stents (BioPol-PES) were implanted, and 7 studies (4491 patients) in whom biodegradable-polymer biolimus-A9 eluting stents (BioPol-BES) were implanted. At 30 days, there was a higher risk of DST ($p=0.04$) and subsequently TLR ($p=0.006$) in the BioPol-BES compared to BioPol-SES, with no significant difference in the other stent comparisons. At 1 year, there was higher risk of TLR in the BioPol-PES ($p=0.01$), and the BioPol-SES ($p=0.04$) compared to BioPol-BES. One-year stent thrombosis was not statistically different between the studied groups (overall $p=0.2$). In another analysis comprising 7 randomised trials comparing BioPol-DES (3778 patients) and PermPol-DES (3291 patients), the risks of TLR and stent thrombosis at 1 year were not significantly different ($p=0.5$ for both).

Conclusion Performance of different BioPol-DES seems to vary from each other. The short and mid-term success rates may not be superimposable. Furthermore, they may not be necessarily better than PermPol-DES.

Keywords Meta-analysis, biodegradable-polymer drug eluting stents, permanent-polymer drug eluting stents, target lesion revascularization, definite stent thrombosis.

INTRODUCTION

Drug eluting stents (DES) represent a major breakthrough in the field of percutaneous coronary interventions (PCI), since they have dramatically reduced the need for repeated revascularization procedures^{1,2}.

Along with the increasing number of patients receiving DES and the availability of long-term follow-up data, concern has arisen regarding the safety of these devices with the potential for increased inflammatory response and stent thrombosis which could have life-threatening consequences³⁻⁵.

Polymers used for the delivery of antirestenotic agents have been accused for the development of late stent thrombosis. This is thought to be secondary to polymer-induced inflammatory reaction, with delayed healing and re-endothelialization of the DES⁶. Given these issues more focus has been placed upon developing bio-degradable polymers, which degrade over time, and therefore possibly eliminate the problems of polymer-induced inflammation.

In some cases, findings from pre-clinical studies can be misinterpreted, especially in cases where the drug may be toxic. The polymer may be blamed for the inflammation or excessive fibrin deposition and lack of endothelialization. Yet the difference in pharmacokinetics and anti-restenotic efficacy of the different drugs could also be held responsible for variation in clinical outcomes. Thus, a "polymer only" control is essential in distinguishing the culpability between polymer versus drug⁷. However, this is a control difficult to implement in clinical studies.

Various studies were conducted to test the clinical performance of a variety of biodegradable polymer-based stents eluting sirolimus (BioPol-SES), biolimus A9 (BioPol-BES) or paclitaxel (BioPol-PES).

The aims of the present meta-analysis were: 1) to compare the short term (1 month) and mid-term (1 year) performance of sirolimus, biolimus A9 and paclitaxel biodegradable-polymer DES and 2) to compare, where information was available, the 1-year performance of biodegradable-polymer DES (BioPol-DES) with permanent-polymer DES (PermPol-DES).

METHODS

Eligibility and search strategies

To be included in this meta-analysis, studies had to meet the following criteria: (a) Implantation of a drug eluting stent with biodegradable polymer; (b) available follow-up data for at least one of the clinical end-points at short term (30 days) and/or mid-term (up to one year). Studies dedicated to specific lesion subsets including; left main stenting, bifurcation lesions, chronic total occlusions, long lesions, in-stent restenosis and venous grafts were excluded.

We searched PubMed, Web of Science, and Embase (OVID) from January 2005 and onwards for studies on biodegradable DES. The PubMed search strategy was formulated as the AND-combination of 1) DES terms and 2) terms denoting biodegradable or permanent polymer as follows: 1) "Drug-Eluting Stents"[Mesh] OR DES[tiab] OR "drug eluting stent"[tiab] OR "drug eluting stents"[tiab] OR "drug eluted stent"[tiab] OR "drug eluted stents"[tiab] OR "drug coated stent"[tiab] OR "drug coated stents"[tiab]; 2) "biodegradable polymer"[tiab] OR "permanent polymer"[tiab] OR "nonbiodegradable polymer"[tiab] OR biodegradable[tiab] OR bioabsorbable[tiab] OR "durable polymer" OR ("Polymers"[Mesh] AND (biodegradable[tiab] OR bioabsorbable[tiab] OR permanent[tiab] OR nonbiodegradable[tiab])). This search strategy was translated to the corresponding vocabulary of Embase and Web of Science. Relevant websites (<http://www.tctmd.com>, www.europcr.com) were searched for pertinent abstracts and expert slide presentations. The search was kept updated until October 2010. No language restriction was applied.

Data abstraction

Two investigators (T.A.N.A. and S.C.B.) independently extracted all data, and disagreements were solved in consultation with a third investigator (J.W.M.P.). A number of 144 papers were identified from PubMed, 52 papers from Web of Science and 125 papers from EMBASE, and 4 additional clinical trials from relevant websites (total of 325 citations) (Figure 1). After reading the titles and abstracts, a total of 25 potentially relevant studies were initially identified from which 22 were eligible for inclusion.

Definitions and end-points

The clinical end-points of the study were the rates of target lesion revascularization (TLR) and definite stent thrombosis (DST) at 30 days and one year follow-up. Even in the few studies with follow-up more than one year only the data at one year were used.

TLR was defined as percutaneous or surgical revascularization of the target lesion. Definite stent thrombosis was defined, whenever available, according to the definition of the Academic Research Consortium⁸.

Statistical analysis

For the comparison of the 3 biodegradable-polymer stent types (BioPol-SES, BioPol-PES and BioPol-BES), 20 studies provided one patient series and 2 studies provided two patient series. Since there were only two studies with two series, we analyzed the 24 patient series as independent studies. For each patient series we extracted from the publications the number of events (TLR or DST within 30 days or one year) and the corresponding number of patients. For each stent type, type of event and follow-up period the exact 95% confidence interval for a binomial proportion was calculated and depicted in a forest plot. If the observed proportion was zero, the one-sided 97.5% confidence interval was given. To compare

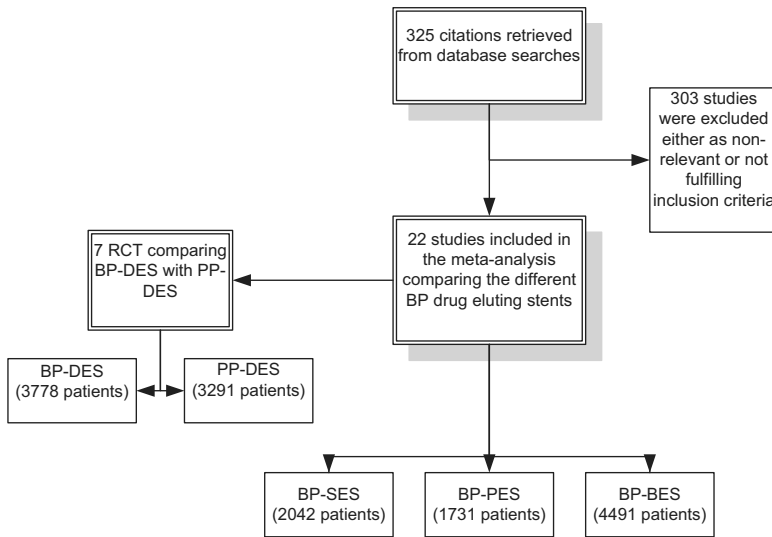


Figure 1: Flow diagram of the review process: Process of identification and selection of the studies for inclusion in the meta-analysis. BP; biodegradable polymer, PP; permanent polymer, SES; sirolimus eluting stents, PES; paclitaxel eluting stents; BES; biolimus eluting stents, DES; drug eluting stents.

the incidences of the different types of events between the different stent types, we used random effects meta-analysis. More specifically, we used random intercept logistic regression with two dummy variables representing the three stent types, as described in Stijnen et al⁹. This analysis assumes that the between studies variance was equal for the different stent types. In the analysis, the random effects take into account the possibility that there may be many differences between the patient populations of the different studies, influencing the risks of the considered endpoints. To adjust for multiple comparisons, we first tested at $\alpha=0.05$ the overall null hypothesis that all three stent types had equal incidence. If this test was significant, the three pair-wise tests were done at $\alpha=0.05$. For the incidence of TLR within 30 days, the estimate of the between studies variance was zero. In that case the analysis reduces to ordinary logistic regression and we used exact tests and confidence intervals for the odds ratios.

Seven studies comprised trials comparing BioPol-DES with PermPol-DES. To make forest plots, we calculated exact 95% confidence intervals for the odds ratio except for studies in which less than 2 events in total were observed. We used random effects meta-analysis to estimate and test the overall odds ratio across studies. Due to the scarcity of data at 30 days among the included studies, we decided to assess the events at 1 year only. Because of the small numbers of events in some of the studies, the hypergeometric-normal model as described in Stijnen et al was used⁹.

All statistical analyses were performed using SAS statistical package version 9.1.3. The procedure NLMIXED was used for the random-effect meta-analysis.

Study Quality assessment

This meta-analysis was especially designed to extract data from various types of available studies: observational studies presenting data about BioPol-DES; randomized clinical trials (RCTs) in which different BioPol-DES are compared among each other, and RCTs in which BioPol-DES is compared with PermPol-DES. Only for the latter category, it was of interest to perform an RCT study quality assessment. We have used the *Delphi list* for the quality assessment of RCTs as described by Verhagen et al¹⁰. In short, the Delphi list allocates 'yes', 'no', or 'do not know' to a total number of nine questions. Quality of RCTs is defined as the likelihood of the trial design to generate unbiased results. When five or more questions are answered 'yes', the RCT is considered to have a low risk of bias. In a respective manner, RCTs may have unclear or high risk to cause bias.

RESULTS

Trials and study characteristics

A total of 22 studies¹¹⁻³³ with a total of 8264 patients were included in this meta-analysis (table 1); 9 trials^{11, 13, 14, 17, 21, 23-25, 30, 32} (2042 patients) with biodegradable polymer sirolimus eluting stents (BioPol-SES), 8 trials^{12, 20, 22, 23, 27, 28, 31, 32} (1731 patients) with biodegradable polymer paclitaxel eluting stents (BioPol-PES) of which two were randomized trials against BioPol-SES^{23, 32}, and 7 trials^{15, 16, 18, 19, 26, 29, 33} (4491 patients) with biodegradable polymer biolimus A9 eluting stents (BioPol-BES). Many of the retrieved trials were observational non-randomized trials. The mean age of the participants in individual trials ranged from 53 to 67 years, with males representing the majority. The percentage of diabetics was 28% among the BioPol-SES, 26% among the BioPol-PES and 28% among the BioPol-BES. The recommended duration of thienopyridine therapy after stent implantation was variable between the studies; 3 months in 2 studies^{19, 30}, 6 months in 12 studies^{12-16, 21, 22, 25-28, 31, 32}, 12 months in 5 studies^{11, 20, 23, 24, 33}, indefinitely in one study¹⁷ and unidentified in 2 studies^{18, 29}. The follow-up (FU) duration ranged from 6 months to 30 months, with only two studies with FU of 6 months^{11, 24}.

Among the included studies there were 10 randomized clinical trials (RCT)^{13-16, 19, 22, 23, 25, 29, 32, 33}, two studies were randomizing BioPol-SES versus BioPol-PES^{23, 32}, two studies; one randomizing BioPol-SES versus permanent polymer sirolimus eluting stent (PermPol-SES)^{13, 25}, and another randomizing BP-SES versus permanent polymer sirolimus (PermPol-SES) plus everolimus eluting stents (PermPol-EES)¹⁴, one study randomizing BioPol-PES versus permanent polymer paclitaxel eluting stent (PermPol-PES)²², two studies randomizing BioPol-BES versus PermPol-SES^{29, 33}, two studies randomizing BioPol-BES versus PermPol-PES^{15, 16}, and finally one study randomizing BioPol-BES versus bare metal stent¹⁹.

Table 1: Characteristics of the source studies

References	Trial Acronym	Year	Stent type	Study design	Number of patients	Inclusion criteria	D.M. (N)	Male (%)	Mean age	Duration of Thienopyridines (months)	Maximum follow-up period (months)
Tin Hay et al ³⁰	CURAMI	2007	SES	OS	49	AMI	15	86	55	3	24
Liu et al ²⁴		2007	SES	OS	97	SA+UA	23	70	58	12	6
Han et al ²¹		2008	SES	OS	100	SA+UA	18	79	59	6	24
Dani et al ¹⁷	SERIES I	2008	SES	OS	100	SA+UA	29	NA	NA	Indefinite	30
Bhargava et al ¹¹	BIORAPID	2008	SES	OS	43	SA+ACS	6	79	53	12	6
Lemos et al ²³	PAINT	2009	SES	RCT	106	SA+UA	37	67	60	12	12
Wessely et al ³²		2007	SES	RCT	46	SA+UA	16	85	67	6	9
Mehilli et al ²⁵	ISAR TEST III	2008,2009	SES	RCT	202	SA+UA	58	78	66	6	24
Byrne et al ¹³											
Byrne et al ¹⁴	ISAR TEST IV	2009	SES	RCT	1299	SA+ACS	376	75	67	6	12
Wessely et al ³²		2007	PES	RCT	45	SA+UA	12	89	67	6	9
Lemos et al ²³	PAINT	2009	PES	RCT	111	SA+UA	32	61	60	12	12
Buszman et al ¹²		2008	PES	OS	116	SA+ACS	25	74	54	6	12
Vranckx et al ³¹	SIMPLE II	2006	PES	OS	103	SA+UA	29	71	58	6	9
Serruys et al ²⁸	PISCES [†]	2005	PES	OS	68	SA+UA	13	76	57	6	12
Kruffoff et al ²²	COSTAR II	2008	PES	RCT	989	SA+UA	271	73	64	6	9
Ostovan et al ²⁷		2008	PES	OS	196	SA+UA	40	67	55	6	12
Grube et al ²⁰	JACTAX	2008	PES	OS	103	SA+UA	22	81	66	12	9
Windecker et al ³³	LEADERS	2008	BES	RCT	857	SA+ACS	223	75	65	12	12
Grube et al ¹⁹	STEALTH I	2005	BES	RCT	80	SA+UA	21	60	62	3	24
Chevalier et al ¹⁵	NOBORI	2007	BES	RCT	85	SA+UA	18	69	65	6	9
Chevalier et al ¹⁶	NOBORI I- 2 nd phase	2009	BES	RCT	153	SA+UA	25	74	63	6	10
Danziet al ¹⁸	NOBORI II	2010	BES	OS	3068	SA+ACS	887	78	64	NA	12
Ostojic et al ²⁶	NOBORI-CORE	2008	BES	OS	54	SA+UA	10	68	57	6	12
Takehita et al ²⁹	NOBORI-JAPAN	2010	BES	RCT	194	SA+UA	75	72	67	NA	12

† In this study the slow release arm only of the BP-PES were included to match the other studies; SES: sirolimus eluting stent; PES: paclitaxel eluting stent; BES: biolimus eluting stent; OS: observational study; RCT: randomized clinical trial; SA: stable angina; UA: unstable angina; AMI: acute myocardial infarction; ACS: acute coronary syndrome; NA: not available.

Clinical end-points at 30 days follow-up (Table 2)

TLR

Among the studied population the incidence of TLR at 30 days was 0.4% in the BioPol-SES, 0.7% in the BioPol-PES and 1.4% in the BioPol-BES. These incidences were statistically significantly different (overall p-value=0.01); the three pair-wise comparisons were; OR= 3.4, 95%CI= 1.3-9.6, p=0.006 for BioPol-BES vs. BioPol-SES, OR= 1.7, 95%CI= 0.6-5.1, p= 0.3 for BioPol-PES vs. BioPol-SES and OR= 2.0, 95%CI= 0.9-4.7, p= 0.08 for BioPol-BES vs. BioPol-PES.

DST

The incidence of DST at 30 days was 0.2% in the BioPol-SES, 0.3% in the BioPol-PES and 0.9% in the BioPol-BES. The overall test on equality of these incidences showed a trend towards statistical significance (p-value=0.06); the three pair-wise comparisons were; OR= 3.9, 95%CI= 1.1-14.0, p=0.04 for BioPol-SES and BioPol-BES, OR=1.4, 95%CI= 0.3-6.0, p= 0.6 for BioPol-SES vs. BioPol-PES and OR= 0.4, 95%CI= 0.1-1.2, p= 0.09 for BioPol-BES vs. BioPol-PES.

Clinical end-points at one year follow-up (Table 2)

TLR

Over a follow-up period up to 12 months, the incidence of TLR among the studied population was 4.9% in the BioPol-SES, 6.1% in the BioPol-PES and 2.3% in the BioPol-BES. These incidences varied significantly among the different stents (overall p-value=0.03). There was almost 3 times higher risk of TLR in the BioPol-PES compared to the BioPol-BES (OR=2.8, 95%CI= 1.3-6.0, p= 0.01), and twice higher risk of TLR in the BioPol-SES compared to BioPol-BES (OR=2.2, 95%CI= 0.2-1.0, p=0.04), and no significant difference in the risk ratio of BioPol-SES vs. BioPol-PES (OR= 1.3, 95%CI= 0.6-2.6, p= 0.5).

DST

The incidence of DST at one year follow-up was 0.3% in BioPol-SES, 1% in the BioPol-PES and 0.8% in the BioPol-BES. The pooled odds-ratio was not significant among the different stent comparisons (overall p-value=0.2).

Clinical end-points at one year in randomized clinical trials of BioPol-DES vs. PermPol-DES (Table 3)

In another analysis, in which clinical end-points were assessed in studies comparing BioPol-DES with PermPol-DES in a randomized manner (seven randomized controlled studies)^{13-16, 22, 25, 29, 33}, it was observed that risk of developing TLR at 1 year follow-up was not significantly different in PermPol-DES compared to BioPol-DES (OR=0.8, 95% CI=0.5-1.4, p= 0.5) (figure 2).

Table 2: Clinical events at 30 days and within 12 months among biodegradable-polymer DES:

References	Trial Acronym	Number of patients at 30 days	TLR (N) at 30 days	DST (N) at 30 days	Number of patients at 1 year follow-up	TLR (N) at 1 year	DST (N) at 1 year
Tin Hay et al ³⁰	CURAMI	49	0	0	49	4	0
Liu et al ²⁴		97	0	0*	97	0	0*
Han et al ²¹		100	0	0*	100	4	0*
Dani et al ¹⁷	SERIES I	100	0	0*	100	4	0*
Bhargava et al ¹¹	BIORAPID	43	0	0	43	2	0
Lemos et al ²³	PAINT	106	NA	0*	106	5	1*
Wessely et al ³²		46	NA	0	46	4	0
Mehilli et al ²⁵	ISAR TEST III	202	NA	NA	202	12	0*
Byrne et al ¹³							
Byrne et al ¹⁴	ISAR TEST IV	1299	7	5*	1299	109	8*
Wessely et al ³²		45	NA	0	45	12	0
Lemos et al ²³	PAINT	111	NA	0*	111	6	2*
Buszman et al ¹²		116	1	1	116	8	1
Vranckx et al ³¹	SIMPLE II	103	0	0	103	5	1
Serruys et al ²⁸	PISCES	68	1	0	68	2	0
Krucoff et al ²²	COSTAR II	989	9	5*	989	80	6*
Ostovan et al ²⁷		196	0	0	196	6	6
Grube et al ¹⁹	JACTAX	103	0	NA	73	2	NA
Windecker et al ³³	LEADERS	857	15	14*	857	46	16*
Grube et al ¹⁹	STEALTH I	80	1	1	80	1	1
Chevalier et al ¹⁵	NOBORI I	85	0	0*	85	4	0*
Chevalier et al ¹⁶	NOBORI I - 2 nd phase	153	0	0*	152	2	0*
Danziet al ¹⁸	NOBORI II †	3068	NA	3 †	2976	65	18 †
Ostojic et al ²⁶	NOBORI-CORE	54	1	1*	54	1	1*
Takeshita et al ²⁹	NOBORI-JAPAN	194	NA	0*	194	1	0*

* Stent thrombosis as defined by the Academic research consortium (ARC); TLR: target lesion revascularization; DST: definite stent thrombosis; NA: not available

† The stent thrombosis (ST) recorded in NOBORI II trial included definite + probable, so we didn't include it in the analysis which was confined to definite ST. However we thought to include it in the table for comparative purposes (see later table 4)

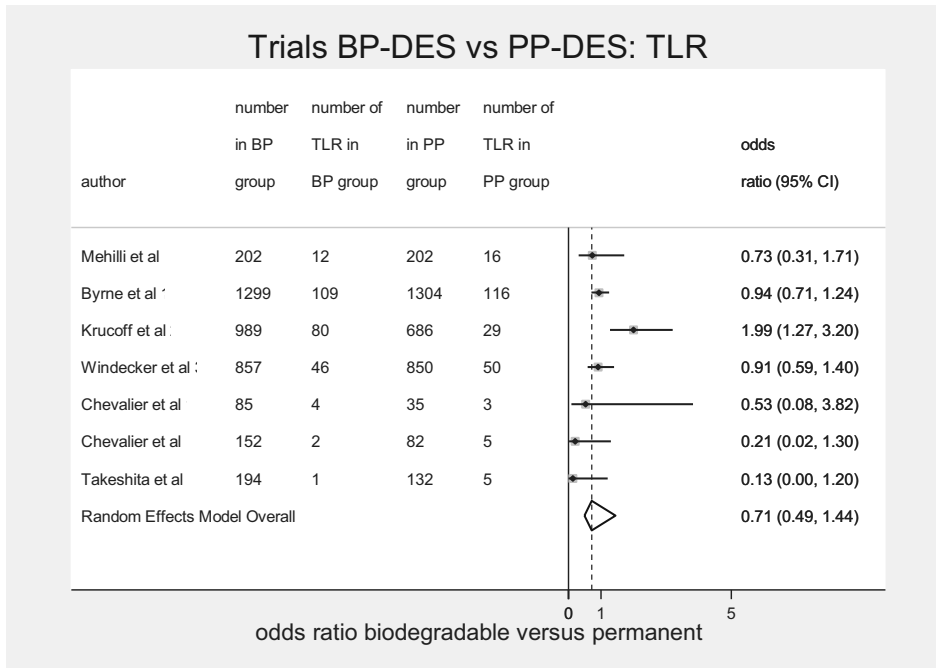


Figure 2: One year TLR in BP-DES vs. PP-DES. TLR; target lesion revascularization, BP; biodegradable polymer, PP; permanent polymer, DES; drug eluting stents.

Similarly, the one year risk of DST was not significantly different in PermPol-DES compared to BioPol-DES (OR=0.7, 95% CI= -0.2-2.4, p=0.5) (figure 3).

Randomized clinical trials quality assessment

Each of the RCTs comparing BioPol-DES with PermPol-DES had five or more questions answered with 'yes' when assessed with the Delphi list. Therefore, all seven RCTs were considered to have a low risk of introducing bias in the assessment of TLR or DST in BioPol-DES vs. PermPol-DES.

DISCUSSION

Three types of biodegradable polymer based DES were analyzed in our study; sirolimus, paclitaxel and biolimus A9.

Rapamycin (sirolimus), is a macrolide with cytostatic properties that blocks progression from G1 to S in the cell cycle and inhibits thus the vascular smooth muscle cell migration and proliferation³⁴.

Biolimus A9 is an analogue of rapamycin that binds to FK binding protein 12 and subsequently to the mammalian target of rapamycin. The formed complex inhibits smooth muscle cells

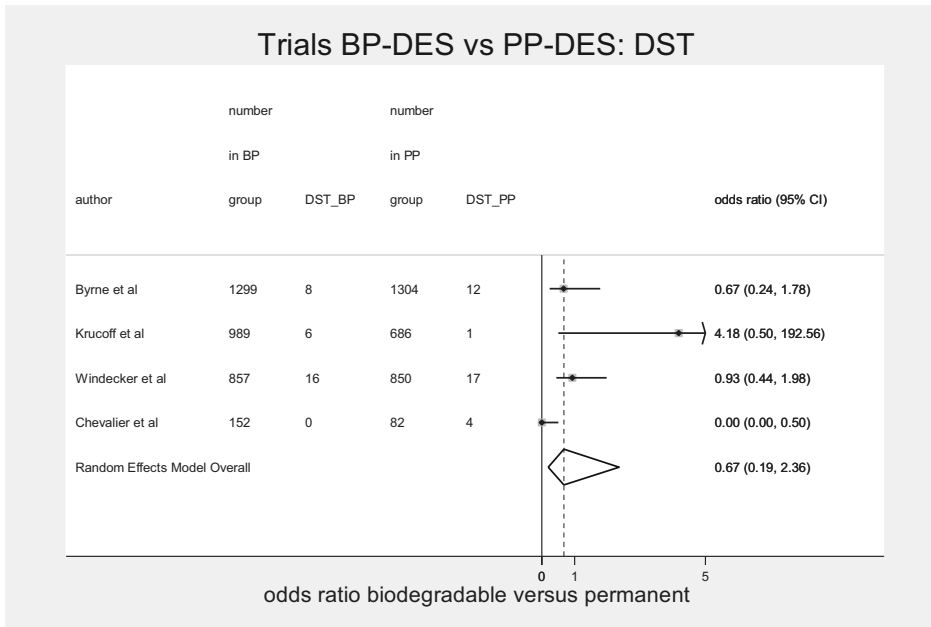


Figure 3: One year DST in BP-DES vs. PP-DES. DST; definite stent thrombosis, BP; biodegradable polymer, PP; permanent polymer, DES; drug eluting stents.

Table 3: Clinical events at 1 year in RCTs of BioPol-DES vs. PermPol-DES:

References	Trial Acronym	Stent	Number of patients	TLR (N)	DST (N)
Mehilli et al ²⁵	ISAR TEST III	BP-SES	202	12	0*
Byrne et al ¹³		PP-SES	202	16	1*
Byrne et al ¹⁴	ISAR TEST IV	BP-SES	1299	109	8*
		PP-SES&PP-EES	1304	116	12*
Krucoff et al ²²	COSTAR II	BP-PES	989	80	6*
		PP-PES	686	29	1*
Windecker et al ³²	LEADERS	BP-BES	857	46	16*
		PP-SES	850	50	17*
Chevalier et al ¹⁵	NOBORI I	BP-BES	85	4	0*
		PP-PES	35	3	0*
Chevalier et al ¹⁶	NOBORI I- 2 nd phase	BP-BES	152	2	0*
		PP-PES	82	5	4*
Takeshita et al ²⁹	NOBORI-JAPAN	BP-BES	194	1	0*
		BP-SES	132	5	0*

BioPol: biodegradable polymer; PermPol: permanent polymer; SES: sirolimus eluting stent; PES: paclitaxel eluting stent; BES: biolimus eluting stent; EES: everolimus eluting stent; TLR: target lesion revascularization; DST: definite stent thrombosis; NA: not available.

* Stent thrombosis as defined by ARC

proliferation by blocking the cell cycle progression between the G1 and S phase. The main difference between biolimus A9 and rapamycin is replacement of hydrogen by alkoxy-alkyl group at 40-O position, increasing its lipophilicity which is expected to optimize the drug distribution¹⁶. Two similar types of biolimus A9 eluting stents were tested in previous studies, The BioMatrix® (Biosensors International- Singapore) and The NOBORI® (TERUMO Europe NV, Leuven, Belgium).

Paclitaxel inhibits vascular smooth muscle cell migration and proliferation mainly as a result of binding to and stabilizing cellular microtubules^{34, 35}.

All stents are coated with a biodegradable poly-lactic acid (PLA) or poly-lactic-co-glycolic acid (PLGA) polymer⁷. In principle, after drug delivery and subsequent complete polymer degradation, only the biologically inert bare-metal platform remains.

To our knowledge this is the first meta-analysis that compares the performance of different DES with biodegradable polymers in a large cohort of patients with similar inclusion criteria, aiming to judge the individual drug performance without the influence of permanent polymer. The key findings were that: a) the risk of TLR and DST were highest in the BioPol-BES group within short term follow-up (30 days); b) The risk of TLR at one year follow-up was three times higher in the BioPol-PES and twice higher in the BioPol-SES when compared to the BioPol-BES; c) There was no significant difference in the one year risk of DST between the studied groups, however we could still observe a higher incidence of stent thrombosis in BioPol-PES compared to BioPol-SES (1% vs. 0.3%).

This meta-analysis is based on comparisons between studies. A consequence is that the results are more amenable to risk of bias than most meta-analyses, which are based on comparisons of meta-analyzed data randomized within studies. Thus our analysis yields valid results only under the assumption that, on the average, throughout these different studies the patient populations are not systematically different, though they are treated with different types of biodegradable-polymer DES. In our view this assumption is likely to be fulfilled since the inclusion and exclusion criteria were very comparable and were not different between the groups of studies with different types of stent.

In an additional analysis performed in randomized trials only, we found that the 1-year risks of TLR and DST were not significantly different between BioPol-DES and PermPol-DES.

Long term follow up results (> 2years) are not yet fully available for the majority of biodegradable polymer DES and therefore we did not perform a long-term analysis.

Early stent thrombosis and target lesion revascularization (TLR)

One of the interesting findings in this study was the significantly higher incidence of early stent thrombosis (EST), within 30 days, in the BioPol-BES group, and the subsequent higher incidence of 30 days-TLR compared to BioPol-SES and BioPol-PES.

These results should be interpreted cautiously, especially in the considerations that polymer- or drug-related stent thrombosis tends to present more likely as a mid- or late-term event,

and that most of the early thrombotic events which have occurred in the BioPol-BES group were encountered in the LEADERS trial³³, which involved a diversity of complex lesions. However, although ISAR TEST-IV trial¹⁴ which tested BioPol-SES, had similar inclusion criteria and diverse complex lesions, yet resulted in less early thrombotic events. Moreover, when comparing the LEADERS³³ and NOBORI-2¹⁸ clinical trials, the 2 leading “all comers” biolimus A9 trials, we could observe that the incidence of EST was obviously different between both trials (1.6% vs. 0.1% respectively, Table 2).

It is still too early to adopt the hypothesis that a more intense antiplatelet regimen should be adopted in patients receiving BioPol-BES. Probably a more dedicated pharmacokinetic study, that addresses the issue of biolimus A9 tissue distribution and polymer degradation rates in different settings as acute coronary syndromes and complex coronary lesions, would shed further light on this issue.

Target lesion revascularization (TLR) at mid-term follow-up (1 year)

From this study it was concluded that the incidence of TLR was significantly lower in the BioPol-BES compared to both BioPol-SES and BioPol-PES. This goes along with the results of the NOBORI series of clinical trials^{15, 16, 26, 29}. A sub-analysis of the LEADERS trial compared outcomes at 1 and 2 years³⁶ in BioPol-BES vs. PermPol-SES patients, stratified according to Syntax score³⁷ tertiles. Authors showed that BES offered significant clinical benefit over SES among patients with high Syntax scores, among which was significantly less TLR at 1 year, with a strong trend at 2 years follow-up. Recently, the 3 years follow-up of the LEADERS trial has been announced, showing the sustained benefit of BES over SES in patients with high Syntax score and among patients with STEMI³⁸. In view of these long-term results, it would be advisable to use BioPol-BES among patients with high-risk lesions.

Biolimus A9 possesses enhanced anti-inflammatory and antiproliferative activity with an improved pharmacokinetic profile. Unlike currently approved drug eluting stents utilizing drugs originally developed for other indications, biolimus A9 has specifically been developed for local delivery to coronary arteries³⁹. Biolimus A9 is a novel rapamycin derivative that, like sirolimus, inhibits smooth muscle cell proliferation via binding to the FK-binding protein and subsequent inhibition of the mammalian target of rapamycin (mTOR)⁴⁰⁻⁴².

The newly developed biolimus A9 eluting stents; Nobori[®] and BioMatrix[®] share several unique features. The most important are biodegradable polymer carrier (poly lactic acid), and coating only on the abluminal stent surface. The later feature allows direct release of biolimus A9 into the vessel wall and, enhanced by its high lipophilicity (~10-fold higher than sirolimus), fast uptake by the surrounding tissue^{15, 16, 33, 43}.

It has been previously reported that sirolimus and paclitaxel drug eluting stents were associated with paradoxical coronary vasoconstriction up to 12 months after implantation⁴⁴⁻⁴⁷. This observation may be attributable to delayed endothelialization caused by the drug and/or endothelial dysfunction caused by polymer-induced inflammation or hypersensitivity reac-

tion. On the contrary, in a recent study, it has been shown that biolimus A9 eluting stents are associated with better preserved endothelial function in coronary arteries compared to the first generation DES, which could be partly explained by the better drug release kinetics⁴⁸. Animal studies showed that after BES implantation, the tissue concentration of the drug in segments 5 mm proximal and distal to the stent edges is almost non-measurable⁴³. In addition, SES and BES have different drug release kinetics: total drug content is released from the SES within 60 days with more than 60% released shortly after stent implantation⁴⁹, versus a small initial burst and sustained simultaneous drug release and polymer degradation taking place over 6-9 months in the BES⁴³, exposing the surrounding tissue at any given time to a lower amount of drug.

Definite stent thrombosis (DST) at mid-term follow-up (1 year)

Because durable polymers have been held responsible for some of the thrombotic events that are assumed to occur as a result of polymer-mediated inflammatory reaction and delayed endothelialization, it was expected that degradation of the polymer will improve arterial healing and thus negate this adverse outcome. This leaves us with the assumption that a higher incidence of thrombotic events, if any, would be a “drug only” effect.

In this meta-analysis, the risk of DST was not significantly different between the different BioPol-DES at one year follow-up; however we could still observe that the incidence of stent thrombosis was numerically 3 times lower in SES vs. PES (0.3% vs.1% respectively). Previous data, comparing first generation DES, have shown that there is higher risk of ST in PES compared to SES^{3,50,51}.

Biodegradable-polymer Biolimus A9 stents (BioMatrix® vs. NOBORI®)

Despite using the same biodegradable polymer (poly-lactic acid) coated on the abluminal stent surface, recent pharmacokinetic studies of the two main biolimus A9 stents; Biomatrix^{®52} and NOBORI^{®43}, have shown that there is an obvious difference between the pharmacokinetics of the the two main biolimus A9 stents, which may be an explanation for the more favourable clinical outcomes encountered with the latter (Table 4).

The NOBORI[®] stent design and coating process differ from that of the BioMatrix[®] stent. The maximum Biolimus A9 concentrations in blood with a median of 18 pg/mL (range <LLOQ to 32 pg/mL) and the AUC_{0-τ} (median 2.9 ng/mL·h, range <LLOQ to 33.1 ng/mL·h) were lower than those after BioMatrix[®] implantation, suggesting that stent design and coating process have an impact on Biolimus A9 release kinetics.

In addition to drug distribution and elimination, biolimus A9 pharmacokinetics are significantly affected by the polymer degradation rate which in turn is influenced by the state of the vessel. In a vessel with inflammation, the pH is expected to be low which will accelerate the degradation of the polymer material and the subsequent drug release into the vessel wall⁷

Table 4: Comparison of pharmacokinetics and clinical end-points of the two main Biolimus A9 DES:

		BioMatrix II	NOBORI
<i>Design & Pharmacokinetics:</i>			
Stent platform and Primer coating		316L Stainless Steel-Parylene C	316L Stainless Steel-Parylene C
Drug-Polymer coating		Abluminal *	Abluminal
Total length (mm)		25.5±10.3	21.4±7.2
Drug concentration(µg/mm)		14.2-17.5	15.6
Total Biolimus A9 dose (µg)		381.7±155.8	336.55±112.99
t _{max} (h)	Mean ± SD	67.2±179.9	178.4±554.3
	Median (min.-max.)	1.0 (0.08-672)	2.0 (0.05-2160)
t _{last} (h)	Mean ± SD	434.7±294.4	984.4±1246.1
	Median (min.-max.)	672 (2-672)	420 (3-4320)
% of patients having measurable concentration of Biolimus A9(>LLOQ) at 28 days		48%	30%
C _{max} (pg/ml)	Mean ± SD	131.5±108.3	17.4±10.2
	Median (min.-max.)	121 (19-394)	17.7 (<LLOQ-32.2)
C _{last} (pg/ml)	Mean ± SD	47.5±34.3	11.7±7.0
	Median (min.-max.)	45 (10-121)	11.4 (<LLOQ-30.3)
AUC _{0-t} (ng/ml-h)	Mean ± SD	16.4±15.6	7.0±10.2
	Median (min.-max.)	13 (0.3-48.7)	2.9 (<LLOQ-33.1)
<i>Clinical end-points:</i>			
TLR 30 days		1.7%	0.3%
TLR 1 year		5.0%	2.1%
DST 30 days		1.6%	0.2% (0.1%) †
DST 1 year		1.8%	0.2% (0.5%) †

t_{max}, time to maximum concentration; t_{last}, time to last quantifiable biolimus A9 concentration (<10 pg/ml); LLOQ, lower limit of quantitation (<10 pg/ml); C_{max}, maximum concentration; C_{last}, last quantifiable concentration; AUC_{0-t}, area-under-the-time-concentration curve over the observation period; TLR, target lesion revascularization; DST, definite stent thrombosis. Values are expressed as mean ± SD and median (minimum -maximum) or as percentages (%).

* Using automatic micropipette coating (AMPC) process.

† Percentages between parentheses show the incidence of DST after including NOBORI-2 results; taking in consideration that they include definite & probable stent thrombosis.

Clinical outcomes in randomized clinical trials of BioPol-DES vs. PermPol-DES

In the sub-analysis confined to randomised clinical trials comparing BioPol-DES and PermPol-DES, it was found that the risks of TLR or late DST at 1 year were not significantly different between both groups.

Unexpectedly, it was found that the presence of biodegradable polymeric coating did not influence the risk of stent thrombosis in DES at 1 year follow-up. A lot of awareness has been raised lately about the biocompatibility of permanent polymer implants and their potential role in contributing to stent thrombosis. Many animal studies have shown that a hypersensi-

tivity reaction may occur as a result of polymer induced inflammation^{7,53}. Given these issues more focus has been placed upon developing biodegradable polymers which degrade over time.

In a previous study, van der Giessen et al has demonstrated that biodegradable polymers may induce marked inflammatory reactions in the porcine coronary arteries, and that this may be attributable to the combination of the parent polymer compound, and biodegradation products⁵⁴. Moreover, there are several factors which influence the velocity of degradation, either by accelerating or slowing it. Accordingly, It is has be stated that a balance between drug release kinetics, the rate of degradation of the polymer and the degradation products are essential for the success of bio-erodible stent systems in coronary vasculature⁷. New families of biodegradable polymers have been tested recently in animal studies implemented by Lockwood and colleagues⁵⁵ which yield fewer acidic by-products than standard biodegradable polymers (PLGA, PLA) used in the currently available BioPol-DES, thus making it well-tolerated *in vivo* by providing a better degradation rate and biocompatibility profile. In an attempt to overcome the problems encountered with polymers or their degradation products, "polymer-free" drug eluting stents have evolved and have been proven to be safe in some clinical studies^{13, 56}, and they were even associated with less late lumen loss compared to biodegradable-polymer and permanent-polymer stents in one study¹³. In a recent animal study, polymer-free biolimus A9 coated stents demonstrated more sustained intimal inhibition, improved healing and reduced inflammation compared with the polymer coated sirolimus eluting Cypher® stent⁵⁷. One would expect that a DES without polymer will release the drug in a relatively short amount of time, resulting in relatively high systemic and tissue peak concentrations, however the superior pharmacokinetics and long half life of Biolimus A9 in the target tissues (Biolimus A9 was present in the coronary tissue until 180 days after stent implantation), made it a suitable drug for coating on non-polymer stents.

LIMITATIONS

To maximize the utilization of all available data, we included abstract presentations that have not been subjected to as much peer review and scrutiny as with full papers, and may not be as of high quality; however, we felt that this was necessary for two reasons. Including abstracts served as an additional tool to avoid any potential publication bias. The second reason is that the magnitude of treatment effect can be overestimated by analyzing only the published data⁵⁸.

In our study only DST was used in the analysis, which may underestimate the true incidence of stent thrombosis among the studied stents. We preferred to use this end-point rather than overall stent thrombosis since not all the included studies reported stent thrombosis as definite, probable or possible according to the ARC definition⁸. In studies not using ARC

definition, they stated in their definition of stent thrombosis that it was angiographically documented which matches definite stent thrombosis as defined by the ARC.

CONCLUSIONS

This meta-analysis, comparing different biodegradable-polymer DES, showed that the risk of early DST and subsequently TLR were highest in the BioPol-BES at 30 days follow-up, whereas at 1 year there was significantly less TLR in the BioPol-BES. We could observe a three times higher incidence of ST in BioPol-PES compared to BioPol-SES at 1 year. On comparing BioPol-DES and PermPol-DES in randomized clinical trials, there was no significant difference in the risk of either TLR or stent thrombosis at 1 year.

These results point to the fact that BioPol-DES do not necessarily perform better than PermPol-DES and that short-mid and long term results are to be carefully judged separately for newly emerging BioPol-DES before they can become a new standard.

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