Guideline Drug Eluting Stents

by the

Dutch Working Group on Interventional Cardiology

JGF Bronzwaer
JW Louwerenburg
JJ Piek
BJWM Rensing
PC Smits (chairman writing committee)
F Zijlstra

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Introduction

Since the results of the RAVEL trial[1] were presented at the European Society of Cardiology Congress in 2001, several randomised controlled trials have documented the antiproliferative effects of sirolimus, paclitaxel, zotarolimus (ABT-578), everolimus and tacrolimus eluting stents. Subsequently, the body of clinical evidence has been increased by the second wave of evidence from trials in more complex lesions like: in-stent restenosis, small vessel disease, chronic total occlusions, multi-vessel disease and patients with diabetes. In the past 12 months, the third wave of evidence has begun to emerge from a series of seven comparative trials involving drug-eluting stents.

This report summarises the available evidence of all reported (presentation at international congresses or published in peer review journals) trials and large observational studies involving drug-eluting stents to assist the Dutch Working Group Interventional Cardiology (WIC) in drawing up guidelines on the use of drug eluting stents (DES) in the treatment of coronary artery disease. Because interventional cardiology is a dynamic profession with multiple new developments and many ongoing studies this guideline has to be revised on a yearly basis.

At present there are two approaches for making recommendations for the use of drug eluting stents (DES). One is based on the results of randomised trials and large observational studies; the other is based on cost-effectiveness. This guideline is primarily focussed on the safety and efficacy data of the available CE marked stents. Since April 2002 and February 2003 the Sirolimus (Cypher®, Cordis) and Paclitaxel (Taxus®, Boston Scientific) eluting stents, respectively, are CE marked and commercial available for clinical use in the Netherlands. The Zotarolimus (Endeavor®, Medtronic) eluting stent received CE mark approval in August 2005 and the Tacrolimus (JANUS®, Sorin Group) eluting stent was approved in October 2004. Therefore the recommendations for the use of DES in this guideline are only focussed on the January 2006 CE approved Sirolimus (Cypher®)-, Paclitaxel (Taxus®)-, Zotarolimus (Endeavor®)- and Tacrolimus (Janus®)-eluting stents.
Other DES that have received CE Mark approval include the paclitaxel-eluting Infinnium® (Sahajanand Medical Technologies [SMT], Surat, India) stent, which received CE Mark approval in late December 2005, and the Axxion® paclitaxel-eluting stent (Biosensors, Singapore). The limiting factor for both of these stents is that they both use paclitaxel as their drug coating, the same drug used on the paclitaxel stent by Angiotech (Vancouver, BC), the manufacturer that supplies the drug to Boston Scientific. As such they cannot be marketed in countries where the drug is patent-protected and licensed for use only on the Taxus® stent and therefore, these stent results are currently not incorporated in this guideline.

Table 1 summarizes all the available evidence in the different subset of lesions and patients.

Table #1: Summary of available evidence	**CYPHER®**	**TAXUS®**	**ENDEAVOR®**	**JANUS®**
Non complex lesions < 30mm / RVD 2.5 -3.5 mm	√	√	√	√
De novo lesions (18-40mm) with RVD 2.5 – 3.5 mm	√	√		
Lesions of moderate length and RVD 2.25mm	√	√	√	
Long lesions > 40 mm	√	√		
AMI lesions	√	√		
Diabetes	√	√	√	
In-stent restenosis	√	√		
Chronic total occlusions	√	√		
Bifurcation lesions	√	√		
Left Main lesions	√	√		
Multi-vessel disease	√	√		
Cost-effectiveness	√	√		

Considering the relative high costs of DES, cost-effectiveness has become an important factor on the implementation of the usage of DES in practice. Based on a thorough cost-effectiveness analysis, the UK NHS NICE (National Institute for Clinical Excellence) recommended in September 2003 the use of DES as follows: “the use of either a Sirolimus eluting stent (SES) or Paclitaxel eluting stent (PES) is recommended in PCI for patients with symptomatic coronary artery disease, 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. Based on these recommendations reimbursement for DES was installed in the UK. Other European countries have different recommendations or reimbursement rules for instance: DES are reimbursed in Switzerland and Portugal for all indications. In France, Spain and Belgium DES are partly reimbursed.

Recommendations based on the level of evidence from large studies and clinical trials are a cumbersome exercise. Primary end-points of the many DES studies are often clinical but different like: target lesion revascularization (TLR), target vessel revascularization (TVR) or target vessel failure (TVF) and major adverse coronary events (MACE) and in some cases not clinical but only angiographic like: late lumen loss or % diameter stenosis. Even the definitions of the different endpoints can differ between the studies. This guideline recognizes the limitations of the different end-points and definitions and in general has adopted the Silber score for its decision making for the recommendations on level evidence. The Silber score is a methodology developed by Sigmund Silber (chairman of ESC guideline committee for percutaneous coronary intervention). It is a system for rating the level of evidence on several criteria, like: primary end point clinical, double blinding, evaluation end point > 6 months, multi-center (>2), clinical event committee/data safety monitoring board independent from steering committee, power of > 80% for primary endpoint reached, follow up > 80% for an angiographic end point and > 95% for a clinical end point. Studies with high scores (maximal 10 points) can be considered as strong evidence in support for their hypothesis.

1. Non complex lesions - non ostial, non calcified and non thrombus containing lesions of <30 mm in native vessels with reference diameter between 2.5 and 3.5 mm - in patients with stable or unstable angina.

Since the results from the First-in-Man (FIM) feasibility studies with sirolimus eluting stents in non complex lesions were published in 2001[2,3], several million patients have now been treated with these drug-eluting stents. With the sirolimus (SES) eluting stent 4 randomized trials in non complex lesions have been published. All 4 trials have shown a significant decrease in MACE, mainly due to the reduction in target lesion revascularization (TVR). In RAVEL[1], the primary endpoint showed a spectacular decrease in loss of minimal lumen diameter or late lumen loss (LLL) at 6 months angiographic follow-up (-0.01 versus 0.80 mm; DES versus BMS), resulting a significant higher minimal lumen diameter (MLD) in the sirolimus stent group (2.42 mm) compared to the bare metal group (1.64 mm). In the United States conducted pivotal sister study of RAVEL: the SIRIUS trial[4] the primary endpoint showed a significant decrease in target vessel failure TVF (cardiac death, MI and target vessel revascularization) at 9 months follow up (8.6 versus 21.0 %). The secondary angiographic endpoints at 8 months follow-up showed significant lower in-stent LLL (0.17 versus 1.00 mm) and in-stent binary restenosis rates (3.2 versus 35.4%). In Europe, a third trial was conducted with the sirolimus stent: E-SIRIUS.[5] This trial compared the sirolimus stent in longer lesions and smaller vessels than in the RAVEL trial. The primary endpoint showed a significant higher in-stent MLD at 8 months angiographic follow-up (2.22 versus 1.33 mm). In Canada a fourth multi-center sirolimus stent trial was conducted in relative small vessel de-novo lesions with 8 months angiographic follow-up (FU): the C-SIRIUS.[6] In this trial again the primary end point showed a significant higher in-stent MLD with the sirolimus eluting stent (2.46 versus 1.49 mm; sirolimus versus BMS). In all these 4 trials the acute myocardial infarction and death rates in the sirolimus stent treated groups were similar compared to the bare-metal stent arm groups.
In the RAVEL[1] and SIRIUS[4] trial pre-dilatation was mandatory. The DIRECT study[7] is a prospective, nonrandomized trial in which a total of 225 patients underwent direct stenting with the sirolimus stent in non complex lesions. The outcomes of these patients were compared with those observed in the 412 patients from the angiographic cohort of the SIRIUS[4] trial who underwent sirolimus stent implantation using the predilatation stent delivery strategy.[1,4] The DIRECT multicenter trial, showed that direct stenting was noninferior to predilatation for all endpoints assessed (primary endpoint in lesions LLL at 8 months FU was similar in both studies: 0.18 mm).

With the paclitaxel (PES) eluting stent 3 randomized trials in non complex lesions have been published. Although less robust, similar outstanding results on the prevention of restenosis are observed. The TAXUS I trial compared the slow release paclitaxel eluting NIR stent versus the bare NIR stent in 61 patients.[8] The primary endpoint showed a similar MACE rate at 30 days of 0 % in both groups. At 1and 3 year FU promising MACE rates were observed for the paclitaxel stent group

with significant less late loss, higher MLD rates and less target lesion revascularization[9]. In TAXUS II, 2 paclitaxel eluting formulas (slow and moderate release) were compared with the BMS arm.[10] The primary endpoint (% in stent volume obstruction with IVUS at 6 months FU) in both paclitaxel arms was comparable and significant better than the BMS groups (7.8 SR and 7.9 MR versus 20.5 and 23.2 % in the BMS groups). Also the binary restenosis (>50%) and TLR rates were significant lower in the paclitaxel groups at 6 months FU. The pivotal TAXUS IV trial conducted in the United States looked primarily at ischemia driven TVR at 9 months FU, with angiographic FU in the first 732 patients.[11] A significant reduction in TVR was observed (4.7 versus 12.0 %; paclitaxel versus BMS). Also significant reduction in-stent LLL (0.39 versus 0.92 mm) and binary in-stent restenosis rates (5.5 versus 24.4%) were obtained. In all these 3 TAXUS trials the acute myocardial infarction and death rates in the paclitaxel stent treated groups were similar compared to the bare-metal stent arm groups. Follow-up data from FIM is now out to 5- years, and the available evidence from the early randomized, controlled trials is now out as far as 4-years (RAVEL) and 3-years TAXUS I, II and IV[9,12]. In these intermediate long-term reports sofar no significant excess of late stent thrombosis or late restenosis have been reported.

With the zotarolimus (Endeavor®) eluting stent 1 multicenter study and 2 randomized trials have been performed in non complex lesions. In comparison with the stainless steel sirolimus SES and paclitaxel PES drug eluting stents , the Endeavor® stent is made from a chromium-cobalt-nickel alloy with thin stent struts. The objectives of the Endeavor I study was to assess safety and MACE at 30 days and second to assess medium and longterm safety and efficacy based on target lesion LLL and neointimal hyperplastic volume at 4 and 12 months[13]. The study showed that the zotarolimus eluting stent platform is safe with persistent low MACE rate at 12 and 24 months FU (2%). Angiographic data however, showed an increasing in-stent LLL of 0.33 and 0.61 mm at 4 and 12 months, respectively. The Endeavor II trial looked primarily at TVF (cardiac death, non fatal MI and TVR) at 8 months angiographic FU and second at LLL and binary restenosis rate[14]. TVF was significant lower in the zotarolimus group with 8.1 versus 15.4%. Also the in-stent LLL and the binary restenosis rate was significant lower in the zotarolimus stent arm (0.62 versus 1.03 mm and 9.5 versus 32.7%), respectively. Apart from the higher late lumen loss in the zotarolimus stent arm compared to the sirolimus and paclitaxel eluting stents, also the third generation bare metal stent group had an unexpected less good angiographic result. Comparable to the sirolimus and paclitaxel stent studies no difference in MI and death was observed between the zotarolimus and bare metal stent arm groups. The ENDEAVOR III trial is a prospective randomized study between the Endeavor® en SES® stent[15]. Four hundred thirty six patients with non-complex lesions were randomized (3:1) between both stents in a non-inferiority study. The primary endpoint (in segment LLL) was significant different between both groups: 0.34 mm versus 0.13 mm, Endeavor® versus SES®, respectively. Therefore, the primary endpoint was not met. Nevertheless, in this non-complex lesion population no clinical significance was observed between both stent groups at 9 months FU. Comparative data in non complex lesions

with the paclitaxel stent will be available in the near future from the ongoing Endeavor IV study, in which the primary end points are: LLL at 8 months and TVF at 9 months, respectively.

The tacrolimus eluting Janus® stent is a stainless steel stent with a passive carbon coating and at the outer circumference of the stent struts crevices that are filled with tacrolimus. In comparison with the above mentioned DES platforms, this stent has no biodegradable or biocompatible polymer for its drug release. At the moment, the results from one small sized safety, feasibility study (JUPITER I) and 1 randomized trial (JUPITER II) are available. The JUPITER 1 is a first-in-man study designed to determine safety and efficacy of the tacrolimus-eluting Janus® stent.[16] In the first phase of the study, 58 patients with non-complex lesions the primary end-point showed no MACE at 30 days FU. The JUPITER II compared the bare-metal Tecnic® carbostent with the Janus® Carbostent in a 1:1 randomized prospective study.[17] Although late loss for the Janus® stent did fall within the range predicted when the trial was designed, late loss for the control Tecnic® stent was lower than expected in this relative low risk non-complex lesion population. The primary endpoint (in segment LLL) was 0.44 mm and 0.40 mm for the Tecnic® and Janus® stent respectively (p=ns). Also the secondary endpoints MACE and TVR at 6 months were similar between both groups.

Trial	**# Centres**	**# Pts**	**Active Arm**	**Control Arm**	**Clop. (mos)**	**RVD (mm)**	**Lesion Length (mm)**	**TLR % DES vs. BMS @ mos f-up**	**Event Free Survival / DES vs. BMS mos f-up**
RAVEL[1,18,19]	19	238	120	118	2	2.60	9.56	5.9 vs. 25. 2 @ 48 mos	78.0% vs. 65.2 % @ 48 mos
SIRIUS [4,20]	53	1058	533	525	3	2.79	14.4	6.8 vs. 23.2 @ 36 mos	87.1% vs. 72.2% @ 36 mos
C-SIRIUS [6]	8	100	50	50	2	2.65	14.5	6.0 vs. 18.0 @ 9 mos	96% vs. 82% @ 9 mos
E-SIRIUS [5,21]	35	352	175	177	2	2.6	14.9	5.1 vs. 26.0 @ 36mos	88.6 % vs. 67.6 % @ 36 mos
DIRECT[7]	na	225	225	412	2	2.77	12.4	1.3 vs. 1.9 @ 8 mos	96.9% vs. 94.7% @ 6 mos
TAXUS II (SR)[9,22]	38	267	131	136	6	2.75	10.5	5.5 vs. 15.5 @ 24 mos	85.8% vs. 75.4% @ 24 mos
TAXUS IV [10,23]	73	1326	667	659	6	2.5 – 3.75	10-28	9.7 vs. 21.0 @ 24 mos	78.7% vs 74.9% @ 24 mos
ENDEAVOR I [11, 24]	8	100	100	n/a	3	2.96	10.9	2.0 @ 24 mos	97% @ 24 mos
ENDEAVOR II [12]	72	1197	600	600	3	2.25 – 3.5	14-27	6.0 vs. 13.1 @ 12 mos	91.2% vs. 84.1% @ 12 mos
JUPITER II [15]	16	332	166	166	2	2.7 – 4.0	$\leq$ 20	5.7 vs. 10.4 @ 6 mos	93.6% vs. 89.4% @ 6 mos

NOTE: DIRECT control arm is the SES angiographic cohort of SIRIUS

NOTE: ENDEAVOR I is a single-arm study. Hence no comparative data with a control arm.

NOTE: 2 years results TAXUS II MR (not incorporated)

2. De-novo lesions (18-40 mm) in native vessels with a reference diameter of 2.5 – 3.5 mm in patients with stable and unstable angina.

In contrast to the treatment of non ostial, non calcified, non thrombus containing and non side branch type lesions in the RAVEL[1], SIRIUS[4], E-SIRIUS[5] and C-SIRIUS[6] trials, the SCANDSTENT (Stenting of Coronary Arteries in Non-STRESS / BENESTENT Disease) investigators from 4 centres in Denmark randomised 322 patients with complex lesions to PCI with the SES stent or a bare metal stent.[25] Complex lesions were defined as those with occlusions longer than 15 mm, lesions with significant side-branches, ostial lesions, and angulated lesions. Only patients with a MI within three days of PCI were excluded from randomisation. At 6 months FU there were no differences in the rates of death, MI, or stent thrombosis, but patients treated with the SES stent had significantly lower rates of target lesion revascularization (TLR) compared with the bare-metal-stent group (Table 1 and 2).
In the single center RESEARCH registry, during 6 months 508 consecutive PCI patients received sirolimus stents in a real world situation.[26] These patients were compared to a historical control group (n=450) who received bare metal stents for de-novo lesions in the preceding 6 months before sirolimus stents were commercial available. In this registry the majority of the lesions were type B2 or C. At 1 year FU the MACE rate was significantly lower in the sirolimus stent treated group (9.7 versus 14.8%), mainly due to reduced target vessel revascularization (5.1 versus 10.9%).

In the TAXUS V trial 1108 patients with de-novo lesions 10-46 mm were randomized between the slow release paclitaxel stent or the bare metal Express® stent.[27] In this pivotal multi-center trial the majority of the treated lesions were long type B2 and C lesions. The primary end-point TVR was significantly less in the paclitaxel stent group (12.1 versus 17.3%). Also MACE was significantly less in the paclitaxel stent group with no difference in death and MI between both groups. The next step in the treatment of complex lesions with paclitaxel eluting stent was investigated in the TAXUS VI trial, in which long lesions were treated with the moderate release formula[28]. In this multi-center, randomized trail, 448 patients with 18-40 mm long de novo lesions were treated with the paclitaxel stent or the bare metal Express® stent. The 9 months TVR (primary endpoint) was 9.1% versus 19.4%, also demonstrating significant improvement in cinical and angiographic outcomes for the moderate release paclitaxel eluting stent as compared to the control stent.

Trial	# Pts	% Overlapping stents	Lesion length (mm)	# stents / lesion	TLR % Active vs. Control	Event Free Survival @ months f-up
Sirolimus						
SIRIUS [4,20]	525	32.5	15 – 30	1.4	6.8 vs. 23.2 @ 36 mos	87.1% vs. 72.2% @ 36 mos
C-SIRIUS [5]	100	36.0	15 – 32	1.8 ± 0.8	4.0 vs. 18	96% vs. 82% @ 9 mos
E-SIRIUS [6,]	352	34.9	15 – 32	1.7 ± 0.7	4.0 vs. 20.9 @ 9 mos	89.7% vs. 70% @ 24 mos
SCANDSTENT[25]	322	n/a	n/a	n/a	2.4 vs. 29.8 @ 6 mos	n/a
Pooled SES data[29]	1084	31.1	28.2 ± 7.2	n/a	4.7 vs. 28.2 @ 360 days	92.9% vs. 68.9% @ 360 days
RESEARCH[26]	958	n/a	30 vs. 38*	1.9 vs. 2.1	3.1 vs. 6.3 @ 360 days	90.3% vs. 85.2% @ 360 days
Multi-centre Korean Registry[30]	297	53.0 vs. 26.0 (BMS)	35.3		2.7 vs. 18.6 @ 6 mos	92.6% vs. 80.2% @ 7 mos
Paclitaxel						
TAXUS IV[11] Tercile 1	397		13.02 – 21.26	1.20 (1.09 – 1.28)	6.1% @ 12 mos	86.3% @ 12 mos
TAXUS V Total Study Population	1172		17.3 ± 9.0	1.83 ± 0.78	8.6 vs. 15.7 @ 9 mos	85% vs. 78.8% @ 9 mos
TAXUS V Multiple Stent Subgroup	379		43.6 ± 10.5		12.6 vs. 28.2 @ 9 mos	79.6 vs. 68.0 @ 9 mos
TAXUS VI	448	28.9	20.6 ± 7.6	1.7 ± 0.6	8.7 vs. 20.6 @ 12 mos	81.7 % vs. 76.2% @ 12 mos
Meta-Analysis[31]	1718		15.2 ± 7.9		6.9 vs. 18.6 @ 36 mos	81.8 vs. 71.7 @ 36 mos
Multi-centre Korean Registry	170	52.0 vs. 26.0 (BMS)	36.3		5.4 vs. 18.6 @ 7 mos	94.0% vs. 80.2% @ 7 mos

3. Lesions in small vessels (reference diameter 2.25 - 3.00 mm).

A diameter smaller than 3 mm has been recognised as an independent predictor of restenosis after stenting, all the more so if the small vessel is associated with a long lesion. In the pre-DES era failures and recurrences were bound to be more frequent with whatever method was used. Using the angiographic substudy of the TAXUS-IV trial, Ellis et al. defined the relationship between in-stent and lesion segment late loss, the shape of the late loss histogram (variance and skewedness), and nine-month TLR. They showed that LLL by several measures was closely related to TLR (area under the receiver-operator curve >0.90). [32] For individual vessels of the size in this study (2.8 +/- 0.5 mm), the likelihood of TLR did not exceed 5% until analysis segment late loss was >0.5 mm, and did not exceed 10% until late loss was >0.65 mm. At greater late losses, the late loss TLR relationship was steep and nearly linear. Several studies have reported now substantial data on the beneficial effect of drug-eluting stents in this challenging lesion subset (see table).

In the SES-SMART trial, 257 patients with the novo lesions in segments < 2.75 mm were randomized between the sirolimus stent and the similar bare metal stent[33]. The primary end-point (binary in-segment restenosis at 8 months) was impressively decreased in the sirolimus eluting stent group (9.8% versus 53.1%). Also significant fewer patients in the sirolimus group experienced MACE (9.3% versus 31.3%), mainly because of fewer TLR, but also surprisingly due to fewer MI.
The SVELTE study also looked at the effect of sirolimus eluting stent on the novo lesions of small arteries (<2.5 mm). The results were compared with the outcomes of the small vessels treatment group in the SIRIUS study[34]. Te primary end-points (8 month in-stent and in-lesion LLL) were 0.22 and 0.20 mm, respectively, and significantly lower then the SIRIUS bare metal control group and similar to the sirolimus treatment group. The same applies for the binary restenosis rate and the TLR rates.
In the RESEARCH registry the effect of sirolimus stents were evaluated in very small vessels with the lowest reported reference vessel diameter of 1.88 mm[35]. Again the 12 months follow results showed historical low LLL (0.07±0.48 mm) and binary restenosis rates (10.7 %), and almost similar to the results of larger sized sirolimus stents (>2.25) in the same patients.
In the PORTO study (a Portuguese prospective, non-randomized, multi-center study) the sirolimus stent in small native coronary arteries of diabetic (PORTO I) and non-diabetic (PORTO II) patients were evaluated.[36] The study assessed the efficacy and safety of the sirolimus stent in reducing angiographic in-stent minimum lumen diameter, late lumen loss and percent stenosis in de novo native coronary lesions in small vessels (<2.50 mm). The six-month findings from the PORTO study showed again low LLL in the non diabetic subset: 0.05 ± 0.38 mm and in the diabetic subset: 0.10 ± 0.38 mm, with similar excellent clinical results.

The sub group analysis of TAXUS IV in which lesions with a reference vessel diameter of < 2.5 mm were treated, showed a significant better outcome in binary restenosis rate in the paclitaxel group at 9 months FU (10.2% versus 38.5%)[37]. Also in the small vessel sub-study of the TAXUS V trial similar good results were obtained[38]. The 9 months results of 2.25 mm stents showed significant

lower LLL in stent (0.49±0.61 versus 0.90±0.63 mm) and in lesion segment (0.36±0.53 versus 0.61±0.59 mm), resulting in significant lower TLR rates in the paclitaxel group.
In the T-SEARCH registry the efficacy of paclitaxel-eluting stents was compared to sirolimus-eluting stents when used without restriction in unselected patients. A total of 576 consecutive patients with de novo coronary artery disease exclusively treated with the paclitaxel stent were compared with 508 patients treated with sirolimus stent from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry.[39] In a sub group analysis of 2.25 mm paclitaxel stents used reasonable good results were obtained, but significantly less than the sirolimus stent.[40] This finding reflects the importance in clinical outcome of late loss in high risk lesions and subsets of patients for restenosis.

In the small vessel subgroup analysis of ENDEAVOR II, lower TLR rates have been presented in the zotarolimus stent group compared to the bare metal control stent group. Currently no additional data on reference vessel diameter, lesion length and statistics is available.

Study	**# Patients**	**# Centres**	**RVD (mm)**	**Lesion Length (mm)**	**TLR % @ follow-up**	**MACE % @ follow-up**
Sirolimus						
SES-SMART[33]	129 vs. 128	20	2.22	13.01	7.0 vs. 21.1 @ 8 mos	9.3 vs. 31.3 @ 8 mos
SVELTE	101vs. 323	9	2.36	14.5	3.0 vs. 22.0 @ 12 mos	7.9 vs. 23.5 @ 12 mos
RESEARCH*	107 vs. 112	1	1.86 ± 0.4	12.3	5.5 @ 12 mos	7.7 @ 12 mos
PORTO	150	na	2.04	11.16	0.8 @ 6 mos	2.9 @ 6 mos
Paclitaxel						
TAXUS IV (≥ 2.5 - ≤ 3.0 mm)	292 vs. 267	73	2.76 ± 0.49 vs. 2.80 ± 0.48	13.8 ± 6.5 vs. 13.9 ± 6.8	3.8 vs. 14.6 @ 9 mos	Not an endpoint
TAXUS V (2.25 mm stent)	108 vs. 95	66	2.07	16.6	10.4 vs. 21.5 @ 9 mos	18.9 vs. 26.9 @ 9 mos
T-SEARCH**	90 vs 107	1	1.95 ± 0.4	Not stated	5.0 @ 12 mos	17.8 @ 12 mos
Zotarolimus						
ENDEAVOR II	na	72	Na	na	7.2 vs. 16.6 @ 9 mos	na

** RESEARCH registry compared 2.25 mm sirolimus stents with >2.25 mm sirolimus stents in the same patient. Only TLR and MACE of 2.25 mm sirolimus eluting stent patients are reported.*

*** T-SEARCH registry compared paclitaxel stent patients with sirolimus eluting stent patients. Only TLR and MACE of 2.25 mm paclitaxel eluting stent patients are mentioned in this table.*

4. Lesions Length > 40 mm

To date there is little randomized data available on the use of drug-eluting stents to treat very long lesions (>40mm). A sub-study from the RESEARCH registry looked at the efficacy of sirolimus stents in lesions > 36 mm[41]. This study comprised of 96 patients with 102 lesions of which 20% chronic total occlusions (CTO). The mean stented length was 61.2 ± 21 mm. FU at 6 months showed a binary restenosis rate of 11.9 % and a low in stent LLL of 0.13 mm. At almost 1 year FU the MACE rate was only 8.3 %. In a Korean multicenter study the efficacy of sirolimus and paclitaxel eluting stents were compared with bare metal stents in long lesions[42]. The study involved 527 patients with de novo long lesions (≥ 24 mm, which were treated with long (≥ 28 mm stents). Lesions in the SES (36.0 ± 14.9 mm, $P < 0.001$) and PES (36.3 ± 14.5 mm, $P < 0.001$) groups were longer than those in the BMS group (32.0 ± 12.3 mm), meaning the two DES groups had longer stented segments than did the BMS group. Six-month angiographic follow-up showed the SES (9.3%, $P < 0.001$) and PES (21.3%, $P < 0.001$) groups had lower in-segment restenosis rates than that of the BMS group (42.5%). The rate of major adverse cardiac events (MACE) including death, myocardial infarction, and target lesion revascularization at 9 months was higher in the BMS group (26.6%) than that in the SES (13.0%, $P < 0.001$) and PES (15.7%, $P < 0.001$) groups. *Posthoc* analysis of the two DES groups showed that the in-segment restenosis rate was lower for the SES than that for the PES group ($P = 0.002$), while the MACE rate was similar.

More data on the paclitaxel stent is available in a sub study of TAXUS V with multiple overlapping stents and total stent length of 43 ± 8 mm, significant lower TVR and MACE rates were obtained in the paclitaxel stent group (n=124) compared to the bare metal stent group (n=124)[43]. Furthermore, in a small subgroup analysis of the TAXUS VI trial similar good results were obtained[44]. In a descriptive "full metal jacket" study form the RESARCH and T-SEARCH registry, the medium long-term FU of 122 patients with at least 64 mm of overlapping DES stents are described (81 pts. with sirolimus and 41 patients with paclitaxel)[45]. The use of these DES stents was associated with low TVR (7.5%) and MACE (18%) rates at 1 year FU.

Study	# Lesions	Stent length	Lesion Length (mm)	TLR % @ follow-up	MACE % @ follow-up
Sirolimus					
RESEARCH	102	61.2	≥ 41	6.2 @ 320 days	8.3 @ 320 days
Very Long Lesions (SJ Park)	294	42.8 vs. 36.0 (BMS)	35.3 vs. 32.0 (BMS)*	2.7 vs. 18.6 @ 7 mos	3.4 vs. 19.8 @ 7 mos
Paclitaxel					
TAXUS V Multiple Stent Subgroup	379	43.6 ± 10.5	25.8 ± 8.9*	9.9 vs. 27.6 @ 9 mos	15.7 vs. 30.1 @ 9 mos
TAXUS VI Long Lesion Subgroup	45	n/a	≥ 26 mm*	4.4 vs. 26.3 @ 9 mos	13.3 vs. 26.3 @ 9 mos
Very Long Lesions (SJ Park)	294	43.1 vs. 36.0 (BMS)	36.3 vs. 32.0 (BMS*)	5.4 vs. 18.6 @ 7 mos	6.0 vs. 19.8 @ 7 mos
Sirolimus & Paclitaxel					
"Full metal jacket''	122	79 (64-168 mm)	79 mm	7.5 @ 12 mos	18 @ 12 mos
* no subset data for lesions longer than 40 mm					

5. Lesions in the setting of STEMI

Percutaneous coronary intervention has become the preferred treatment option for patients with acute ST Elevation Myocardial Infarction (STEMI). Routine stent implantation has been shown to have a better procedural outcome than balloon angioplasty in this patient group[46]. There is little information available as to the efficacy and long-term safety of drug-eluting stents in STEMI lesions in randomized controlled studies.

With the sirolimus eluting stent the STRATEGY trial evaluated the clinical and angiographic impact of single high-dose bolus tirofiban plus sirolimus-eluting stenting vs. standard-dose abciximab plus bare-metal stenting in patients with STEMI[47]. The primary end point was a composite of death, nonfatal myocardial infarction, stroke, or binary restenosis at 8 months. In the sirolimus stent group only 19 % reached the primary end point as compared to the 50% in the bare metal stent group (CI 0.18-0.60, $p<0.001$). In a subgroup of the RESEARCH registry, also significant lower TLR and MACE rates were observed in the sirolimus eluting stent group, compared to the previous bare metal stent group[48]. Weber et al. compared 50 consecutive STEMI patients treated with sirolimus stent with 50 matched control patients who received bare metal stent[49]. The 6 months angiographic and clinical outcome was significantly superior in the sirolimus stent group (binary restenosis 4.0 vs. 18.0%, MACE 6.0 vs. 22.0%).

Apart from a randomized two center study from the Netherlands (PASSION trial)[50], a small sized, uncontrolled study reporting safety and promising early outcome data with the paclitaxel stent[51], and a subgroup analysis of the T-SEARCH registry is of importance for the efficacy of the paclitaxel stent in patients with acute myocardial infarction[52].

In the PASSION trial, 620 STEMI patients with native coronary artery culprit lesions were randomised between the paclitaxel stent and the equivalent bare metal stent. The primary endpoint was the composite endpoint of MACE. Baseline characteristics and the acute primary outcome (eg TIMI flow) was in both groups similar. At 6 months FU, the MACE rate in the paclitaxel stent group was significantly lower compared to the bare metal stent group (7.6 versus 12.6 %), mainly due to less TLR . No subacute stent thrombosis occurred in the paclitaxel stent group.

In the T-SEARCH registry 136 consecutive STEMI patients were treated with the paclitaxel stent and compared with the 186 STEMI patients treated with sirolimus stent in the preceding period. No significant differences in MACE were observed between both stent groups (9.8 vs. 15% at 1 year FU, sirolimus vs paclitaxel respectively). Results form the ongoing randomized HORIZON trial will bring extended data on the safety and efficacy of the paclitaxel eluting stent in this subset of patients.

Study	**# Patients**	**AMI (%)**	**TLR % @ follow-up**	**MACE % @ follow-up**
Sirolimus				
STRATEGY	87 vs. 88	100	9 vs. 36* @ 8 mos	18 vs. 32 @ 8 mos
RESEARCH	186 vs 183	100	1.1 vs. 8.2 @ 300 days	9.4 vs. 17.0 @ 300 days
Weber AMI sub-study	50 vs 50	100	2.0 vs. 16 @ 6 mos (TVR)	6.0 vs. 22.0 @ 6 mos
Paclitaxel				
PASSION	310 vs 310	620	1.0 vs. 3.6 @ 6 mos	7.6 vs. 12.6 2 6 mos
T-SEARCH AMI	136	100	5.1 @ 30 days (TVR)*	15.0 @ 12 mos
HORIZON	ongoing			
* No 12 mos data available and only sirolimus stent data is mentioned in the table.				

6. Lesions in patients with diabetes

Regardless of age, the diabetic patient has a much higher incidence of coronary artery disease than the general population, and does worse after revascularisation as borne out by evidence from historic trials such as RITA, EAST, CABRI and BARI. However, despite the use of DES, diabetes mellitus still remains an independent risk factor of restenosis, need for revascularization and MACE.

Several different randomized trials have investigated the effect of sirolimus stent in the diabetes population. The Spanish multicenter DIABETES trial randomized 180 DM patients between sirolimus stent or its bare metal equivalent[53]. The primary end point of the trial was in-segment late lumen loss at 9-month follow-up. In-segment late lumen loss was reduced from 0.47+/-0.5 mm for standard stents to 0.06+/-0.4 mm for sirolimus stents (P<0.001). Target-lesion revascularization and major adverse cardiac event rates were significantly lower in the sirolimus group. Non-insulin- and insulin-requiring patients demonstrated similar reductions in angiographic and clinical parameters of restenosis after sirolimus-eluting stent implantation. The ISAR-DIABETES trial randomly assigned 250 DM patients to receive paclitaxel-eluting stents or sirolimus-eluting stent[54]. The primary end point was in-segment late luminal loss at 9 months FU. Although the angiographic results in the sirolimus stent group was significantly better then the paclitaxel stent group, in both groups low TLR rates were obtained (6.4% for sirolimus vs 12.0% for paclitaxel).
In the DM subgroup analysis of the SIRIUS trial the 9 months TLR and MACE rates were also significantly reduced[55]. Additional data derived from 3 non controlled studies in DM patients showed equivalent beneficial data on the use of sirolimus stents[56,57,58].

Sofar with the paclitaxel stent only sub-group analyses are available from the three large sized randomized controlled trials TAXUS IV, V, VI. All subgroup analyses show consistent beneficial outcomes of the paclitaxel stent group compared to the equivalent bare metal stent in a variety of lesion subsets[59,60,61,62]. Additional data derived from the non controlled RESEARCH/T-SEARCH registry in DM patients show equivalent beneficial data on the use of paclitaxel stents[39,58].

Study	# pts	# DM pts	IDDM	NIDDM	LESION LENGTH	RVD	TLR % @ f-up (mos)	MACE % @ f-up (mos)
Sirolimus								
DIABETES	160	100	53	107	15.0	2.34	7.3 vs. 31.3 @ 9 mos	11.3 vs 36.3 @ 9 mos
ISAR-DIABETES	125	125	45	79	13.8	2.70	6.4 @ 9 mos	
SIRIUS	1058	279	82	197	14.93	2.77	6.9 vs 22.3 @ 9 mos	9.2 vs 25.0 @ 9 mos
PORTO	120	120	34	86	11.2	2.04	1.7 @ 6 mos	5.0 @ 6 mos
BRIDGE	628	605	30.4	65.9	18.4	2.8	5.7 @ 12 mos	9.7 @ 12 mos
RE/T-SEARCH	145	145						20.4 @ 12 mos
Paclitaxel								
TAXUS IV	1314	318	105	213	14.2 $\pm$ 6.2	2.72 $\pm$ 0.47	8.0 vs. 22.0 @ 24 mos	15.6 vs 27.7 @ 12 mos
TAXUS V	1156	356	102	254	17.97	2.55 $\pm$ 0.59	9.6 vs. 17.5 @ 9 mos	16.9 vs 24.6 @ 9 mos
TAXUS VI	448	89	39	50			2.6 vs. 22.0 @ 9 mos	15.4 vs 28.0 @ 9 mos
Meta-analysis [63.]	1718	398	120	278			7.9 (oral agents) vs 19.4 (control) @ 9 mos	
ISAR-DIABETES	125	125	36	89	12.4	2.75	12.0 @ 9 mos	
RE/T-SEARCH	148	148					5.7 @ 12 mos	15.6 @ 12 mos
Zotarolimus								
ENDEAVOR II		118	35	84			7.5 @ 9 mos	

** Meta-analysis of pooled data from PES II, IV, V and VI*

7. In-stent restenosis

In-stent restenosis (ISR) continues to represent one of the most important limitations to the long-term success of percutaneous coronary intervention with an estimated 20% to 40% of patients requiring repeat treatment, depending on lesion and patient-related factors. In-stent restenosis is mainly due to intimal proliferation. Thus, the introduction of drug-eluting stents coated with antiproliferative agents, able to reduce neointimal hyperplasia, could represent a valid rationale for the use of DES in the treatment of ISR.

The ISAR-DESIRE is the only randomized trial on this topic[64]. Three hundred patients with angiographic ISR were randomized between the balloon angioplasty, sirolimus and the paclitaxel stent. Primary end-point (in segment binary restenosis rate at 6 months) showed significant improvement in the sirolimus and paclitaxel stent compared to the balloon angioplasty group (14.3 vs 21.7 vs 44.6%, respectively). Also inboth group clinical outcome at 1 year FU was significantly better then the balloon angioplasty group, mainly due to the decreased TVR rate.
The SIRO-ISR, TROPICAL and RESEARCH-subgroup registries all showed that sirolimus stents are highly effective in prevention of recurrent ISR with low MACE rates[65,66,67].

With paclitaxel stent, apart from the ISAR-DESIRE trial, less robust data is currently available. The TAXUS III trial was a single-arm, 2-center safety, feasibility study that enrolled only 28 patients with ISR meeting the criteria of lesion length ≦30 mm, 50% to 99% diameter stenosis, and vessel diameter 3.0 to 3.5 mm[68]. In this high risk population for recurrent ISR the lesions were treated with one or more slow release NIRx paclitaxel-eluting stents.

Study	**# pts**	**# ISR lesions**	**DM %**	**Focal / Diffuse %**	**TLR %**	**MACE %**
Sirolimus						
ISAR-DESIRE	200	200	31	Focal 60 / 40 Diffuse	8 vs. 33 @ 12 mos	11 vs 36 @ 12 mos
SIRO-ISR	332	436	41	46/ 29	12.0 @ 12 mos	13.4 @ 12 mos
TROPICAL	162		30	57% LAD lesions	7.4 @ 9 mos	9.8 @ 9 mos
RESEARCH	44	53	25	Focal 42 / 58 Diffuse	11.6 @ 12 mos	20.9 @ 12 mos
Paclitaxel						
TAXUS III	28	28	14.3	Focal 32.1 / 67.9 Diffuse	21.4 @ 12 mos	29 @ 12 mos
ISAR-DESIRE	200	200	27	Focal 51 / 49 Diffuse	19 vs. 33 @ 12 mos	22 vs 36 @ 12 mos

8. Chronic Total Occlusion Lesions

Chronic total occlusion (CTO) continues to represent a significant challenge more than 20 years after the first PTCA, accounting for up to 15% of activity in the catheterisation laboratory. This rate is largely dependent on patient selection. The most important technical limitation is lesion crossing using a suitable guide wire through the occlusion. With recent advances in technology and increased operator experience, better results have been reported. As yet, there are only a handful of clinical studies in which the potential role of drug-eluting stents has been evaluated in this very challenging lesion subset. Continued improvement to the wires and devices used for crossing CTOs will be the main driver of increased percutaneous CTO revascularizations.

With the sirolimus-eluting stent, PRISON II is the only randomised controlled trial comparing the SES stent to the Bx Velocity bare metal stent[69]. Other studies are one small registry involving 25 patients (SICTO)[70], and two registries[71,72].

PRISON II addressed a primary end point of angiographic binary in-segment restenosis at six months. A total of 200 patients were randomized to a bare BX Velocity stent or to the sirolimus-eluting stent. The clinical event rate was higher in the bare-metal-stent group (20% vs. 4%), driven primarily by target lesion revascularization (TLR) (19% vs. 4%) and target vessel failure (22% vs. 8%). At 12 months the MACE results remained significantly better for the sirolimus-eluting stent group. Six-month angiographic follow-up also pointed to significant differences between the two stents. Notably, in-segment (41% vs. 11%) and in-stent restenosis (36% vs. 7%), as well as re-occlusions (13% vs. 4%), were significantly higher in the bare-metal-stent group.

The SICTO study assessed the safety and effectiveness of the SES stent in reducing angiographic in-stent late loss in totally occluded native coronary arteries. At 6-month follow-up absolute late lumen loss was -0.03 ± 0.28 mm with a restenosis rate of 0%. The IVUS follow-up revealed in-stent obstruction volume of 4.9 ± 6.8%. Target lesion revascularisation at 12 months was 4%, with target vessel revascularisation of 12%. Similarly, Major Adverse Cardiac Events at 12 months was 4.0%.

The aim of the CTO subset (n=56) of RESEARCH registry was to assess SES stent implantation for the treatment of CTO. The CTO cohort was compared with a similar group of patients (n=28) treated in the preceding 6-month period. At 1-year, the cumulative survival-free of MACE was 94.4% in the SES group compared with 82.8% in the control bare metal stent group. At 6-months, 33 (58.9%) patients in the SES group underwent follow-up angiography (none in the bare metal stent group). The binary restenosis rate was 9.1%. At 12-month follow-up the MACE rate was 3.6. Similarly, the Milan group identified 122 patients who underwent revascularisation in CTO lesions. A control group consisted of 259 consecutive patients with CTO lesions treated with bare metal stents in the preceding 24 months. At 6-month follow-up the Milan group reported the cumulative MACE rate of 16.4% in the SES group as compared with 35.1% in the control group. The incidence of restenosis was 9.2% in the SES group and 33.3% in the bare metal stent group. The need for revascularization in the SES

group was significantly lower, both target lesion (7.4% vs. 26.3%) and target vessel revascularization (9.0% vs. 29.0%).

With the paclitaxel-eluting stent there are two studies in which the paclitaxel-eluting stent was used to treat patients with a confirmed CTO lesion. Buellesfeld and colleagues evaluated both safety and efficacy of the polymer-based paclitaxel-eluting PES stent for treatment of chronic total coronary occlusions[73]. Forty-five consecutive symptomatic patients with chronic total coronary occlusions were included in this observational single-arm study. Only patients with successfully crossed occlusions were enrolled. Primary endpoints were binary restenosis and late lumen loss at 6-month angiographic follow-up. Secondary endpoints were MACE at 30-day and 6-month follow-up. The 30-day MACE rate was 0%. At 6 months, the cumulative MACE-free survival was 84.4%. There were no deaths, myocardial infarctions, or stent thrombosis up to 6 months post-stenting. At angiographic follow-up, the in-stent restenosis rate was 13.2% (5/38). There was a total of five in-stent restenoses, with three focal and two diffuse restenosis patterns. The in-segment late lumen loss was 0.13 +/- 0.58 mm. The stent edge analyses revealed a late loss of 0.21 +/- 0.66 proximally and a negative late loss of -0.10 +/- 0.67 at the distal edge segment.

In a second study, Werner GS et al. assessed the effect of paclitaxel-eluting stents in CTO's in a strategy of extensive stent coverage and the optional use of additional bare metal stents (BMS) [74]. In 82 consecutive patients, a CTO (duration > 2 weeks) was successfully recanalized with implantation of one or more paclitaxel stents. These patients underwent a repeat angiography after 5.0 +/- 1.5 months and were assessed by quantitative angiography. The patients were compared with 82 clinically and lesion-matched patients from a consecutive series of 148 patients with CTOs treated by BMS in the preceding time period. In 21 of the 82 patients, additional lesions in the target artery not directly related to the original occlusion site were treated with BMSs (hybrid approach). The history of diabetes, extent of coronary artery disease, clinical symptoms, and angiographic features were similar in the PES and BMS group. Peri-procedural adverse events were 3.3% with PES and 3.3% with BMS, but 12 months MACE was significantly lower in the group with exclusive use of PES (13.3% vs. 56.7%; P < 0.001), mainly due to a lower TLR of 10.0% as compared to 53.4% (P < 0.001). There was only one late re-occlusion with PES (1.7%) as compared to 21.7% with BMS (P < 0.05). However, in the hybrid group, the MACE rate was considerably higher, with 33.3%.

Study	# Pts	# DM	% MVD	Lesion Length	# stents / pt	Mean length of occlusion	TLR %	MACE %
Sirolimus								
PRISON II	100	10.0	53.0			16.0 ± 9.26	4 @ 6 mos	4 @ 6 mos
SICTO	25			30.2± 12.0			0	
RESEARCH	56	14.3	46.3		2.0	11.3	1.8 vs 3.6 @ 12 mos	3.6 vs. 17.2 @ 12 mos
Milan Registry	122						7.4 vs. 26.3 @ 6 mos	16.4 vs 35.1 @ 6 mos
Paclitaxel								
PES CTO	45							15.6 @ 6 mos
Werner et al. (PACTO study)	82	33	23		1.7	18±13	10.0 vs. 53.4 @12 mos	13.3 vs 56.7 @ 12 mos

9. Bifurcation lesions

Bifurcation lesions continue to represent a major challenge for interventional cardiologists. Understanding the crucial role of an appropriate strategy using the quality of the immediate results will continue to dictate the long term outcome – even in the era of drug-eluting stents.

Currently, only little and non-controlled data on the sirolimus stent has been reported. Researchers from the Center Cuore Columbus, Milan, Italy evaluated the use of SES stents in the treatment of bifurcation lesions[75]. Between April 2002 and May 2004, 174 consecutive patients who underwent percutaneous coronary intervention of bifurcational lesions with sirolimus-eluting stents were identified. Two strategies were used: stenting only 1 branch (group 1S, n = 57) or stenting both branches (group 2S, n = 117). The incidence of major adverse cardiac events was evaluated in the hospital and at 9-month follow-up. There were no statistically significant differences between the 2 groups with regard to the incidence of target lesion revascularization (5.4% vs 8.9%, p = 0.76), target vessel revascularization (5.4% vs 11.1%, p = 0.51), and cumulative major adverse cardiac events (18.9% vs 23.3%, p = 0.76) at 9 months.

The SES-Bifurcation prospective study evaluated the safety and efficacy of sirolimus-eluting stents for treatment of coronary bifurcation lesions[76]. Patients were randomly assigned to either stenting of both branches (group A) or stenting of the main branch with provisional stenting of the side branch (SB) (group B). Eighty-five patients (86 lesions) were enrolled. There was 1 case of unsuccessful delivery of any device at the bifurcation site. Given the high crossover, more lesions were treated with 2 stents (n=63) than with stent/balloon (n=22). Clinical follow-up at 6 months was completed in all patients and angiographic follow-up in 53 patients in group A (85.5%) and 21 in group B (95.4%). One patient died suddenly 4.5 months after the procedure. There were 3 cases of stent thrombosis (3.5%). The total restenosis rate at 6 months was 25.7%, and it was not significantly different between the double-stenting (28.0%) and the provisional SB-stenting (18.7%) groups. Fourteen of the restenosis cases occurred at the ostium of the SB and were focal. Target lesion revascularization was performed in 7 cases; target vessel failure occurred in 15 cases (17.6%). Overall low TLR and MACE rates are reported with the sirolimus eluting stent in bifurcations lesion, however, MACE rate increases dramatically in case both branches are stented.

In another paper from Milan the results from the crush stenting technique with DES is reported[77]. In order to guarantee full coverage of the ostium of the side branch, the crush stent technique was introduced. In 106 patients 110 bifurcations were treated with the sirolimus eluting stent and 75 patients with 75 bifurcations with the paclitaxel eluting stent. In 116 patients with 118 bifurcations a final kissing balloon procedure was performed, whereas in 65 patients with 67 bifurcations a final kissing balloon procedure was not done. The absence of a final kissing balloon procedure together with the presence of diabetes and premature discontinuation of dual antiplatelet therapy were identified as independent predictors for target lesion revascularization and stent thrombosis during the 9 months follow up. With the crush technique the restenosis rate in the side

branch of 21% in the SES bifurcation study was reduced to 11.1 % when a final kissing balloon procedure was performed. Though little is mentioned about outcome of the specific sirolimus and paclitaxel stents, there was no difference in post procedural stent thrombosis between sirolimus and paclitaxel eluting stents.

Hoye et al. reported the outcome of a single center non controlled comparison study of 144 consecutive patients with 167 bifurcation lesions treated with the sirolimus eluting stents followed by 104 patients with 133 bifurcation lesions that were treated with the paclitaxel eluting stent[78]. Though better then the historical bare metal stent results, the MACE rate and the TLR rate was significant higher for the paclitaxel group compared to the sirolimus stent group, although different stenting techniques were used between both groups and less GP2a3b inhibitors in the paclitaxel stent group.

Study	# Pts	# DM	# Lesions	Stent Strategy 1 branch vs. 2 branches		TLR % 1 branch vs. 2 branches		MACE % 1 branch vs. 2 branches	
Sirolimus									
Milan BIF	174			N=57	N=117	5.4 @ 9 mos	8.9 @ 9 mos	18.9 @ 9 mos	23.3 @ 9 mos
SES-BIF study	85		86	N=43	N=43	4.5 @ 6 mos	9.5 @ 6 mos		
RESEARCH[79]	56	14.3	65		N=65				10.3 @ 6 mos
Hoye et al.	144	18.8	167	N=22	N=145		9.1 @ 9 mos*		13.3 @ 9 mos*
Paclitaxel									
DES crush†	181	22.1	185		N=185		14.9 @ 9 mos		26.5 @ 9 mos
Hoye et al.	104	17.3	113	N=17	N=87		18.4 @ 9 mos*		21.4 @ 9 mos*

** TLR and MACE rates are reported for the single and multiple stent groups together.*

†DES crush study results are sirolimus and paclitaxel eluting stents together.

10. Left main lesions

The expansion of drug-eluting stent technology is having a major impact on 'real world' clinical practice. More and more patients are switching from surgery to angioplasty based on the results of clinical trials of drug-eluting stents in a wide variety of patient subsets and lesion types – including those with unprotected left main coronary artery disease. The principal major adverse cardiac event in survivors of left main coronary angioplasty (LMCA) with drug-eluting stents remains the need for target vessel revascularisation. With the exception of the CORPAL study, the evidence in support of the use drug-eluting stents in the treatment of left main disease is currently restricted to registries / single centre studies.

In the Spanish CORPAL study, de Lezo et al. studied a series of 52 patients with LM lesions treated with SES[80]. Forty-seven patients presented with de novo stenoses, and 5 had in-stent restenosis; 19 patients required combined stent treatment for other remote lesions in the coronary tree, 6 of them at the level of proximal right coronary artery. The SES stent was implanted directly at the LM in 39 patients; 13 others needed pre dilatation. Once deployed, the SES was over expanded with short balloons adjusted to the LM length in 44 patients. Quantitative coronary angiograms were analyzed in the same view before and immediately after treatment and at follow-up. Patients were followed-up at 6-month or earlier in the presence of symptoms. At follow-up study, quantitative coronary angiography and motorized intravascular ultrasound analyses were performed in 35 (67%) patients. Dr de Lezo and colleagues reported that primary success was obtained in 50 patients (96%). Two patients (4%) developed a non-Q-wave myocardial infarction. All patients were symptom-free at discharge. After a mean follow-up of 12 +/- 4 months, 50 patients (96%) remain asymptomatic. No late death or acute thromboses were reported. Two patients became symptomatic 2 and 4 months after treatment, respectively. One had restenosis at a remote site, while the other had in-segment restenosis. None of the remaining 33 angiographically evaluated patients developed restenosis at any site. Target lesion revascularization was 1/52 (2%).

A second study by SJ Park and colleagues was designed to compare the clinical and angiographic outcomes of the SES stent and bare metal stent implantation for unprotected left main coronary artery stenosis[81]. Elective SES implantation for de novo unprotected LMCA stenosis was performed in 102 consecutive patients with preserved left ventricular function from March 2003 to March 2004. Data from this group were compared to those from 121 patients treated with BMS during the preceding two years. Compared to the BMS group, the SES group received more direct stenting, had fewer debulking atherectomies, had a greater number of stents, had more segments stented, and underwent more bifurcation stenting. The procedural success rate was 100% for both groups. There were no incidents of death, stent thrombosis, Q-wave myocardial infarction (MI), or emergent bypass surgery during hospitalization in either group. Despite less acute gain (2.06 +/- 0.56 mm vs. 2.73 +/- 0.73 mm, $p < 0.001$) in the SES group, SES patients showed a lower late lumen loss (0.05 +/- 0.57 mm vs. 1.27 +/- 0.90 mm, $p < 0.001$) and a lower six-month angiographic restenosis rate (7.0% vs. 30.3%, $p < 0.001$)

versus the BMS group. At 12 months, the rate of freedom from death, MI, and target lesion revascularization was 98.0 +/- 1.4% in the SES group and 81.4 +/- 3.7% in the BMS group (p = 0.0003).

Alaide Chieffo and colleagues studied consecutive patients electively treated from April 2002 to April 2004 in the EMO Centro Cuore Columbus and San Raffaele Hospital with implantation of an SES or a PES in the ULM on de novo lesions were analyzed[82]. Patients treated with a DES were compared with the historical group of consecutive patients treated with a BMS from April 1993 to June 2001. Eighty-five patients were treated with a DES (41 with an SES, and 44 with a PES); 64 received a BMS. The authors do not provide any comparative results between the two DES used in this study. Compared with BMS patients, those treated with a DES had a lower ejection fraction (51.1±11% versus 57.4±13%, respectively; *P*=0.002) and were more often diabetic (21.2% versus 10.9%, *P*=0.12) with more frequent distal left main involvement (81.2% versus 57.8%, *P*=0.003). High mortality risk scores (Euroscore >6 and/or Parsonnet >15) were present in 38 DES patients (45%), as compared with 22 BMS patients (34%; *P*=0.23). Moreover, in the DES group, smaller vessels (3.33±0.6 versus 3.7±0.7 mm; *P*=0.0001) with more lesions (2.94±1.6 versus 2.25±1.3, *P*=0.004) and vessels (2.03±0.69 versus 1.8±0.72, *P*_0.05) were treated during the index procedure with longer stents (24.3±12 versus 15.8_8.6 mm, *P*=0.0001). At the 6-month clinical follow-up, the incidence of MACE was significantly lower in the DES group (17 of 85) than in the BMS group (23 of 64) (20.0% versus 35.9%, respectively; *P*=0.039). In addition, the incidence of cumulative MACE was lower in the DES than in the BMS group (24.7% versus 42.1%, respectively; *P*=0.03). Nine patients (14.1%) in the BMS group died, as compared with 3 (3.5%) in the DES group (*P*=0.03). Cardiac deaths occurred in 3 patients (3.5%) in the DES group, as compared with 6 (9.3%) in the BMS group (*P*=0.17), resulting in a 63% relative reduction in the occurrence of cardiac death in the patients treated with DES.

In a second registry to report findings from the use of DES in the treatment of left main lesions without providing a breakdown between DES, Marco Valgimigli and colleagues studied 181 patients who underwent percutaneous coronary intervention for LM stenosis at the Thorax Center, Rotterdam[83]. The first cohort consisted of 86 patients (19 protected LM) treated with bare metal stents (pre-DES group); the second cohort comprised 95 patients (15 protected LM) treated exclusively with DES. The 2 cohorts were well balanced for all baseline characteristics. At a median follow-up of 503 days (range, 331 to 873 days), the cumulative incidence of major adverse cardiovascular events was lower in the DES cohort than in patients in the pre-DES group (24% versus 45%, respectively; hazard ratio [HR], 0.52 [95% CI, 0.31 to 0.88]; P=0.01). Total mortality did not differ between cohorts; however, there were significantly lower rates of both myocardial infarction (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; P=0.006) and target vessel revascularization (6% versus 23%, respectively; HR, 0.26 [95% CI, 0.10 to 0.65]; P=0.004) in the DES group. On multivariate analysis, use of DES, Parsonnet classification, troponin elevation at entry, distal LM location, and reference vessel diameter were independent predictors of major adverse cardiovascular events.

The main findings of the most recent published reports are summarised in the following table.

	# pts	SAT / Late/Death	TLR	TVR	MACE
Sirolimus					
CORPAL	52	0% @ 12 mos	2% @ 12 mos	2% @ 12 mos	4% @ 12 mos
Korean study	102	0% in hospital	2% @ 12 mos	Nd	2% vs. 18.6% @ 12 mos
Chieffo	85 (41 SES)	1.2%	14.1%	18.8%	24.7% vs. 42.1% @ 6 mos
RESEARCH and T-SEARCH	95 (52 SES)	0% in hospital	nd	6% vs. 23% @ 18 mos	24% vs. 45% @ 18 mos
Torino University LMCA registry	96	0	TLR / TVR 4.2%		5.2%
Paclitaxel					
Chieffo	85 (44 PES)	1.2%	14.1%	18.8%	
RESEARCH and T-SEARCH	95 (43 PES)	0% in hospital	Nd	6% vs. 23% @ 18 mos	24.7% vs. 42.1% @ 6 mos
LM TAXUS pilot study[84]	166	2.1% @ 7 mos		5.2 @ 7 mos	24% vs. 45% @ 18 mos

11. Multi-vessel disease

Numerous studies have shown multi-vessel disease to be a strong predictor of major cardiovascular and cerebral events and target lesion revascularisation. Historically, percutaneous coronary intervention in these patients was associated with high rates of revascularisation although rates were reduced following the introduction of stents. Further improvements in stent technology, notably the introduction of drug-eluting stents, have helped to level the playing field between surgery and angioplasty, including patients with diabetes who often have multi-vessel involvement. The benefits of drug-eluting stents are only now beginning to be felt in multi-vessel disease. ARTS II was the first trial to evaluate a drug-eluting stent trial in multi-vessel disease, and the first to have been published[85]. ARTS II compared the outcomes of 607 patients with multi-vessel disease and treated with sirolimus-eluting stents with the historical results of the two arms of the ARTS I trial. It showed that sirolimus eluting stents are safe and efficacious in multivessel disease and significantly better then the results obtained with BMS in ARTS I. Compared to the historical surgery study arm in ARTS I, ARTS II results still yielded higher TLR rates, but overall had a similar MACCE rate.

With the paclitaxel stent the ongoing pivotal SYNTAX trial will address in a larger and true randomized controlled study the value of paclitaxel stents in multivessel and left main coronary artery disease.

Characteristic	**ARTS II * SES**	**ARTS I PCI (BMS)**	**ARTS I CABG**
# Pts	607	600	605
Male (%)	77	77	76
Age (years ± SD)	63 ± 10	61 ± 10	61 ± 9
Myocardial Infarction (%)	34	44	42
Diabetes (%)	26	19	16
Hypertension (%)	67	45	45
Hypercholesterolemia (%)	74	58	58
Family history of MI (%)	36	39	42
Current Smoker (%)	19	28	26
Peripheral Vascular Disease (%)	7	6	5
No. diseased vessels			
1	0	4	4
2	46	69	66
3	54	27	30
Lesion Classification			
A	7	6	7
B1	23	26	31
B2	56	60	54
C	14	8	8
No stents implanted ± SD	3.7 ± 1.5	2.8 ± 1.3	-
Total stent length	72.5 ± 32.1	47.6 ± 21.7	-
Max. dilation pressure (atm ± SD)	16.4 ± 2.9	14.6 ± 3.0	-
Direct Stenting (%)	34.6	3.3	-
Glycoprotein IIb/IIIa inhibitors during procedure	33	-	-
Clinical Endpoints out to 1-year (97% follow-up)			
Death (%)	1.0	2.7	2.7
CVA (%)	0.8	1.8	1.8
MI (%)	1.2	5.0	3.5
Re- CABG (%)	2.0	4.7	0.7
Re-PCI (%)	5.4	12.3	3.0
Any MACCE (%)	10.4	26.5	11.6

12. Antithrombotic therapy in PCI with DES

a. Platelet inhibition

Acetylsalicyl acid. So far all studies with DES have been performed with the combination therapy of acetylsalicyl acid (100-325 mg daily) and clopidogrel (75 mg daily). Acetylsalicyl acid is usually given life long after the procedure. ***Recommendation class 1, level C***.

Clopidogrel. In DES studies clopidogrel is only given for 3 (Cypher™, Endeavor™ and Janus™ stent studies) to 6 months (all Taxus™ studies), except for the E-Sirius trial (2 months). Considering the late complete healing of the vessel wall after drug eluting stenting, and the reported occurrences of stent thrombosis shortly after early discontinuation of clopidogrel (< 6 months post PCI), the Dutch Working Group on Interventional Cardiology advises - according to the European Guidelines on PCI (Eur HJ 2005) - to use clopidogrel (in combination with acetylsalicyl acid) for at least 9-12 months after the PCI. ***Recommendation level class1, level C***.

b. Anticoagulants

Heparin. Heparin has been used in almost all DES studies during the PCI procedure. Heparin is still considered the standard regimen for PCI procedures in which the operator aims at achieving an activated clotting time between 250 and 350 sec or between 200 and 250 in case 2b3a GP blockers are administrated. ***Recommendation level class 1, level C***.

Bivalirudine. Little data is available on the effect of bivalirudine on drug eluting stenting. Only 1 single center study has prospectively investigated the safety and feasibility of bivalhirudin during with DES (SES and PES)[86]. No specific interactions between bivalhirudin and DES were observed in this non randomized study. More data on the effect of bivalhirudin with the PES stent is expected from the ongoing HORIZON trial. ***Recommendation level class 2b, level C***.

Fractionated Heparin. To date little data is available on the use of fractionated heparin during PCI with DES. There is no compelling data that fractionated heparin is superior to unfractionated heparin during bare metal stent PCI with or without 2b3a GP blockers. Whether DES stents have a different interaction with fractionated heparin compared to unfractionated heparin is probably unlikely, but more information is needed to advice for standard fractionated heparin usage during PCI with DES. ***Recommendation class 2b, level C.***

13. Recommendations based on Cost effectiveness

There is limited published information available on cost effectiveness of DES stents. The main reasons are the many variables that are involved like the local price of the DES stent, the amount of revascularization procedures for in-stent restenosis, the availability of brachytherapy, the local costs for PCI and CABG etc. The latest evidence on the cost-effectiveness of DES comes from the BASKET trial[87] and the paper by van Hout et al.[88].

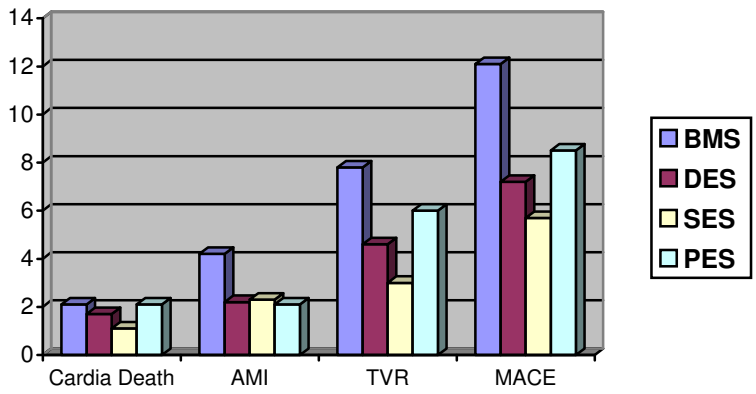
BASKET is the first prospective randomized trial to compare DES and BMS in consecutive, non-selected patients on an "all-comer" basis. Between May 2003 and June 2004 all patients referred for interventional therapy of coronary disease were randomized to receive either sirolimus-eluting, paclitaxel-eluting or BMS irrespective of clinical presentation or lesion characteristics. The only exclusion criteria were no patient consent, in-stent-restenosis and vessel size ≥4mm. Clinical follow-up for major events is performed after 6 and 18 months including stress myocardial perfusion scintigraphy after 6 months. This first analysis compares in-hospital major events, i.e. death, non-fatal myocardial infarction and target lesion/vessel revascularization (TLR/TVR) up to discharge. A total of 806/988 patients (82%) were enrolled, while 46 patients were treated for in-stent-restenosis and 136 did not consent or appropriate stent sizes were not available. Overall in-hospital mortality was 1.2%, infarction rate 1.5% and the rates of TVR 2.2% or TLR 0.9% for a total event rate of 4.0% (Table 1).

TABLE 1: BASKET TRIAL (ESC 2005)

In-Hospital MACE:	All n= 806	SES n = 261	PES n = 276	BMS n=269	P value
Death (%)	1.2	0.8	1.1	1.5	
Non-fatal MI (%)	1.5	1.5	0.7	2.2	
TVR (%)	2.2	1.5	2.6	2.6	
TLR (%)	0.9	0.8	0.7	2.2	
Any event (%)	4.0	3.1	3.2	5.6	0.25
Stent thrombosis (%)	0.7	0.8	0.7	0.7	

Although the trial was not powered to show any statistical differences between the two DES, Dr Pfisterer reported a trend in favor of SES at the 6-month follow-up point (Figure 1). Major predictors of in-hospital events were acute infarction, 3 vessel-disease and number of stented segments.

Figure 1: BASKET Trial: Rate of MACE at 6 months – a comparison of DES vs. BMS, and the two subgroups of DES (SES & PES) – ESC 2005



The total costs at six months for the DES group (10,544 Euros) were higher than the bare metal stents (9,639 Euros) demonstrating increased costs for the initial procedure could not be off-set by reductions in event-related follow-up costs. This point was highlighted by Dr Petr Widimsky who, in his discussion of the BASKET Trial, noted that the cost analysis data could have been skewed by the use of one of the more expensive bare metal stents in the trial (Vision list price €1260). 'Since the risk of adverse events is reduced by 40 percent, patients would clearly prefer a DES," he said. "Healthcare systems and industry should find financial solutions to allow routine use of these devices," he added. Another issue is the relative high cost price of the DES stents used. Cypher list price was €2380and Taxus list price was €1935.

In BASKET, it cost 18,311 Euros to avoid one major event with DES and the cost per quality-adjusted life-year (QUALY) gained from DES-use was more than 50,000 Euros. However, sub-group analysis of high-risk elderly patients and people with three-vessel disease, multiple lesions, long lesions and small vessels proved more cost effective. Commenting on these findings, Dr Pfisterer said: "Under present restricted budgets cardiologists have to use what they can afford and on the basis of this data there's still no reason to use DES in all patients. Until prices fall they should be reserved for high risk patients." Currently, the price of DES has fallen considerably in the Netherlands and still continues to fall.

14. Longterm effects of DES

Although all landmark trials have shown no adverse late effects with DES compared to the bare metal stents, some recent reports on late[89,90] (> 30 days < I year) and very late[91] (> 1year) stent thrombosis in the real world situation have fuelled the debate on long term safety of DES in daily practice.

Stent thrombosis is a rare (0.5-1.5%) but serious and often lethal complication of PCI.[89] Multivariate analysis of several large DES studies have indicated that stent thrombosis with DES is associated with (pre-mature) discontinuation of dual anti-platelet therapy, renal failure, stent bifurcations and in-stent restenosis.[89,90, 92] Hypersensitivity reactions on the polymer coating of the DES has been proposed as one of the reasons for lack of intimal healing and stent thrombosis.[93]

The recent presented late (18 months) results of the BASKET-LATE study observed a trend in more stent thrombosis and higher long-term mortality with the Cypher™ or Taxus™ stent compared to the Vision™ bare metal stent.[94] The BASKET investigators followed the remaining 746 'all-comer' patients who were MACE free at 6 months (end-point of the cost-effectiveness BASKET trial) for an additional 12 months, when the clopidogrel was stopped in these patients. The outcome between 7 and 18 months after PCI of the pooled Taxus™ and Cypher™ stent group was compared to the BMS group. In this time period a surprising higher nonfatal MI and cardiac death was noted in the DES group. The investigators stated that using this kind of drug eluting stent in 100 patients may avert five target vessel revascularizations, but at a price of three late deaths/myocardial infarctions. However, the outcome of the BASKET-LATE study is heavily questioned by the lack of statistic power to look at these infrequent events in this relative small study and by the use of unclear defined 'thrombosis related events'. Furthermore, another recent long term report of the Rotterdam RESEARCH registry on the usage of DES in the 'real world' didn't show an increase in mortality and in stent thrombosis within 2 years.[95] Nevertheless, the long-term outcome of DES in strict controlled trials may differ from the outcome in the real world and whether long-term requirement of clopidogrel is needed are two issues that still need to be addressed.

15. New and future developments

Following in the footsteps of Cordis, Boston Scientific, Medtronic and Sorin, Guidant, has received Conformite Europeene (CE) Mark approval for the XienceV® Everolimus Eluting Coronary Stent System in January 2006. This regulatory certification allows Guidant to begin marketing the drug eluting stent in the 25 countries of the European Union.

Guidant's rapid-exchange XienceV® everolimus-eluting stent is currently still being tested in the ongoing SPIRIT II and SPIRIT III pivotal trials. The results from the multi-center randomized safety and efficacy SPIRIT I trial (n=60), demonstrated an angiographic in-stent late loss of 0.10 mm at 6 months (primary endpoint) and 0.24 mm at 12 months, comparable to one-year results from the early pivotal trials with the sirolimus and paclitaxel stent[96,97.]

SPIRIT I: 6-month Angiographic and clinical end points [97]			
End point	**Everolimus (n=23)**	**Bare-metal-stent (n=27)**	**P**
In-stent Late loss (mm)	0.10	0.87	<0.001
In-segment Late loss (mm)	0.07	0.61	<0.001
% volume obstruction	8±10	28±14	<0.001
In-segment binary restenosis (%)	4.3	33.3	0.01
% MACE (overall)	7.7	21.4	

SPIRIT I: 12-month angiographic and clinical end points [96]			
End point	**Everolimus (n=16)**	**Bare-metal stent (n=21)**	**P value**
In-stent Late Loss (mm)	0.24	0.84	<0.001
In-segment Late Loss (mm)	0.14	0.59	<0.001
% volume obstruction	10±7	28±12	<0.001
In-stent binary restenosis (%)	4.5	28.0	0.05
% MACE (Device related*)	3.8	21.4	
% MACE (overall)	15.4	21.4	

**three non study device related events occurred (one non-Q MI in non-target vessel, one TLR due to dissection during the procedure and one non-Q MI during IVUS at FU).*

Following the entry of Guidant, the next wave of drug-eluting stents is likely to include products from Conor MedSystems, OrbusNeich, Biosensors and Devax, all of whom have released data in support of their respective drug-eluting stent programs.

Two clinical trials involving the CoStar Stent (Conor MedSystems) have reported at international congresses. EuroStar (EUROpean cobalt chromium Stent with Anti-proliferative for Restenosis) is a prospective, multi-centre, sequentially controlled, non-randomised, two-arm dose-ranging pivotal trial designed to evaluate the safety and effectiveness of the CoStar stent for the treatment of restenosis.

EuroStar (6-month follow-up)	**Arm 1**	**Arm 2**
Paclitaxel dose	10mcg	30mcg
In-stent binary restenosis (%)	3.4	6.9
In-stent late loss (mm)	0.26	0.39
TLR (%)	1.7	3.6
MACE (%)	4.8	9.2

EuroStar (12-month follow-up) --- Keith Dawkins, EuroPCR 2005: Oral Presentation	
	Arm 1 (n= 142# patients)
Death	2.1%
Myocardial Infarction: Q-Wave Non Q-Wave	 0.7% 1.4%
Emergent CABG	0.0%
TLR* (%)	2.9%
Cumulative MACE (%)	7.6%
Stent Thrombosis (0- -6 M)	0.7%
Stent Thrombosis (6- -12 M)	0.0%
* Clinically Driven TLR based on number of lesions # One patient was a failure to cross and followed only to 30 days	

COSTAR I (Cobalt chromium Stent with Antiproliferative for Restenosis) is a three-arm, dose-ranging registry is a pilot study designed to evaluate the safety and efficacy of the CoStar stent with the formulations of 3mcg, 10mcg and 30 mcg of Paclitaxel. A total of 122 lesions were treated in 87 patients. Nearly 50% of the patients had a prior myocardial infarction and approximately 25% were diabetic.

The final results of the HEALING II study (Orbus-Neigh) were presented at the 2005 Transcatheter Cardiovascular Therapeutics (TCT). The HEALING II study evaluated the safety and efficacy of the Genous Bio-engineered R-stent. Unlike drug eluting stents (DES) which inhibit tissue growth, the manufacturers claim that Genous captures a patient's endothelial progenitor cells (EPCs) to accelerate the natural healing process. Once attached, EPCs rapidly form a protective endothelial layer over the stent, providing immediate protection against thrombus and minimizing restenosis. During the course of this trial, 63 patients were treated at 10 centers in Belgium, Germany, and The Netherlands. The index lesions had an average reference diameter of 2.63mm, a minimal lumen diameter of 0.98mm, and an average lesion length of 9.83mm. 57% of all lesions were Type B2/C. The clinically driven target lesion revascularization (TLR) rate at six months was 6.3% with an overall major adverse cardiac events (MACE) rate of 7.9%. Additionally, no subacute or late thrombosis was reported even with a recommended 30 days of dual antiplatelet therapy. HEALING III will assess the effect of statin therapy combined with EPC capture and bare metal stents. HEALING III will be initiated in early 2006.

At the 2005 TCT, (DEVAX) reported positive results on its AXXESS PLUS trial, a first in man study for AXXESS(TM) Drug Eluting Bifurcation Stent which included 139 patients from 13 international study centres. Mean lesion length was 16.28 mm in the parent vessel, 7.4 mm in the side

branch; average number of stents used was 1.8 in the parent vessel and 0.58 in the side branch. At 210 days, TVR rate was 7.5%; late loss was 0.11 mm, a 75% reduction from rates achieved with AXXESS bare-metal stent. The AXXESS Stent is the first to show clinical results with a drug eluting stent designed specifically for bifurcation lesions. The Devax AXXESS technology is a proprietary self-expanding nickel titanium alloy stent specifically engineered for the treatment of coronary and vascular bifurcation lesions. The conical shape of the stent conforms to the bifurcation anatomy and provides full access to both branches for additional interventional procedures. DEVAX has licensed the drug Biolimus A9 and a bioabsorbable polymer coating from Occam International, an affiliate of Biosensors International.

The STEALTH study is the first in man study to assess the safety and efficacy of the bioabsorbable-polymer coated Biolimus A9 eluting BioMatrix™ stent as compared to a bare metal stent control (S-Stent™).

STEALTH Trial: All MACE to 6 Months (Hierarchical)			
	Control BMS (n=40)	Biolimus A9 (n=80)	P value
MACE (Death, MI or TLR)	7.5%	5.0%	0.68
Death	0%	0%	NA
Q-wave MI	0%	0%	NA
Non Q Wave MI	7.5%	3.8%	0.40
Emergent CABG	0%	0%	NA
TLR-CABG	0%	0%	0.0000
TLR-PTCA	0%	1.3%	>0.99
• Non-Q Wave MI: Spiral dissection during stent implantation; Pt. received 3 non-study stents • TLR: RCA acute stent thrombosis, clinical driven re-PCI, no MI			

STEALTH Trial: Angiographic Follow-Up to 6 Months			
	Control BMS (n=40)	Biolimus A9 (n=80)	P value
In-stent % Diameter Stenosis	27.38	11.86	p < 0.001
In-stent Late Loss (mm)	0.74	0.26	p <0.005
In-lesion % Diameter Stenosis	30.85	22.03	p < 0.001
In-lesion Late Loss (mm)	0.40	0.14	p = 0.004
In-stent binary restenosis (%)	7.7	3.9	0.40
In-lesion binary restenosis (%)	7.7	3.9	0.40
Ref: E. Grube: TCT 2005 Oral Presentation			

16. Conclusions

Recommendations are based on in-exclusion criteria of randomised trials and large observational studies. Conform European Guidelines, the usefulness or efficacy of the usage of DES will be presented according to three classes and the strength of evidence will be ranked according to three levels of evidence.

Classification of usefulness or efficacy

Class 1 Evidence and/or general agreement that treatment is beneficial, useful and effective

Class 2 Conflicting evidence and/or a divergent of opinion about the usefulness /efficacy of the treatment:

- Class 2a Weight of evidence/opinion is in favour of usefulness/efficacy
- Class 2b Usefulness/efficacy is less well established by evidence/opinion

Level of evidence

Level A Data derived from randomised trials or meta-analyses

Level B Data derived from a single randomised trial or non-randomised studies (registries) or single meta-analysis

Level C Consensus opinion of experts and/or small studies.

	Sirolimus	**Paclitaxel**	**Zotarolimus**	**Tacrolimus**
Non Complex	*Class 1, Level A*	*Class 1, Level A*	*Class 2a, Level B*	*Class 2b, Level B*
Moderate Complex	*Class 1, Level A*	*Class 1, Level A*		
Small Vessel (2.25-3.0 mm)	*Class 1, Level B*	*Class 1, Level B*		
Long Lesion (> 40 mm)	*Class 1, Level B*	*Class 1, Level B*		
STEMI Lesions	*Class 2a, Level B*	*Class 2a, Level B*		
DM Patients	*Class 1, Level A*	*Class 1, Level A*	*Class 2a, Level C*	
In Stent Restenosis Lesions	*Class 1, Level A*	*Class 1, Level B*		
CTO lesions	*Class 1, Level A*	*Class 1, Level B*		
Bifurcation Lesions	*Class 1, Level C*	*Class 1, Level C*		
Left Main Lesions	*Class 1, Level B*	*Class 1, Level B*		
Multi Vessel Treatment	*Class 1, Level B*	*Class 1, Level C*		

The above mentioned recommendations are by no means absolute requirements for the use of DES in the different subsets of lesions or patients. Individual circumstances can require that BMS can be used in stead of DES. For instance the likelihood of increased bleeding risk, the need for early discontinuation of dual anti-platelet therapy or potential increased risk for in stent thrombosis may favour the use of BMS. Furthermore, in relative low risk lesions for re-stenosis the additional benefit of DES is proven, however at high initial costs and disputable cost-effectiveness. Daily usage of DES or BMS in these circumstances is at discretion of the individual operators.

In conclusion, drug eluting stents irrefutably reduces restenosis, morbidity and patient discomfort in the majority of clinical settings.

Peter Smits, 23june 2006.

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