FDA Clinical Overview for Panel Packet
DES Thrombosis Panel
December 7-8, 2006

I. Introduction

FDA has been monitoring the use of drug eluting stents (DES) since they were approved for use in the United States market in 2003 (Cypher® Sirolimus-Eluting Coronary Stent) and 2004 (Taxus™ Express^2™ Paclitaxel-Eluting Coronary Stent). Recent presentations at scientific meetings have suggested a small but significant increase in the rates of: (1) death or myocardial infarction (possibly due to stent thrombosis) and (2) non-cardiac mortality in DES-treated patients compared to patients treated with bare metal stents (See Section VII: *Camenzind*, European Society of Cardiology Scientific Congress, September 2006; *Nordmann, et al.,* Eur Heart J 2006, in press). FDA has also been evaluating the use patterns of clopidogrel, a drug used in combination with aspirin in patients to reduce/prevent stent thrombosis in DES patients. Although the duration of clopidogrel use appeared to be adequate for the selected patient population in the original clinical trials that supported FDA approval, the optimal duration of clopidogrel in more complex patients has not been established. Though much of the current data that have raised questions regarding the safety of DES have been publicly presented at scientific meetings, relatively little has appeared in peer-reviewed publications or has been independently reviewed by FDA. Nevertheless, DES thrombosis concerns have important public health implications that warrant open an open dialogue among the DES manufacturers, investigators, physicians, and the FDA.

FDA is convening this public meeting of the Circulatory System Devices Advisory Panel in an effort to fully characterize the risks, timing and incidence of DES thrombosis. The purposes of this meeting are: (1) to provide a forum for the presentation of clinical data relevant to the issue of DES thrombosis (both when DES are used according to their label and in more complex patients beyond their labeled indication) and (2) to address the appropriate duration of clopidogrel use in DES patients.

II. DES: Pathophysiologic insights into restenosis prevention and stent thrombosis

In catheter-based percutaneous coronary intervention (PCI), lumen enlargement is created by splitting the atherosclerotic plaque and is often accompanied by stretching (and frequently disruption) of the arterial media and stretching of the adventitia. The endothelial arterial lining is invariably damaged during PCI. The arterial responses to PCI follow an injury-and-repair sequence of events (*Farb, et al*. Circulation 1999; 99: 44-52). Within the initial 72 hours, platelet and fibrin deposition are present associated with acute inflammation. Over the next 2 weeks, chronic inflammatory cells (lymphocytes and macrophages) replace neutrophils and proliferating vascular smooth muscle cells (SMC's) migrate from the media and intima. These SMC's synthesize extracellular matrix (collagen and proteoglycans) to form the neointima, which becomes endothelialized. Adventitial fibrosis is commonly observed. The greater the degree of arterial injury, the greater the resultant inflammatory responses and the greater the expansion of the neointima (*Farb, et al*. Circulation 2002; 105: 2974-80).

Clinical restenosis after arterial balloon injury occurs as a result of luminal re-narrowing secondary to: (1) expansion of the neointima and (2) adventitial fibrosis-induced arterial constriction (negative remodelling). Deployment of metal stents prevents arterial constriction that occurs post-balloon angioplasty so that restenosis occurs as a consequence of neointimal

growth alone. Compared to balloon angioplasty, bare metal stents improve PCI outcomes via: (1) reducing rates of acute vessel closure and recoil and (2) modestly reducing long-term restenosis rates by preventing the constrictive effects of negative remodelling. Deployment of a metallic foreign body within an artery creates a thrombosis risk; antiplatelet therapy prevents thrombosis in the vast majority of cases until the stent struts are covered by an endothelialized neointima.

Residual high restenosis rates after bare metal stenting (approximately 25%) combined with an understanding of the pathogenesis of restenosis lead to investigations of interventions aimed to inhibit neointimal growth. Systemic therapies proved to be ineffective, most likely due to the inability to target drugs in adequate doses to the treatment site. Local delivery of anti-restenosis therapy appeared to be a more promising approach. Success in inhibiting neointimal thickening was achieved via the local delivery of agents that specifically targeted the cell cycle; these agents inhibit cellular proliferation and have anti-inflammatory properties. Pre-clinical studies demonstrated that antimitogenic agents (such as sirolimus and paclitaxel) eluted over time from a polymer coating reduced in-stent stenosis at 28 days (*Carter, et al*. Circulation. 2001; 104: 1188-93).

Effects on healing. Interventions that inhibit of SMC proliferation and extracellular matrix synthesis may also inhibit re-endothelialization of injured arterial surfaces as well as prevent neointimal coverage of stents. The therapeutic benefit of restenosis prevention is thus accompanied by a delay in arterial healing resulting in a prolongation of the window of risk for stent thrombosis. Compared to bare metal stents examined at the similar time points post-deployment, DES typically demonstrate reduced endothelialization, increased inflammation, and increased peri-strut fibrin deposition, and these changes are more pronounced in DES with thrombosis compared to DES without thrombosis (*Joner, et al.* J Am Coll Cardiol 2006; 48: 193–202). In additional, specific lesion morphologies (such as bifurcation lesions and highly necrotic atherosclerotic plaques) are associated with delayed neointimal healing and may be inherently at increased risk for stent thrombosis (for both bare metal stents and DES). Rare cases of very late stent thrombosis associated with aneurysm formation and a hypersensitivity-like reaction (possibly in response to the DES non-biodegradable polymer) have been identified (*Virmani, et al.* Circulation 2004; 109: 701-5). Finally, stent thrombosis may occur in the setting of severe in-stent stenosis produced by aggressive neointimal thickening.

Resistance to antiplatelet therapy is a potential risk factor for stent thrombosis. Responsiveness to the antiplatelet effects provided by aspirin and thienoyridines vary widely in the population, and relative antiplatelet hyporesponsiveness has been associated with cardiovascular events such as unstable angina, MI, myonecrosis post-PCI, and cardiac death. ADP released from adhering platelets activates the $P2Y_{12}$ receptor resulting in further platelet recruitment and aggregation; thienoyridines antagonize the $P2Y_{12}$ receptor (*Dorsam, et al*. J. Clin. Invest.*2004;* 113: 340–5). Retrospective data suggest that high post-PCI platelet reactivity and incomplete platelet $P2Y_{12}$ receptor inhibition increase the risk for subacute stent thrombosis (*Gurbel, et al.* J Am Coll Cardiol 2005; 46: 1827–32).

III. Clinical importance of stent thrombosis: Death and MI

Whether or not there is an increased risk of stent thrombosis with DES use compared to other revascularization techniques, there is a clear consensus that stent thrombosis is a clinically relevant adverse outcome. Multiple studies have documented a high rate of death or non-fatal myocardial infarction (MI) secondary to stent thrombosis occurring early or late after stenting.

In the pre-DES era, a stent thrombosis rate of 0.9% (the sum of angiographically confirmed and clinically defined thrombosis events in the absence of angiography) through 30-days post stent implantation was reported from an analysis of a pooled population of 6186 patients who received bare metal stents as part of either randomized trials or non-randomized registries. At 6 months follow-up, stent thrombosis was associated with a 69.8% incidence of death or MI and a mortality rate of 20.8% (*Cutlip et al*. Circulation. 2001; 103:1967-1971). In a study by Heller et al., late stent thrombosis (defined as an acute MI >30 days post-stenting) was observed in 12 patients (incidence 0.65% of the total number of stented subjects followed) with patients presenting 73±23 days (range, 33 to 270 days) after stenting. Significant mortality and morbidity was observed; 2 of 12 (17%) patients died, and of the 10 patients with initially successful percutaneous interventions, 4 patients developed abrupt or threatened arterial closure (leading to coronary bypass surgery in 2), 1 experienced a stroke, and there was 1 late death (*Heller et al*. Catheter Cardiovasc Interv. 2001; 53: 23–28).

Considering stent thrombosis occurring at any time point post-DES placement, a recent registry study of DES use reported 29 of 2229 (1.3%) patients with initially successful DES implantation had stent thrombosis by 9-month follow-up. Of these, 14 patients had subacute thrombosis (0.6%), and 15 patients had late thrombosis (0.7%). Seven patients (24%) presented with death, 20 (69%) with nonfatal MI, and 2 (7%) with unstable angina. At follow-up, of the 29 total DES thrombosis patients, 13 died, corresponding to a 45% case fatality rate (*Iakovou et al*., JAMA 2005; 293: 2126-2130). Similar rates of mortality and morbidity associated with DES thrombosis have been observed in other studies. There was a 31% mortality rate within 6 months among 38 patients DES thrombosis (*Kuchulakanti et al*., Circulation 2006; 113: 1108-1113). Ong et al. reported a 25% case fatality rate for patients with late DES thrombosis, defined as thrombosis occurring at least one month after DES implantation (*Ong et al*., J Am Coll Cardiol 2005; 45:2088-92).

IV. On-label use of DES

A. Pivotal studies submitted to support PMA approval

In the pivotal studies for the two currently approved DES (SIRIUS for CYPHER and TAXUS IV for TAXUS) that were submitted to FDA for PMA approval, both DES successfully met their primary endpoints [significant reduction in 9 month target vessel failure (TVF) for CYPHER and 9 month target vessel revascularization (TVR) for TAXUS], and major adverse cardiac events (MACE) rates were also reduced for both devices (driven by reduced revascularization rates) (*Moses, et al*. N Engl J Med 2003; 349: 1315-23; *Stone, et al*. N Engl J Med 2004; 350: 221-31).

Data from the pivotal SIRIUS trial are shown in the following table. TVF was a composite endpoint comprised of cardiac death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization. MACE was a composite endpoint comprised of death, Q-wave or non Q-wave MI, or target vessel revascularization.

SIRIUS: Principal Effectiveness and Safety Results (to 360 Days)

	CYPHER Stent (N=533 Patients N=533 Lesions)	**Control** (N=525 Patients N=531 Lesions)	**Difference** [95% CI]	**p-Value**
TVF to 9 Months (Primary Endpoint)*	8.8% (47/533)	21.0% (110/525)	-12.1% [-16.4/o, -7.9%]	<0.001
Clinical Endpoints to 270 Days				
TLR-Free	95.8%	83.2%	12.6%[8.5%, 16.7%]	<0.001
TVR-Free	93.5%	81.1%	12.4% [8.0%, 16.8%]	<0.001

TVF-Free	91.1%	78.9%	12.2% [7.5%, 16.8%]	<0.001
MACE-Free	92.8%	81.0%	11.8% [7.4%, 16.3%]	<0.001
Clinical Endpoints to 360 Days				
TLR-Free	95.0%	79.5%	15.5% [t1.4%, 19.7%]	<0.001
TVR-Free	92.7%	76.9%	15.8% [11.4%,20.1l%]	<0.001
TVF-Free	90.1%	74.9%	15.2% [10.6%, 19.9%]	<0.001
MACE-Free	91.7%	77.4%	14.2% [9.8%, 18.7%]	<0.001
TVF to 360 days*	9.8% (52/533)	24.8% (130/525)	-15.0%[-19.5%, -10.5%]	<0.001
Stent Thrombosis to 30 days	0.2% (1/533)	0.2% (1/525)	0.0% [40.5%, 0.5%]1	1.000
Late Thrombosis to 360 days	0.2% (1/533)	0.6% (3/525)	-0.4% [-1.1%, 0.4%/o]	0.371

Results of the pivotal TAXUS IV trial are shown in the following table. MACE was a composite of cardiac death, MI and TVR. TVR was classified as ischemia-driven if the target vessel diameter stenosis was ~50% by quantitative coronary angiography and any of the following were present:

- A positive functional study corresponding to the area served by the target vessel
- Ischemic ECG changes at rest in a distribution consistent with the target vessel
- Ischemic symptoms referable to the target lesion

TAXUS IV Principal Safety and Effectiveness Results Through 12 months

	TAXUS n=662	**Control n=652**	**Difference [95% CI]**	**P**
Clinical Endpoints to 9 months				
TVR-Free	95.25%	87.89%	7.36% [4.35%, 10.37%]	<0.0001
TLR-Free	96.93%	88.51%	8.42% [5.62%, 11.22%]	<0.0001
TVF-Free	92.40%	85.48%	6.92% [3.54%, 10.30%]	0.0001
'MACE-Free	91.51%	84.88%	6.63% [3.14%. 10.12%]	0.0003
Clinical Endpoints to 12 months				
TVR-Free	92.87%	82.88%	9.99% [6.41%. 13.57%]	<0.0001
TLR-Free	95.58%	84.89%	10.69% [7.46%, 13.92%)	
TVF-Free	90.03%	80.57%	9.46% [5.61%, 13.31%]	<0.0001
MACE-Free	89.15%	79.97%	9.18% [5.26%, 13.10%]	<0.0001
In-hospital MACE	2.4% (16/662)	2.1% (14/652)	0.3% [-1.3%, 1.9%]	0.854
MACE to 9 months	8.5% (561655)	15.2% (98/ 645)	-6.6% [-lO.l%, -3.1%	0.0002
MACE to 12 months	10.7% (70/ 653)	20.0% (129/ 644)	-9.3% [-13.2%, -5.4%]	<0.0001
TVR to 9 months (Primary Endpoint)	4.7% (311655)	12.1% (781645)	-7.4% [-10.4%, -4.4%]	<0.0001
TVR to 12 months	6.9% (451653)	16.9% (109/ 644)	-10.0% [-13.5%. -6.5%]	~0.0001
TVF to 9-months	7.6% (50/655)	14 6% (94/645)	-6.9% [-10.3%, -3.5%]	0.0001
TVF to 12-months	9.7% (64/ 653)	19.2% (1251644)	-9.6% f-13.4%, -5.8%]	~0.0001
Stent Thrombosis to 30 days	0.3% (2/ 662)	0.6% (4/ 652)	-0.3% [-1 .O%, 0.4%]	0.4487
Stent Thrombosis to 9 months	0.6% (41655)	0.8% (5/ 645)	-0.2% [-l.l%, 0.7%]	0.7513
Stent Thrombosis to 12 months	0.6% (4/ 653)	0.8% (5/ 644)	-0.2% [-1 .l%, 0.7%]	0.7515

B. Pivotal studies submitted to support PMA approval: Stent thrombosis

For the CYPHER stent studies, stent thrombosis was defined as:

- Subacute closure or unexplained death or Q-wave MI through 30-days
- Late thrombosis was defined as MI occurring >30 days after the index procedure and attributable to the target vessel with angiographic documentation and freedom from an interim revascularization of the target vessel.

The stent thrombosis rate through 12 months in the SIRIUS trial was 0.4% for CYPHER (vs. 0.8% for controls, p=NS).

For the TAXUS stent studies, stent thrombosis was defined as:

- Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis
- Angiographic documentation of a complete occlusion (TIM1 flow 0 or 1) of a previously successfully treated artery and/or angiographic documentation of a flow limiting thrombus within or adjacent to a previously successfully treated lesion
- Acute Ml in the distribution of the treated vessel
- Death within first 30 days (without other obvious cause) was considered a surrogate for stent thrombosis when angiography was not available

The stent thrombosis rate through 12 months in the TAXUS IV trial was 0.6% for TAXUS (vs. 0.8% for controls, p=NS).

The definitions of stent thrombosis differed between the SIRIUS and TAXUS studies with the TAXUS definition being somewhat more inclusive as it attributed an acute Ml in the distribution of the treated vessel to stent thrombosis if angiography was not performed. In a pooled analysis of 10 randomized studies of DES deployment (Moreno et al. *J Am Coll Cardiol*. 2005; 45: 954-9), the rate of DES thrombosis (through 9 or 12 months follow-up) was 0.58% (vs. 0.54% for BMS, p = 1.000) with similar rates for sirolimus- or paclitaxel-eluting stents (0.57% vs. 0.58%, respectively, p = 1.000).

C. Labeling

Based on results for the pivotal and supporting trials, the CYPHER and TAXUS stents were approved for the following limited anatomic indications:

- The CYPHER Sirolimus-eluting Coronary Stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete *de novo* lesions of length ≤ 30 mm in native coronary arteries with reference vessel diameter of ≥2.5 mm to ≤3.5 mm.
- The TAXUS Express Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter for the treatment of de novo lesions ≤28 mm in length in native coronary arteries ≥2.5 to ≤3.75 mm in diameter.

The complete labeling for the CYPHER and TAXUS stents may be found at the following websites:

http://www.fda.gov/cdrh/pdf2/P020026.html for CYPHER and
http://www.fda.gov/cdrh/pdf3/P030025.html for TAXUS

V. Longer-term follow-up of on-label DES use (randomized clinical trials)

As a condition of approval, patients participating in the studies for both DES submitted for FDA review were to be followed through 5-years post-enrollment. The most recent long-term follow-up data submitted to the FDA are summarized below. *The data on stent thrombosis utilized the definitions presented above for each DES.*

A. CYPHER

1. The RAVEL study was a randomized study of the Sirolimus-eluting BX velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions.

There were 238 patients in the trial, 120 randomized to Sirolimus-eluting BX velocity and 118 to BX velocity bare metal stent (control):

RAVEL effectiveness and safety results (n=238) to 1460 days

Measure	Sirolimus-eluting BX Velocity (n=120)	Bx Velocity n=118)	Difference [95% CI]
TLR-free at 1460 days	96.7% (116/120)	93.1% (108/116)	3.6% [-2.1%,9.2%]
TVR-free at 1460 days	92.7% [86.1%,99.3%]	84.0% [74.9%, 93%]	
TVF-free at 1460 days	90.9% [83.5%, 98.2%]	81.3% [71.8%, 90.9%]	
MACE at 1460 days	85.5% [76.7%, 94.4%]	74.6% [64.2%, 85%]	
Stent thrombosis	0% (0/118)	0% (0/115)	0%
Late thrombosis	0% (0/118)	0% (0/115)	0%

2. In the SIRIUS study, among 1058 patients in the intent-to-treat population, 994 (94.0%) patients (CYPHER vs. Bx VELOCITY Control: 502/533 vs. 492/525) had 4 year follow-up (≥1410 days). Results are shown in the following table.

SIRIUS Cumulative incidence (CI) and Kaplan-Meier (KM) estimate of freedom from outcome at 1440 days

	CYPHER	Bx Velocity	p-value
Target vessel failure (CI)	19.6% (99/506)	33.5% (168/501)	<0.001
Target vessel failure (KM)	80.8%	67.5%	<0.001
Major adverse cardiac events (CI)	17.2% (87/505)	31.9% (160/501)	<0.001
Major adverse cardiac events (KM)	83.2%	69.2%	<0.001
Target lesion revascularization (KM)	91.7%	75.4%	<0.001
Late thrombosis (incidence 31-1440 days)	0.8% (4/502)	0.6% (3/493)	1.00

For the CYPHER stent, a pooled analysis of SIRIUS, E-SIRIUS, and C-SIRIUS trials showed a 2 year stent thrombosis rate of 0.9% in the CYPHER–treated subjects vs. 0.7% in the bare metal stent group.

B. TAXUS

1. TAXUS IV pivotal study 3 years follow-up. The 3 year MACE rate for the TAXUS IV study was 18.9% (116/614) and 29.0% (178/613) for the TAXUS and control arms, respectively. In both treatment groups, MACE was driven primarily by TVR. Between 2 and 3 years of follow-up, an additional 21 events were reported for the TAXUS arm (4.2%) and 17 events for the control arm (3.8%).

TAXUS IV Principal Efficacy Results

Measure	Control % (n)	TAXUS % (n)	Difference [95% CI]	p-Value
9-Month MACE	15.0% (98/652)	8.5% (56/ 662)	-6.6% [-10.0%, -3.1%]	0.0002
TVR	12.0% (78/ 652)	4.7% (31/ 662)	-7.3% [-10.2%, -4.3%]	<0.0001
TLR	11.3% (74/ 652)	3.0% (20/ 662)	-8.3% [-11.1%, -5.6%]	<0.0001
1-Year MACE	19.8% (129/ 652)	10.6% (70/ 662)	-9.2% [-13.1%, -5.4%]	<0.0001
TVR	16.7% (109/ 652)	6.8% (45/ 662)	-9.9% [-13.4%, -6.5%]	<0.0001
TLR	14.7% (96/ 652)	4.2% (28/ 662)	-10.5% [-13.6%, -7.4%]	<0.0001
2-Year MACE	25.2% (161/640)	14.7% (95/645)	-10.4% [-14.8%, -6.1%]	<0.0001
TVR	21.1% (135/640)	10.4% (67/645)	-10.7% [-14.6%, -6.8%]	<0.0001
TLR	17.5% (112/640)	5.6% (36/645)	-11.9% [-15.4%, -8.5%]	<0.0001
3-Year MACE	29.0% (178/613)	18.9% (116/614)	-10.1% [-14.9%, -5.4%]	<0.0001

Cardiac Death	2.6% (16/613)	2.6% (16/614)	-0.0% [-1.8%, 1.8%]	1.0000
MI	6.5% (40/613)	5.9% (36/614)	-0.7% [-3.4%, 2.0%]	0.6380
Q-Wave MI	0.8% (5/613)	1.3% (8/614)	0.5% [-0.7%, 1.6%]	0.5790
Non-Q-Wave MI	6.0% (37/613)	4.7% (29/614)	-1.3% [-3.8%, 1.2%]	0.3148
TVR, Overall	24.1% (148/613)	13.7% (84/614)	-10.5% [-14.8%, -6.1%]	<0.0001
TLR	19.1% (117/613)	7.0% (43/614)	-12.1% [-15.8%, -8.4%]	<0.0001
Non-TLR	7.5% (46/613)	7.3% (45/614)	-0.2% [-3.1%, 2.8%]	0.9137

The stent thrombosis rate through 3 years was 1.2% (7/595) for the TAXUS group and 0.8% (5/594) for the control group. Of these thrombosis events, 3 (0.5% 3/641) occurred between 1 and 2 years for the TAXUS group with no additional stent thromboses beyond 2 years; there were no additional stent thromboses after 6 months in the control group.

2. TAXUS V label expansion study 1 year follow-up. The objective of the TAXUS V trial was to expand the indication for use of the TAXUS stent to include the use of small diameter (2.25 mm) stents, large diameter (4.00 mm) stents, and overlapping stents (lesions up to 46 mm) in de novo coronary arteries. *These data and the request for label expansion for the TAXUS stent are currently under FDA review.*

Principal Efficacy Results, Intent-to-Treat, All Patients (N=1156)

Measures	Control (N=579)	TAXUS (N=577)	Difference [95% CI]	p-Value
1-Year MACE	25.9% (146/563)	18.9% (105/556)	-7.0% [-11.9%, -2.2%]	0.0052
Cardiac Death or MI	5.7% (32/563)	6.1% (34/556)	0.4% [-2.3%, 3.2%]	0.8004
Cardiac Death	1.1% (6/563)	1.1% (6/556)	0.0% [-1.2%, 1.2%]	1.0000
MI	4.6% (26/563)	5.4% (30/556)	0.8% [-1.8%, 3.3%]	0.5852
Q-Wave MI	0.2% (1/563)	0.5% (3/556)	0.4% [-0.3%, 1.1%]	0.3712
Non-Q-Wave MI	4.4% (25/563)	4.9% (27/556)	0.4% [-2.1%, 2.9%]	0.7777
TVR, Overall	21.8% (123/563)	15.8% (88/556)	-6.0% [-10.6%, -1.5%]	0.0116
TLR, Overall	19.0% (107/563)	11.2% (62/556)	-7.9% [-12.0%, -3.7%]	0.0003
TVF	25.0% (141/563)	18.7% (104/556)	-6.3% [-11.2%, -1.5%]	0.0114
Stent Thrombosis to 1 Year	0.7% (4/553)	0.7% (4/546)	0.0% [-1.0%, 1.0%]	1.0000
In-Hospital	0.2% (1/579)	0.5% (3/577)	0.3% [-0.3%, 1.0%]	0.3735
Out of Hospital to 30 Days	0.5% (3/576)	0.2% (1/569)	-0.3% [-1.0%, 0.3%]	0.6244
31 - 180 Days	0.2% (1/575)	0.0% (0/569)	-0.2% [-0.5%, 0.2%]	1.0000
181 - 284 Days	0.0% (0/563)	0.0% (0/557)	0.0% [NA%, NA%]	Undef
285 - 365 Days	0.0% (0/556)	0.0% (0/550)	0.0% [NA%, NA%]	Undef
All Death to 1 Year	1.8% (10/561)	2.2% (12/553)	0.4% [-1.2%, 2.0%]	0.6726
Non-Cardiac Death to 1 Year	0.7% (4/555)	1.1% (6/547)	0.4% [-0.7%, 1.5%]	0.5442

Stent thrombosis rates in selected higher risk TAXUS V lesions/patients are shown in the following table.

Lesion Length ≥18 mm	Control N=265, % (n/N)	TAXUS N=265, % (n/N)	Difference [95% CI]	P Value
Stent Thrombosis	0.4% (1/255)	0.8% (2/255)	0.4% [-0.9%, 1.7%]	1.0000
Multiple stents	Control N=184, % (n/N)	TAXUS N=195, % (n/N)	Difference [95% CI]	P Value
Stent Thrombosis	0.6% (1/180)	1.1% (2/190)	0.5% [-1.3%, 2.3%]	1.0000
Medically treated diabetics	Control N=173, % (n/N)	TAXUS N=183, % (n/N)	Difference [95% CI]	P Value
Stent Thrombosis	1.8% (3/170)	0.6% (1/177)	-1.2% [-3.5%, 1.1%]	0.3630

VI. New considerations in the definition stent thrombosis

As noted above, definitions of stent thrombosis differed between the two approved DES (and varies among other published studies, see Section VIII), and identifying cases of DES thrombosis to determine the true frequency of this adverse event is problematic. Although stent thrombosis detected during coronary angiography or at autopsy is unequivocal evidence, many patients do not undergo follow-up angiography, and autopsy rates in the US are exceedingly low among both hospitalized patients and in cases of out-of-hospital sudden death. Thus, counting only cases of unequivocal stent thrombosis (confirmed by angiography or autopsy) underestimates the true rate. Conversely, ascribing all new myocardial infarctions or sudden cardiac deaths to stent thrombosis inflates the rate of DES thrombosis; coronary atherosclerosis is a multifocal, often progressive disease, and patients may have events secondary to rupture of a de novo plaque or die suddenly due to a lethal arrhythmia in the absence of stent thrombosis. In recognition of the limitations inherent in establishing the precise incidence of stent thrombosis, FDA has participated in the Academic Research Consortium (ARC) roundtable of investigators, industry, and regulators to propose working definitions of stent thrombosis (based on available clinical evidence in each case) and the timing of the occurrence of the thrombotic event. These definitions are summarized as follows:

Definite stent thrombosis is considered to have occurred by *either* angiographic or pathologic confirmation.

1. Angiographic confirmation of stent thrombosis based on TIMI flow and at least one of the following criteria has been fulfilled within a 48 hours time window:
    - A) new acute onset of ischemic symptoms at rest
    - B) new ischemic ECG changes suggestive of acute ischemia
    - C) typical rise and fall in cardiac biomarkers as evidence for an acute MI
2. Pathologic confirmation of recent stent thrombosis either at autopsy or via examination of tissue retrieved following thrombectomy

Probable stent thrombosis

1. Any unexplained death within the first 30 days
2. Irrespective of the time after the index procedure, any MI which is related to acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible stent thrombosis: Any unexplained death from 30 days following intracoronary stenting until end of trial follow-up

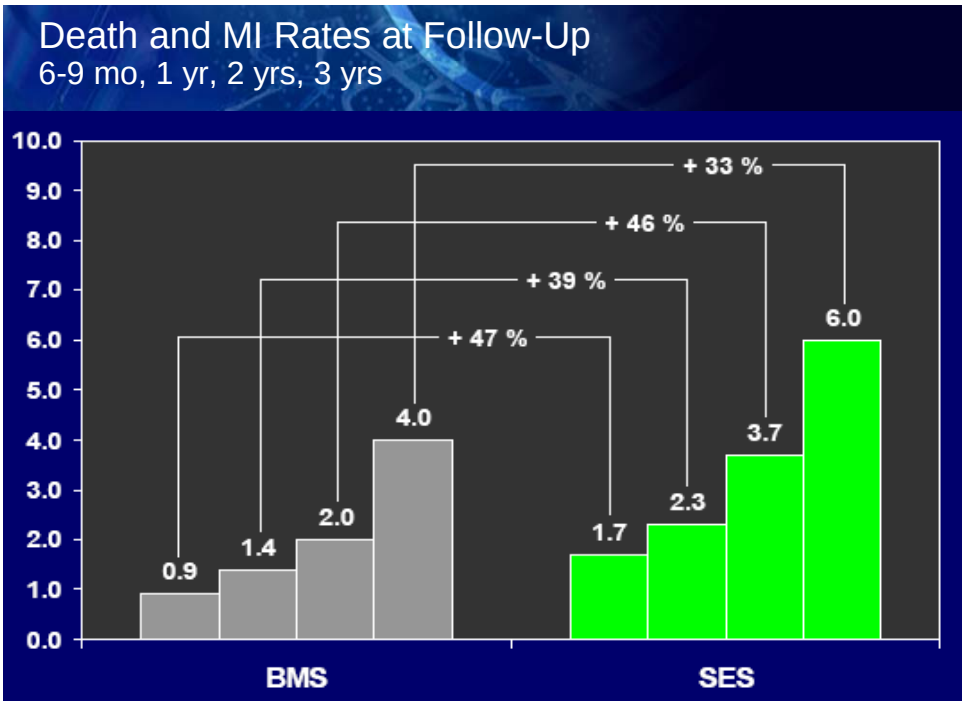
Timing of stent thrombosis:

1. Early stent thrombosis: 0 – 30 days post stent implantation
2. Late stent thrombosis: >30 days – 1 year post stent implantation
3. Very late stent thrombosis: >1 year post stent implantation

FDA recognizes that other definitions of stent thrombosis may also be appropriate and proposed for use in clinical studies. For the purposes of the discussion at the FDA Advisory Panel meeting, we believe that the ARC definitions are acceptable and have requested Sponsors and investigators to apply them to their datasets when possible. We expect that both DES Sponsors will utilize the ARC definitions in their presentations at the Panel meeting.

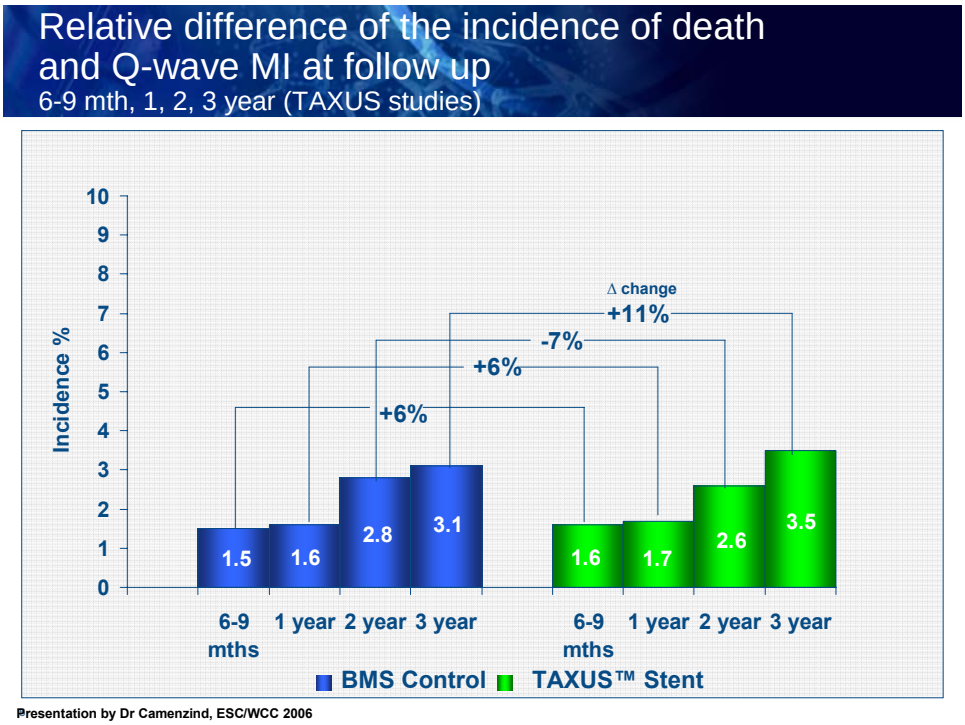
VII. DES late thrombosis concerns: Recent meta-analyses of randomized clinical trials of DES

At the European Society of Cardiology (ESC) Scientific Congress, September 2006, Dr. Edoardo Camenzind presented a paper entitled: "Safety of Drug Eluting Stents: a meta analysis of 1st Generation DES programs." In his study, the rates of death, Q-wave MI, and the composite of death or Q-wave MI were determined from a meta-analysis of published randomized trials of DES. This meta-analysis compared long-term outcomes of the CYPHER and TAXUS stents to their respective bare metal control stents. The trials included were RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS [sirolimus-eluting stents (SES, CYPHER); n = 878 for SES and n = 870 for bare metal stents (BMS)] and TAXUS I, II, IV, V, and VI [paclitaxel-eluting stents (PES); n = 1,675 for PES and n = 1,685 for BMS]. Results of this meta-analysis are summarized in the following slides that were presented at ESC:

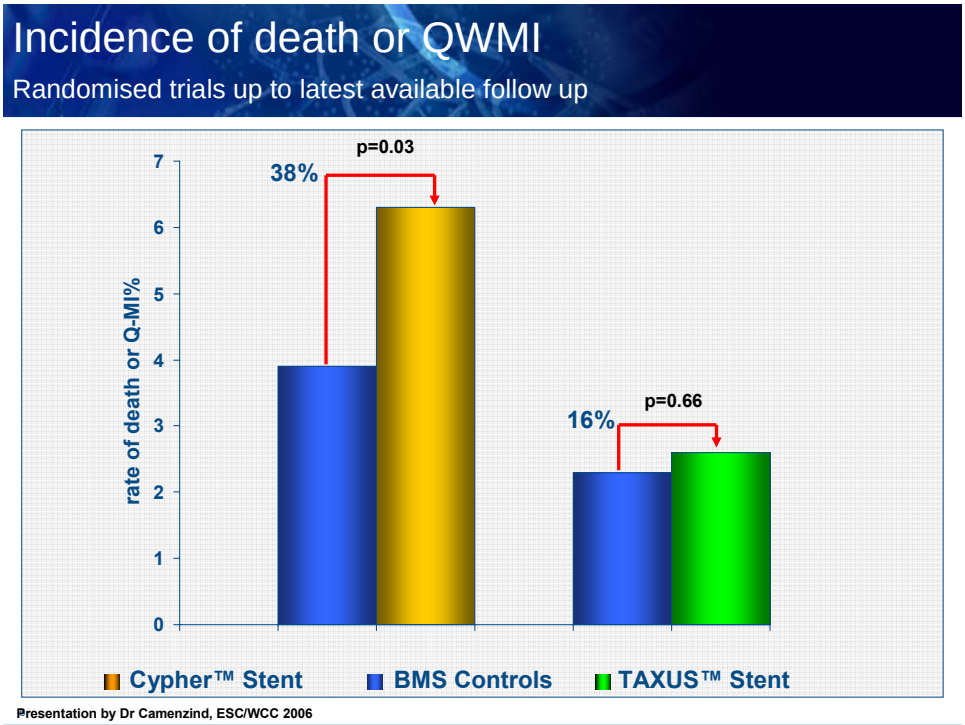


Presentation by Dr Camenzind, ESC/WCC 2006

As seen above, the rate of death or Q-wave MI was 0.9% for BMS versus 1.7% for SES at 6-9 months (p = 0.21), 1.4% for BMS versus 2.3% for SES at 1 year (p = 0.30), 2.0% for BMS versus 3.7% for SES at 2 years (p = 0.09), and 4.0% for BMS versus 6.0% for SES at 3 years (p = 0.06).



The rate of death or Q-wave MI was 1.5% for BMS versus 1.6% for PES at 6-9 months (p = 0.88), 1.6% for BMS versus 1.7% for PES at 1 year (p = 0.80), 2.8% for BMS versus 2.6% for PES at 2 years (p = 0.78), and 3.1% for BMS versus 3.5% for PES at 3 years (p = 0.60).

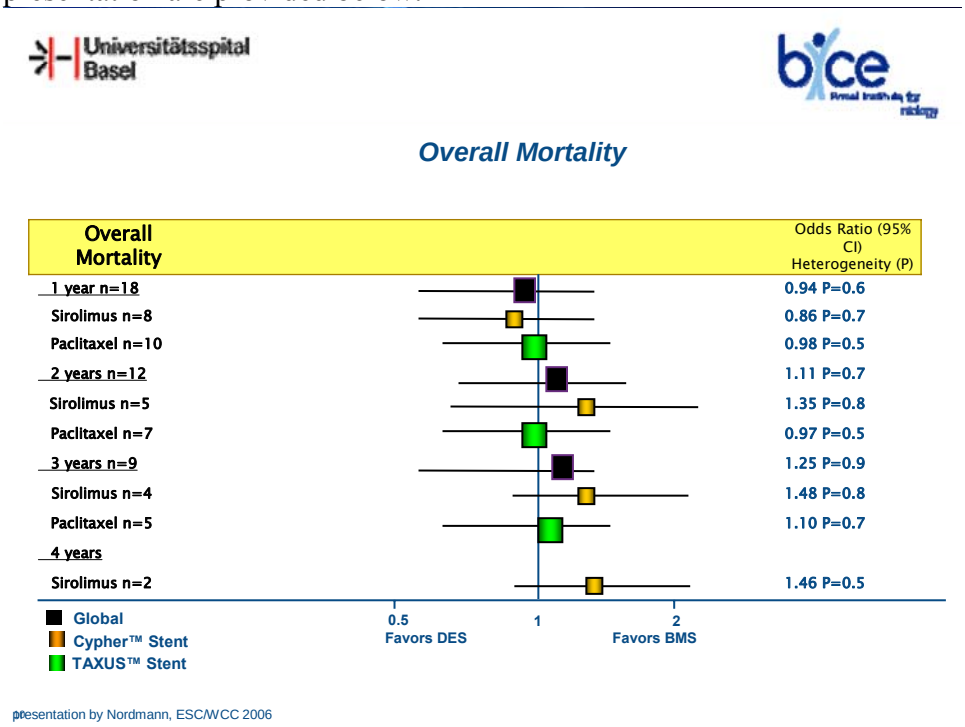


As noted above, at last available follow-up, death or Q-wave MI was significantly higher in the SES group compared with the BMS group (6.3% vs. 3.9%, relative risk [RR] 1.38, p = 0.03).

The rate of death or Q-wave MI at last follow-up did not differ significantly for PES compared with BMS (2.6% vs. 2.3%, RR 1.16, p=0.68).

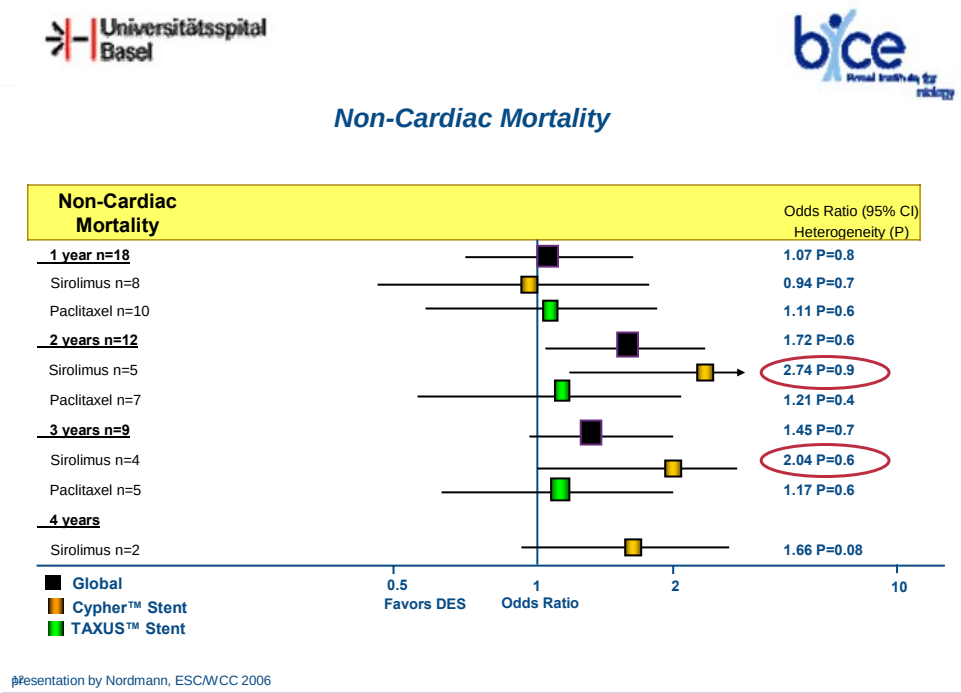
In summary, the Camenzind meta-analysis reported outcomes through three years post-stent implantation and suggested a small but significant increase in death or Q-wave MI in patients treated with CYPHER stents *possibly* due to stent thrombosis compared to those treated with bare metal stents (with increases in rates not reaching statistical significance with TAXUS stents).

An additional meta-analysis of 17 DES vs. bare metal stent (BMS) randomized clinical trials was presented by Dr. Alain J Nordmann at the ESC Scientific Congress, September 2006 (and subsequently published online in the Eur Heart J 2006, in press). Slides from this ESC presentation are provided below.



presentation by Nordmann, ESC/WCC 2006

Data was available out to 3 years for Taxus and 4 years for Cypher. As seen above, total mortality at did not differ between BMS compared with DES (both SES and PES combined) or for the individual DES analyzed separately. Similarly, there were no differences in cardiac mortality between BMS and DES combined or for the individual DES (data not shown).



As shown above, noncardiac mortality at 2 and 3 years was with significantly higher in patients treated with SES compared with BMS (2 years OR 2.74, 95% CI 1.22-6.13, $p < 0.05$; and 3 years OR 2.04, 95% CI 1.00-4.15, $p < 0.05$). The increased risk for non-cardiac death associated with sirolimus-eluting stents at 2 and 3 years post-implantation was mainly attributed to cancer (15 of 36 deaths), stroke, or lung disease. There is no known pathophysiologic mechanism to link the CYPHER stent to non-cardiac mortality.

It should be noted that neither the Camenzind nor the Nordmann meta-analysis utilized patient-level data from the original study datasets. At the Transcatheter Cardiovascular Therapeutics (TCT) 2006 meeting in Washington, DC in October 2006, Drs. Gregg Stone and Martin Leon presented meta-analyses of patient-level data from the CYPHER and TAXUS randomized clinical trails**. In their presentations, Drs. Stone and Leon noted a small but significant increase in the rate of late stent thrombosis for both DES (compared with bare-metal-stent controls) after one year follow-up. This increased rate of DES thrombosis was not associated with an increased risk of death or MI in their analyses.** For the Taxus randomized clinical trials, the cumulative increase in stent thrombosis rate was 0.5% between one and four years after stent implantation (approximately 0.15% per year). For the Cypher trials, the cumulative stent late-stent-thrombosis rate was 0.6% between one and four years (approximately 0.2% per year). Commenting on these meta-analyses, Dr. Stuart Pocock noted that after one year, 5 CYPHER patients and no bare metal stent patients experienced late thrombosis. After one year, stent thrombosis occurred in 9 TAXUS patients compared with 2 bare metal stent patients. Combining the two DES, there were 14 DES vs. 2 bare metal stent thromboses ($p=0.01$). As estimated by Dr. Pocock, the stent thrombosis rates in the randomized DES trials correspond to approximately 1 event per 500 patient-years of follow-up.

In considering the meta-analyses based on patient-level data presented at TCT 2006, it should be recognized that: (1) the cumulative randomized trial data reflect a limited number of DES patients [n=878 CYPHER (RAVEL, SIRIUS, C-SIRIUS, E-SIRIUS) and 1332 TAXUS (I, II-SR, IV, V)]; (2) only a subset of patients have been followed ≥3 years; and (3) the patients

enrolled in the randomized trials generally reflect a clinically stable population with non-complex coronary lesions.

VIII. Broader use of DES and stent thrombosis

DES have been enthusiastically embraced by interventional cardiologists in the US and are used in >80% of PCI procedures. Like many promising medical interventions, however, DES use has eclipsed the relatively narrow anatomic subsets treated in the pivotal trials (see above approved Indications for Use, **section IV.C**). It is believed that a majority (likely >60%) of current DES use is beyond the labeled intended uses. This off-label use typically involves patient and lesion subsets that are more complex than those represented in the randomized trials (i.e., submitted for DES PMA approval) including left main (LM) disease, bifurcation lesions, chronic total occlusions, thrombus containing lesions (in acute MI), saphenous vein bypass grafts, post-PCI restenosis lesions, long lesions requiring overlapping stents, patients with multivessel disease, and patients with renal dysfunction.

It may be anticipated that the rate of serious adverse events (*including subacute **and** late stent thrombosis*) would be greater in more complex clinical settings compared with more straightforward patients (e.g., single vessel de novo disease treatable with a single stent in stable subjects) enrolled in the pivotal trials. Although diabetic patients were included in the randomized control trials submitted for DES approval, neither of the approved DES has a specific labeled indication for use in diabetics (either insulin-requiring or non-insulin requiring); concern has been raised whether there is a significantly greater DES thrombosis risk in this high cardiovascular risk subgroup. Information is emerging that suggests increased rates of DES thrombosis in more complex patient and lesion subsets including bifurcation lesions, thrombus containing lesions (acute MI), multiple stents per vessel and in patients with diabetes, multivessel disease, and renal dysfunction. It should be recognized, however, that most DES data are from single-armed registries and lack a control group, and few long-term data (≥1 year) are available. Further, there are only limited data on bare metal stent thrombosis (see Section X), death, MI in more complex patients are available to make comparisons to events in DES subjects.

A. Condition of approval studies

As a condition of approval, both DES manufacturers were required to conduct registry studies of at least 2000 patients followed for 12 months. These studies were designed as "all-comers" registries to reflect a broad range of clinical use:

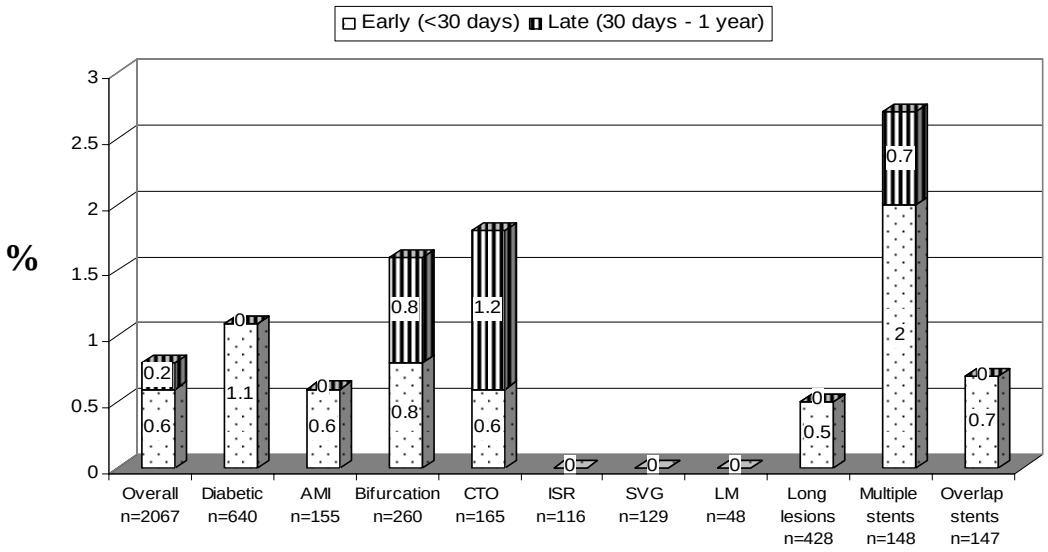
1. CYPHER

A. The e-Cypher US Registry. The purpose of the prospective multi-center e-CYPHER stent registry was to collect post marketing surveillance data on the CYPHER stent. Thirty-eight clinical sites provided 12-month follow-up on 2067 patients. MACE events were adjudicated by an independent CEC, rates are shown in the following table.

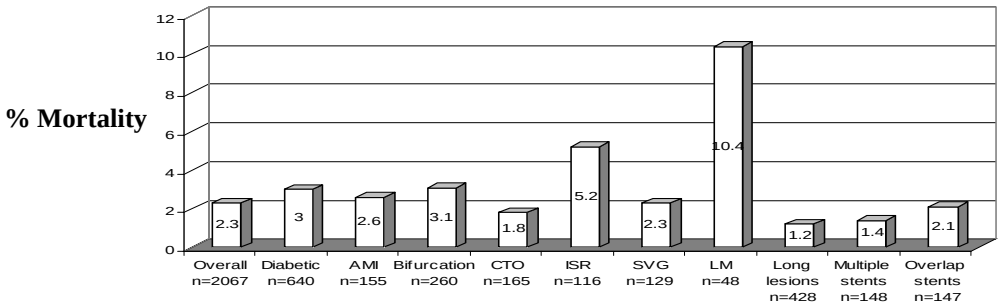
Outcome	Cumulative incidence	95% Confidence interval
Major adverse cardiac event at 30 days	1.4% (28/2067)	[0.9%, 2.0%]
Major adverse cardiac event at 180 days	4.2% (86/2067)	[3.3%, 5.1%]
Major adverse cardiac event at 360 days	7.3% (150/2067)	[6.2%, 8.5%]
TLR at 360 days	4.6% (95/2067)	[3.7%, 5.6%]
Combined acute and subacute thrombosis at 30 days	0.6% (12/2067)	[0.3%, 1.0%]
Late thrombosis through 360 days	0.2% (5/2067)	N/A

Higher rates of major cardiac events and stent thrombosis were observed in the more complex patient/lesion group vs. the rates for all patients as a whole as shown in the following graphs.

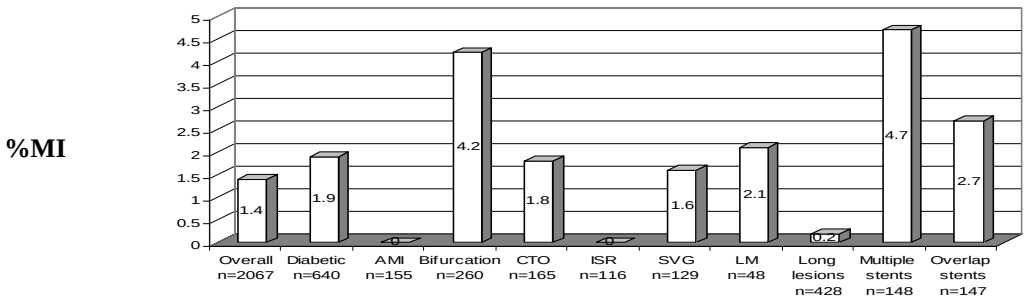
Stent Thrombosis rates (%) at 1 year: e-CYPHER-US subgroup analysis



Mortality at 1 Year: e-CYPHER-US subgroup analysis



MI (Q- and Non-Q wave) at 1 year: e-CYPHER-US subgroup analysis

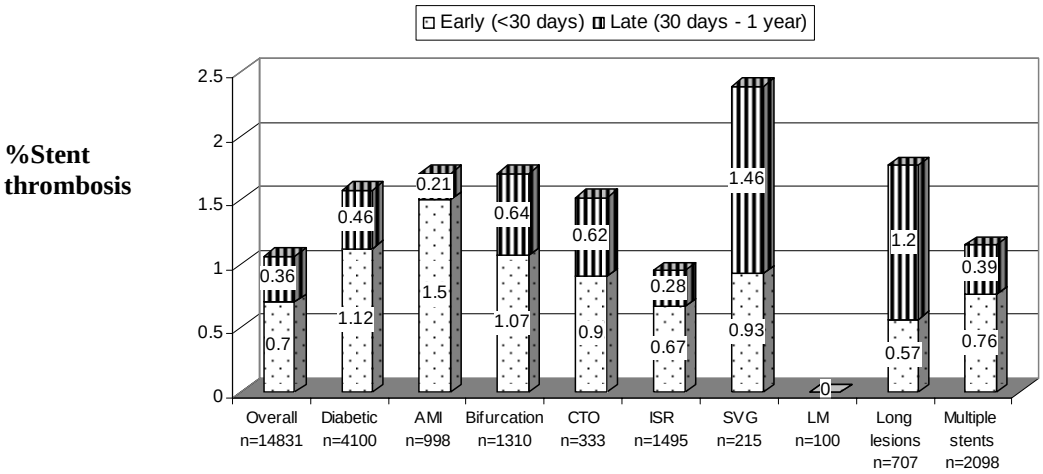


B. <u>The e-Cypher OUS registry</u>. The purpose of the e-CYPHER OUS Registry was to collect additional postmarket surveillance data on the CYPHER stent. The e-CYPHER OUS study was a prospective, international, multi-center study, designed to include 15,000 consecutively enrolled patients in 41 countries, but not in the US or Japan. This registry was independent from the e- CYPHER US registry. There were 291 clinical sites which enrolled 15,157 analyzable patients, and from those 88% were followed for 12 months postprocedure.

Outcome	Cumulative incidence	95% Confidence interval
Major adverse cardiac event at 30 days	1.4% (196/14381)	[1.2%, 1.6%]
Major adverse cardiac event at 180 days	3.4% (480/14190)	[3.1%, 3.7%]
Major adverse cardiac event at 360 days	5.8% (779/13437)	[5.4%, 6.2%]
TLR at 360 days	3.1% (412/13437)	[2.8%, 3.7%]
Combined acute and subacute thrombosis at 30 days	0.7% (100/14381)	[0.6%, 0.8%]
Late thrombosis through 360 days	0.2% (26/13437)	N/A

Higher rates of stent thrombosis were observed in the more complex patient/lesion group vs. the rates for all patients as a whole as shown in the following graph..

Stent thrombosis: e-CYPHER-OUS subgroup analysis



2. TAXUS: The ARRIVE 1 registry. The ARRIVE 1 peri-approval registry was a prospective multicenter study that enrolled 2585 patients. Subjects/treatment were categorized as uncomplicated or complex with uncomplicated subjects/treatments defined as subjects without acute MI, LM disease, coronary bypass grafts, chronic total occlusions, in-stent restenosis, failed brachytherapy, bifurcations, ostial lesions, severe tortuosity, multiple stents, multivessel stenting, RVD <2.5mm, RVD >3.5mm, or lesion length >26mm. Complex patients/treatments were defined by the presence at least one of the above characteristics and accounted for 66% of patients enrolled in the registry. Some of these clinical features are shown in the following table.

ARRIVE 1 Stenting Characteristics (N=2585 Patients)

	Uncomplicated Patients/ Treatment N= 880 Patients	Complex Patients/ Treatment N=1705 Patients
Urgent/Emergent Procedure	12.5% (110/880)	19.7% (336/1705)
De Novo Lesions	99.9% (879/880)	91.6% (1562/1705)
Acute MI	0.0% (0/880)	15.3% (261/1705)
Left Main Stenting	0.0% (0/880)	4.5% (76/1705)
Graft Stenting	0.0% (0/880)	8.5% (145/1705)
Chronic Total Occlusion	0.0% (0/880)	3.4% (58/1705)
In-stent Restenosis	0.0% (0/880)	9.9% (169/1705)
Failed Brachytherapy	0.0% (0/880)	0.9% (15/1705)
Bifurcated Lesion	0.0% (0/880)	12.0% (205/1705)
Ostial Lesion	0.0% (0/880)	15.7% (268/1705)

All events were adjudicated by a CEC. Higher rates of major cardiac events and stent thrombosis were observed in the more complex patient/lesion group (see following table).

ARRIVE 1 12 Month TAXUS Related Cardiac Events by Risk (N=2585 Patients)

	Uncomplicated Patients/ Treatment * N= 880 Patients	**Complex Patients/ Treatment ** N=1705 Patients**
Cardiac Events		
Related to TAXUS Stent	4.0% (33/833)	8.4% (136/1625)
Death	2.6% (22/833)	4.1% (66/1625)
Cardiac Death	1.6% (13/833)	2.7% (44/1625)
Related to TAXUS Stent	0.5% (4/833)	1.4% (23/1625)
Non-Cardiac Death	1.1% (9/833)	1.4% (22/1625)
Myocardial Infarction	1.1% (9/833)	3.1% (51/1625)
Related to TAXUS Stent	1.0% (8/833)	2.2% (35/1625)
Q-Wave MI	0.2% (2/833)	0.9% (15/1625)
Related to TAXUS Stent	0.2% (2/833)	0.9% (14/1625)
Non Q-Wave MI	1.0% (8/833)	2.3% (37/1625)
Related to TAXUS Stent	0.8% (7/833)	1.3% (21/1625)
Reintervention (by patient)	5.0% (42/833)	8.0% (130/1625)
Related to TAXUS Stent	3.5% (29/833)	6.3% (103/1625)
Stent Thrombosis(by patient)	1.0% (8/833)	2.6% (43/1625)

Increased rates of stent thrombosis in selected higher risk groups are presented in the following table.

Stent thrombosis rates through 12 months in selected ARRIVE 1 complex patient/lesion subsets

	Long Lesions (> 20 mm)	Patients with Multiple TAXUS Stents	Lesions with Multiple TAXUS Stents	Multi-vessel Stenting	Bifurcations	Acute MI	Diabetics	Insulin-Requiring Diabetics
Stent Thrombosis	3.7% (23/624)	3.4% (34/1009)	4.1% (14/340)	3.8% (16/421)	3.5% (7/198)	2.9% (7/242)	3.1% (23/750)	6.3% (15/238)

Diabetics: The ARRIVE 1 registry

Diabetes patients experienced an 8.4% (63/750) TAXUS stent-related cardiac event rate through the 12 months including a TAXUS stent-related cardiac death rate of 1.9% (14/750) and a TAXUS stent related MI rate of 2.9% (22/750). The MI group consisted of 6 or 0.8% (6/750) Q-wave MI's and 16 or 2.1% (16/750) non Q-wave MI's. TAXUS stent related re-interventions of the target vessel were observed in 5.7% (43/750) of patients. Diabetics had an angiographically confirmed stent thromboses rate of 1.7% (13/750) and 1.3% (10/750) rate of presumed stent thromboses **(total 3.1%)**.

For the subset of insulin requiring diabetics, the TAXUS stent related cardiac event rate was 13.0% (31/238) at 12 months. Insulin requiring diabetics had a TAXUS stent related cardiac death rate of 3.4% (8/238) and a TAXUS stent related MI rate of 6.3% (15/238). Of the latter, there were 5 or 2.1% (5/238) Q-wave MI's and 10 (4.2%, 10/238) non Q-wave MI's. TAXUS stent related re-interventions of the target vessel were observed in 8.8% (21/238) of patients. Insulin-requiring diabetics had 10 or 4.2% (10/238) angiographically confirmed stent thromboses and 2.1% (5/238) presumed stent thromboses **(total 6.3%)**.

B. Other "real world" DES experience: Selected published studies relevant to DES thrombosis

1. *Ong et al*. J Am Coll Cardiol 2005; 45; 947-53. The study population consisted of consecutive series of 1,017 patients treated with sirolimus-eluting stents (SES), and 989 patients treated with paclitaxel-eluting stents (PES). Patients were followed for a minimum of one year to determine the incidence of late stent thrombosis. Patients were advised to maintain lifelong aspirin therapy. Patients who received SES were prescribed clopidogrel for three or six months depending on the complexity of the procedure, whereas patients treated with PES were given a six-month prescription. **Late stent thrombosis was defined by the presence of acute symptoms plus angiographic confirmation**. At baseline, 57% of patients had multivessel disease, 22% had acute MI, and 18% had bifurcation lesions. There were eight angiographically confirmed late stent thrombosis events in seven patients: three with SES (at 2, 25, and 26 months) and five with PES (at 6, 7, 8, 11, and 14.5 months) **corresponding to an incidence of 0.35%** (95% CI 0.17% to 0.72%). All patients presented with an acute STEMI. Three cases were related to complete cessation of antiplatelet therapy, two cases occurred while patients were on aspirin therapy within one month of cessation of clopidogrel, and three cases occurred at a time when patients were apparently clinically stable on aspirin monotherapy.

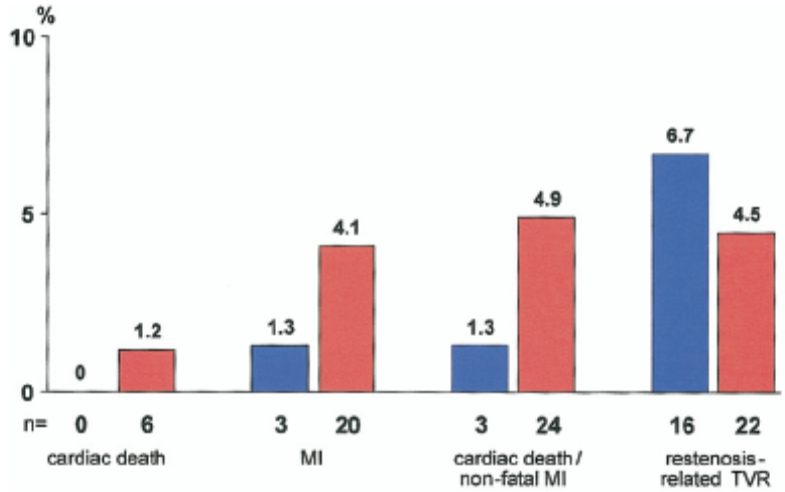
2. *Iakovou et al*. JAMA 2005; 293 :2126-2130. A total of 2229 consecutive patients underwent successful implantation of sirolimus-eluting (1062 patients, 1996 lesions, 2272 stents) or paclitaxel-eluting (1167 patients, 1801 lesions, 2223 stents) stents. All patients were

pretreated with ticlopidine or clopidogrel and aspirin. Aspirin was continued indefinitely and clopidogrel or ticlopidine was administered for at least 3 months after sirolimus-eluting and for at least 6 months after paclitaxel-eluting stent implantation. **Stent thrombosis was defined as any of the following events: angiographic documentation within 30 days of the procedure (an acute ischemic event in addition to angiographic documentation had to be present when the event occurred after 30 days), or sudden cardiac death or post-procedural MI after successful stent implantation not clearly attributable to another coronary lesion. At 9-month follow-up, 29 patients (1.3%) had stent thrombosis** (9 [0.8%] with sirolimus and 20 [1.7%] with paclitaxel; *P*=.09), of which 13 died (case fatality rate, 45%). A total of 71% (10/14) of the subacute (within 30 days) cases occurred within 1 week of the procedure (median, 4 days) and 53% (8/15) of the late thrombosis (>30 days) cases occurred within 3 months of the procedure (median, 57 days). **Independent predictors of stent thrombosis were renal failure (rate 5.5%, HR, 6.49; *P*<0.001), bifurcation lesions (rate 3.5%, HR, 6.42; *P*<0.001), diabetes (rate 2.6%, HR, 3.71; *P*=.001), and a lower ejection fraction (HR, 1.09; *P*<0.001 for each 10% decrease).**

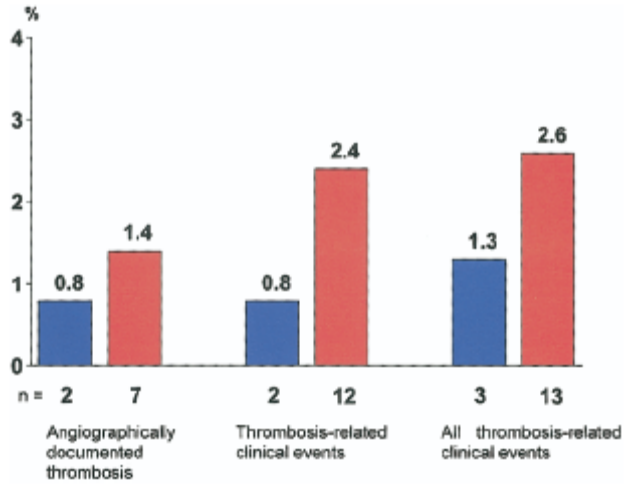
3. *Hoye et al.* J Am Coll Cardiol 2006; 47: 1949 –58. The authors identified 231 consecutive patients treated with drug-eluting stent implantation with the "crush" technique for 241 de novo bifurcation lesions. **Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation, or in the absence of angiographic confirmation, either acute AMI in the distribution of the treated vessel or death not clearly attributable to other causes. At 9 months, 10 (4.3%) patients had an event consistent with stent thrombosis**.

4. *Kuchulakanti et. al.* Circulation 2006; 113: 1108-1113. From a total cohort of 2974 consecutive patients treated with DES, the authors identified 38 patients who presented with **angiographic evidence** of stent thrombosis (1.27%). Stent thrombosis ST occurred acutely in 5 patients, subacutely (≤30 days) in 25 patients, and late (>30 days) in 8 patients. **Multivariate predictors of stent thrombosis were renal failure, bifurcation lesions, and in-stent restenosis**.

5. *Pfisterer et al.* J Am Coll Cardiol 2006; 48: in press. The BASKET study was a randomized controlled trial of DES (TAXUS or CYPHER stents) compared to bare metal stents in a "real-world" consecutive series of patients with the only angiographic exclusion criteria consisting of in-stent restenosis lesions or target vessel diameter vessels ≥4 mm. Of the 826 patients enrolled in the BASKET study, 746 patients with a total of 1,133 stented lesions who survived the first 6 months without nonfatal MI or repeat TVR were enrolled in the present BASKET-LATE study and followed for an additional 12 months. The BASKET-LATE patients included 21.0% with STEMI, 36.7% with unstable angina, and 66.8% with multivessel disease; they were treated with a mean of 1.9±1.0 stents per patient and a mean of 33±20 mm total stent length per patient. Importantly, clopidogrel treatment was stopped 6 months post-stent placement**. Late events were defined as occurring between 7 and 18 months after stenting and consisted of any cardiac death and documented nonfatal MI. All sudden cardiac deaths and all MI's attributable to the target vessel were considered to be "thrombosis-related."** Event data are presented in the following graphs.

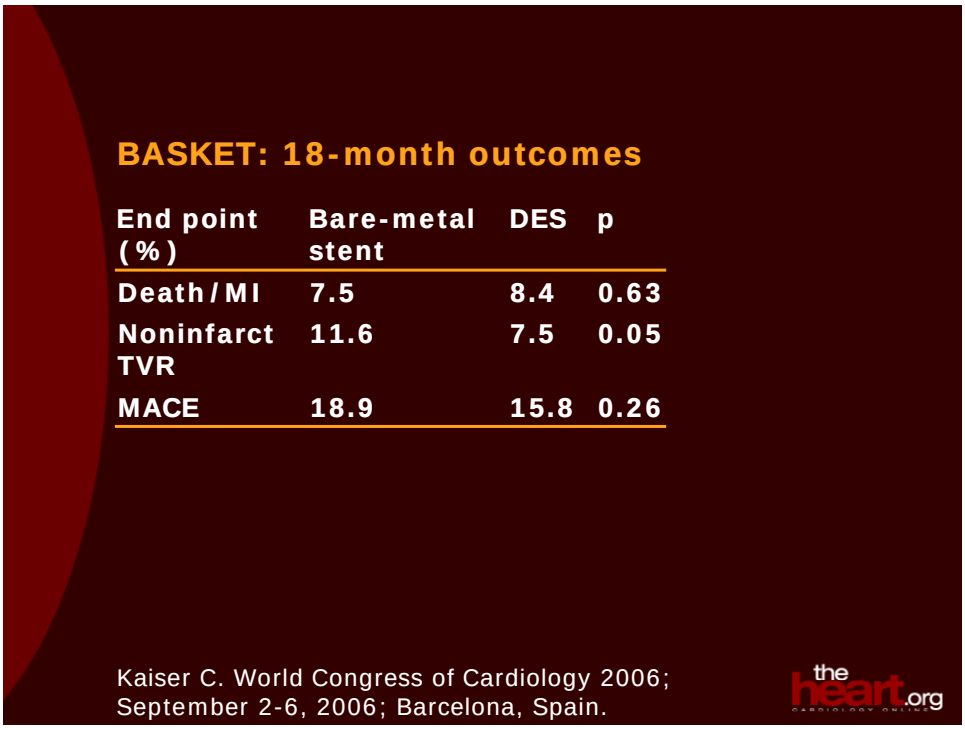


As shown above, of late major cardiac events occurring between months 7 to 18 post-stenting, cardiac death or nonfatal MI, was greater in DES (red) versus bare-metal stent (blue) groups, with a lower restenosis-related target vessel revascularization (TVR) rate after DES.



As noted above, late angiographically documented stent thrombosis and thrombosis-related clinical events were greater for DES (red) versus bare-metal (blue) stent-treated patients. These differences were not statistically significant.

The authors concluded that after the discontinuation of clopidogrel, the benefit of DES in reducing target vessel revascularization is maintained; however, this benefit is mitigated by an increase in the rate of late cardiac death or nonfatal MI, possibly related to late stent thrombosis. *[At the European Society of Cardiology Scientific Congress, September 2006, Dr. Christoph Kaiser presented the full 18-month results on all 826 patients in the BASKET study. Rates of noninfarct-related target vessel revascularization were lower in DES-treated patients, and there were no significant differences in rates of death/MI or overall MACE between treatment groups (see following figure).]*

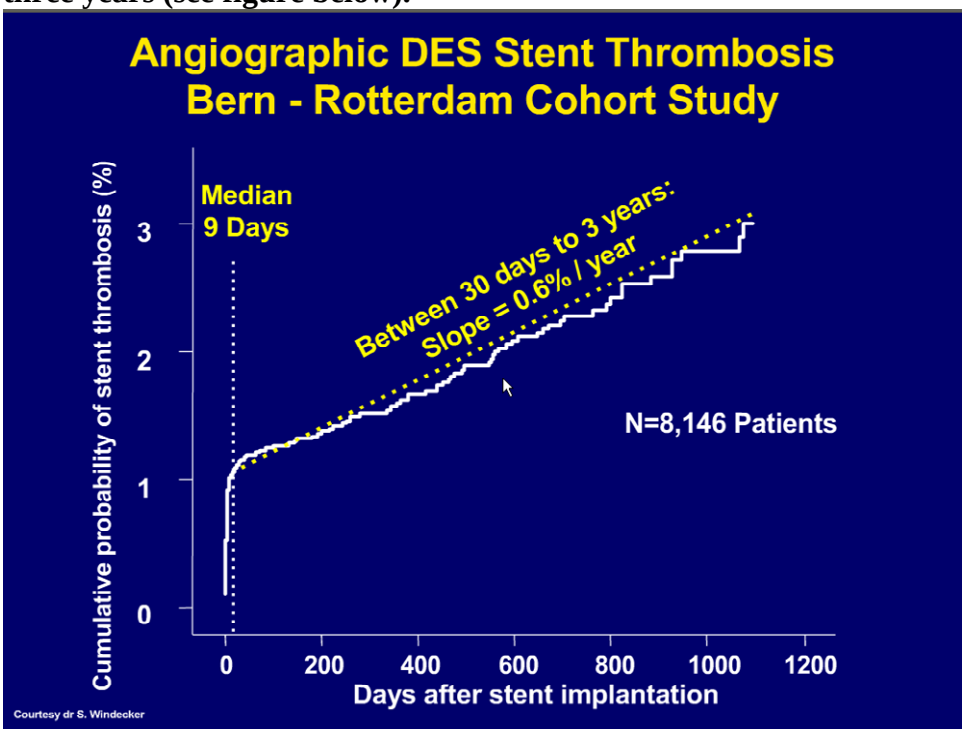


6. *Williams et al.* Circulation 2006; 114: in press. The DEScover registry enrolled 6906 patients who underwent PCI at 140 medical centers. Baseline characteristics and outcomes were compared on the basis of treatment with ≥1 bare-metal (BMS; n=397), sirolimus-eluting (SES; n=3873), or paclitaxel-eluting (PES; n=2636) stent. **Definite stent thrombosis was defined as the presence of angiographic thrombus accompanied by an acute coronary syndrome. Probable stent thrombosis is defined as unexplained sudden cardiac death or Q-wave MI in the distribution of the stented artery.** Information on antiplatelet therapy use was not collected. Patients frequently had complex clinical and procedural features including >30% with diabetes, >25% with prior MI, >20% with acute MI, and >25% with multivessel PCI. At 1 year, the unadjusted cumulative incidence of death/MI was higher in BMS than in DES patients (9.0% versus 5.2%; P=0.002) but similar in SES and PES patients (5.2% versus 5.3%). After adjustment for baseline covariates, the risk of death/MI was similar in DES- compared with BMS-treated patients (adjusted hazard ratio, 0.74; 95% CI, 0.52 to 1.07). Target vessel revascularization occurred less often in DES patients (9.5% versus 6.0%; P=0.007), and rates were similar between SES and PES patients (6.3% versus 5.5%). **Rates of stent thrombosis were similar among BMS (0.8%), SES (0.5%), and PES (0.8%) patients.**

C. Other real world DES experience: Selected recent presentation

At the European Society of Cardiology Scientific Congress, September 2006, Dr. Peter Wenaweser presented data on stent thrombosis rates in 8,146 patients enrolled in the SIRTAX and Post-SIRTAX registries in Bern and the RESEARCH and T-SEARCH registries in Rotterdam. **Only angiographically documented stent thromboses were included**. In Bern, patients were prescribed clopidogrel and aspirin for three to six months, while in Rotterdam, patients were prescribed dual antiplatelet therapy for three to 12 months (with actual use based on local practice). There were a total of 152 stent thromboses in 8146 patients. The cumulative incidence of stent thrombosis was 2.9% (1.3 per 100 patient-years). **The rate of stent**

thrombosis was 1.2% at 30 days, 1.7% at one year, 2.3% at two years, and 2.9% at three years, corresponding to a stent thrombosis rate of 0.6% per year between 30 days and three years (see figure below).



In a follow-up presentation at Transcatheter Cardiovascular Therapeutics 2006 meeting in Washington, DC October 2006, Dr. Wenaweser reported that acute coronary syndromes and diabetes were the only independent predictors of overall stent thrombosis.

IX. Antiplatelet therapy.

It should be recalled that in the pivotal SIRIUS trial (CYPHER stent), patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for only 3 months. In the pivotal TAXUS IV trial (TAXUS stent), aspirin was given indefinitely and clopidogrel or ticlopidine were administered for 6 months. These antiplatelet regimens are reflected in the current DES labeling.

Two major issues associated with antiplatelet therapy use post-DES implantation have emerged: (1) patient non-compliance with or early discontinuation of recommended antiplatelet therapy and (2) uncertainty regarding the optimal duration of dual antiplatelet therapy. Multiple studies demonstrate increased rates of DES thrombosis, MI, or mortality associated with premature discontinuation of dual anti-platelet therapy.

A. <u>Clinical data</u>

1. *ARRIVE 1 Registry*. Twelve month follow-up data from the ARRIVE 1 registry of the TAXUS stent demonstrate significantly increased stent thrombosis rates associated with non-compliance with antiplatelet therapy. At one year post-TAXUS stent placement, the per patient stent thrombosis rate was 4.4% (4.7% per stented vessel) in patients who were not taking dual antiplatelet therapy at 6 months (see following table).

	Patients with ASA/Clopidogrel or ASA/Ticlopidine at:	Patients without ASA/Clopidogrel or ASA/Ticlopidine at:	
	Discharge	**Discharge**	**P-Value**
1-Year Stent Thrombosis			
Stent Thrombosis (by patient)	1.9% (44/2272)	3.8% (7/186)	0.1034
Stent Thrombosis (by vessel)	1.8% (49/2699)	5.2% (11/212)	0.0034
	30-day	**30-day**	**P**
1-year Stent Thrombosis			
Stent Thrombosis (by patient)	1.8% (42/2278)	5.0% (9/180)	0.0102
Stent Thrombosis (by vessel)	1.8% (48/2707)	5.9% (12/204)	0.0007
	6-month	**6-month**	**P-Value**
1-Year Stent Thrombosis			
Stent Thrombosis (by patient)	1.7% (37/2143)	4.4% (14/315)	0.0045
Stent Thrombosis (by vessel)	1.7% (43/2549)	4.7% (17/362)	0.0010

2. *Iakovou et al.,* JAMA 2005; 293 :2126-2130 (see study details above). An independent predictor of stent thrombosis was premature antiplatelet therapy discontinuation [rate 29% (5/17 patients), HR 89.78; 95% CI, 29.90-269.60; P<0.001].

3. *Kuchulakanti et al.* Circulation 2006; 113: 1108-1113 (see study details above). The incidence of discontinuation of clopidogrel was significantly higher in patients with stent thrombosis compared to those without stent thrombosis (36.8% vs. 10.1%, *P*<0.001), and clopidogrel discontinuation was an independent predictor of stent thrombosis (OR 0.21, 95% CI 0.09-0.49, p=0.0003).

4. *Pfisterer et al.* J Am Coll Cardiol 2006; 48: in press. The BASKET LATE study (see above).

5. *Spertus et al.* Circulation 2006; 113: 2803-2809. The PREMIER Registry studied 500 DES-treated acute MI patients who were discharged on thienopyridine therapy. By 30 days, 68 patients (13.6%, 1 in 7) stopped therapy. Patients who stopped thienopyridine therapy by 30 days were more likely to die during the next 11 months (7.5% versus 0.7%, *P*<0.0001). Compared to those who continued taking thienopyridines, those who stopped were older, less likely to have completed high school or be married, more likely to avoid health care because of cost, and more likely to have had preexisting cardiovascular disease or anemia at presentation. They were also less likely to have received discharge instructions about their medications or a cardiac rehabilitation referral.

While the placement of DES in acute MI patients clearly represents off-label use, PREMIER Registry data demonstrate patient education and medication cost challenges associated with compliance with long-term dual antiplatelet medications that should be considered if the recommended duration of dial antiplatelet therapy is increased.

B. Recognition of anti-platelet compliance issues, current recommendations, and future concerns

As early reports of DES thrombosis emerged, it was recognized that patients may have their anti-platelet medications stopped inadvertently prior to elective procedures or need to have

these agents stopped secondary to clinically significant bleeding. In response, FDA worked collaboratively with DES manufacturers to inform cardiologists and patients of the need to continue anti-platelet therapy, without interruption, for its full recommended course. Patients have been further advised to consult their physician before stopping antiplatelet therapy for any reason. With respect to clopidogrel, FDA has also recommended that patients continue this agent for its other currently approved indications (recent myocardial infarction, acute coronary syndrome, recent stroke, or established peripheral arterial disease).

The current ACC/AHA/SCAI PCI Practice Guidelines recommend clopidogrel therapy for at least 3 months after CYPHER stent implantation, at least 6 months after TAXUS stent implantation (reflecting the recommendations in the present label for the CYPHER and TAXUS stents, respectively), and ideally up to 12 months in patients who are not at high risk of bleeding (Class IB recommendation). The European Society of Cardiology recommends clopidogrel administration for 6 to 12 months after DES implantation (Class IC recommendation).

Although premature discontinuation of dual antiplatelet therapy been identified as an important risk factor for DES thrombosis, the optimal duration of administration (particularly in higher risk patent and lesion subsets) is unknown. Further, it is not clear that extended duration of dual-antiplatelet therapy will prevent late thrombosis. In a presentation at the Transcatheter Cardiovascular Therapeutics 2006 meeting in Washington, DC October 2006, Dr. Alaide Chieffo reported that of 16 patients among 3021 consecutive DES recipients treated in Milan, Siegburg, and Naples who had late DES thrombosis (≥6 months post-stenting), 9 had been taking clopidogrel. Finally, a consideration for a longer duration of dual antiplatelet therapy must weigh a potential benefit of a reduction in the incidence of stent thrombosis versus a potential increase in the risk of major bleeding.

X. Bare metal stent thrombosis

In the initial studies of bare metal stent deployment, there were significant concerns regarding the high incidence (3-5%) of acute and subacute stent thrombosis. However, the frequency of acute and subacute coronary stent thrombosis, defined as stent thrombosis within 30 days of deployment, has been reduced to <1% to 2% as a result of improved deployment techniques (that fully appose stent to vessel wall) and the use of dual antiplatelet therapy. Most contemporary bare metal stent thrombosis data reflect relatively short-term follow-up. Overall, rates of BMS stent thrombosis generally range from 0.5% to 1.8%, and rates vary among different lesion and patient subsets (e.g., 2.9% in an acute MI study). The following studies are provided for background informational purposes but should not be used to make direct statistical comparisons to DES.

A. *Cutlip et al.* Circulation 2001; 103: 1967-71. This analysis pooled data from 6 coronary stent trials and associated nonrandomized registries that enrolled 6186 patients (6219 treated vessels) treated with ≥1 coronary stent followed by antiplatelet therapy with aspirin and ticlopidine. Clinical stent thrombosis was defined as any of the following within 30 days of the procedure: angiographic documentation of stent occlusion, unexplained sudden death when the stent was not known to be patent, myocardial infarction, or urgent target lesion revascularization within 30 days of the procedure. **Within 30 days, clinical stent thrombosis developed in 53 patients (0.9%).** The variables most significantly associated with the probability of stent thrombosis were persistent dissection NHLBI grade B or higher after stenting (OR, 3.7; 95% CI,

1.9 to 7.7), total stent length (OR, 1.3; 95% CI, 1.2 to 1.5 per 10 mm), and final minimal lumen diameter within the stent (OR, 0.4; 95% CI, 0.2 to 0.7 per 1 mm).

B. *Heller, et al*. Cathet Cardiovasc Intervent 2001; 53: 23–8. From a single center cath lab registry, 1855 patients treated with intracoronary stenting between January 1, 1998 and January 31, 1999 were identified. A total of 2,022 vessels and 2,475 lesions were stented (1.3 stents/patient); none received brachytherapy. All patients were treated with aspirin and either ticlopidine and clopidogrel for a minimum of 3 weeks post-procedure. Stent thrombosis was defined as (1) acute myocardial infarction plus (2) angiographic confirmation. Half of all stent thromboses occurred within the first week and 22 occurred within 15 days. An additional 12 patients presented with late stent thrombosis between 33 and 270 days post-procedure (mean 72.9 ± 23 days). The overall incidence of stent thrombosis (subacute plus late) was 1.8% (34/1855).

C. *Wang et al.* Cathet Cardiovasc Intervent 2002; 55: 142–147. The incidence of stent thrombosis causing MI was studied. Stent thrombosis was defined angiographically associated with symptoms, biochemical markers, and ECG changes consistent with a myocardial infarction. Antiplatelet therapy consisted of aspirin indefinitely and thienopyridines for 4 weeks**. Of 1,191 patients undergoing coronary stenting, acute (< 24 hr) plus subacute (1–30 days) stent thrombosis occurred in 0.92% (11 of 1,191 patients). A further 0.76% (9 of 1,191 patients) developed late stent thrombosis after 30 days.** There were no clinical or angiographic features at the time of the initial procedure that were associated with stent thrombosis.

D. *Ong et al*. J Am Coll Cardiol 2005; 45: 947-953. The 30-day incidence of stent thrombosis was studied in three sequential cohorts of 506 consecutive patients with bare metal (BMS), 1,017 consecutive patients with sirolimus-eluting (SES), and 989 consecutive patients treated with paclitaxel-eluting (PES) stents. Stent thrombosis was considered to have occurred when confirmed angiographically. A clinical definition of "possible stent thrombosis" was used for patients who within the first 30 days experienced sudden death, who suffered a fatal out-of-hospital cardiac arrest, or who suffered a MI that was not attributable to another coronary lesion and who did not undergo repeat angiography. **Including possible cases, 7 BMS (1.4%, 95% CI 0.7% to 2.8%) had stent thrombosis**, an incidence similar to the DES-treated patients. Bifurcation stenting in the setting of acute MI was an independent risk factor for angiographic ST in the entire population (OR 12.9, 95% CI 4.7 to 35.8, p<0.001).

E. *Katayama et al*. Circ J 2006; 70: 151–5. In a study of acute 381 consecutive **acute MI** patients treated with direct PCI using bare metal stents, angiographically confirmed subacute thrombosis was observed in 10 patients **(2.6%**).

XI. Benefits of reduced in-stent restenosis

The relative benefits DES implantation compared with bare metal stents was demonstrated by a significant reduction in the composite endpoint consisting of death, MI and target vessel revascularization. For both approved DES, however, the difference in outcome of DES vs. bare metal stents was essentially due to a reduction in the rate of ischemia-driven repeat revascularization. There were no differences in the rates of death and MI between treatment groups at 9 to 12 months post-stenting; death and MI rates in DES studies have been relatively

low, and these studies have not been powered to detect differences in these endpoints. No claims have been made in the device label that MI's and deaths are prevented with DES use. Similarly, there are no labeled claims of reduced death or MI rates with the other approved PCI revascularization techniques (balloon angioplasty and bare metal stents). The reduction in the rates of repeat revascularization favoring DES have been maintained during long-term follow-up (3 to 4 years) of randomized patients.

It is understood that the composite endpoint is non-hierarchical and does not equate the clinical importance of clinical restenosis with death or MI. Given the high case fatality and MI rates associated with stent thrombosis, it is reasonable to re-assess the risk/benefit ratio of reduced repeat revascularization rates if there is a significant increase in DES thrombosis-induced death and MI. While it is often expressed that clinical restenosis is a "benign" condition, this assertion is an area of uncertainty. Recurrent symptoms of myocardial ischemia present quality of life considerations if repeat revascularization is not attempted. Repeat PCI or referral for CABG for in-stent restenosis exposes the patient to the additional safety risk of repeat revascularization procedures (death, MI, other procedural complications), which can be avoided if clinical restenosis is prevented in the first place. The efficacy of repeat revascularization for ISR is less than for denovo lesions. Thus, there will be a reservoir of patients who will have recurrent restenosis after a second PCI; these individuals may face the risks associated with additional PCI procedures or CABG and/or have residual symptoms.

There are few data on the clinical consequences of in-stent restenosis. In a recent publication by Chen et al. (Am Heart J 2006; 151: 1260-4), the authors retrospectively identified 1186 cases of bare metal in-stent restenosis in 984 patients treated at the Cleveland Clinic. Of the in-stent restenosis episodes, 9.5% presented as acute MI (7.3% as non–ST-segment elevation MI and 2.2% as ST-segment elevation MI), 26.4% as unstable angina requiring hospitalization before angiography, and 64.1% as exertional angina. The clinical implication of this study is that the reduction in in-stent restenosis rates by DES would reduce these clinically significant events. However, in this study, unstable angina was not defined. Further, in-stent restenosis was defined as any "restenosis" severe enough to warrant repeat PCI. The duration from the index stent procedure to presentation was not stated. Thus, it is not known how many lesions had typical restenosis (due to neointimal growth, which is inhibited by DES) or had other underlying pathologic mechanisms (such as in-stent thrombus formation, dissection, or plaque prolapse), which is not prevented by DES use.

In considering the clinical significance of a reduction in restenosis and repeat revascularization rates associated with DES implantation, it would be important for the Sponsors to provide information on the clinical presentations of patients who underwent ischemia driven revascularization (stable angina, Braunwald class unstable angina, non-STEMI, or STEMI). Additionally, major adverse cardiac events that occur after repeat revascularization attempts should be considered.

XII. Passive surveillance MDR data

A. *Background.* The Medical Device Reporting (MDR) system reporting is a nationwide passive surveillance system which includes both mandatory and voluntary reporting. The MDR regulation, 21 CRF 803, effective 12-13-84, requires manufacturers to submit reports of device-related deaths or serious injuries and events involving a device malfunction that could cause or contribute to a death or serious injury, to the FDA. All medical device adverse event reports are entered into the Center's Manufacturer and User Facility Device Experience database

(MAUDE). As a condition of approval, manufacturers are required to submit a summary every 6 months of adverse events deemed reportable, those deemed non-reportable, and a summary of anticipated versus un-anticipated events.

A few months after the approval of the Cypher stent, there was an influx and clustering of sub-acute thrombosis reports. The Agency, in conjunction with Cordis, issued a letter notifying physicians of these initial reports in July 2003. In October 2003, upon receipt of approximately 300 cases of sub-acute thrombosis through MDR, the agency issued a public health notification which reminded clinicians to follow the product's labeling, including patient selection, sizing of the stent and concomitant antiplatelet therapy.[1]

B. *Methods.* The MAUDE database was queried on all brand name permutations of both commercially available drug-eluting stents, Cypher and Taxus, since their approval dates, April 24, 2003 and March 4, 2004, respectively. Further query identified reports of thrombosis. Finally, a more comprehensive query included reports mentioning thrombosis and/or associated patient signs/symptoms (e.g., ST segment elevation or chest pain) or cardiac events (e.g., myocardial infarction).

C. *Results.* The total number of reports for both DES entered into the database is depicted over time in Figure 1. Reports of thrombosis over time are illustrated in Figure 2. The highest number of reports was entered into the database in fall of 2003 concurrent with the release of FDA's public health notification (http://www.fda.gov/cdrh/safety/cypher3.html). Figure 3 represents reports mentioning thrombosis and/or associated with patient signs/symptoms (e.g. ST segment elevation and chest pain) and/or cardiac events (e.g. myocardial infarction). Table 1 enumerates the total number of reports for each of the three categories entered into the database.

[1] Muni NI, Gross TP; Problems with Drug-eluting Coronary Stents- the FDA Perspective. N Engl J Med 2004 Oct 14; 351(16): 1593-4.

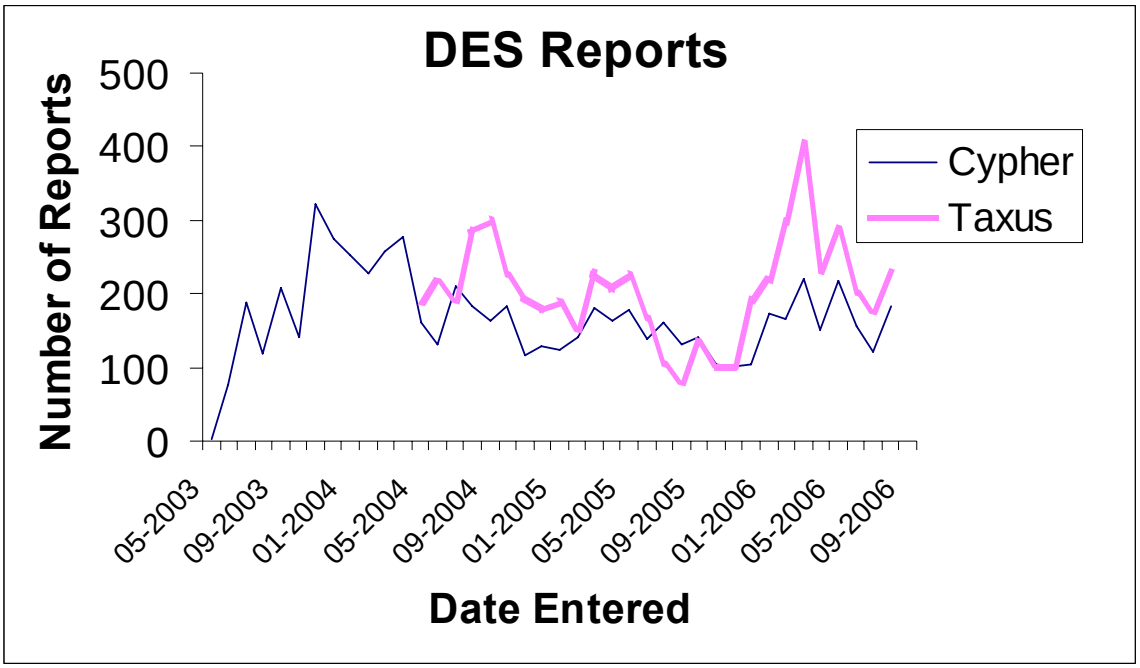


Figure 1. DES reports entered into the MAUDE database since May 2003.

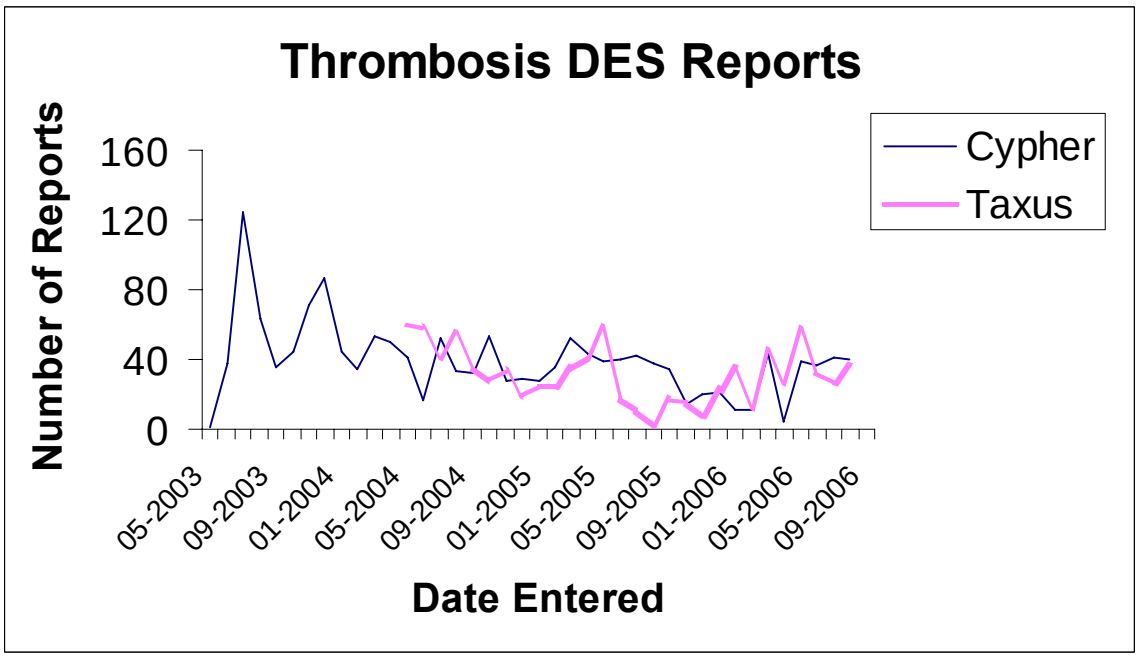


Figure 2. DES reports entered into the MAUDE database since May 2003 associated with thrombosis.

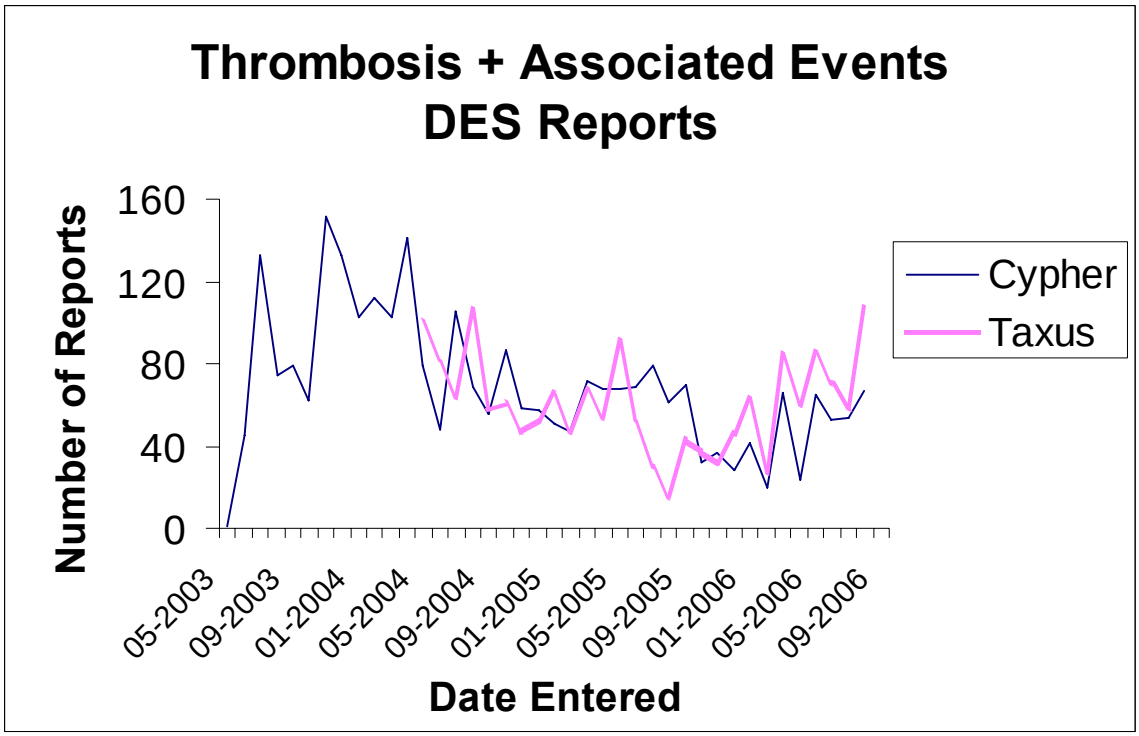


Figure 3. DES reports entered into the MAUDE database since May 2003 associated with thrombosis and related signs/symptoms/cardiac events.

	Overall	Thrombosis N (%)	Thrombosis and Associated Events N (%)
Cypher	6696	1570 (23)	2775 (41)
Taxus	5700	882 (16)	1702 (30)

Table 1. DES reports entered into the MAUDE database since May 2003.

D. *Assessment.* No discernable trend in reports of thrombosis (or associated events) is noted for either Cypher or Taxus stents. Analyses using differing definitions and search criteria are expected to produce dissimilar aggregate results as shown in the Figures and the Table 1. The important limitations of MDR data as described below (Section XIII.C) should be considered.

XIII. Limitations of data

A. Post-approval registries

There are several epidemiologic study designs that can be employed to answer remaining questions of safety and effectiveness for drug-eluting stents. It may be costly and impractical to collect long-term effectiveness data in a randomized clinical trial. Multi-year registries designed as cohort studies are an important way to study issues postmarket. (Nested case-control designs can be incorporated into these cohorts to study emerging and unexpected safety issues.)

There are several limitations to post-approval registries as currently designed for DES. These patient registries were designed as to capture early postmarket experience in the "real world" of diverse patients and users. They were meant to be descriptive (non-hypothesis driven) and non-comparative (i.e., without controls) and were only "powered" to confidently detect adverse events rates on the order of one percent.

As the Agency and industry grows in their experience with the use of registries, it is anticipated that post-approval registries will be more sophisticated and rigorous (e.g., incorporate data validation, controls, and be sufficiently sized to address specific hypotheses when appropriate).

B. Meta-analyses

There have been a number of recently presented meta-analyses of clinical trials related to drug-eluting and bare metal stents. The following discussion will outline some of the key issues that should be considered in the evaluation of these studies.

There are many benefits of meta-analysis, including the ability to increase the power of small trials, and the ability to identify sources of diversity across various types of studies. There are two methods of meta-analyses that have been used to study drug-eluting stent trials, individual patient- and group-level meta-analyses or meta-regressions.

Group-level meta-analyses are those where data are only available at the level of the published study. In patient-level meta-analyses, data are accessible at the level of the individual patient (this may also be referred to as a type of data pooling). Meta-analysis of patient-level data offers several potential advantages over study-level analysis including: (1) the ability to use more appropriate statistical methods not always feasible using study-level analysis to study patients who may have been excluded from the original publications, and (2) to adjust for prognostic variables that may have confounded the original treatment comparisons. Although patient-level analysis has, in some instances, led to different conclusions than the corresponding study-level analysis, that has not always been the case. For examining the overall treatment effects, it has been demonstrated that, given the same studies included in both types of analysis, study level analysis and patient-level analysis produce the same results, at least for certain types of statistical models focusing on overall estimates of treatment or exposure effects. However, comparisons of study-level analysis and patient-level analysis for the same clinical questions are often confounded by the inclusion of different studies and, thus, different patients in the analyses.[2]

Patient-level meta-analysis is the preferred method, when feasible. If such an analysis is conducted on all randomized clinical trials, regardless of publication status, the limitation of publication bias has been eliminated. There are also many limitations that come from data abstraction that is minimized when one is able to pool individual data. The main limitation that remains is that there still may be some heterogeneity across studies that cannot be corrected for ad-hoc. If the difference between study results is not significantly different, then the meta-analysis should be statistically valid.

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[2] Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI; Anti-Lymphocyte Antibody Induction Therapy Study Group. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. Stat Med. 2002 Feb 15;21(3):371-87.

C. Limitations of MDR Data

Passive surveillance, while providing signals to actual and potential device-related problems, has four significant limitations. **First**, under-reporting of adverse events is a well-known and recognized phenomenon. Events reported through the system represent a subset of the total occurrence of events. In addition, manufacturers are not required to submit denominator information such as number of devices manufactured, distributed and implanted. Thus accurate incidence rates are unable to be determined based on report data alone. **Second**, report data are often incomplete and invalid, though there is a regulatory requirement for a minimum dataset, event narrative descriptions vary in completeness and complexity. Furthermore, FDA is often not able to obtain failure analysis information as devices may be discarded or not returned to the manufacturer for testing. In addition, data are not independently corroborated by FDA. **Third**, due to device complexity and the use environment, causality cannot be determined. Reports only provide signals of actual or potential device problems, which further investigation needs to refine. **Fourth**, reports are not representative of the universe of adverse events because reporting is subject to various biases. For instance, reports may vary by source of report, by severity of event, or by presence of litigation or publicity.

XIV. Conclusion

Developed to address the important clinical problem of restenosis, drug-eluting stents are the product of advances in biomedical engineering, pharmacology, toxicology, polymer chemistry, and vascular biology built on a foundation of bare metal stent technology. Data from multiple randomized clinical trials supported by large registry studies provide convincing evidence that the currently approved DES significantly reduce the rate of repeat revascularization rates in the treatment of obstructive coronary atherosclerosis.

In recognition of the novelty of DES technology and the mechanism of restenosis prevention by DES, extended follow-up (5 years) of patients enrolled in the DES randomized trials submitted for PMA approval was required to address long-term safety and effectiveness questions. Additionally, with an expectation that DES would be widely adopted by interventional cardiologists, FDA requested that the DES manufacturers conduct large registry studies that reflect real-world DES use. Recent analysis of these long-term and broad DES use datasets has suggested a DES safety issue that requires further discussion and investigation.

Concerns regarding stent thrombosis have lead FDA to convene a public meeting of the Circulatory System Devices Advisory Panel in an effort to explore the risks, timing and incidence of DES thrombosis. It is hoped that this meeting will enhanced our understanding of the benefits and risks of DES.

The Agency believes that the data currently available from the extended follow-up of patients in the industry sponsored randomized PMA trials and post-approval registries supplemented other published literature and presentations indicate the following:

1. When used in accordance to their labeled intended uses, the currently approved DES (CYPHER and TAXUS) are associated with a small but significant risk of late stent

thrombosis (emerging 1-year post stent placement) compared to bare metal stents. The total number of patients ≥3 years post-stenting remains relatively small, and it is uncertain whether cases of late stent thrombosis will continue to accrue with longer-term follow-up.

2. Whether DES are associated with an overall long-term increased rate of death or MI is an area of uncertainty. Meta-analyses based on published literature suggest an increased death or MI risk associated with the CYPHER stent. In contrast, meta-analyses based on patient-level data bases from the DES manufactures have not shown an increased risk either CYPHER or TAXUS stents. Reconciliation of the results of these meta-analyses is needed.

3. DES use has eclipsed the relatively narrow anatomic subsets treated in the pivotal trials with a majority of current DES use in patient and lesion subsets that are more complex than those represented in the randomized trials. Increased rates of stent thrombosis have been observed in more complex patient and lesion subsets (e.g., bifurcation lesions, multiple stents per vessel, diabetics, and patients with acute MI, multivessel disease and renal dysfunction). However, most data are from single-armed registries of DES use and lack a control group for comparison, and few long-term data (≥1 year) are available.

4. Valuable information on DES thrombosis, death and MI rates in more complex lesion and patient subsets can be expected from ongoing and planned registry studies. However, there is consensus among investigators, the NIH, and FDA that randomized controlled trials are the best approach to address optimal revascularization strategies in certain high risk patient cohorts. To that end, multivessel revascularization (including left main disease) with DES vs. coronary bypass surgery is being explored in the SYNTAX Trial (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) using a non-inferiority design. Additionally, a randomized controlled superiority design of multivessel stenting (CYPHER or TAXUS) vs. CABG focused on diabetics is being employed in the FREEDOM Trial (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease). PCI with bare metal stents is the standard treatment for most individuals with acute ST-segment elevation MI (STEMI), but the safety and efficacy of deploying a DES in a thrombus-containing lesion associated with an acutely disrupted plaque has not been established. To investigate this issue, STEMI subjects in the HORIZONS AMI Trial (Harmonizing Outcomes with Revascularization and Stents) are randomized to either the TAXUS stent or the bare metal EXPRESS stent. The results of these important trials will have broad public health implications.

5. The current labeling for dual antiplatelet therapy for DES reflects the duration of use in the pivotal trials (3 months for CYPHER and 6 months for TAXUS). Multiple studies indicate increased rates of DES thrombosis, MI, or mortality associated with premature discontinuation of dual anti-platelet therapy. The optimal duration of dual antiplatelet therapy particularly in more complex patient and lesion subsets that may be inherently at increased risk of late stent thrombosis is unknown.

6. It is not known whether an extended course of dual-antiplatelet therapy will prevent late thrombosis. Consideration for a longer duration of dual antiplatelet therapy must weigh a potential benefit of a reduction in the incidence of stent thrombosis versus a potential increase in the risk of major bleeding.

7. Since stent thrombosis is a serious adverse event associated with high rates of death and MI, continued efforts to clarify the mechanisms of stent thrombosis and interventions to reduce the risk of its occurrence will have public health benefits.

In the other sections of this Panel Package, you will find data and analyses presented by Cordis and Boston Scientific. FDA has requested that each company provide a minimum set of analyses using the ARC definitions. However, due to the time needed to accomplish the requested data readjudication and analyses for this meeting, these materials have not been reviewed by FDA prior to their inclusion in this package.

FDA welcomes the Panel's expert opinion on the issues raised above; specific questions for your consideration are included in Section 4 of this binder.