


DES: Benefit or hazard?

Abstract


Although rare, stent thrombosis remains a severe complication after stent implantation owing to its high morbidity and mortality. Since the introduction of drug-eluting stents (DES), most interventional centers have noted stent thrombosis up to 3 years after implantation, a complication rarely seen with bare-metal stents. Some data from large registries and meta-analyses of randomized trials indicate a higher risk for DES thrombosis, whereas others suggest an absence of such a risk. Several factors are associated with an increased risk of stent thrombosis, including the procedure itself (stent malapposition and/or underexpansion, number of implanted stents, stent length, persistent slow coronary blood flow, and dissections), patient and lesion characteristics, stent design, and premature cessation of antiplatelet drugs. Both the polymers used to coat the devices and the drugs released from DES exert distinct biological effects, such as the induction of local hypersensitivity reactions and inhibition of cell proliferation. As a result, although primarily aimed at preventing vascular smooth muscle cell proliferation and migration (ie, key factors in the development of restenosis), DES also impair reendothelialization, which leads to delayed arterial healing, and induce tissue factor expression, which results in a prothrombogenic environment. Finally, DES impairs endothelial function of the coronary artery distal to the stent, which potentially promotes the risk of ischemia and coronary occlusion. Although several reports raise the possibility of a substantially higher risk of stent thrombosis in DES, evidence remains inconclusive; as a consequence, both large-scale and long-term clinical trials, as well as further mechanistic studies, are needed. Extended dual anti-platelet therapy is recommended in certain patients treated with DES.

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Drug Eluting Stents: Benefit or Hazard


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“Science never solves a problem without creating ten more”


George Bernard Shaw

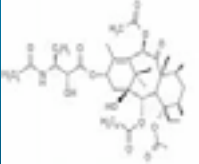

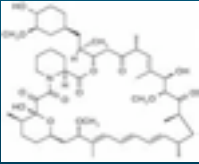

Objectives



- Review efficacy data of drug-eluting stents
- Review safety data of drug-eluting stents
- Make sense of the drug-eluting stent roller coaster

Current Drug Eluting Stents



	DRUG	POLYMER	STENT
TAXUS	 Paclitaxel	SIBS with paclitaxel Stainless Steel	 Liberte
CYPHER	 Cypher	PEVA/PBMA PEVA/PBMA with sirolimus Parylene C Stainless Steel	 BX Velocity

Purpose of Drug Eluting Stents

To eliminate the neointimal proliferation that occurs with bare metal stents



The Problem of Restenosis

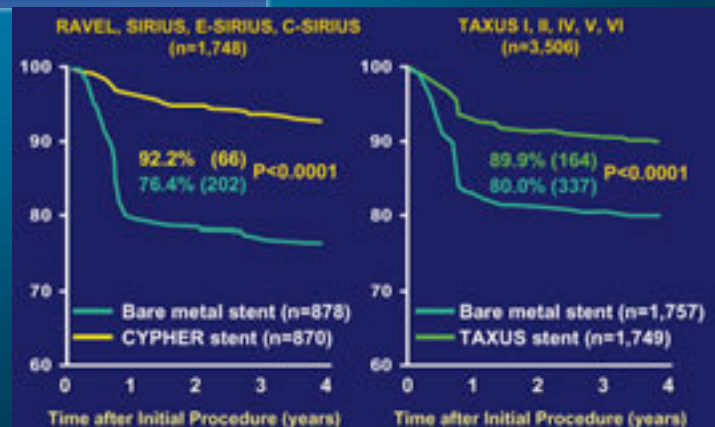
- **Coronary interventions worldwide 2003:**
2.0 million (~ 50% in US)
- **Angiographic Recurrence:**

PTCA	40-45 %	
Stents	20-30 %	500,000/yr
- **Clinical Events:** 300,000/yr
- **Recurrent Restenosis:** 150,000/yr

Drug Eluting Stents

- **Efficacy**
 - Durability
- **Safety**
 - Death and MI
 - Stent thrombosis (especially late)

Freedom From Ischemic TLR 9 prospective, double-blind, randomized trials

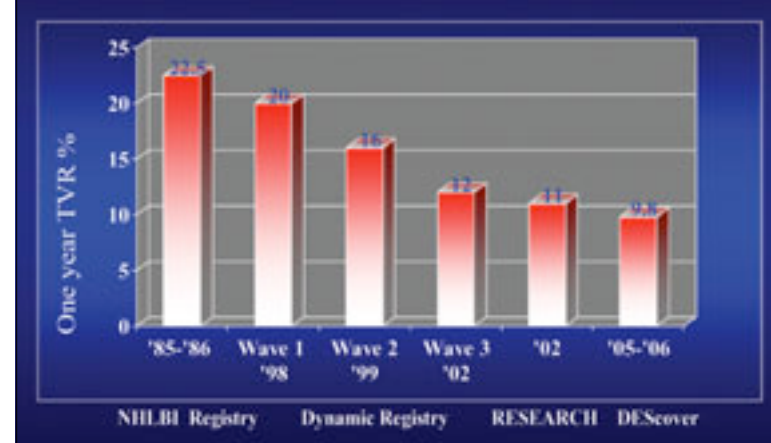


Independent patient-level meta-analysis

Penetration of Drug Eluting Stents



Reduction in Clinical Restenosis with Bare Metal Stents



Drug Eluting Stents

- Efficacy
 - Durability
- Safety
 - Death and MI
 - Stent thrombosis (especially late)

Bare metal and drug-eluting stent explant



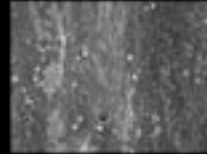
Guagliumi et al. Circulation 2003;107

Bare metal and drug-eluting stent explant

BMS



confluent endothelium



confluent endothelium, sparse adherent platelets



minute platelet aggregates

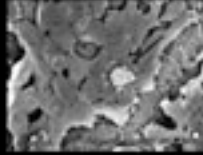
DES



abnormal EC morphology



focal loose cell junctions



small platelet aggregates

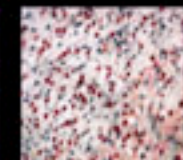
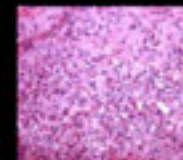
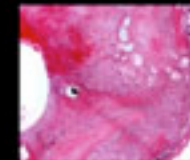
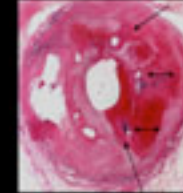
Guagliumi et al. Circulation 2003;107

Hypersensitivity reaction to DES polymer

prox stent



distal stent



Marked inflammation extending to adventitia

Virmani et al. Circulation 2004;109

New York Times – Wednesday July 9, 2003

Warning on Artery Stent Cites Some Cases of Clots

By MICHAEL ROSENBERG

Johnson & Johnson said it today is warning that its coronary artery stents may be associated with a higher risk of blood clots than other stents, according to a new study. The study, published in the medical journal *Journal of the American Medical Association*, found that patients who received a Johnson & Johnson stent had a higher risk of dying from a heart attack or stroke within 30 days of the procedure than those who received a bare metal stent. The study also found that patients who received a Johnson & Johnson stent had a higher risk of dying from a heart attack or stroke within 30 days of the procedure than those who received a bare metal stent. The study also found that patients who received a Johnson & Johnson stent had a higher risk of dying from a heart attack or stroke within 30 days of the procedure than those who received a bare metal stent.



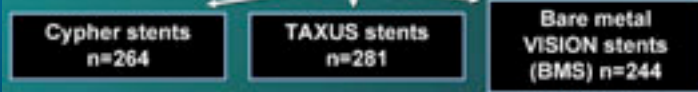
The Cypher stent, made by Johnson & Johnson, is coated with a drug meant to prevent clots from clogging again.

Five deaths are reported in patients who got a Johnson & Johnson product.

Five deaths are reported in patients who got a Johnson & Johnson product.

BASKET Trial: Study Design

826 patients all undergoing PCI irrespective of indication (of 988 (84%) consecutive pts – only excluded were RVD >4.0 mm (n=23), ISR lesions (n=49), and no consent (n=90))
1281 de novo lesions



Clopidogrel for 6 months in all patients

Primary endpoint: Cost-effectiveness at 6 months
Cost per MACE prevented
MACE = cardiac death, nonfatal MI, and TVR

Kaiser C et al. Lancet 2005;366:921-29

BASKET Trial: 6 Month MACE N=824 with 6 month follow-up



Kaiser C et al. Lancet 2005;366:921-29

BASKET LATE Trial: Study Design

743 patients randomized in the BASKET trial and WITHOUT AN EVENT DURING THE 6-MONTH CLOPIDOGREL PHASE

Drug-eluting stents (DES)
(pooled paclitaxel and sirolimus DES groups)
n=499

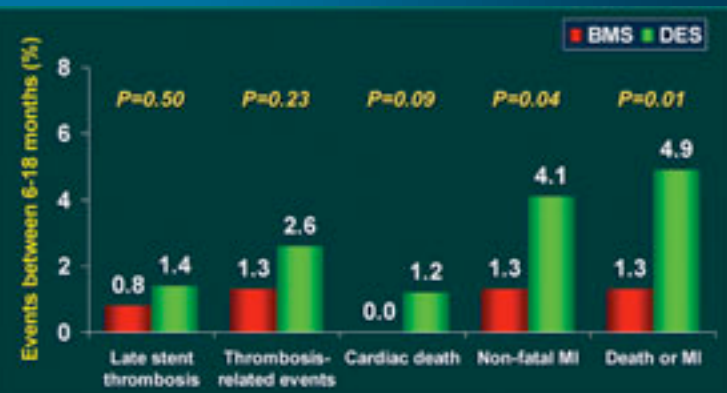
Bare metal
VISION stents (BMS)
n=244

Followed for 1 year off clopidogrel

- Primary Endpoint: Composite cardiac death or nonfatal MI.
- Other Endpoints: "Thrombosis-related events"

Pfisterer M et al. J Am Coll Cardiol 2006;48:2584-91

BASKET LATE Trial: 6-18 Month MACE N=743 (pts with early events excluded)



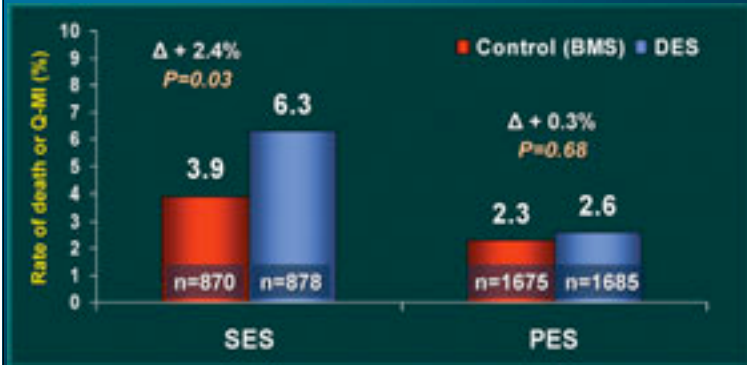
Pfisterer M et al. J Am Coll Cardiol 2006;48:2584-91

"An Epidemic of Madness"



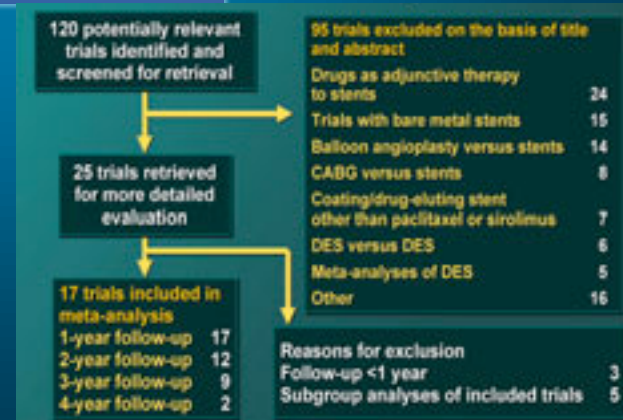
Incidence of Serious or Adverse Events Death or Q-Wave MI

All randomized studies up to latest available follow-up



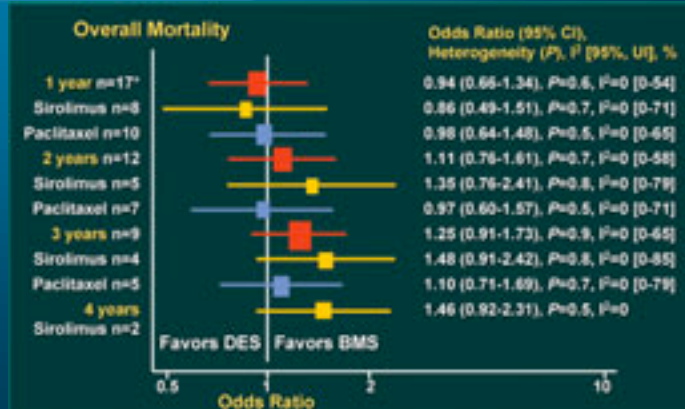
Camenzind E, ESC 2006

DES Meta-Analysis



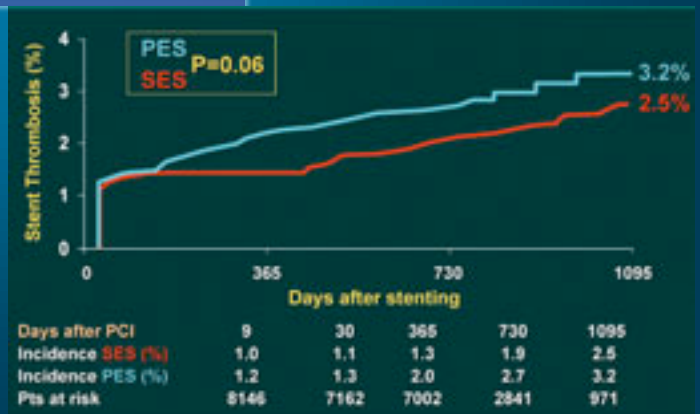
Nordmann AJ et al. Eur Heart J 2006;27:2784-814

Mortality from 17 Randomized Controlled Trials Comparing DES vs BMS: Overall Mortality



Nordmann AJ et al. Eur Heart J 2006;27:2784-814

Bern/Rotterdam - 2 Center Experience

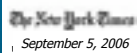


Daemen J et al. Lancet 2007;369:619-21

Hype and Hysteria: "If it Bleeds it Leads"



Studies linking drug eluting stents to mortality/MI spark impassioned pleas and calls for calm



Cardiologists Question the Risks Using Drug-Coated Stents



Boston Scientific Risks Tied to Stent



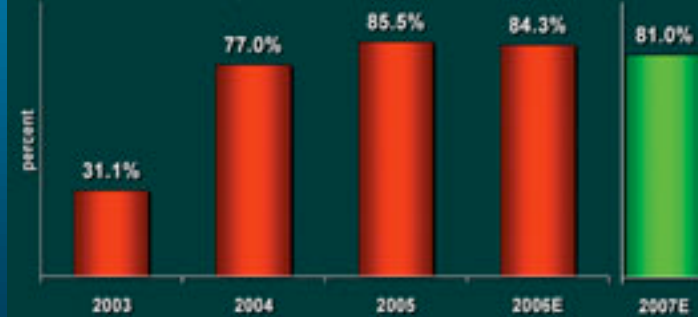
Stent Safety Near Boiling

Problems with the Camezind Meta-Analysis

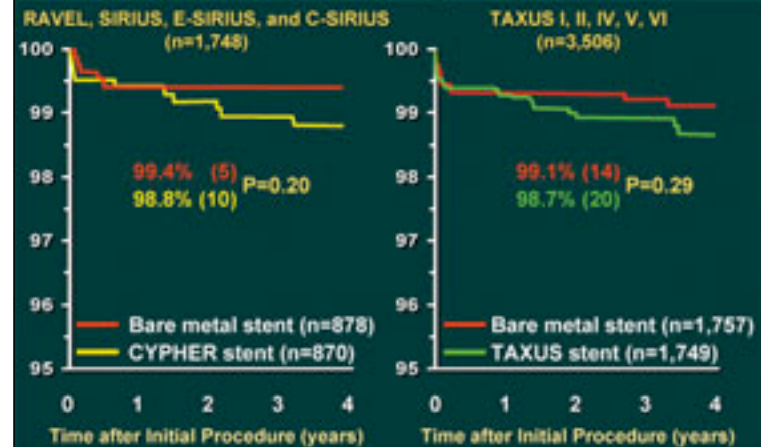
- Biased selection of trials
- Variable follow-up
- Included un-published data (abstract)
- Various definitions of thrombosis

US Penetration of DES: Falling!

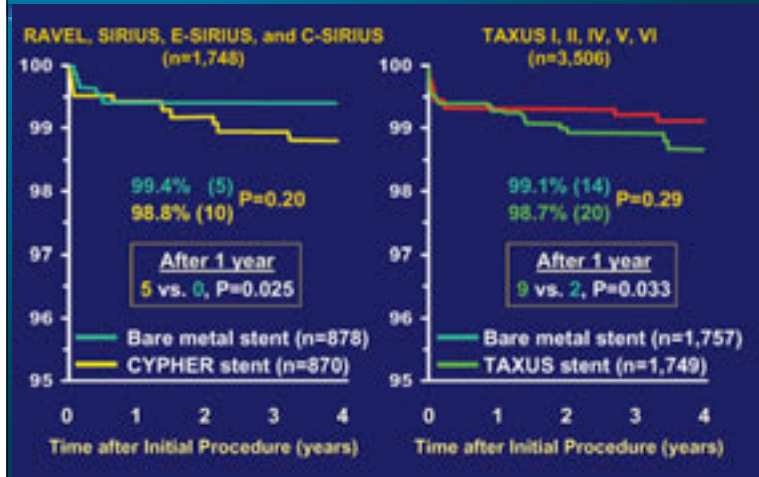
Source: JP Morgan



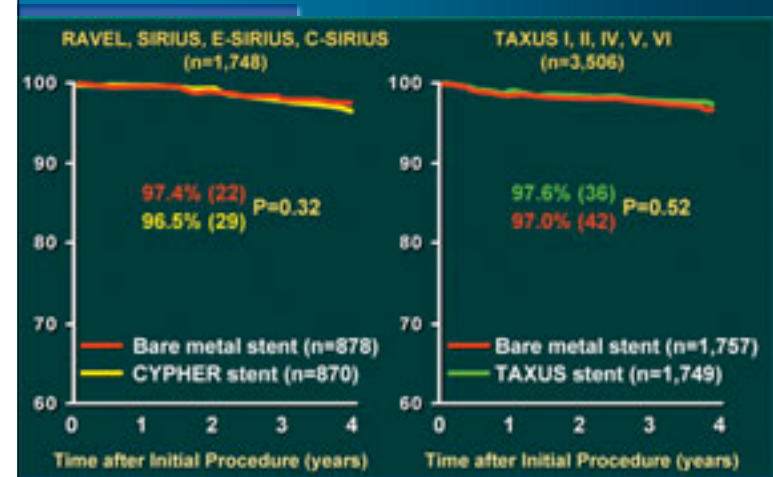
Freedom From (Protocol) Stent Thrombosis 9 prospective, double-blind, randomized trials



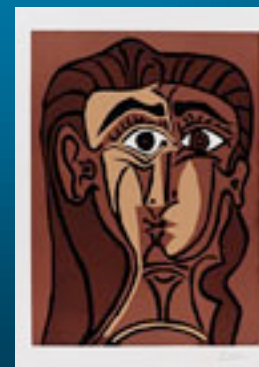
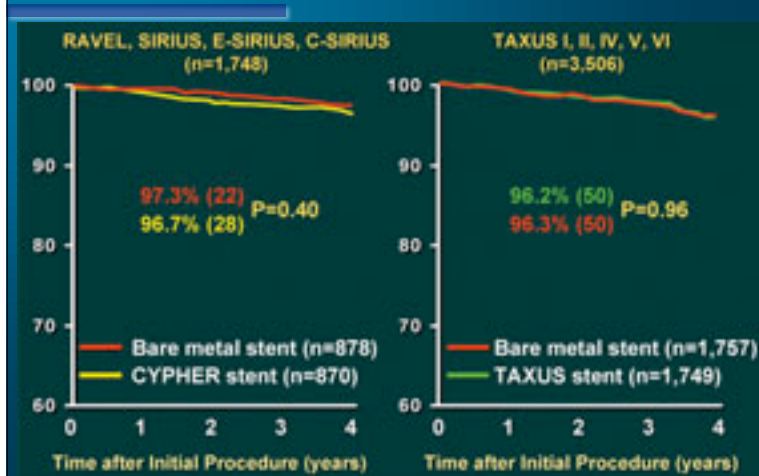
Freedom From (Protocol) Stent Thrombosis 9 prospective, double-blind, randomized trials



Freedom From Cardiac Death 9 prospective, double-blind, randomized trials

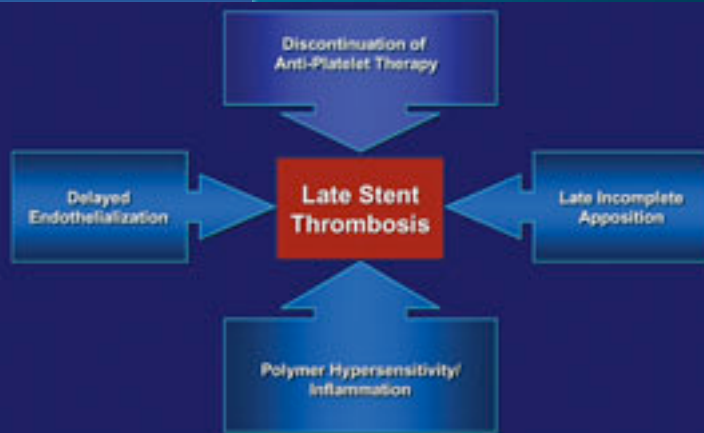


Freedom From Non Cardiac Death 9 prospective, double-blind, randomized trials



What is stent thrombosis?

Late Stent Thrombosis



Stent Thrombosis Definition

Expanded Stent Thrombosis Definition

1. Definite/Confirmed

Autopsy evidence or angiographic confirmed stent thrombosis (definite) is considered to have occurred if:

1. TIMI flow is:

- a. Grade 0 with occlusion originating in the stent or segment 5mm proximal or distal to the stent region in the presence of thrombus
- b. Grade 1, 2, 3 originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of thrombus

AND at least one of the following criteria within 48 hrs:

2. New onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes)
3. New ischemic ECG changes suggestive of acute ischemia
4. Typical rise and fall in cardiac biomarkers (>2x ULN of CK)

The incidental angiographic documentation of stent occlusion in the absence of clinical syndromes is not considered a confirmed stent thrombosis (silent thrombosis).

Stent Thrombosis Definition

Expanded Stent Thrombosis Definition

2. Probable

Probable stent thrombosis is considered to have occurred in the following cases:

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

3. Possible

Possible stent thrombosis is considered to have occurred with any unexplained death beyond 30 days.

Stent Thrombosis Definition

Expanded Stent Thrombosis Definition

Timing

Acute Thrombosis*:	0 – 24 hrs. post
Sub-acute Thrombosis*:	>24 hrs – 30 days post
Late Thrombosis:	30 days – 1 year post
Very Late Thrombosis:	> 1 year post

1. Definite/Confirmed
2. Probable
3. Possible

* Acute/Sub-acute can also be replaced by early stent thrombosis. Early stent thrombosis = 0-30 days.

Stent Thrombosis Study

10,000 consecutive pts receiving DES
at up to 12 sites

Aspirin and Clopidogrel responsiveness evaluated
(Accumetrics VerifyNow system)

Clinical FU for 2-5 years

Angiographic core lab assessment of all
stent thromboses and 1:3 matching controls

Pis: Gregg W. Stone and Chuck Simonton
Sponsors: CRF and the Dickinson Inst.
Principal study group: STENT Registry investigators

Supported by grants from Boston Scientific
(lead contributor), Accumetrics, Abbott
Vascular, Cordis, and Medtronic

Final Thoughts

- The use of drug eluting stents has led to decreased rates of restenosis, however with improvements in bare metal stents and stenting techniques the relative benefit is narrowing
- There is a clear signal that late stent thrombosis occurs more frequently with current DES than BMS - >0.4% increase per year in the first 4 years
- Based on available meta-analysis from randomized trials, the cumulative frequency of cardiac death and MI are NOT significantly increased, although more "real world" data is necessary

Final Thoughts

- There are no convincing data to suggest that there are important differences in early or late stent thrombosis when comparing Cypher and Taxus DES
- The causes of late stent thrombosis are multifactorial – but the majority of events are probably due to biologic DES responses (drug/polymer)
- **Safer DES are needed**