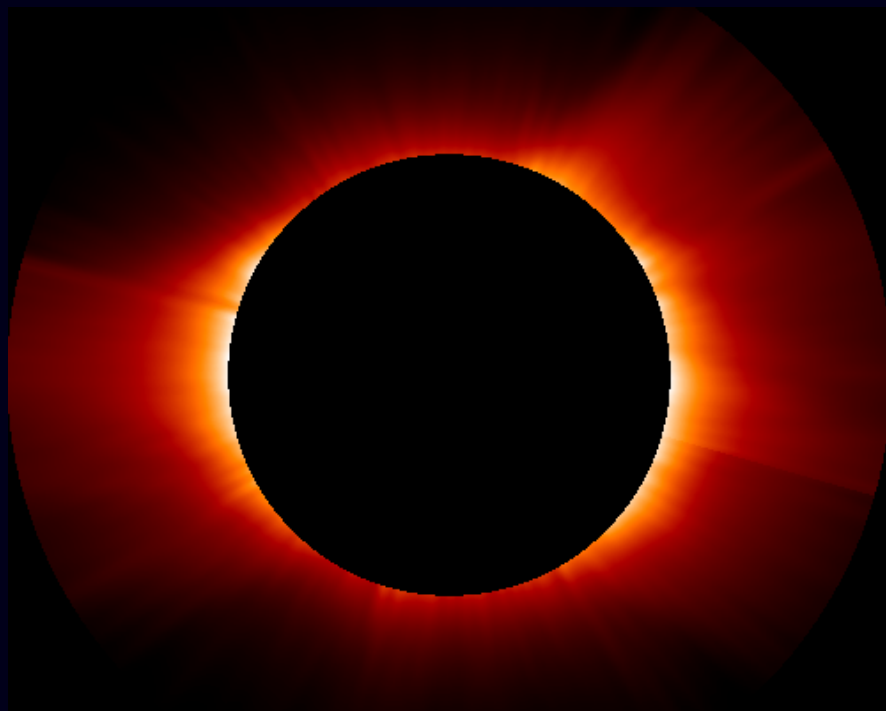


DES Controversy

Stent Thrombosis, Not Time to Panic



Dual Anti-platelet Therapy, How Long?

Cheol Whan Lee, MD
University of Ulsan,
Asan Medical Center,
Seoul, Korea

A landscape photograph showing a dark, silhouetted horizon against a gradient sky. The sky transitions from a dark, muted blue at the bottom to a lighter, hazy grey at the top. A small, bright white light source is visible on the horizon line, slightly to the right of the center. The overall mood is quiet and contemplative.

Disclosure

Nothings

RAVEL, ZERO Trial

You do 100 patients and 0 come back.

	Sirolimus-stent (N=118)	Bare-stent (N=120)	P value
Lesion Length, mm	9.6	9.6	NS
Pre-MLD, mm	0.94	0.95	NS
Post-MLD, mm	2.43	2.41	NS
Follow-up MLD, mm	2.42	1.64	< 0.001
Late Loss, mm	-0.01±0.33	0.80±0.53	< 0.001
Angiographic Restenosis, %	0	27	< 0.001
1-Year TLR, %	0	23	< 0.001
Death, %	2	2	NS
MACE- free survival, %	97	73	< 0.001

SIRIUS Trial

Bright Star in Cardiology

Dramatic reductions in odds ratio for restenosis were seen across all subgroups of patients in the SIRIUS trial.

A degree of efficacy rarely have been seen for any particular therapy in medicine history.



**Dramatic changes across
the therapeutic landscape**

DES Euphoria

To Open or Not To Open

**Restenosis, the Achilles heel of bare-metal stenting,
had finally been cured.**

**Based on pivotal clinical trial evidence,
the US FDA approved both CYPHER in 2003
as well as TAXUS in 2004.**

Prevalence of DES Usage

DES for All Kinds of Patients

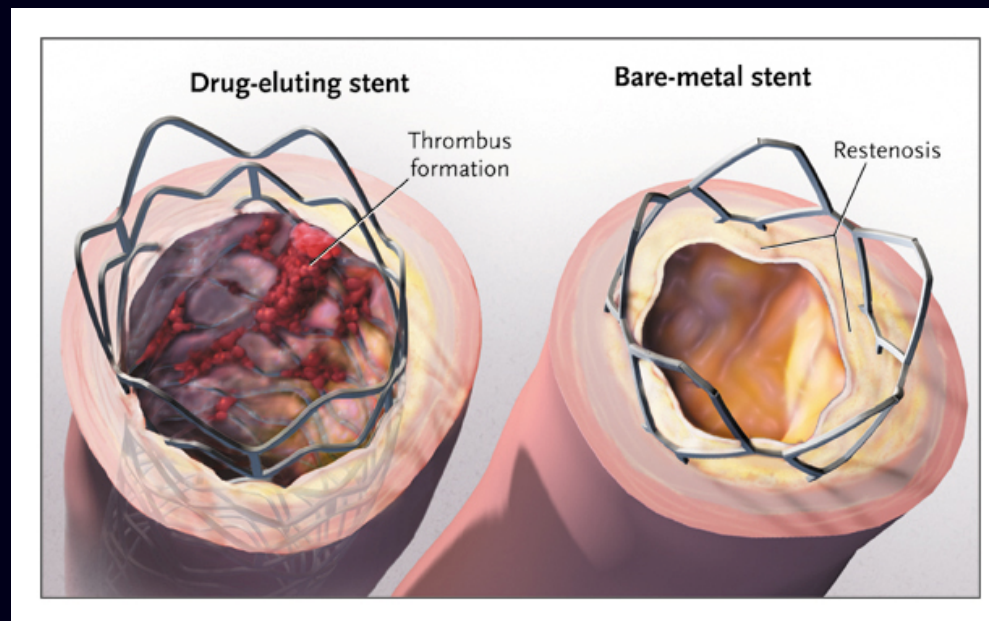
- On-label use of DES is estimated to account for <40% of DES use.
- More than 60% of the DES is currently used for off-label indications, such as more complex lesions or higher risk clinical setting.

Late Stent Thrombosis

Two Sides of The Same Coin



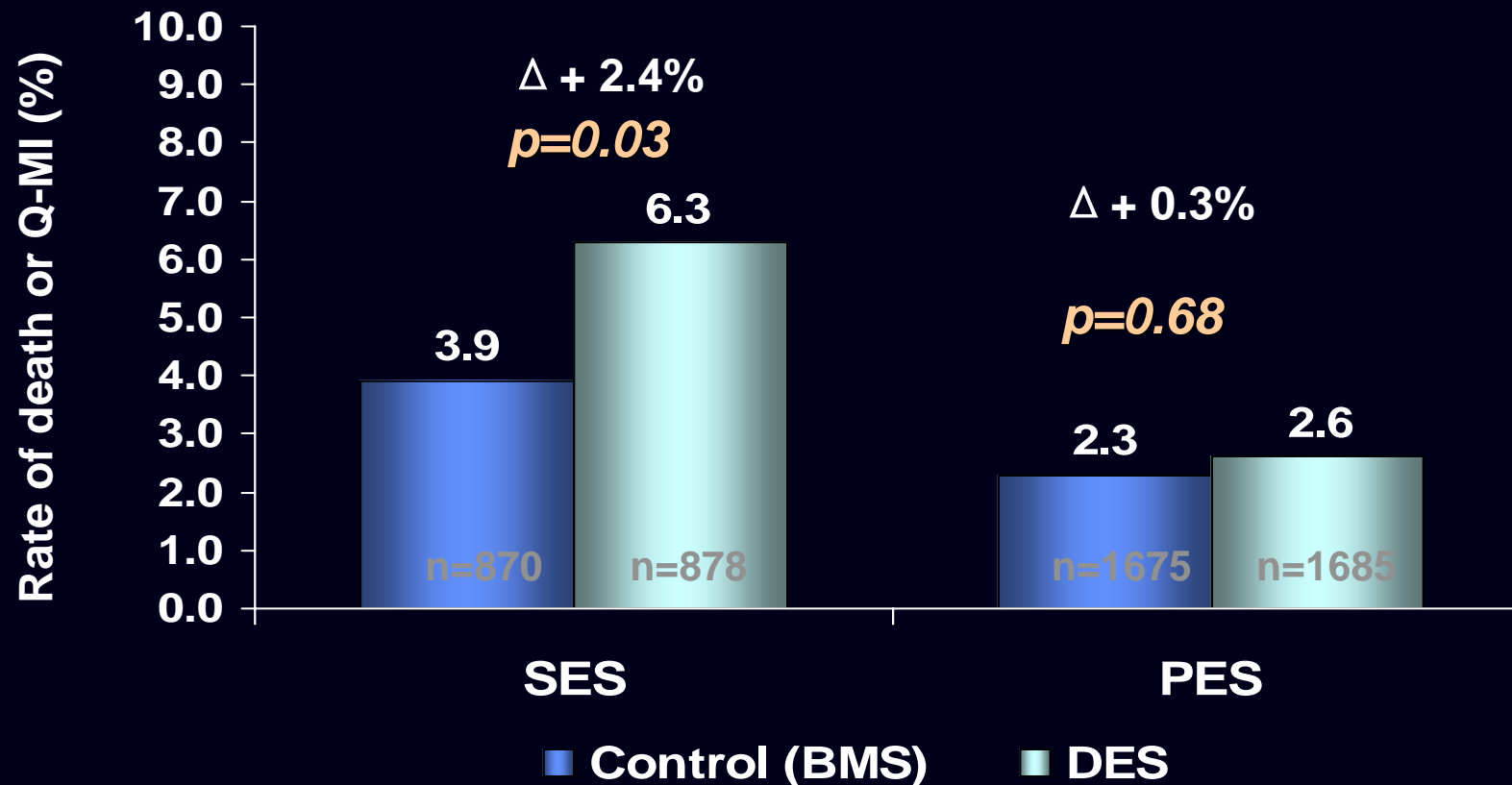
A 73-year-old man received Taxus stent implantation 14 months ago. Aspirin was discontinued before resection of a newly diagnosed colon carcinoma. 1 week later, on the evening of surgery, he developed a big anterior AMI.



Doubts were emerging.

Incidence of All Death or MI in Pooled DES Data

All randomized studies up to latest available follow-up



Swedish Shock

DES euphoria cool down!



Safety Issues, swirling around the world.

After 6 months, the DES-group compared to the BMS group:

Mortality: 32% ↑, 0.5%/year ↑

Death/MI: 20% ↑, 0.5-1%/year ↑

No interval differences → **Is it a permanent problem?**

	Time (years)					
BMS	9556	8744	8541	6465	4154	2213
DES	3432	3179	3092	1897	932	347

“Real-life experience, from an entire country”

Fashionable topic!



The **NEW ENGLAND**
JOURNAL of MEDICINE

A Topic Leader

An Epidemic of Violent Language

Clot magnet

Lethal gun

Malignant disease

Monster

Time bomb

Vulnerable strut

.....

A rare but life-threatening disease

Purpose of FDA Meeting

December 7 - 8, 2006

1st day: on-label, 2nd day: off-label

- **Assess safety and efficacy of DES**
- **Assess objective data presented by FDA, industry, professional societies, academic physicians**
 - **stent thrombosis (BMS vs DES)**
 - **mortality risk (BMS vs DES)**
 - **on-label vs off-label usage of DES**
 - **length of continuation for dual antiplatelet therapy**

ORIGINAL ARTICLE

Safety and Efficacy of Sirolimus- and Paclitaxel-Eluting Coronary Stents

Gregg W. Stone, M.D., Jeffrey W. Moses, M.D., Stephen G. Ellis, M.D.,
[Joachim Schofer, M.D.](#), Keith D. Dawkins, M.D., Marie-Claude Morice, M.D.,

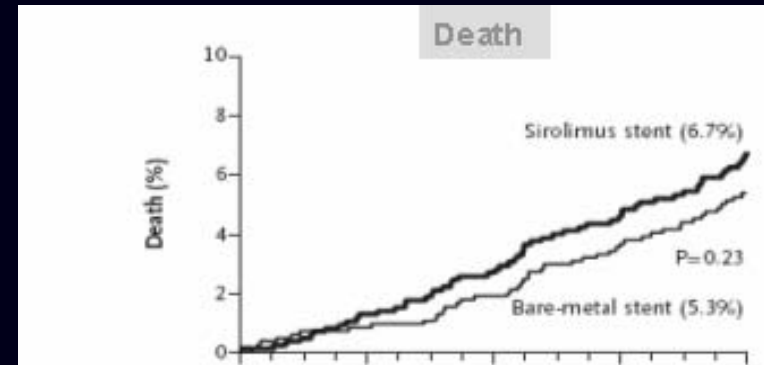
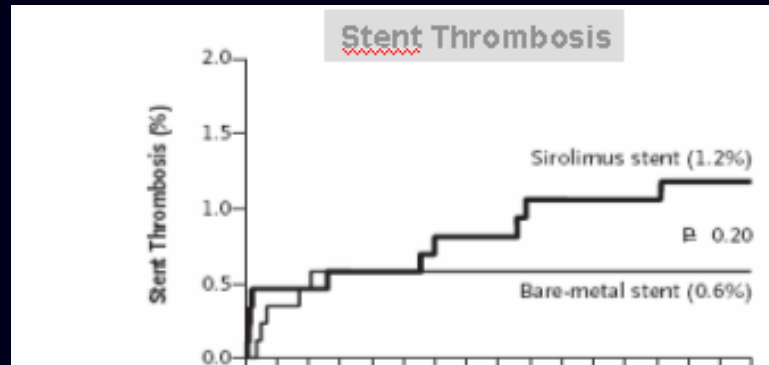
1,748 patients in 4 RCT treated with SES or BMS
3,513 patients in 5 RCT treated with PES or BMS

Analyzed the major clinical end points of the trials

NEJM 2007;356:998-1008

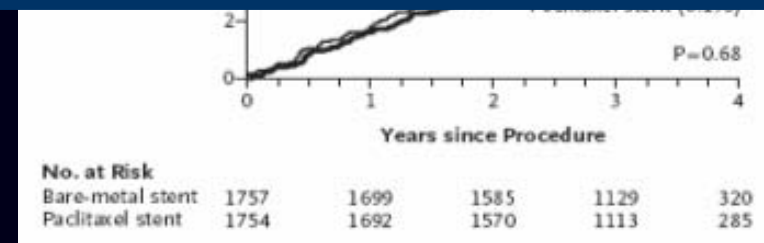
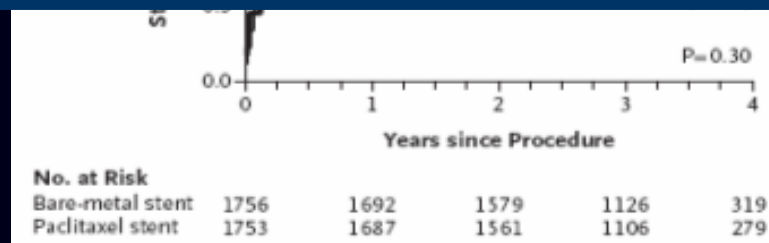
All smoke but no fire

Cypher stent vs Bare-metal stent



There were no significant differences in the cumulative rates of death/MI at 4 years

Stent thrombosis after 1 year was more common with both SES and PES than with BMS.



ORIGINAL ARTICLE

Analysis of 14 Trials Comparing Sirolimus-Eluting Stents with Bare-Metal Stents

Adnan Kastrati, M.D., Julinda Mehilli, M.D., Jürgen Pache, M.D.,
Christoph Kaiser, M.D., Marco Valgimigli, M.D., Ph.D., Henning Kelbæk, M.D.,

4,985 patients in 14 RCTs comparing SES with BMS

Mean F/U interval ; 12.1 to 58.9 months

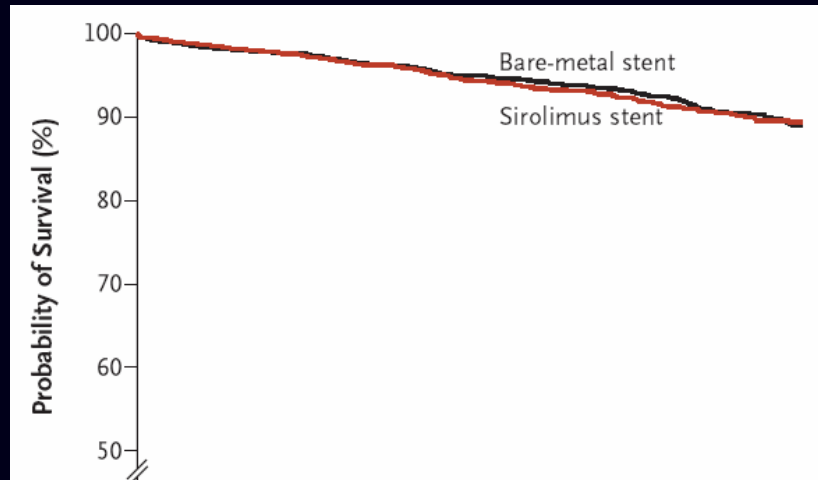
Primary End point: death from any cause

Other outcomes: death/MI, death/MI/reintervention

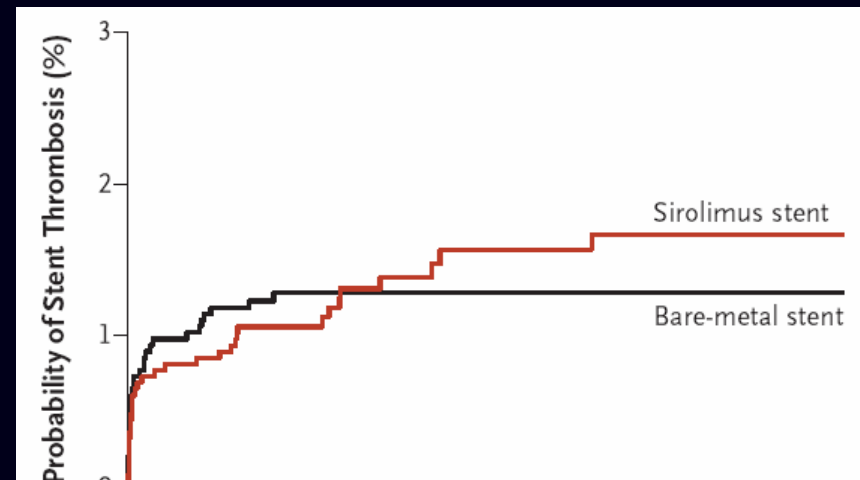
NEJM 2007;356:1030-9

All smoke but no fire

Death, Death/MI



Stent thrombosis

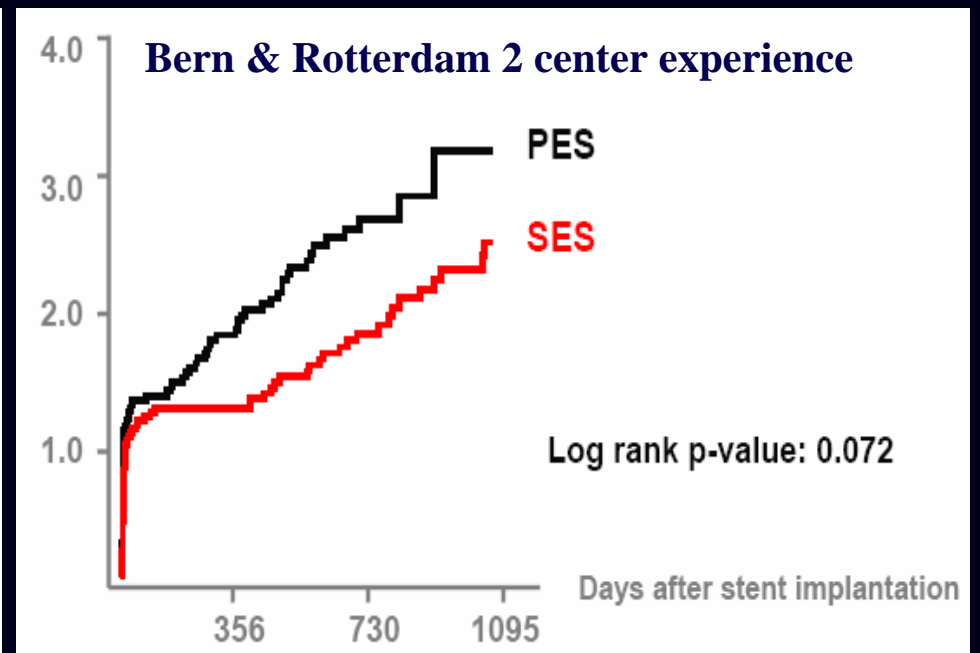
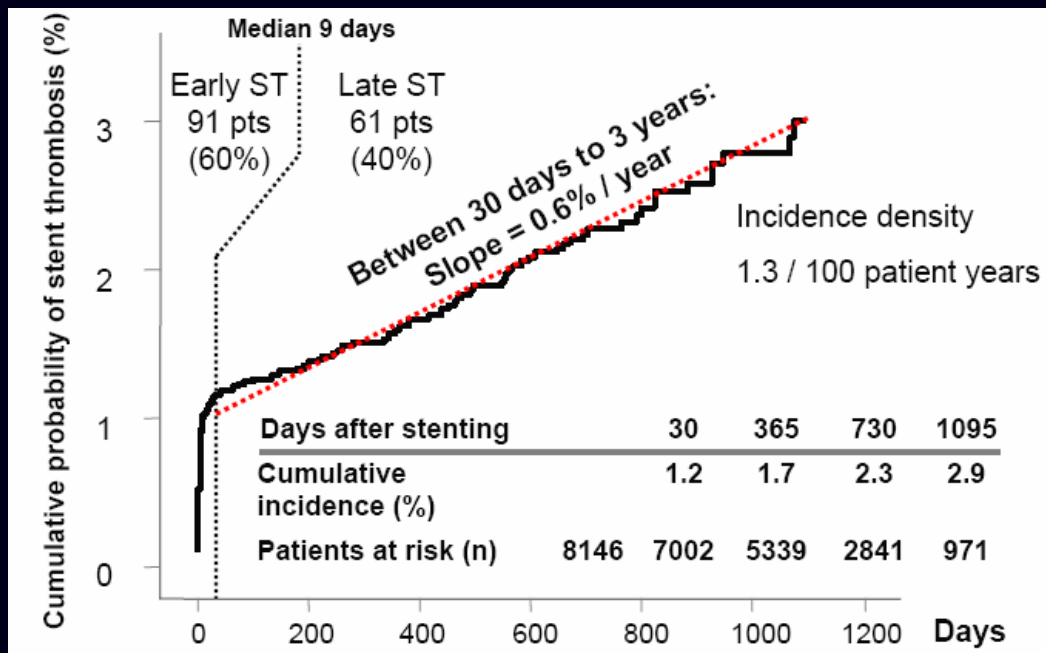


The use of SES does not have a significant effect on overall long-term survival and survival free of MI, as compared with BMS.

There was a slight increase in the risk of ST associated with SES after the first year.

“Window of vulnerability”
No Safe Period!

Late Stent Thrombosis Real-World Data (n=8,146)



These data reflect higher stent-thrombosis rates than seen elsewhere, but they also reflect a higher-risk population.

Clopidogrel Use and Long-term Clinical Outcomes After Drug-Eluting Stent Implantation

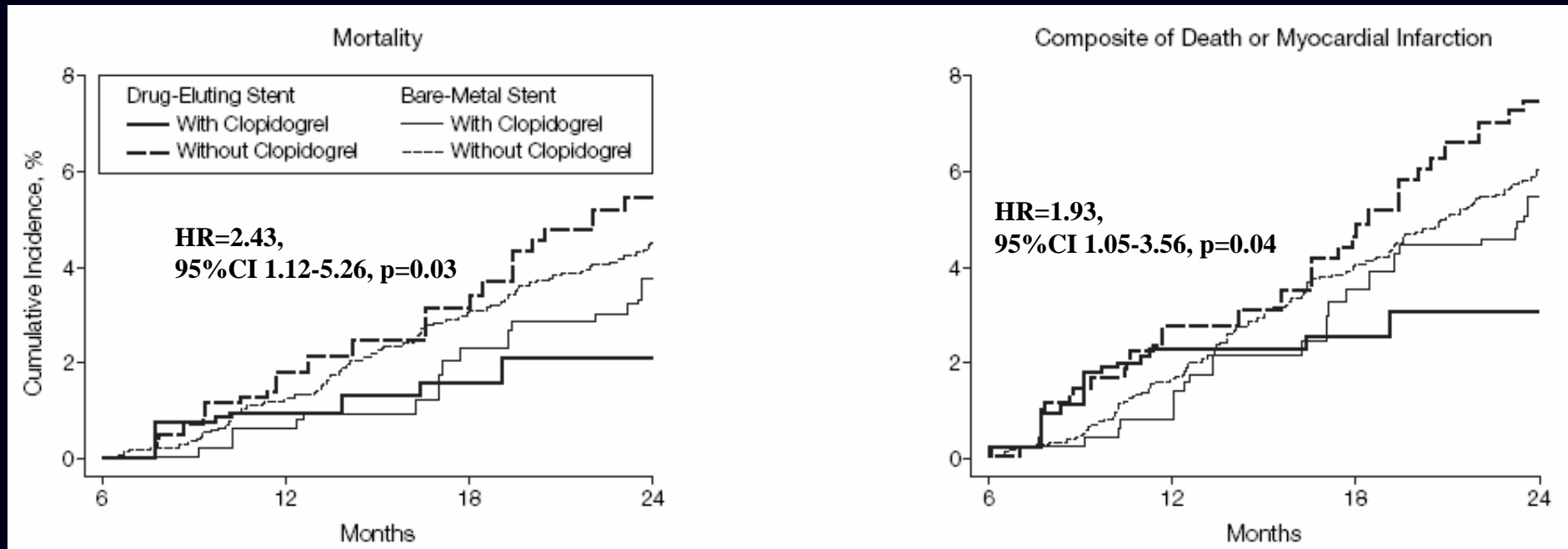
An observational study examining consecutive patients receiving coronary stents at Duke Heart Center (BMS, n=3165; DES, n=1501).

Landmark analyses(6, 12, 24m): death/MI, death/MI/revascularization

JAMA 2007; 297:159

A Greater Sense of Optimism

The overall risk of mortality & MI is probably OK



- **Death, death/myocardial infarction:**
 - no difference in BMS group, big difference in DES group
- **The extended use of clopidogrel in patients with DES may be associated with a reduced risk for death & death/MI.**

Inadequate Data

FDA Panel Summary

Major conclusion _ neither here nor there

RCT data are insufficient to really make any concrete recommendations about either the appropriateness of off-label use of DES, or the most appropriate length of time to administer dual anti-platelet therapy.

Still hungry?

Visit at FDA website: **open public hearing**, Dec 7, 2006

http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4253oph1_index.htm

Urgent Need for More Data

- **ZEST trial**
comparison of the efficacy of Endeavor vs Cypher vs Taxus stent for native coronary lesions in 2,640 real-world patients

“Window of Vulnerability” for ST

The safety and efficacy of FDA’s 1 year-recommendation should be formally tested.

VLST, small but real!

AMC Data, Incidence of ST (Any ARC)



Clopidogrel, How long?

Dual anti-platelet therapy should be continued through at least 1 year in patients at low risk of bleeding.

Dual anti-platelet therapy for > 1 year may be needed for sicker patients (AMI, CRF, diabetes) & complex lesions.

The appropriate duration for clopidogrel administration can only be determined by a large-scale RCT.

The debate on DES will continue!

Safety and Efficacy of Drug-Eluting Stents Reaffirmed in
New England Journal of Medicine Articles and Editorial
Boston Scientific Press Release September 13, 2006

"DES world, the growing fear factor"

Based on available patient-level meta-analysis,
the overall risk of mortality & MI is no different for DES & BMS,
even if LST does appear to be more of a problem with DES.

The DES landscape has changed considerably in the past few months.
LST certainly occurs more frequently with current DES than BMS.

drug-coated stent
September 14, 2006

Sign of hope!

Moving Forward Future Is Bright!

Solution, upcoming soon!

Polymer is enemy, but drugs are OK.
It is just a matter of how to use it!

The LST issue may ultimately be resolved
by a safer smart DES.