FDA Advisory Panel

Drug-Eluting Stent Safety Profile
Stent Thrombosis

Campbell Rogers, M.D.

Chief Technology Officer

Cordis
a Johnson & Johnson company

Agenda

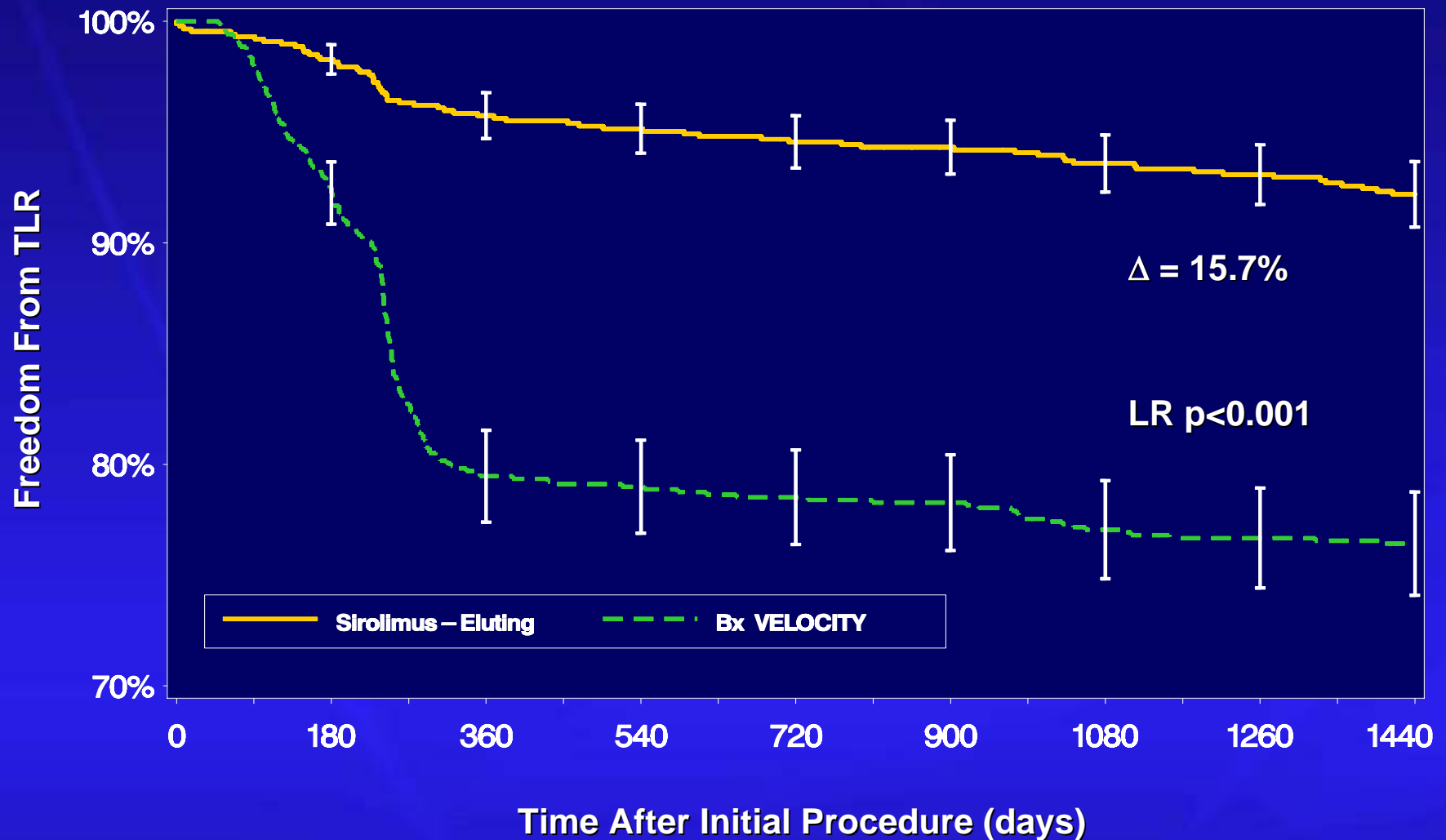|	
CYPHER® Stent Benefits	**Campbell Rogers, MD** **Chief Technology Officer** **Cordis Corporation**
Safety Profile: Death and MI	**Dennis Donohoe, MD** **Worldwide Vice President** **Clinical Research & Regulatory Affairs** **Cordis Corporation**
Stent thrombosis	**Laura Mauri, MD, MSc** **Chief Scientific Officer** **Harvard Clinical Research Institute**
Conclusions	**Campbell Rogers, MD**

Freedom From TLR Through 4-Years

Freedom From TLR (y-axis)

100%
90%
80%
70%

$\Delta = 15.7\%$

LR p<0.001

Sirolimus – Eluting — — — Bx VELOCITY

0   180   360   540   720   900   1080   1260   1440

Time After Initial Procedure (days)

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS
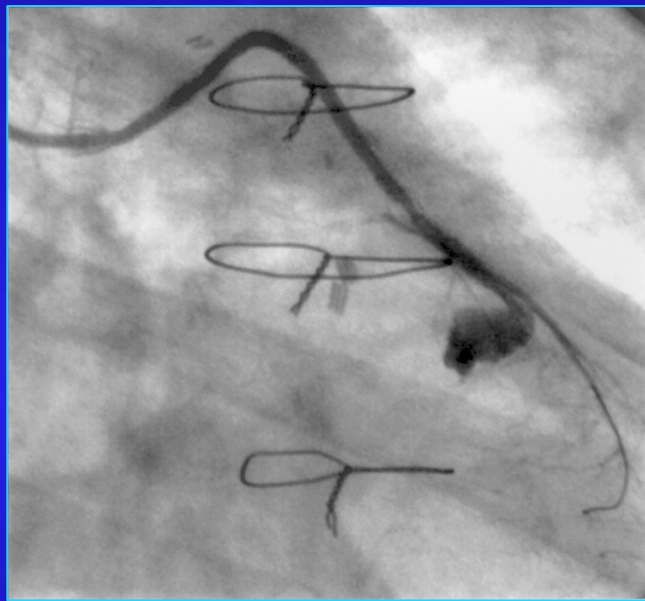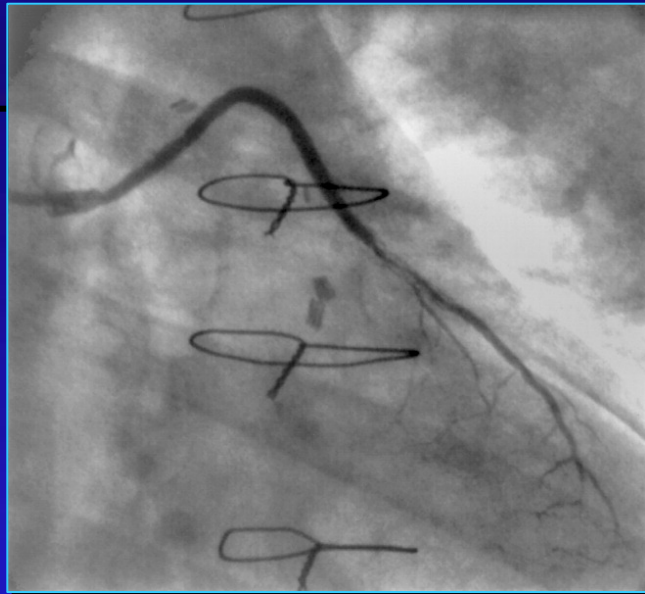
Coronary Artery Perforation by Cutting Balloon Resulting in Dissecting Subepicardial Hematoma and Avulsion of the Vasculature

Vu H. Quan,[1] MD, James R. Stone,[2] MD, PhD, Gregory S. Couper,[3] MD, and Campbell Rogers,[1*] MD
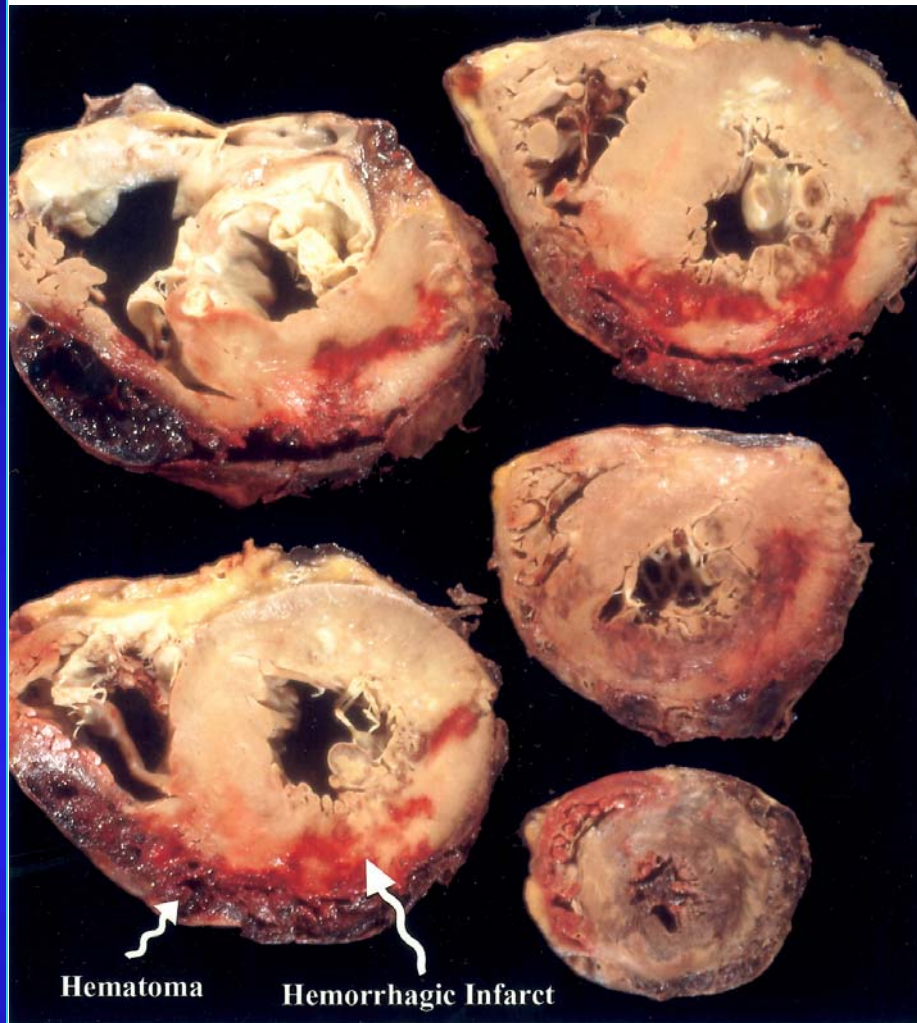
Hematoma   Hemorrhagic Infarct

Restenosis and Late Mortality

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Consecutive Patients

P = 0.02

Mortality at 4-Years (%)

- No Restenosis: 6
- Yes Restenosis: 8.8

Restenosis: No / Yes
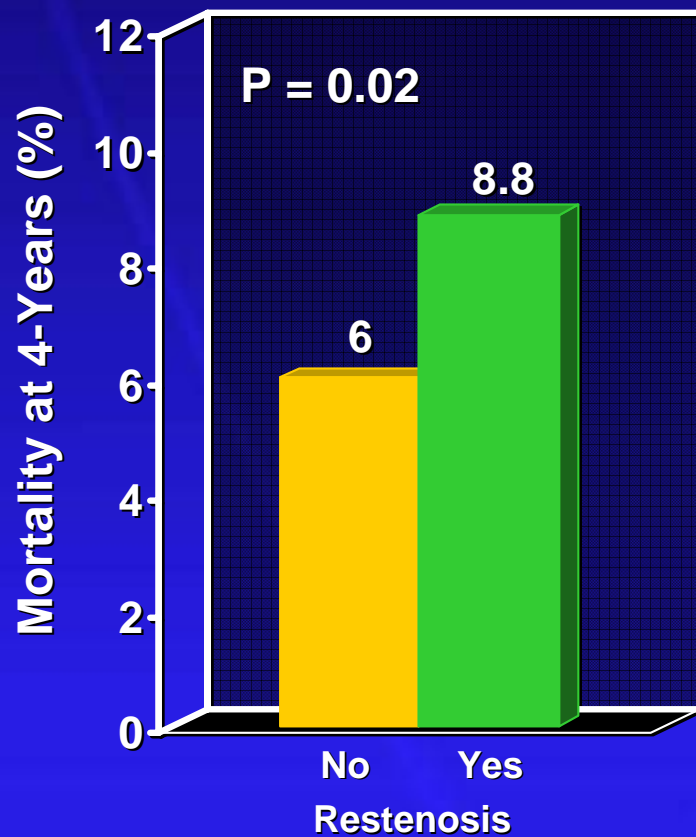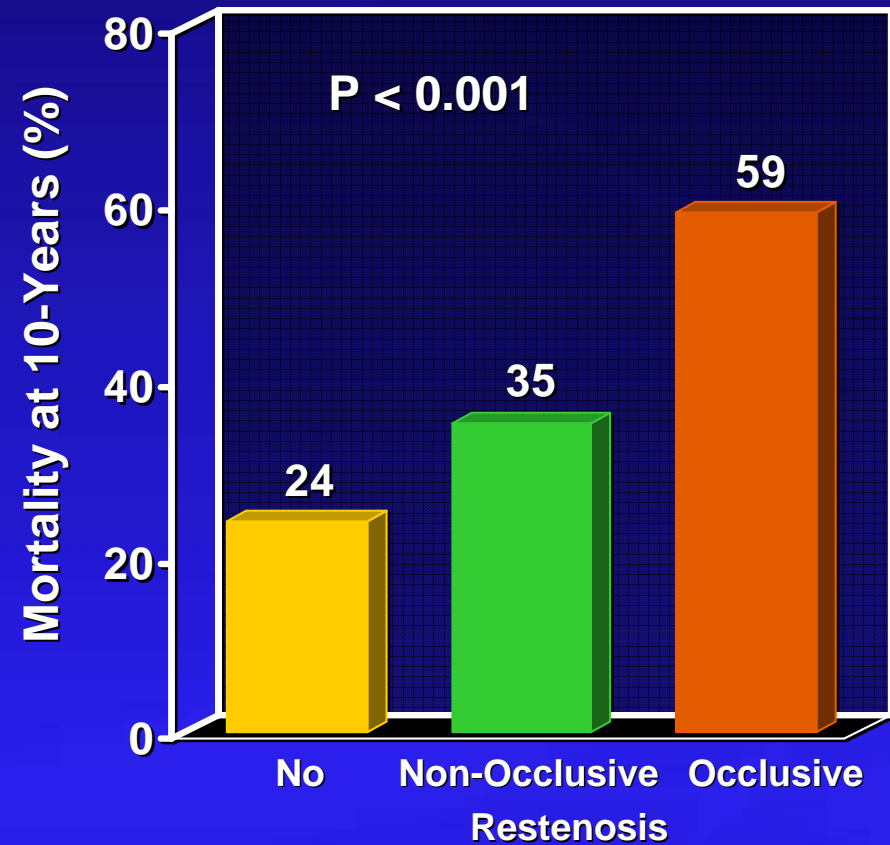
2,272 patients undergoing BMS implantation between 1992-1996

Schühlen H et al. Am Heart J 2004;147:3174.

Diabetics

P < 0.001

Mortality at 10-Years (%)

- No: 24
- Non-Occlusive: 35
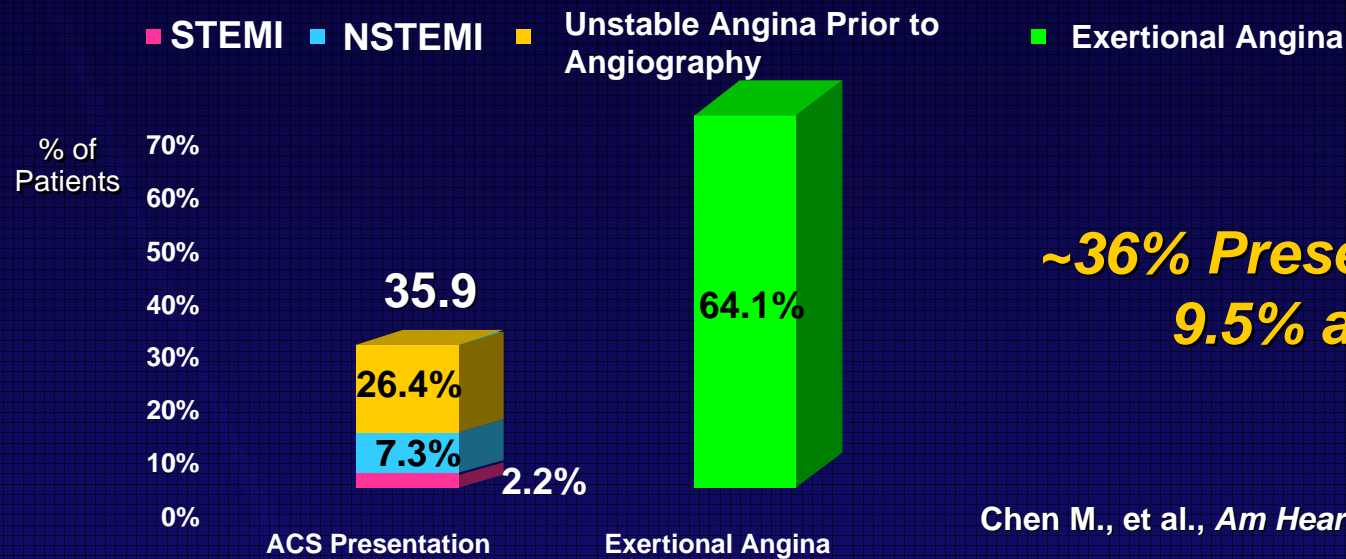- Occlusive: 59

Restenosis: No / Non-Occlusive / Occlusive

603 diabetic patients undergoing PTCA between 1987-1995

Van Belle E et al. Circulation 2001;103:1218.

Clinical Presentation of BMS Restenosis

■ STEMI   ■ NSTEMI   ■ Unstable Angina Prior to Angiography   ■ Exertional Angina

% of Patients

**~36% Present as ACS
9.5% as AMI**

35.9
26.4%
7.3%
2.2%
64.1%

ACS Presentation   Exertional Angina

Chen M., et al., *Am Heart J* 2006;151:1260-64.

**10% of BMS
In-Stent Restenosis Cases
Presented as an MI**

Nayak AK., et al., *Circ* 2006;70:1026-9.

■ AMI   ■ NSTEMI   ■ ACS
■ All myonecrosis

% of Patients

21%
10%
12%
5.7
4.7
n=12
n=10

ACS Presentation
AMI or CK $\geq$ 2 with associated CKMB elevation

ACS (Troponin I)
$\geq$ 2 fold increase

Any Sign of Myonecrosis
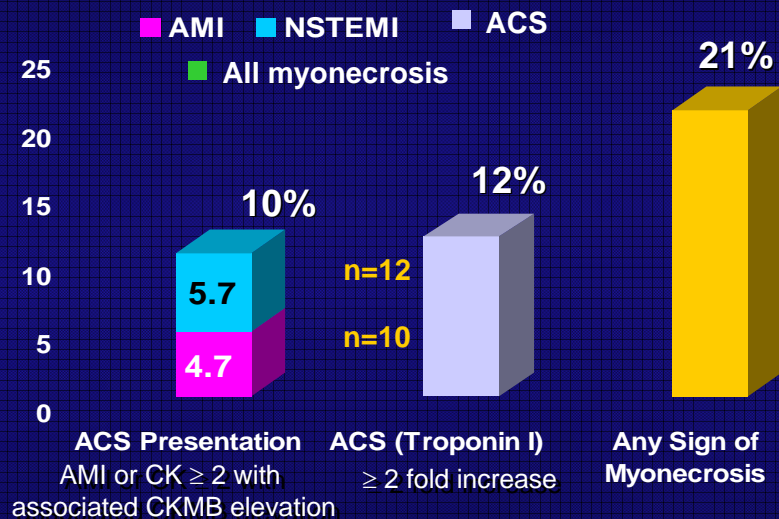
Clinical Consequences of Acute Coronary Syndrome in BMS Restenosis

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Acute Coronary Syndrome May Occur With In-Stent Restenosis and Is Associated With Adverse Outcomes (The PRESTO Trial)

Abid R. Assali, MD[a], Ali Moustapha, MD[b], Stefano Sdringola, MD[d,*], Ali E. Denktas, MD[c], James T. Willerson, MD[d], David R. Holmes, Jr., MD[c], and Richard W. Smalling, MD, PhD[d]
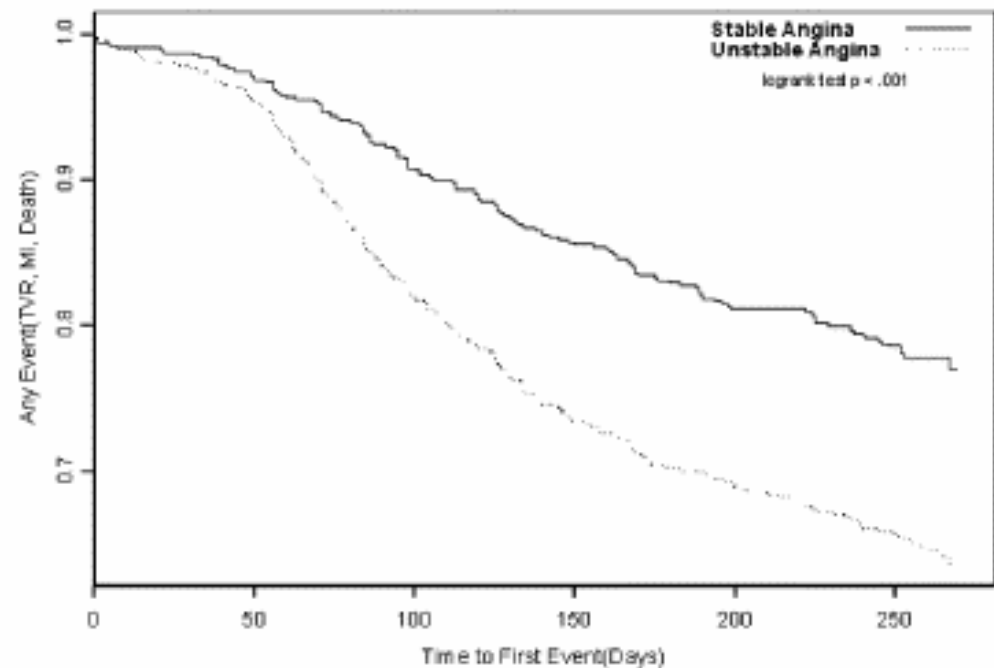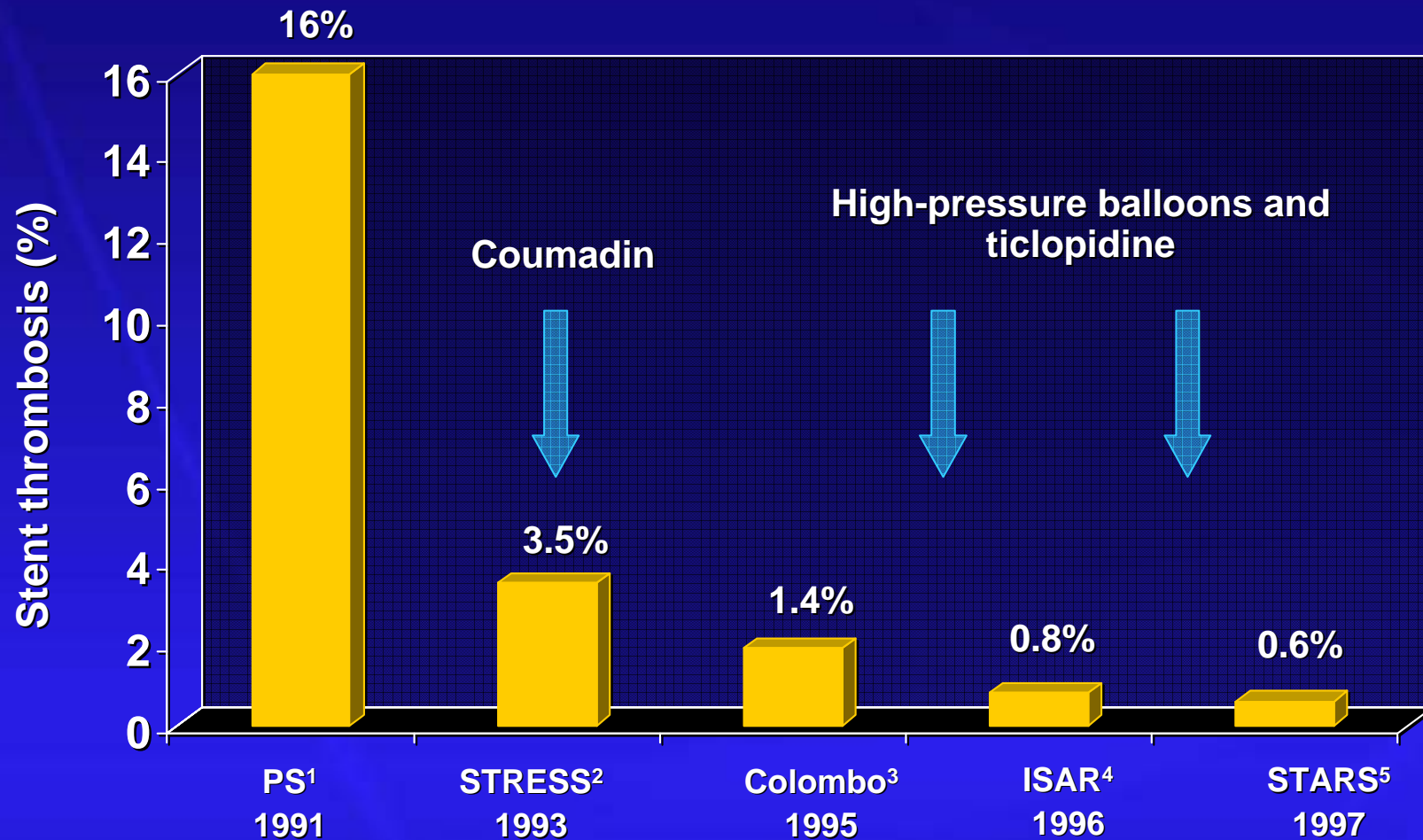
(Am J Cardiol 2006;98:729–733)

Table 3
Clinical events

	Stable Angina (n = 617)	ACS (n = 824)	p Value
In-hospital events			
Any event	4 (1%)	3 (0.3%)	0.4
Myocardial infarction	2 (0.3%)	2 (0.2%)	0.66
Target vessel revascularization	2 (0.3%)	1 (0.1%)	1.00
Death	0 (0%)	0 (0%)	N/A
Follow-up events			
Any event	135 (22%)	285 (35%)	<0.001
Myocardial infarction	13 (2%)	16 (2%)	0.83
Target vessel revascularization	130 (21%)	271 (33%)	<0.001
Death	3 (0.5%)	18 (2%)	0.008
Restenosis defined by ≥50% narrowing*	42 (42%)	78 (56%)	0.043
Restenosis defined by ≥50% loss of gain*	50 (51%)	90 (64%)	0.033

*Restenosis measurements are from a subset of the angiographic substudy patients (n = 99, stable angina group; n = 140, ACS group).

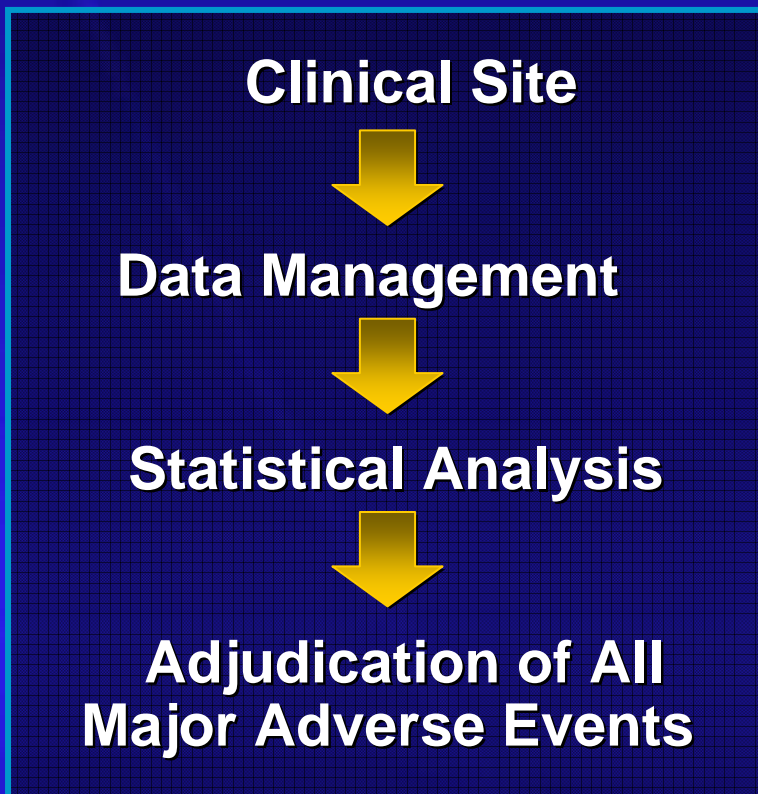### Any Event Before Nine Months by Unstable Angina Status

Stable Angina ———
Unstable Angina ········
logrank test p < .001

Any Event(TVR, MI, Death) vs Time to First Event(Days)

History of Stent thrombosis

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16%

Stent thrombosis (%)

High-pressure balloons and ticlopidine

Coumadin

3.5%

1.4%

0.8%

0.6%

| PS[1] | STRESS[2] | Colombo[3] | ISAR[4] | STARS[5] |
| 1991 | 1993 | 1995 | 1996 | 1997 |

1. Schatz et al. Circulation.1991;83:148; 2. Fischman et al. N Engl J Med. 1994;331496; 3. Colombo et al. Circulation.1995;91:1676; 4. Schömig et al.Circulation.1994,90:2716; 5. Leon et al. N Engl J Med. 1998;339:1665;

Clinical DES Data

- **Data accurately analyzed and reported**
  - **Need for independence and transparency**

Clinical Site

↓

Data Management

↓

Statistical Analysis

↓

Adjudication of All Major Adverse Events

Independent

All analyses shown done by HCRI

Pooled Data from RAVEL, SIRIUS, C-SIRIUS, E-SIRIUS

Clinical DES Data

- **Data accurately analyzed and reported**
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- **A common set of definitions**
  - **ARC definitions**

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- **A common set of definitions**
  - **ARC definitions**

- **Patient based clinical end-points**
  - **Vigilance for safety signals**

Clinical DES Data

- **Data accurately analyzed and reported**
  - Need for independence and transparency

- **A common set of definitions**
  - ARC definitions

- **Patient based clinical end-points**
  - Vigilance for safety signals

- **Opinions of experts with deep domain expertise**

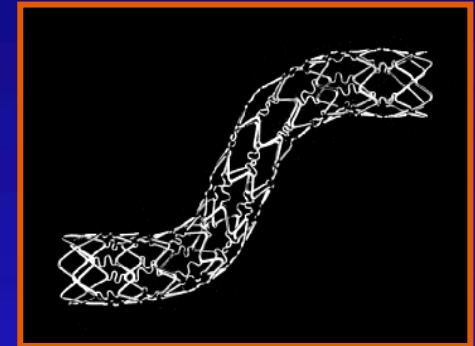|		
Ralph D'Agostino, Ph.D.	Harvard/BU	Director Biostatistics
Elazer Edelman, M.D., Ph.D	Harvard/MIT	Vascular biology and DES
Daniel Simon, M.D.	Case Western	Antiplatelet therapies
Frederic Resnic, M.D., MSc	Harvard	Registry and Outcomes

Evidence on CYPHER® Stent

1. **Wide range of levels of evidence will be seen by panel**

Evidence on CYPHER® Stent

1. **Wide range of levels of evidence will be seen by panel**

2. **Need to consider each device as a discrete entity**
   - **Different drugs**
   - **Different polymers**
   - **Different rate and duration of drug delivery**
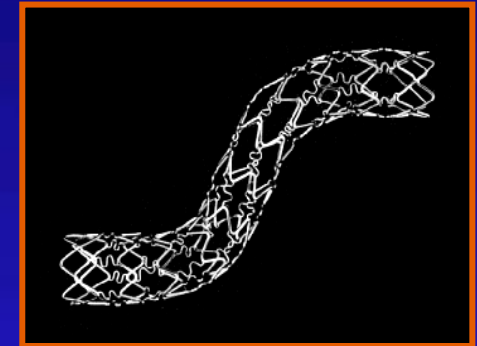
Evidence on CYPHER® Stent

1. **Wide range of levels of evidence will be seen by panel**

2. **Need to consider each device as a discrete entity**
   - **Different drugs**
   - **Different polymers**
   - **Different rate and duration of drug delivery**

3. **Strong evidence of Safety and Efficacy of the CYPHER® Stent**
   - **Wide variety of clinical settings**
   - **Data from more 45,000 patients enrolled in clinical trials**
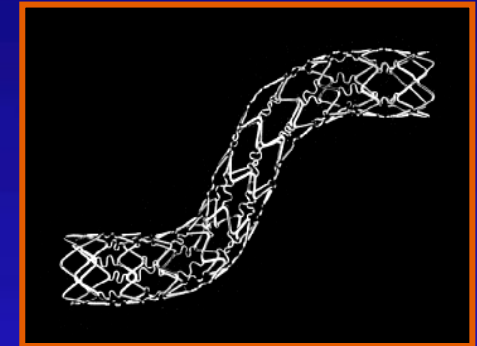
Overview

- **Patient level pooled analysis of RCTs in patients treated with the CYPHER® Stent Sirolimus-eluting Stent vs. BMS through 4-year follow-up demonstrates no significant differences in Death or MI**

- **Patients treated with CYPHER® Stent and BMS have a similar overall risk of stent thrombosis over 4-years**

- **Although early, late and very late events occur in both arms, there are more events before year one for BMS and more events after year one for CYPHER® Stent**

- **Commitment to continued research and education to improve patient outcomes**

Review Of Safety Data

Dennis Donohoe, MD
Vice President, Clinical Research & Regulatory Affairs

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Patient Level Pooled Analysis of 4 RCTs

	RAVEL*	SIRIUS*	C-SIRIUS	E-SIRIUS
Study Type	Prospective, Multi-Center, Blinded, Randomized			
# of Patients	238 (120 CYPHER®, 118 BMS)	1,058 (533 CYPHER®, 525 BMS)	100 (50 CYPHER®, 50 BMS)	352 (175 CYPHER®, 177 BMS)
Lesion Type	Single *de novo* lesion in native coronary artery			
RVD	$\geq$2.5 to $\leq$3.5 mm		$\geq$2.5 to $\leq$3.0 mm	
Lesion Length	Lesion had to be covered with a single 18 mm stent	15 to 30 mm in length coverable with 2 stents	15 to 32 mm in length coverable with 2 stents	
Aspirin	Indefinitely			
Clopidogrel or Ticlopidine	2 months	3 months	2 months	2 months
Compliance to 4-year follow-up	CYPHER® – 94.2% BMS – 94.1%	CYPHER® – 96.8% BMS – 97.0%	CYPHER® – 98.0% BMS – 98.0%	CYPHER® – 97.1% BMS – 98.3%

Summary of Safety Events

- **Analysis of 4-year follow-up data across the 4 RCTs was conducted**

- **No significant differences noted in death and non-fatal MI combined, death or MI rates**

- **Multiple subgroup analyses were conducted and a significant finding was noted only in the diabetic subgroup**

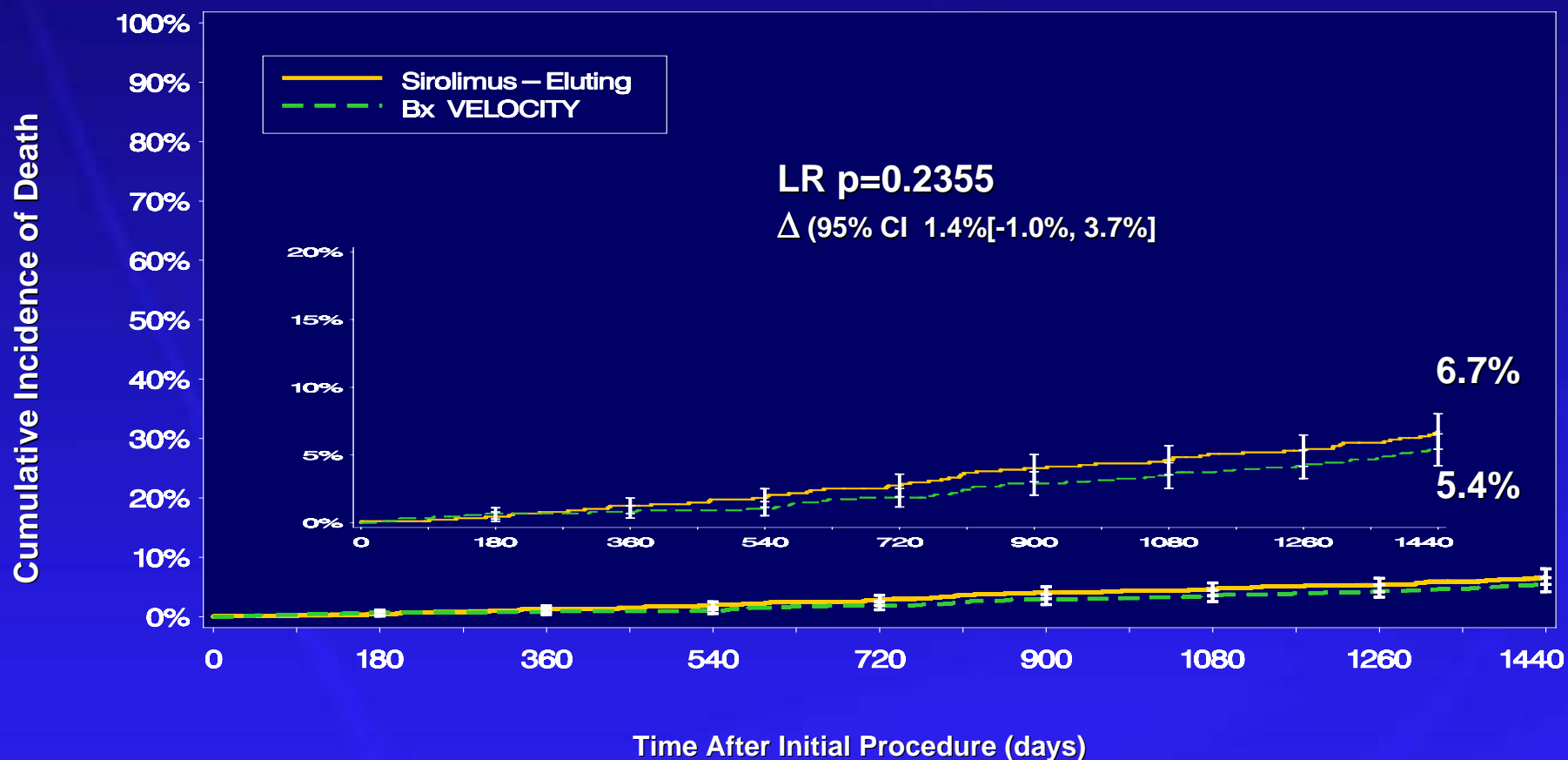# Cumulative Incidence of Myocardial Infarction*: 0 – 1,440 Days (4-Years)

LR p=0.8672

Δ (95% CI 0.2%[-2.2%, 2.6%]

6.4%

6.2%

Cumulative Incidence of MI

Time After Initial Procedure (days)

Legend: Sirolimus – Eluting; Bx VELOCITY
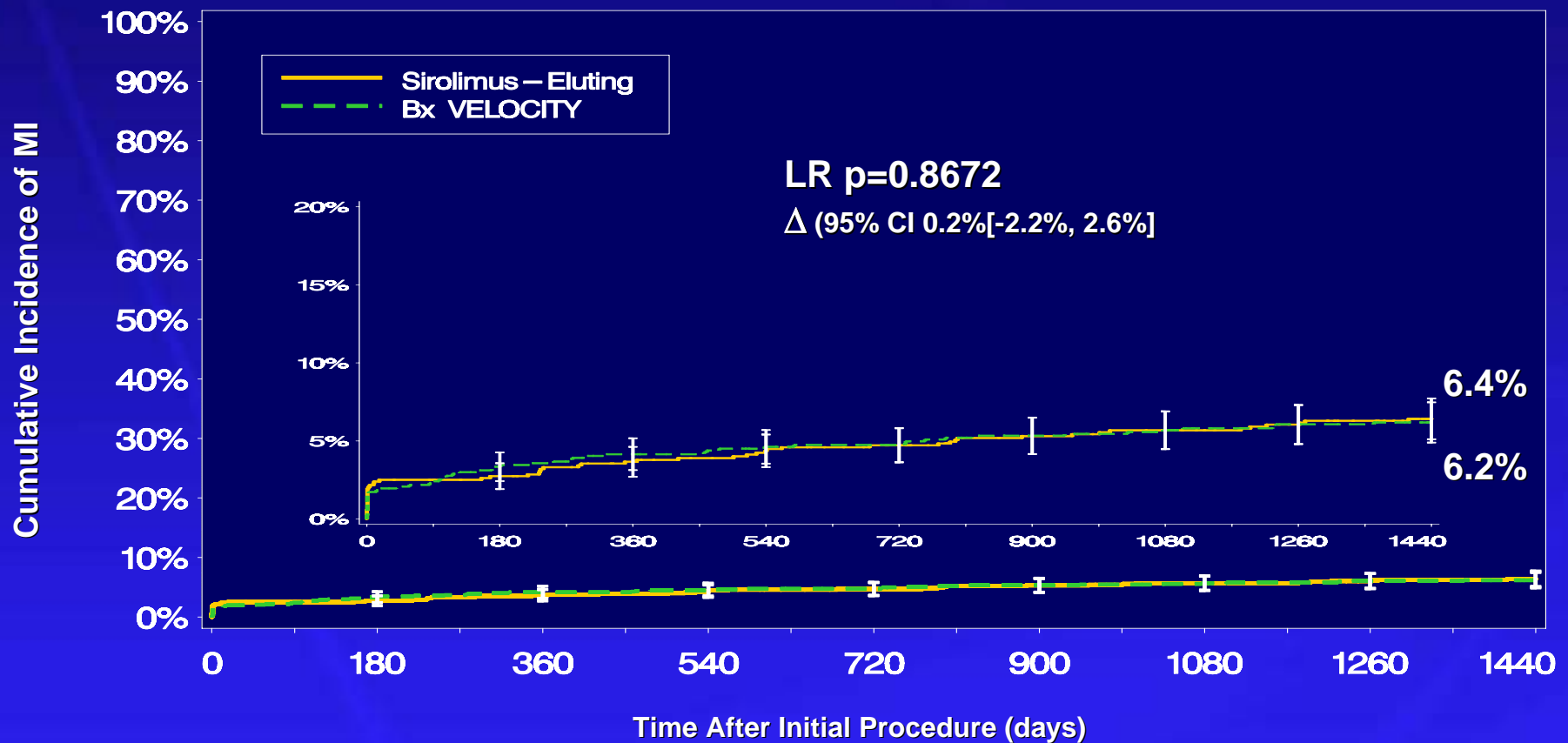
# Entered	0 D	180 D	360 D (1-yr)	720 D (2-yr)	1080 D (3-yr)	1440 D (4-yr)
Sirolimus	878	847	832	807	779	741
Bx Velocity	870	837	824	806	782	740

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS
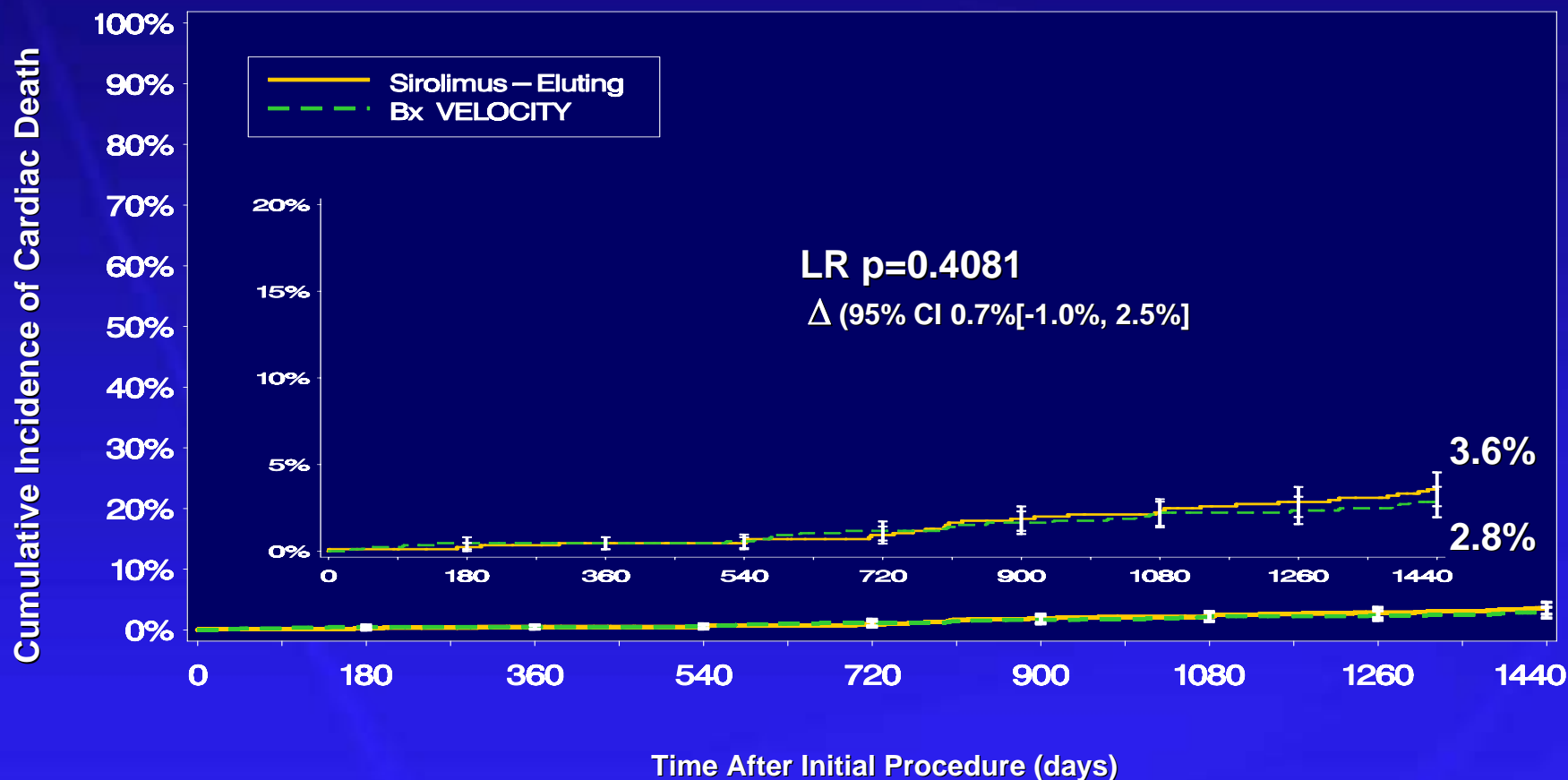* Non –Q wave CK levels greater then 2 times normal with elevated CKMB

Cumulative Incidence of Death: 0 – 1,440 Days (4-Years)

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LR p=0.2355

Δ (95% CI 1.4%[-1.0%, 3.7%])

- Sirolimus – Eluting
- Bx VELOCITY

6.7%

5.4%

Cumulative Incidence of Death

Time After Initial Procedure (days)

# Entered	0 D	180 D	360 D (1-yr)	720 D (2-yr)	1080 D (3-yr)	1440 D (4-yr)
Sirolimus	878	870	863	842	817	776
Bx Velocity	870	863	857	843	824	781

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS

Cumulative Incidence of Cardiac Death: 0 – 1,440 Days (4-Years)

Sirolimus — Eluting
Bx VELOCITY

LR p=0.4081
Δ (95% CI 0.7%[-1.0%, 2.5%]

3.6%

2.8%

Cumulative Incidence of Cardiac Death

Time After Initial Procedure (days)

# Entered	0 D	180 D	360 D (1-yr)	720 D (2-yr)	1080 D (3-yr)	1440 D (4-yr)
Sirolimus	878	870	863	842	817	776
Bx Velocity	870	863	857	843	824	781

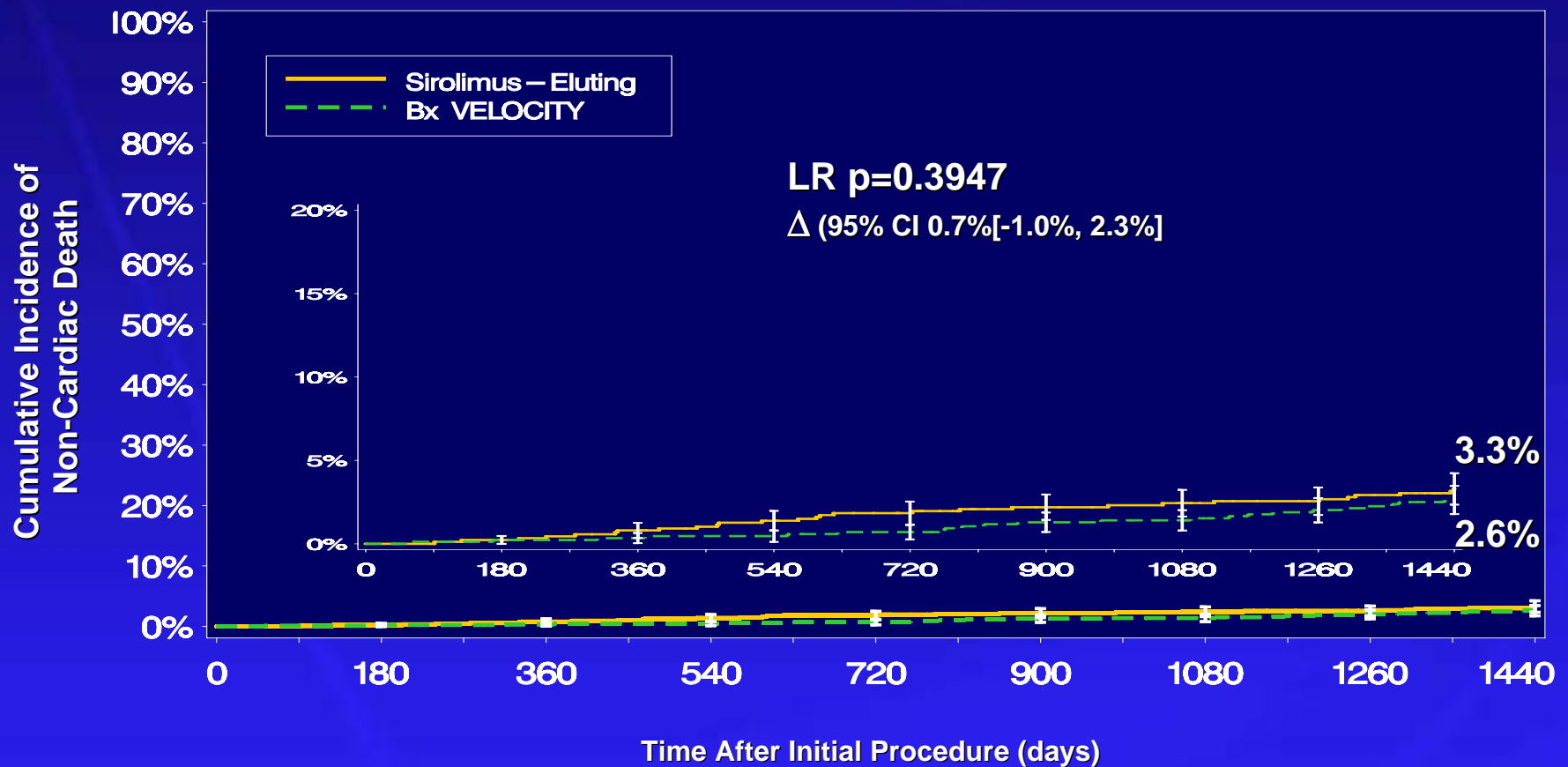**Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS**

Cumulative Incidence of Non-Cardiac Death: 0 – 1,440 Days (4-Years)

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Cumulative Incidence of Non-Cardiac Death

Legend:
— Sirolimus – Eluting
- - - Bx VELOCITY

LR p=0.3947
Δ (95% CI 0.7%[-1.0%, 2.3%]

3.3%

2.6%

Inset axis: 20%, 15%, 10%, 5%, 0% vs 0, 180, 360, 540, 720, 900, 1080, 1260, 1440

Main Y-axis: 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 0%

X-axis: 0, 180, 360, 540, 720, 900, 1080, 1260, 1440

Time After Initial Procedure (days)

# Entered	0 D	180 D	360 D (1-yr)	720 D (2-yr)	1080 D (3-yr)	1440 D (4-yr)
Sirolimus	878	870	863	842	817	776
Bx Velocity	870	863	857	843	824	781

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS

4-Year Mortality in CYPHER® Stent Trials

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| Mortality	CYPHER® Stent	Control	*p*-Value
Cardiac			
RAVEL (n=238)	3 (2.7%)	5 (4.6%)	0.493
SIRIUS (n=1058)	17 (3.4%)	12 (2.4%)	0.452
C-SIRIUS (n=100)	1 (2.0%)	1 (2.0%)	1.00
E-SIRIUS (n=352)	8 (4.7%)	5 (2.9%)	0.409
Non-Cardiac			
RAVEL (n=238)	10 (8.9%)	2 (1.9%)	0.034
SIRIUS (n=1058)	15 (3.0%)	13 (2.6%)	0.849
C-SIRIUS (n=100)	1 (2.0%)	2 (4.1%)	1.00
E-SIRIUS (n=352)	2 (1.2%)	5 (2.9%)	0.449

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS

Exploratory Post-Hoc Subgroup Analyses

- **Multiple subgroups within these 4 RCTs were evaluated for mortality and MI rates**
  - **Multiple stents, overlapping stents, long lesions (>20mm), small vessels (2.5mm stent), diabetics and non-diabetics**

- **There were no pre-specified subgroup analyses or sub-randomizations in these four trials**

- **All subgroups demonstrated similar mortality and MI rates except for the diabetic subgroup**

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS

Summary of Contemporary Diabetic Mortality Data
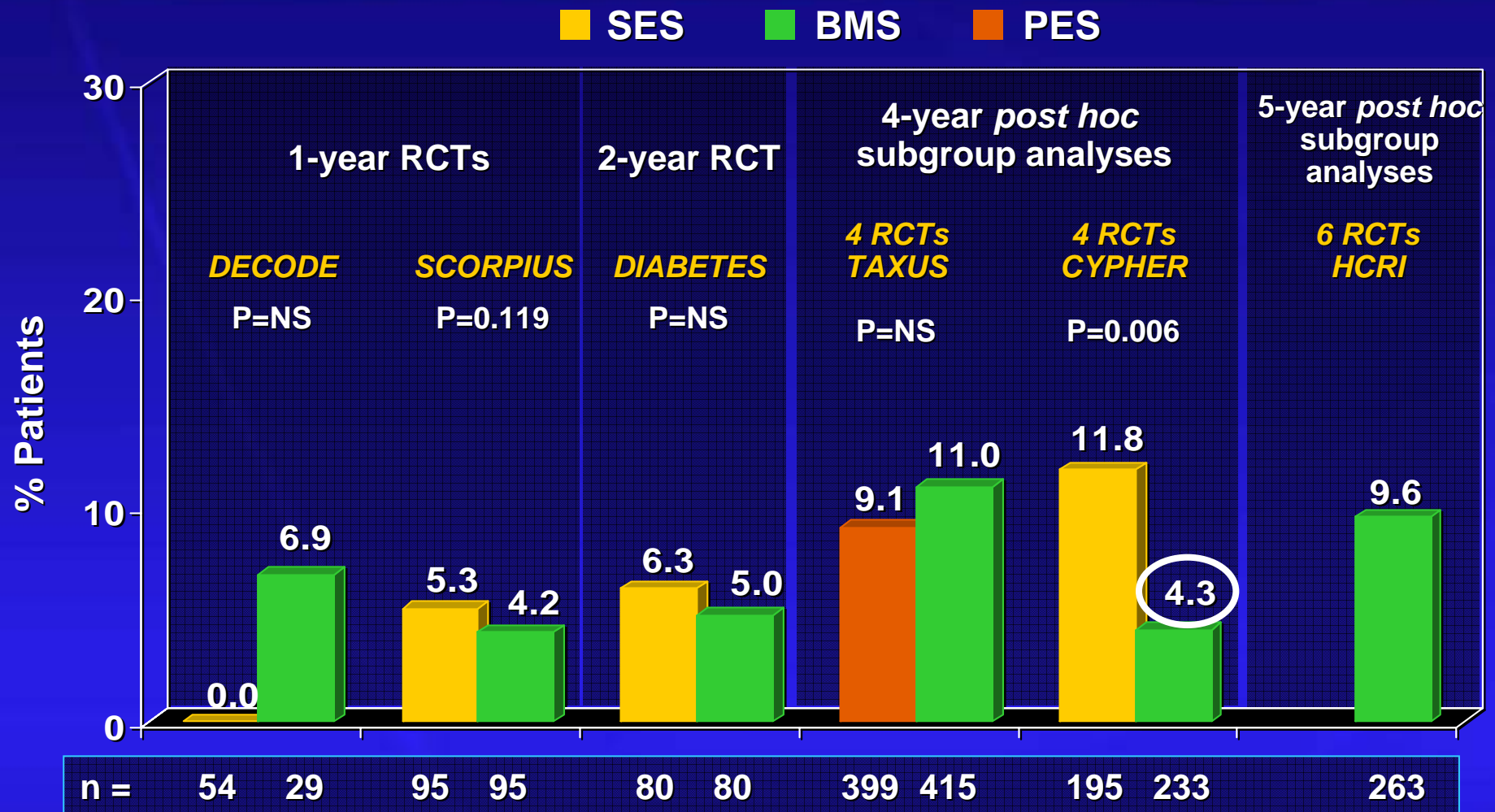
*Lee T et al., Am J Cardiol, 2006; 98:718-721
$DIABETES: Sabaté M., et al., *ESC* 2006; Oral Presentation.
SCORPIUS: Baumgart D., et al., *TCT* 2006; Oral Presentation.
Letter from Don Baim, M.D.

DECODE: Chan C., et al., AHA 2005; Oral Presentation.
4 RCTs CYPHER: Internal Data, Cordis Corporation.

Diabetic Mortality

- **The difference at 4-years in post hoc subgroup analysis appears to be an anomalous finding**
  - **This difference was driven by the SIRIUS study (P=0.037) and at 5-years the difference no longer significant (P=0.21)**
  - **BMS-treatment group had an unusually good outcome compared to published data**
  - **A Cox regression analysis of these data indicates that presence of diabetes lowered the risk of death**
- **Three randomized prospective trials in diabetics did not support this observation**

Conclusions: Safety

- **Patient level pooled analysis of randomized controlled multi-center studies in patients treated with the CYPHER® Sirolimus-eluting Stent vs. BMS through 4-year follow-up demonstrates no significant differences in:**
    - **Death (cardiac and non-cardiac)**
    - **MI**
    - **Death and non-fatal MI**
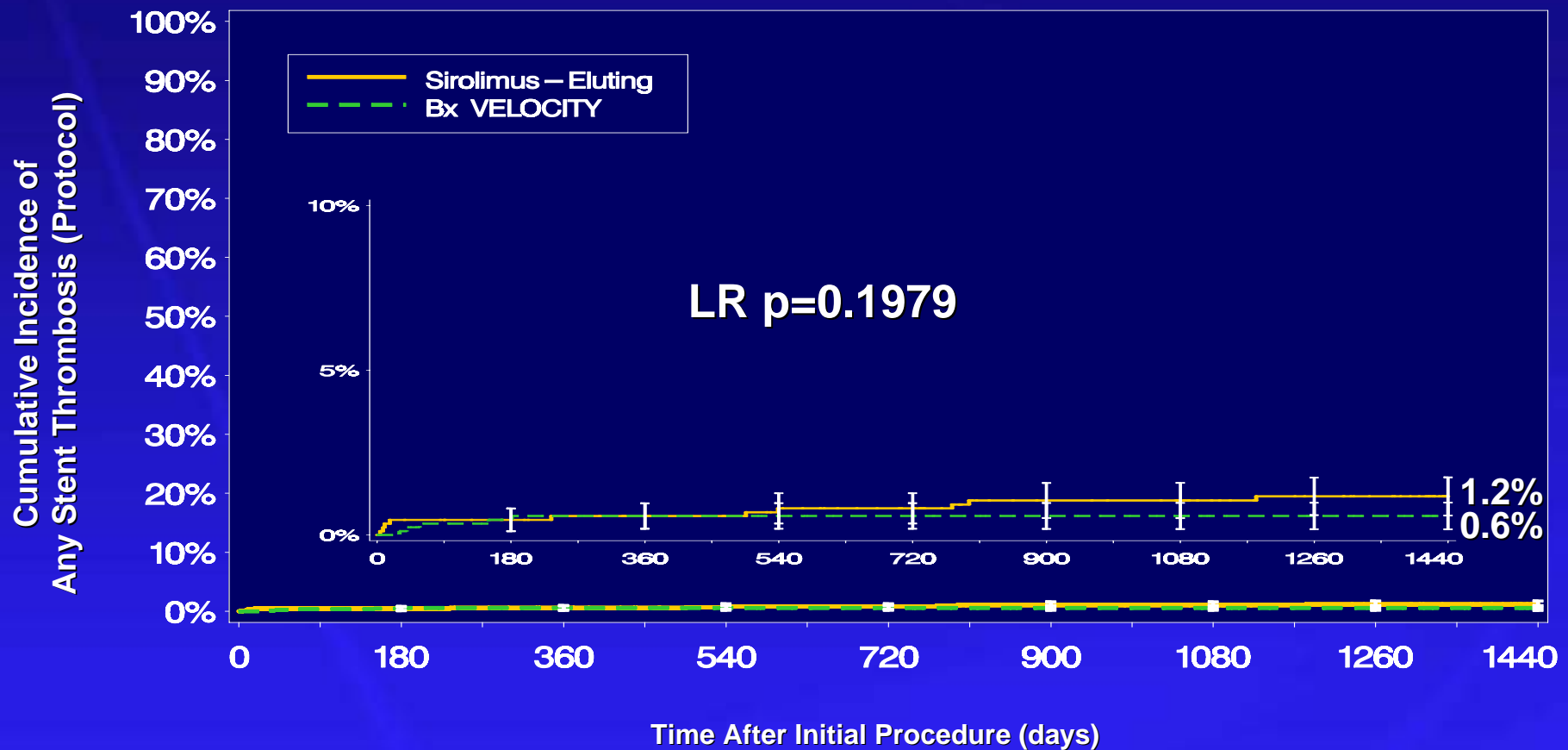
Stent Thrombosis

- **Academic Research Consortium Definition**

- **Results of Blinded Adjudication**
  - **Overall results**
  - **Relationship of target lesion revascularization to subsequent stent thrombosis**
  - **Relationship of stent thrombosis to clinical endpoints (death, myocardial infarction)**
  - **Relationship to antiplatelet therapy**

- **Conclusions**

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS

Is There An Optimum Definition For Stent Thrombosis

- **Protocol Definition**
  - **Most restrictive**
  - **Excluded intervening TLR, potential bias**

- **Definite ARC**
  - **More reliable to distinguish mechanism, but may miss some stent thrombosis events**

- **Possible ARC**
  - **Driven by unexplained death**
  - **Best captured by clinical endpoints**

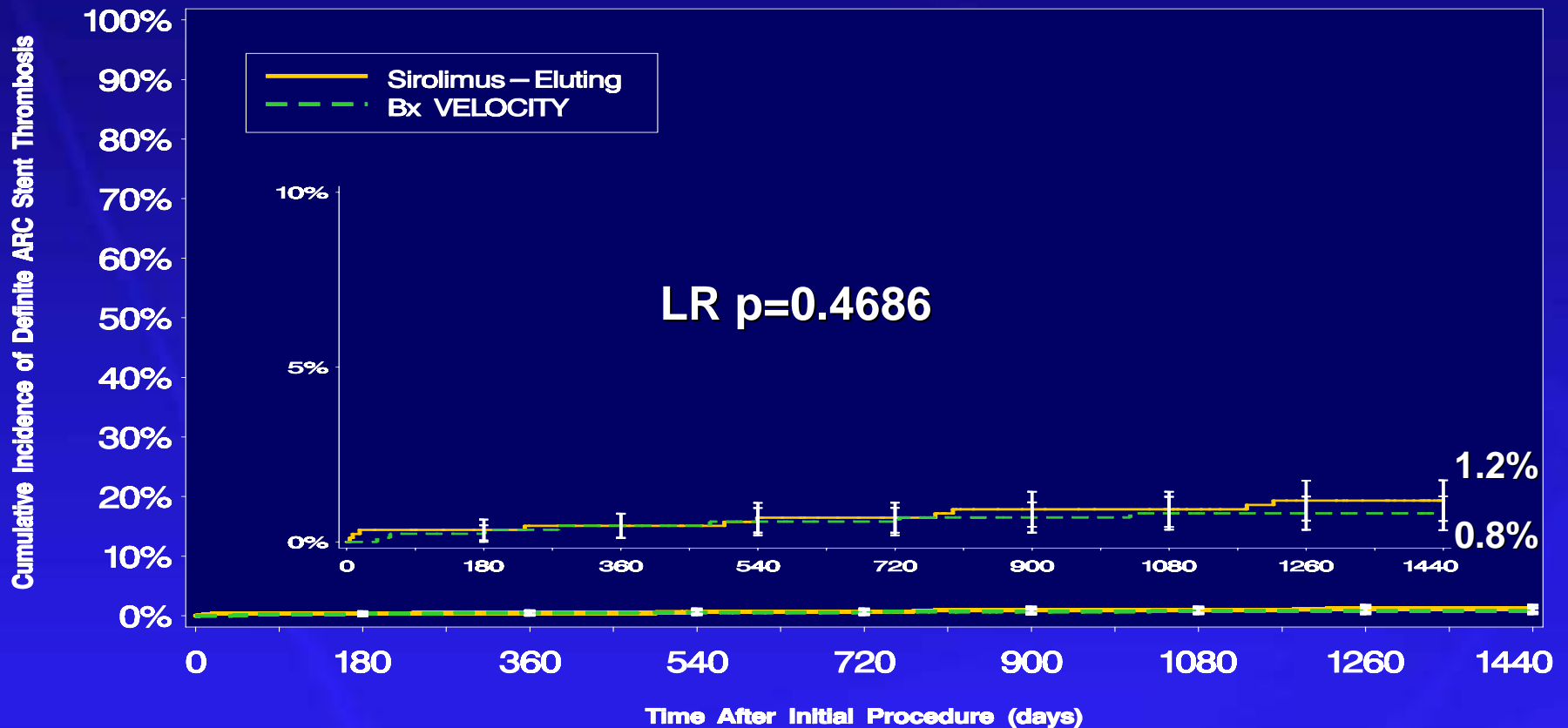- **Definite + Probable ARC**
  - **Balances sensitivity and specificity**

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS

Cumulative Incidence of Stent Thrombosis (Protocol Definition): 0 – 1,440 Days (4-Years)

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LR p=0.1979

Legend:
— Sirolimus – Eluting
- - - Bx VELOCITY

1.2%
0.6%

Y-axis: Cumulative Incidence of Any Stent Thrombosis (Protocol)

X-axis: Time After Initial Procedure (days)

# Entered	0 D	180 D	360 D (1-yr)	720 D (2-yr)	1080 D (3-yr)	1440 D (4-yr)
Sirolimus	878	866	858	836	811	770
Bx Velocity	870	860	853	839	820	777

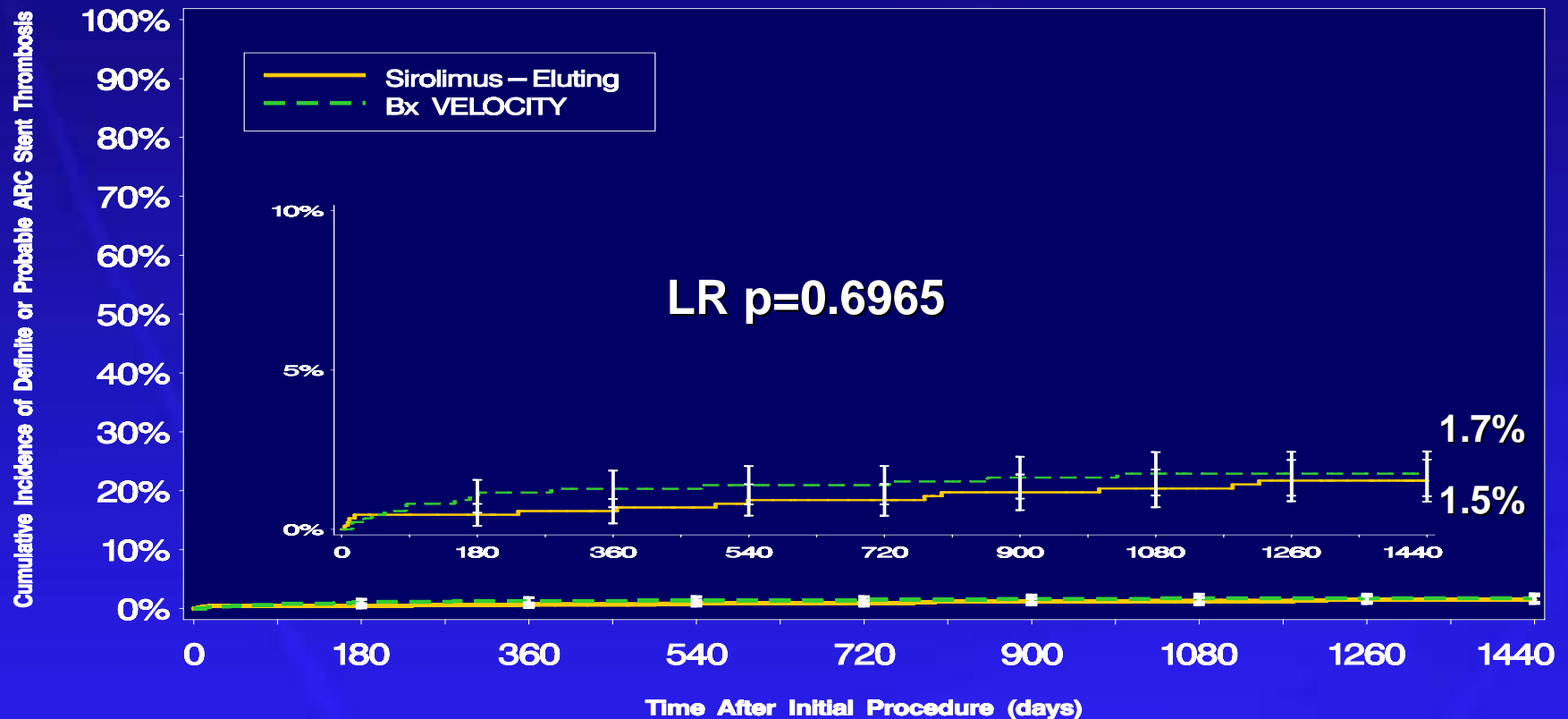**Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS**

Cumulative Incidence of Definite ARC Stent Thrombosis: 0 – 1,440 Days (4-Years)

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LR p=0.4686

1.2%

0.8%

# Entered	0 D	180 D	360 D (1-yr)	720 D (2-yr)	1080 D (3-yr)	1440 D (4-yr)
Sirolimus	878	867	859	837	811	769
Bx Velocity	870	861	853	838	818	775

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS

Cumulative Incidence of Definite or Probable ARC Stent Thrombosis: 0 – 1,440 Days (4-Years)

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LR p=0.6965

1.7%

1.5%

Legend: Sirolimus – Eluting / Bx VELOCITY

Y-axis: Cumulative Incidence of Definite or Probable ARC Stent Thrombosis

X-axis: Time After Initial Procedure (days)

# Entered	0 D	180 D	360 D (1-yr)	720 D (2-yr)	1080 D (3-yr)	1440 D (4-yr)
Sirolimus	878	866	858	835	809	768
Bx Velocity	870	856	848	834	813	772

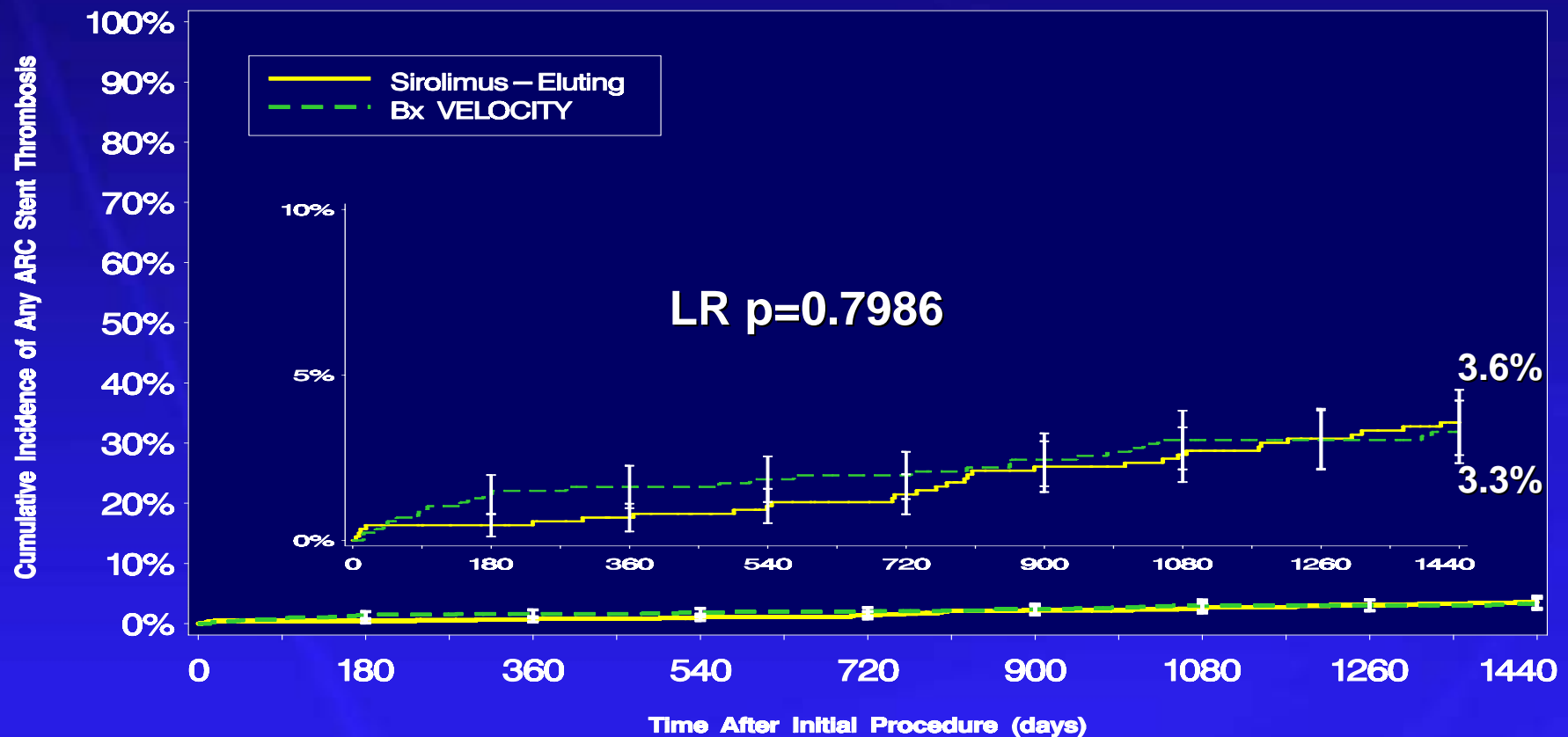**Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS**

Thrombosis Incidence Analysis: ARC Definite or Probable

ARC Definite or Probable Stent Thrombosis	SES (N=878 Patients)	BMS (N=870 Patients)
Acute Thrombosis (0-1)	0.0% (0/878)	0.0% (0/870)
Sub Acute Thrombosis (2-30)	0.4% (4/877)	0.3% (3/870)
Late Thrombosis (31-360)	0.1% (1/874)	1.0% (8/865)
Very Late Thrombosis (361-1440)	0.9% (8/848)	0.5% (4/843)
Any Thrombosis (0-1440)	1.5% (13/848)	1.8% (15/843)

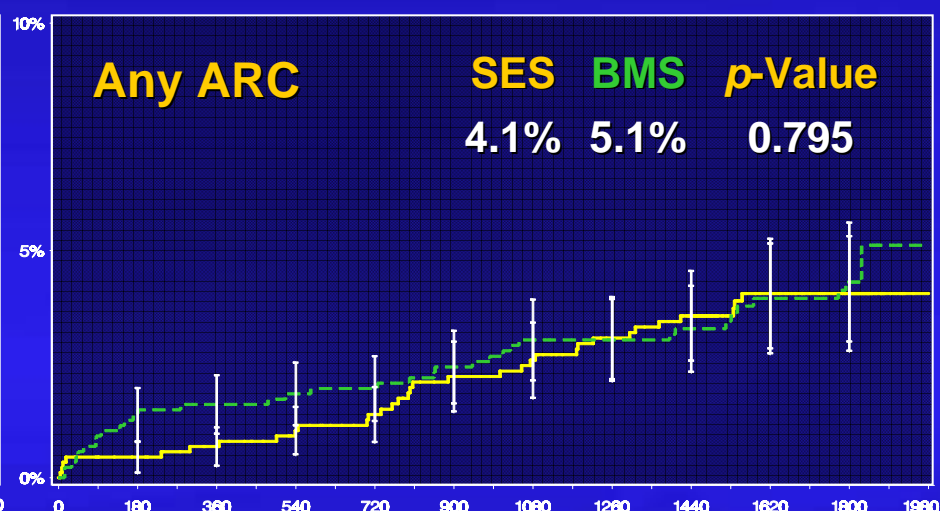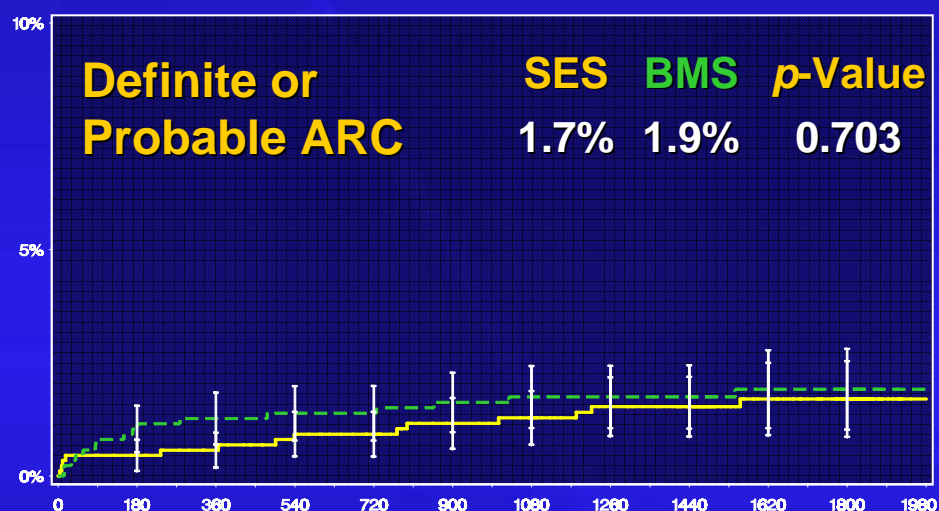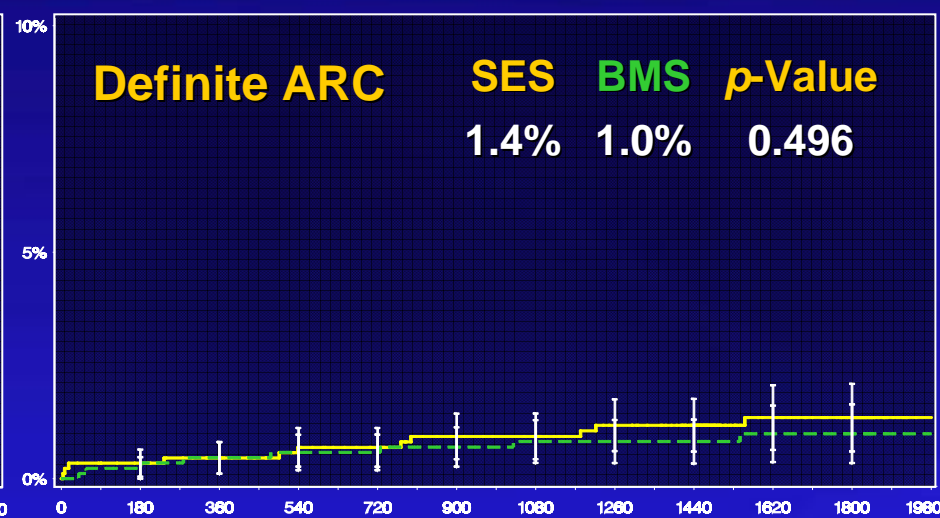**Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS**

Cumulative Incidence of Any ARC Stent Thrombosis: 0 – 1,440 Days (4-Years)

LR p=0.7986

3.6%

3.3%

Cumulative Incidence of Any ARC Stent Thrombosis (y-axis)

Time After Initial Procedure (days) (x-axis)

Legend:
- Sirolimus – Eluting
- Bx VELOCITY

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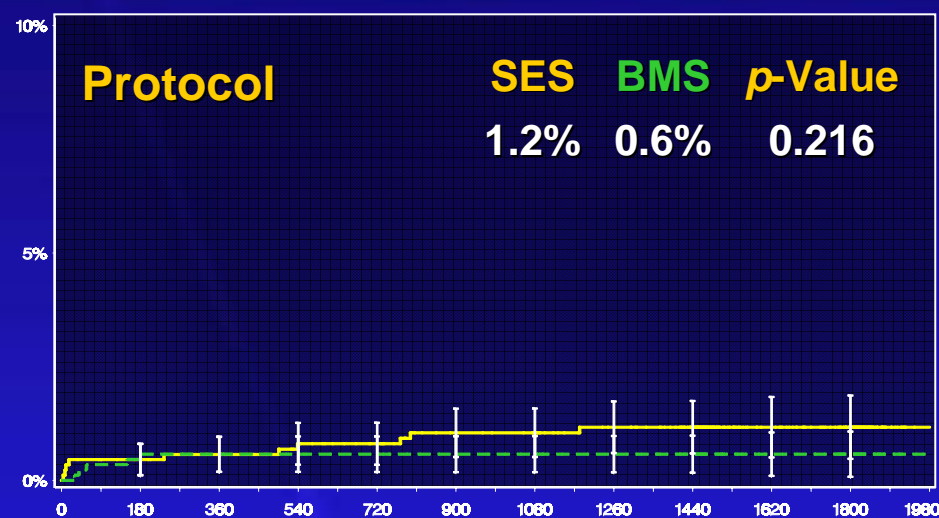
Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS

Prior TLR and Stent Thrombosis: 4-Year Data

	CYPHER®Stent ST N=30	BMS ST N=28
Prior TLR	0	10
Time from TLR to ST, days, median (min,max)	N/A	269 (15, 1141)
ST Classification		
Definite/Probable (N=13 vs. 15)	0	6
Possible (N=17 vs. 13)	0	4
TLR Procedure	0	10
BMS only	0	0
Any SES	0	1
PTCA only	0	2
Brachytherapy/PTCA	0	5
Brachytherapy/BMS Stent	0	2

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS

Relationship of Stent Thrombosis (Definite and Probable) to Clinical Endpoints

	SES (N=13)	BMS (N=15)
Death	4	5
Myocardial Infarction	13	13
Fatal MI	4	4
Q Wave MI	8	5
Non-Q Wave MI	5	8

Similar mortality observed for SES and BMS thrombosis

Pooled Data from RAVEL, SIRIUS, C-SIRIUS, E-SIRIUS

Antiplatelet or Warfarin Therapy at Time of Event for Patients with Stent Thrombosis (0-1,440 days)

	SES	BMS
Patients with <u>Any ARC</u> Stent Thrombosis	30	28
Yes		
ASA, Clopidogrel/Ticlopidine	27% (8)	43% (12)
ASA only	37% (11)	18% (5)
Clopidogrel only	1	0
Coumadin	1	1
No*	6% (2)	11% (3)
*Stopped at 7, 17, 58, & 403 days prior to ST, with 1 unknown stop date)		
Unknown**	23% (7)	25% (7)
** Last known dose between 82 – 1325 days prior to ST – 5 unknown stop dates		

Pooled Data from RAVEL, SIRIUS, C-SIRIUS, E-SIRIUS

Stent Thrombosis

- Patients treated with CYPHER® Stent and BMS have a similar overall risk of stent thrombosis over 4-years, and to last available follow-up beyond 4-years

- Although early, late and very late events occur in both arms, there are more events before year one for BMS and more events after year one for CYPHER® Stent

- Evaluation of varying frequencies over time is limited by small numbers of events (proportional hazards assumption was not rejected)

- Patients with BMS were more likely to have ST if they had TLR

- Although rare, patients with TLR following CYPHER® Stent did not have an increased frequency of stent thrombosis

- Clinical outcomes following ST were similar for CYPHER® Stent and BMS

Time Course of Events in SES Does Not Support a Single Simple Hypothesis

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Stent Thrombogenicity
Material
Designs
(open vs. closed cell)
Surface coating
Adjunctive therapies
(drug, radiation)

Bio-Compatibility

Patient/Lesion Factors
Vessel size, Lesion length
ACS
Plaque characteristics
Intrinsic platelet/
coagulation activity
Ejection fraction/CHF

**Multiple stents
Stent length**

Blood Flow

Procedure-Related Factors
Morphometric and/or morphologic abnormalities
(under-expansion /
dissection, incomplete apposition, thrombus, tissue
protrusion), Mechanical vessel injury
Antithrombotic therapy

Kereiakes D., et. al., Rev Cardiovasc Med. 2004;5(1):9-15.

Final Conclusion

- **The CYPHER® Stent has demonstrated impressive, sustained benefit in reducing the need for repeat revascularizations**

- **No difference in overall risk of stent thrombosis**
  - **No significant difference in death, and death or MI**
  - **Temporal distribution of stent thrombosis may vary between CYPHER® Stents and BMS**

- **Cordis will continue to work with the FDA to:**
  - **Provide physician and patient education**
  - **Generate the appropriate data to understand better how to reduce the risk of stent thrombosis**

Recommendations and Commitments

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- **Endorse ACC/AHA/SCAI PCI Guidelines regarding dual antiplatelet therapy (up to 12 months for suitable patients)**

- **Educate on the need for dual antiplatelet therapy**
  - **Primary cardiologists, gastroenterologists and dentists**

- **Exploring patient programs to enhance compliance**
  - **Financial assistance, education, awareness**

- **Define optimal stent procedural technique**

Recommendations and Commitments

- **Extend follow-up of 3 SIRIUS trials to 8-years**

- **Coordinate the extended follow-up of 10 RCTs (n=4,500 patients) to 5-years**

- **Conduct appropriately powered CYPHER® Stent PMS study with randomization to 2 durations of dual APT pending recommendations from panel**

- **Continue to examine the mechanisms of thrombosis and to optimize device design**