

“Real-World” Use of the CYPHER® Sirolimus-Eluting Stent

Data from Randomized Controlled Trials and Registries

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Studies On Real-World Use Of The CYPHER[®] Stent



- CYPHER[®] Stent rapidly adopted
- Use includes patient and lesion types not currently in label
- Unmet clinical need
 - Shift from open surgical to less-invasive interventions
 - Desire to reduce need for revascularization
 - Diabetic patients
 - Acute MI
 - SVG
 - Renal insufficiency
 - Multi-vessel stenting
 - Bifurcation
 - CTO
 - In-stent restenosis
 - Long-lesions
 - Multiple non-overlapping stents
- **Goal:** to review safety and efficacy of CYPHER[®] Stent in these subgroups using data from randomized trials and from Cordis sponsored registries
 - **Strength:** Data from studies that enrolled >45,000 patients
 - **Limitation:** 1-year data

Agenda: Safety Data in Subgroups



- 6 trials undertaken in higher-risk subgroups to expand the CYPHER® Stent label
- 16 RCTs which enrolled >5,000 patients in CYPHER® Stent vs. Bare Metal Stent (BMS) control
 - Meta-analysis of safety (Death, MI, Thrombosis)
 - 9 trials on AMI, small vessel, diabetes, & CTO
- 6 registries sponsored by Cordis enrolled >40,000 patients with 1-year follow-up in >25,000 patients
 - Safety profile:
 - Individual registry results
 - Pooled results – examine patient & lesion subsets
 - Compare subset outcomes in registry vs. randomized data
- Additional safety data on CYPHER® Stent and TAXUS

Executive Summary

- Real-world use compared to 4 RCTs:
 - Same marked benefit (60-80% ↓ TLR)
 - Elevated risk - ↑ rates of death, MI, stent thrombosis
 - Same elevation seen with bare metal stents (BMS)
 - Related to higher-risk nature of patient/lesion subgroups
- Data on dual anti-platelet therapy insufficient to propose patient- or lesion-specific labeling in these subgroups

Cordis Studies of CYPHER® Stent in Higher Risk Sub-Groups



- Small vessel stent * – SIRIUS 2.25 Trial¹
- Large vessel stent * – SIRIUS 4.0 Trial
- Direct stenting * – DIRECT Trial²
- In-stent Restenosis * – SISR Trial³
- Acute Myocardial Infarction – TYPHOON⁴
- Chronic Total Occlusions – ACROSS Trial

*** PMA supplement submitted to FDA**

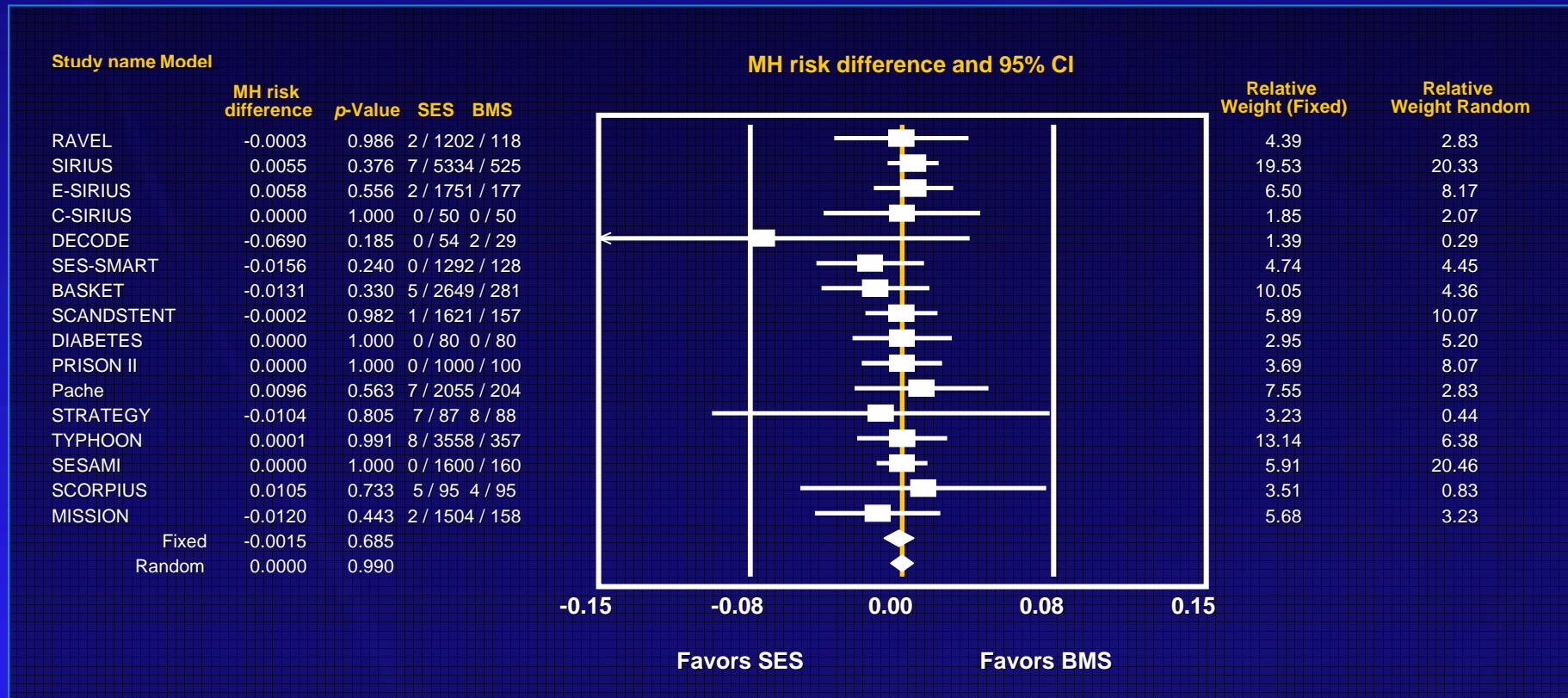
¹ Moses et al., Am J Cardiol 2006;98:1455–1460

² Hirohata et al., Am J Cardiol 2006; 98:1464-1467

³ Holmes et al., JAMA 2006;295:1264-1273

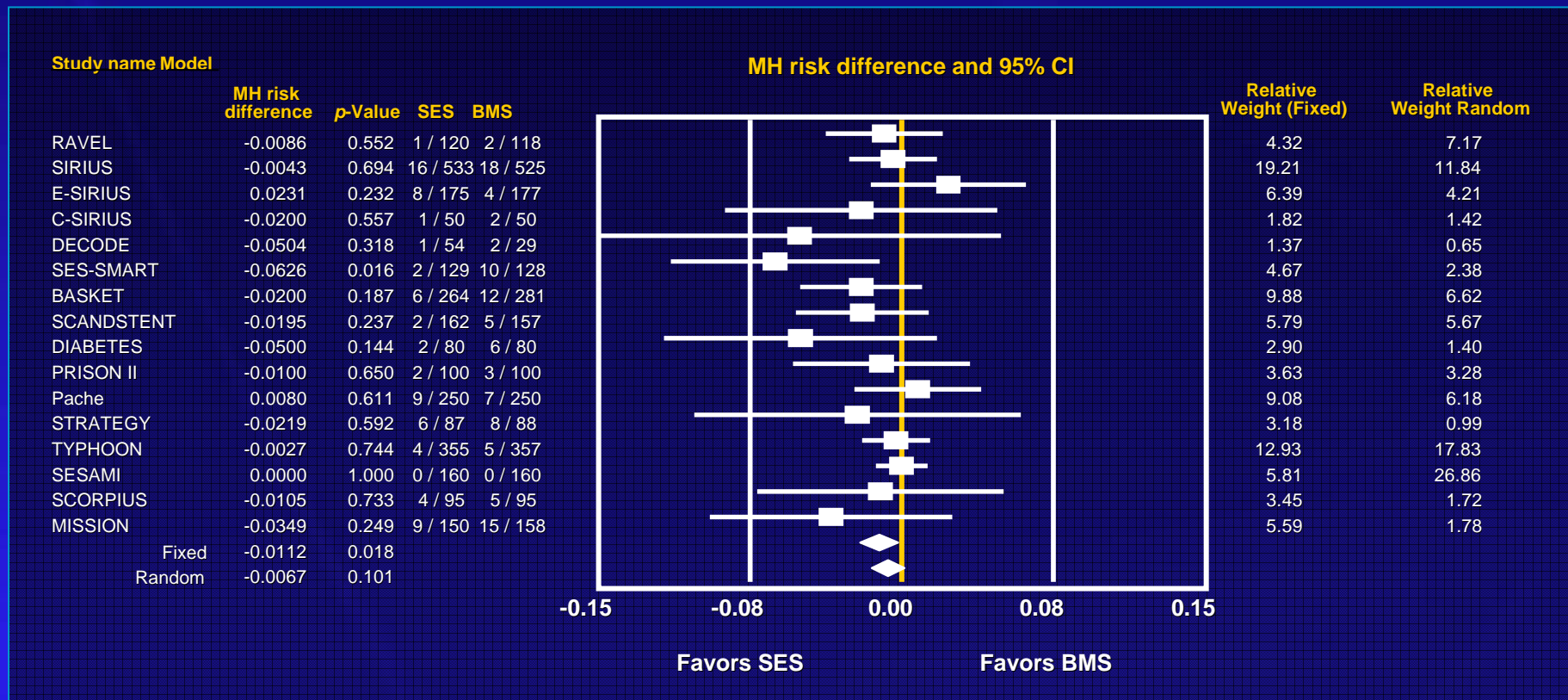
⁴ Spaulding et al., NEJM 2006;355:1093-104

Meta-Analysis: All Cause Mortality up to 1-Year in SES vs. BMS RCTs



	Q-Values	Degree of freedom (Q)	I ²	p-Value
Heterogeneity	6.614	15	0.000	0.9675

Meta-Analysis: Any MI up to 1-Year in SES vs. BMS RCTs



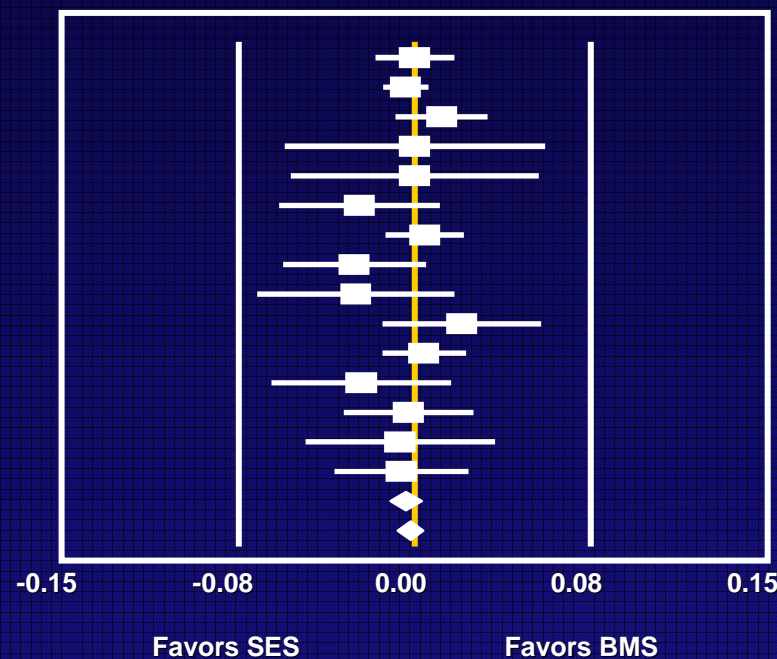
	Q-Values	Degree of freedom (Q)	I ²	p-Value
Heterogeneity	16.514	15	9.169	0.3487

Meta-Analysis: Thrombosis up to 1-Year in SES vs. BMS RCTs

Study name Model

	MH risk difference	p-Value	SES	BMS
RAVEL	0.0000	1.000	0 / 120	0 / 118
SIRIUS	-0.0039	0.403	2 / 533	4 / 525
E-SIRIUS	0.0114	0.242	2 / 175	0 / 177
C-SIRIUS	0.0000	1.000	1 / 50	1 / 50
DECODE	0.0000	1.000	0 / 54	0 / 29
SES-SMART	-0.0235	0.172	1 / 129	4 / 128
BASKET	0.0042	0.606	3 / 264	2 / 281
SCANDSTENT	-0.0257	0.093	1 / 162	5 / 157
DIABETES	-0.0250	0.236	0 / 80	2 / 80
PRISON II	0.0200	0.238	2 / 100	0 / 100
Pache	0.0040	0.653	3 / 250	2 / 250
STRATEGY	-0.0227	0.238	0 / 87	2 / 88
TYPHOON	-0.0026	0.850	12 / 35513	3 / 357
SESAMI	-0.0063	0.759	5 / 160	6 / 160
MISSION	-0.0057	0.693	2 / 150	3 / 158
Fixed	-0.0037	0.281		
Random	-0.0018	0.505		

MH risk difference and 95% CI



Relative Weight (Fixed)	Relative Weight Random
4.47	11.09
19.89	35.83
6.62	8.05
1.88	0.98
1.42	1.08
4.83	2.59
10.24	11.33
6.00	3.28
3.01	1.72
3.76	2.67
9.40	9.69
3.29	2.07
13.39	4.03
6.02	1.85
5.79	3.73

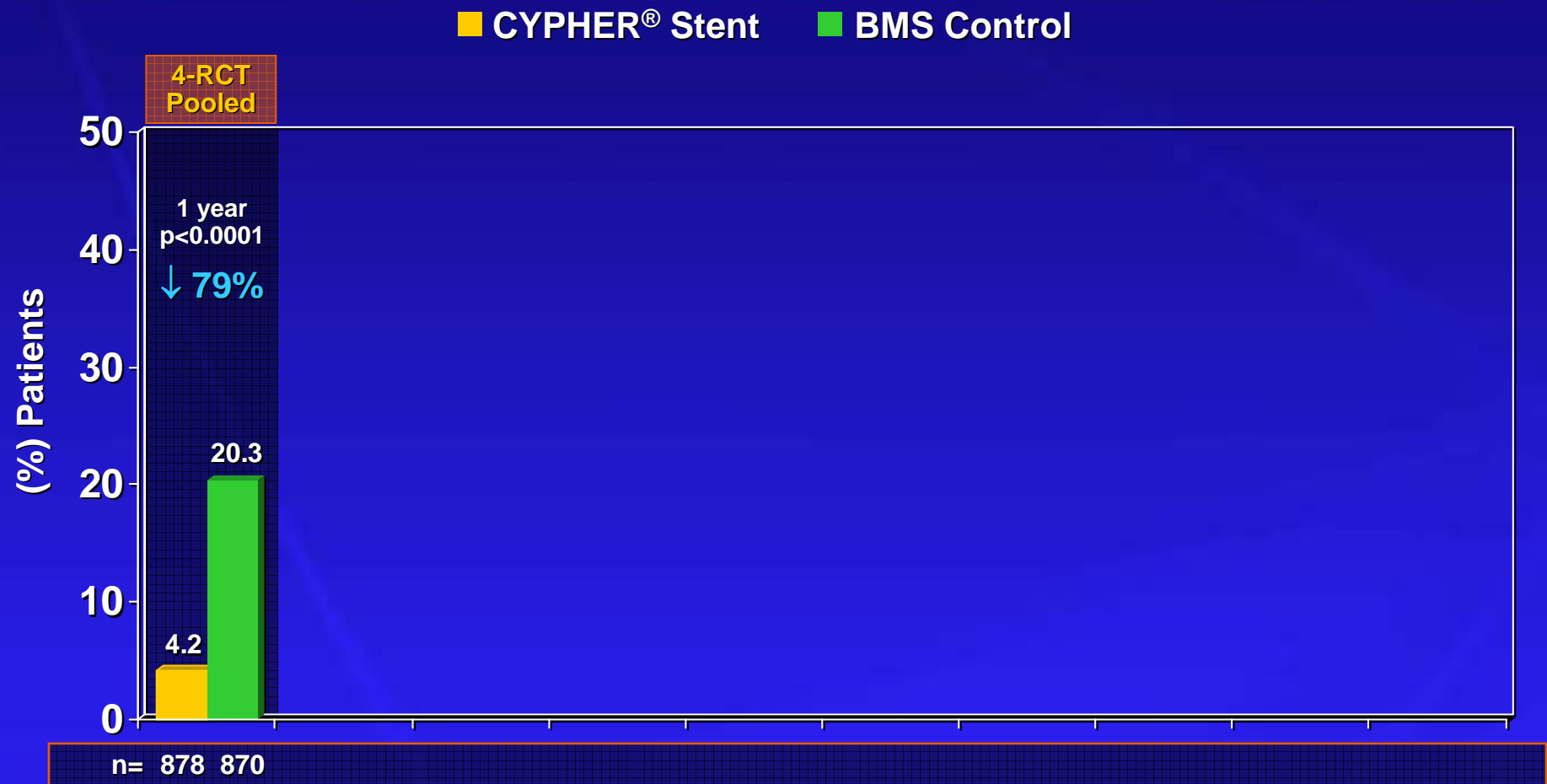
	Q-Values	Degree of freedom (Q)	I ²	p-Value
Heterogeneity	11.681	14	0.000	0.6319

9 CYPHER® Stent vs. BMS Trials in 4 Key Subsets



	Number of CYPHER®/BMS)	# of Sites / Location	Key Entry Criteria	Duration of Follow-up	Duration of Dual APT
PRISON 2	100 / 100	2 sites / Holland	CTO \geq 2 weeks with evidence of ischemia	1-year	\geq 6 months
SES-SMART	129 / 128	20 sites / Italy	RVD \leq 2.75 mm	2-years	> 2 months
DIABETES	80 / 80	4 sites / Spain	Diabetics	9 months	12 months
DECODE	54 / 29	11 sites / U.S. & Asia	Diabetics	1-year	3 months
SCORPIUS	95 / 95	16 sites / Germany	Diabetics	1-year	N/A
TYPHOON	355 / 357	48 sites / EU & Australia & Israel	Acute MI < 12 hours	1-year	\geq 6 months
SESAMI	160 / 160	1 site / Italy	Acute MI < 12 hours	1-year	N/A
STRATEGY	87 / 88	1 site / Italy	Acute MI < 12 hours or < 24 hours with ongoing ischemia	8 months	\geq 3 months
MISSION	150 / 158	1 site / Holland	Acute MI < 9 hours	1-year	12 months

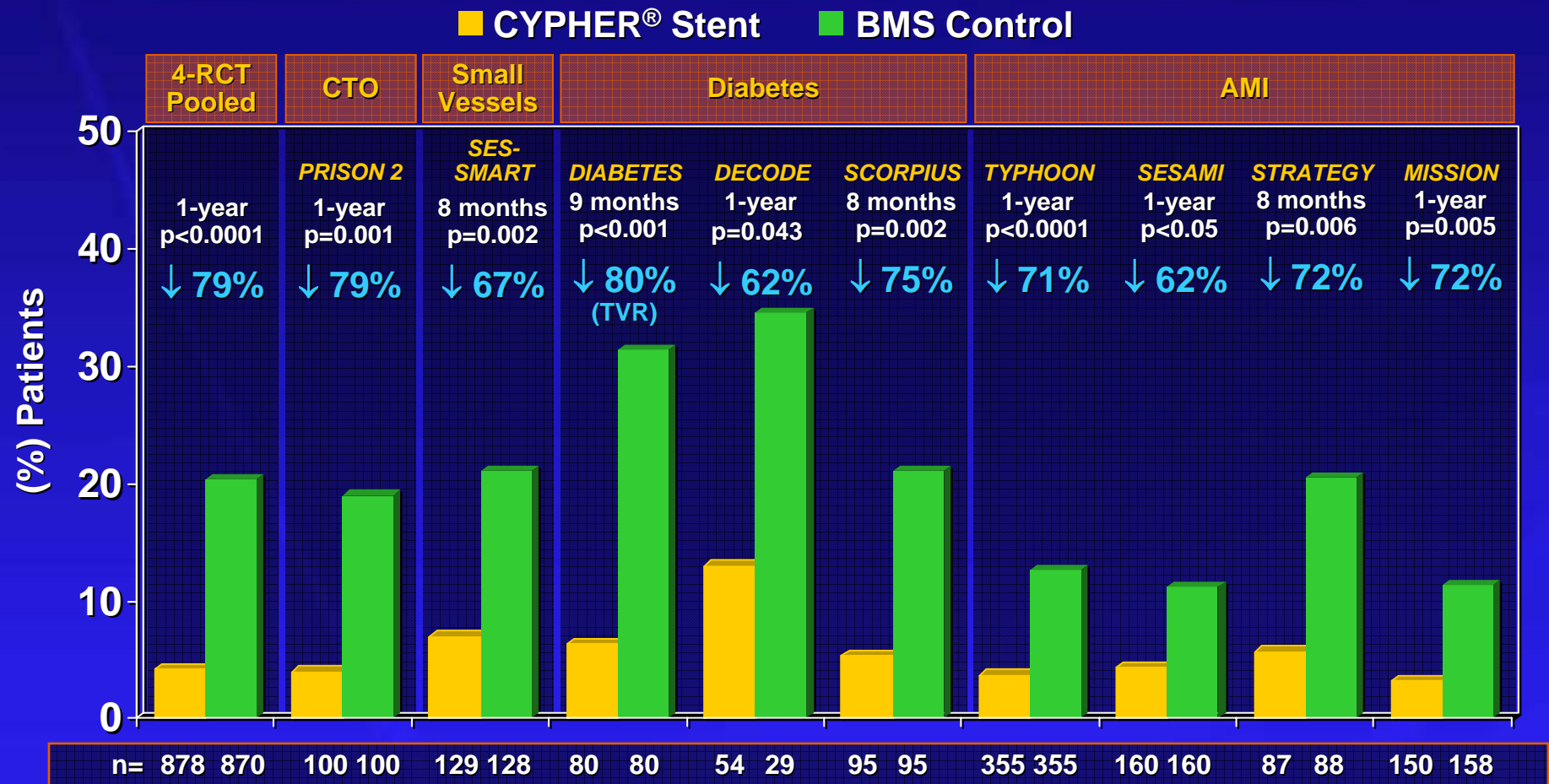
TLR in Randomized Clinical Trials of CYPHER® Stent vs. BMS Control



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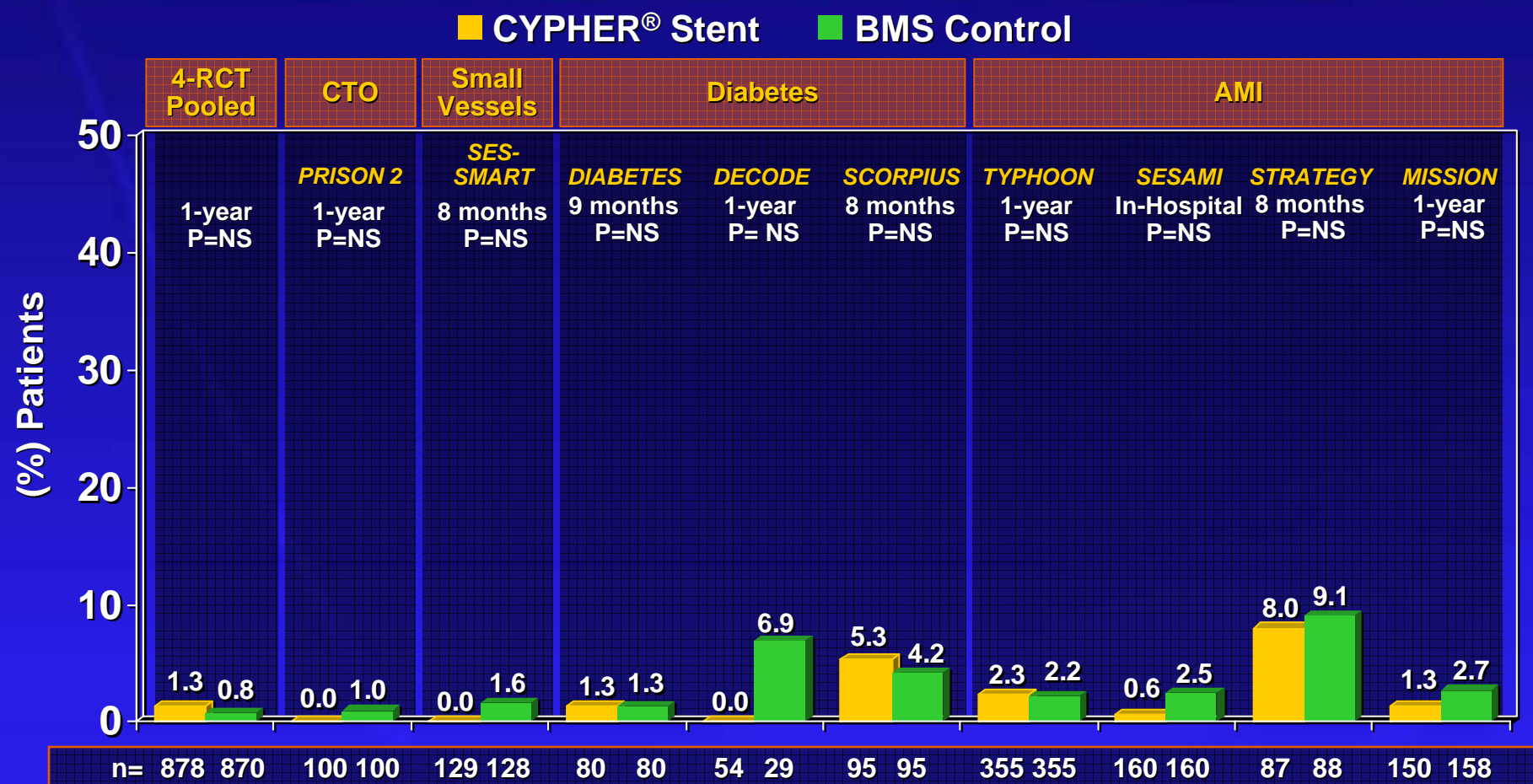
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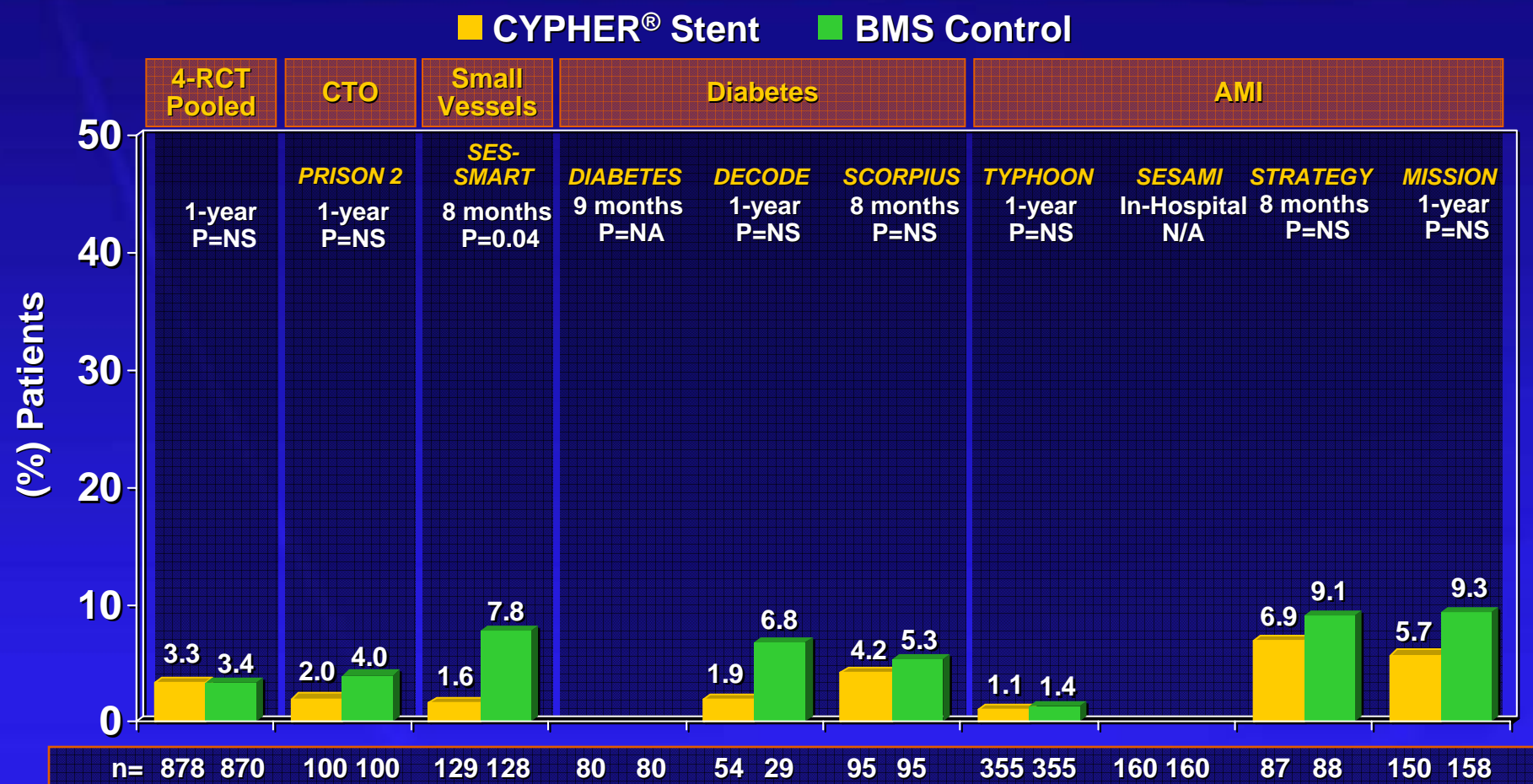
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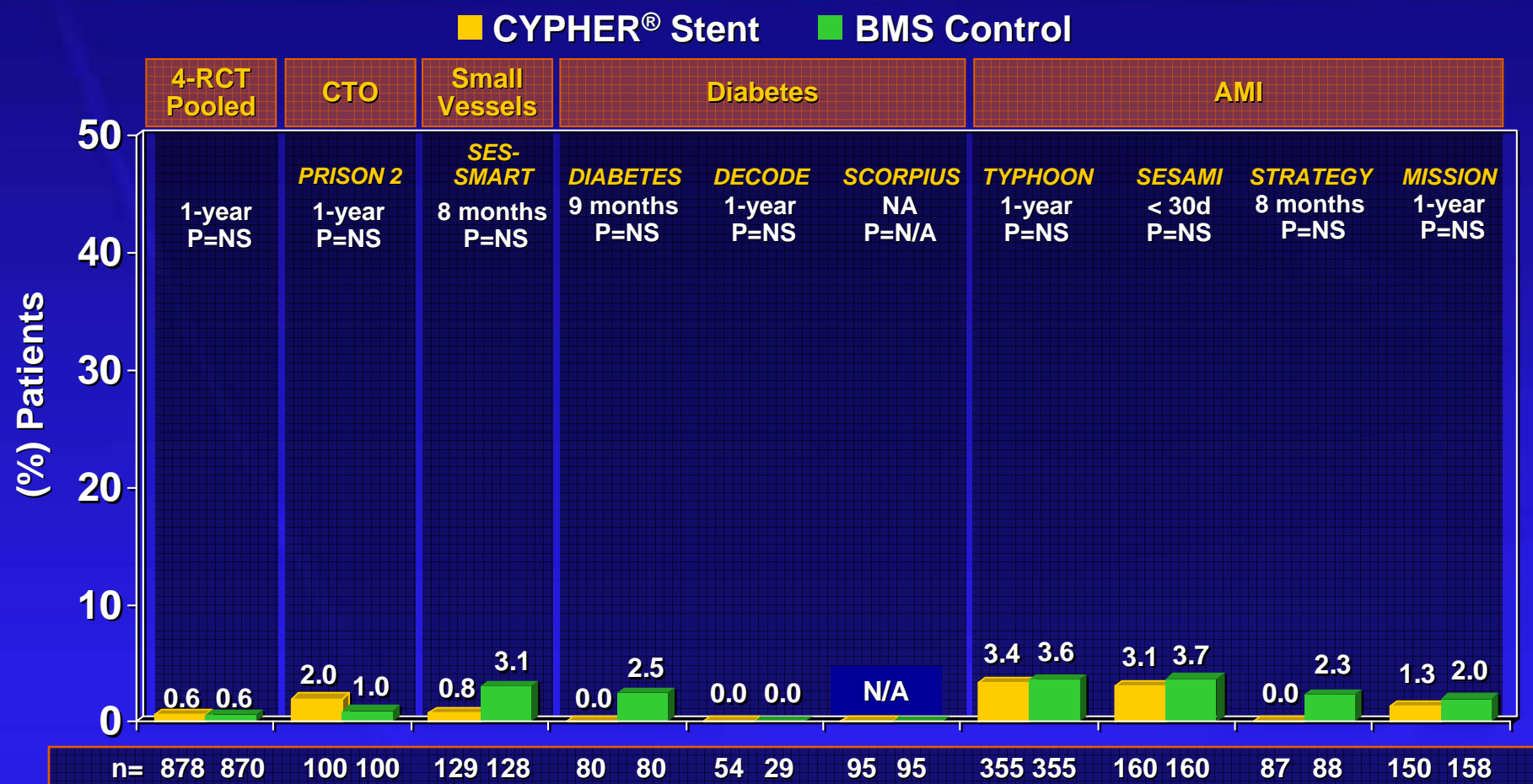
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Summary – RCT Involving Use Of CYPHER[®] Stent In High Risk Subgroups



Different risk: benefit ratio compared to RAVEL/SIRIUS:

- Benefit similar to lower risk groups:
 - 62% – 80% relative reductions in TLR/TVR with CYPHER[®] Stent vs. BMS
- Risk:
 - Rates of death, MI, or stent thrombosis numerically higher than on-label trials:
 - No significant differences between the CYPHER[®] Stent and BMS
 - Elevated risk related to patient and lesion subgroups

CORDIS CYPHER[®] Stent Registries



- **Six post-marketing surveillance registries to determine:**
 - **Safety of CYPHER[®] Stent in routine clinical use**
 - **Benefit seen in RCT reproduced in clinic**
 - **Pattern of CYPHER[®] Stent use worldwide in daily practice**
- **Enrolled all patients receiving ≥ 1 CYPHER[®] Stent**
- **Recorded data on both on- and off-label use**

6 CYPHER® Stent Registries



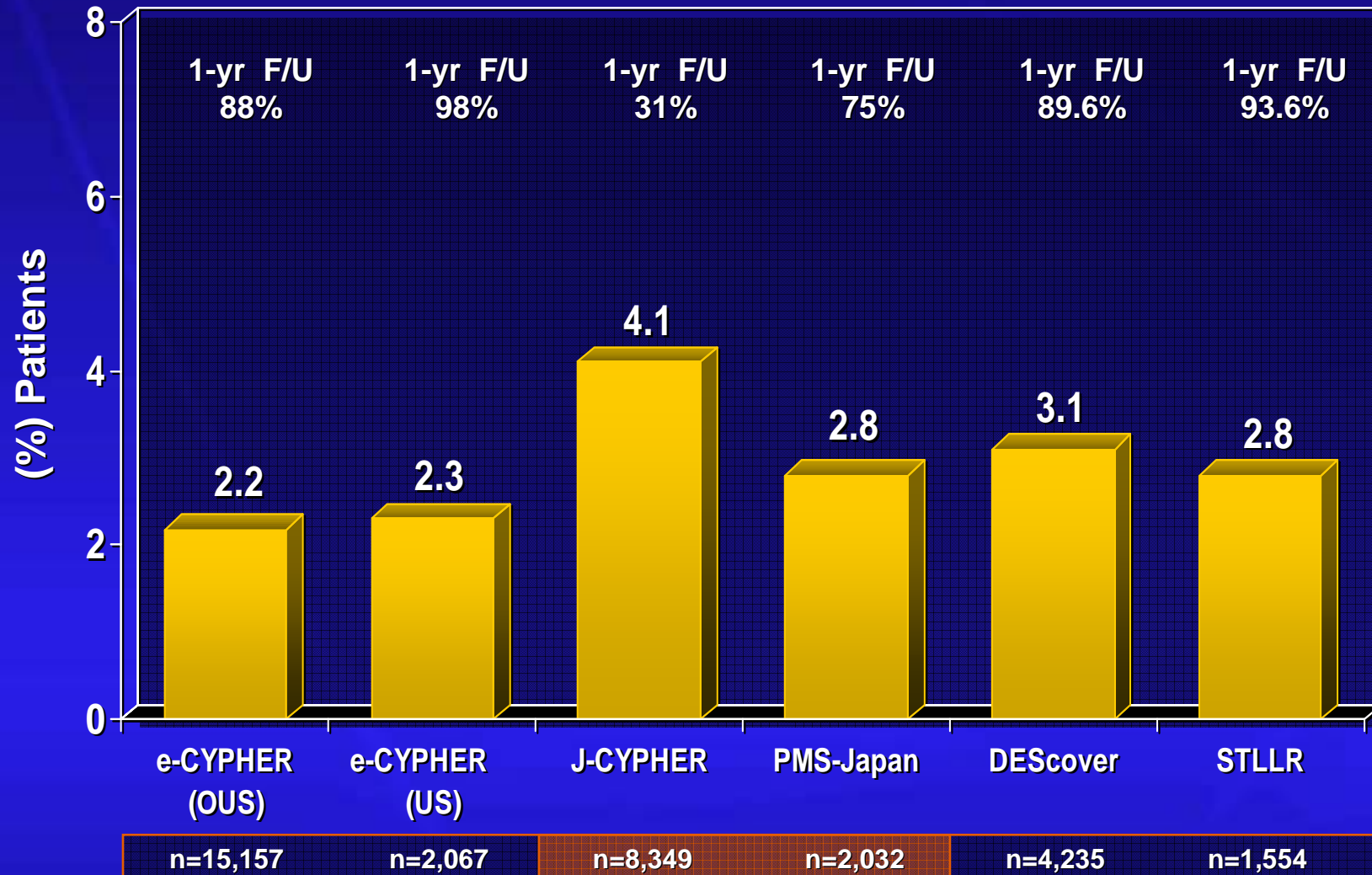
	OUS e-CYPHER	US e-CYPHER*	D.E.S. COVER	S.T.L.L.R.	Japan- PMS	J-CYPHER
Study Type	Open Enrollment Registry	Open Enrollment Registry	Open Enrollment Registry	Angio eval: stent deployment on TVR	Open Enrollment Registry	Open Enrollment Registry
Enrollment	2002-2005	2003-2004	2004-2005	2004-2005	2004-2005	2004-2005
# of Patients	15,157	2,067	4,235	1,554	2,032	14,087
# of Sites	279	38	140	41	50	41
Location	41 Countries	United States	United States	United States	Japan	Japan
Independent CEC	Yes	Yes	Yes	Yes	Yes	Yes
Independent Data Mgmt	Yes	Yes	Yes	Yes	Yes	Yes
Monitoring	3%	100%	-	-	100%	3%
Anti-platelet Medications	ASA, Ticlopidine, Clopidogrel				ASA, Ticlopidine	
Clinical Follow-up	1, 6, and 12 months					Also yearly f/u to 5-years

* FDA mandated PMS

Mortality Rates Across Six Registries

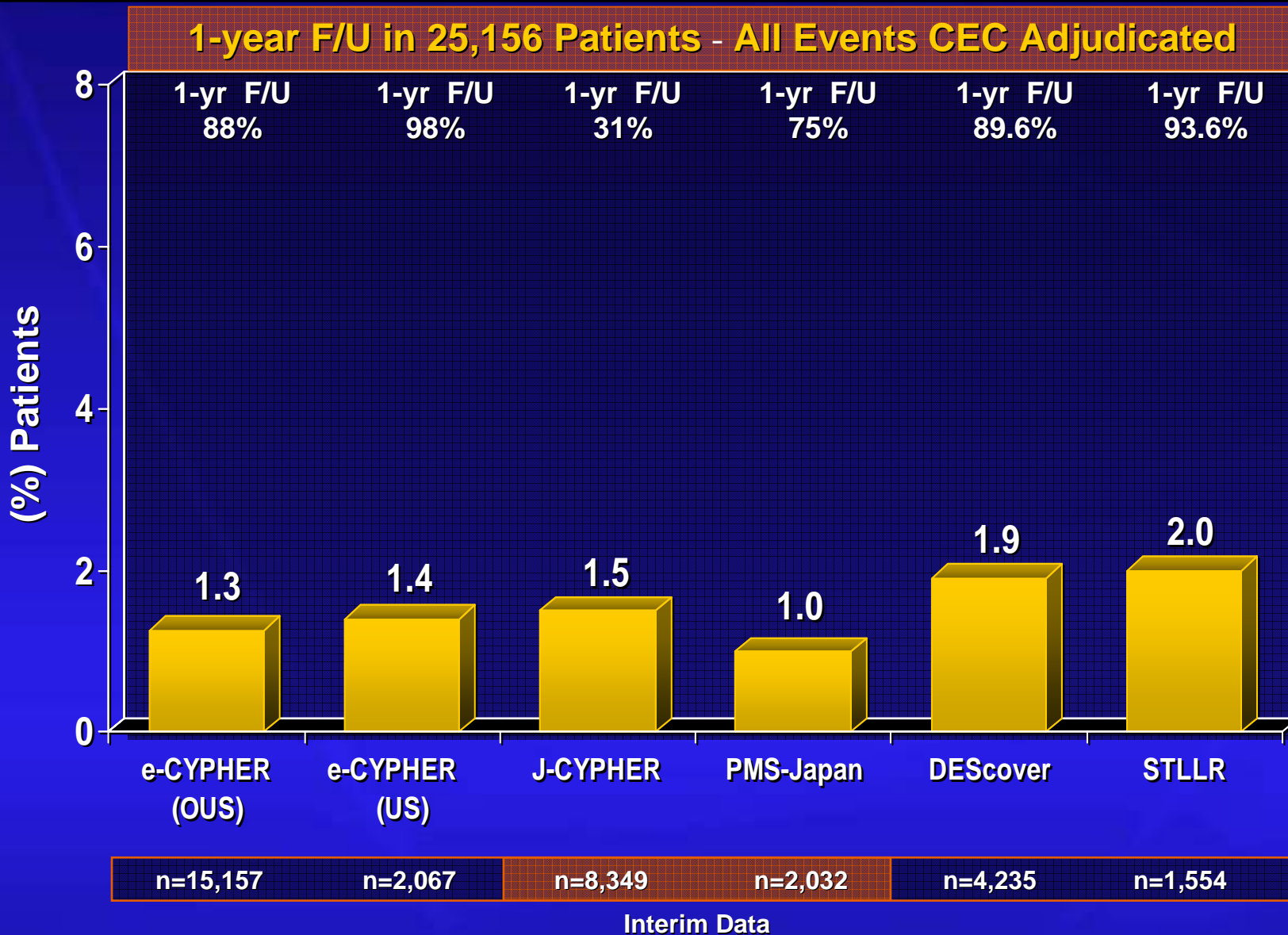


1-year F/U in 25,156 Patients - All Events CEC Adjudicated



Interim Data

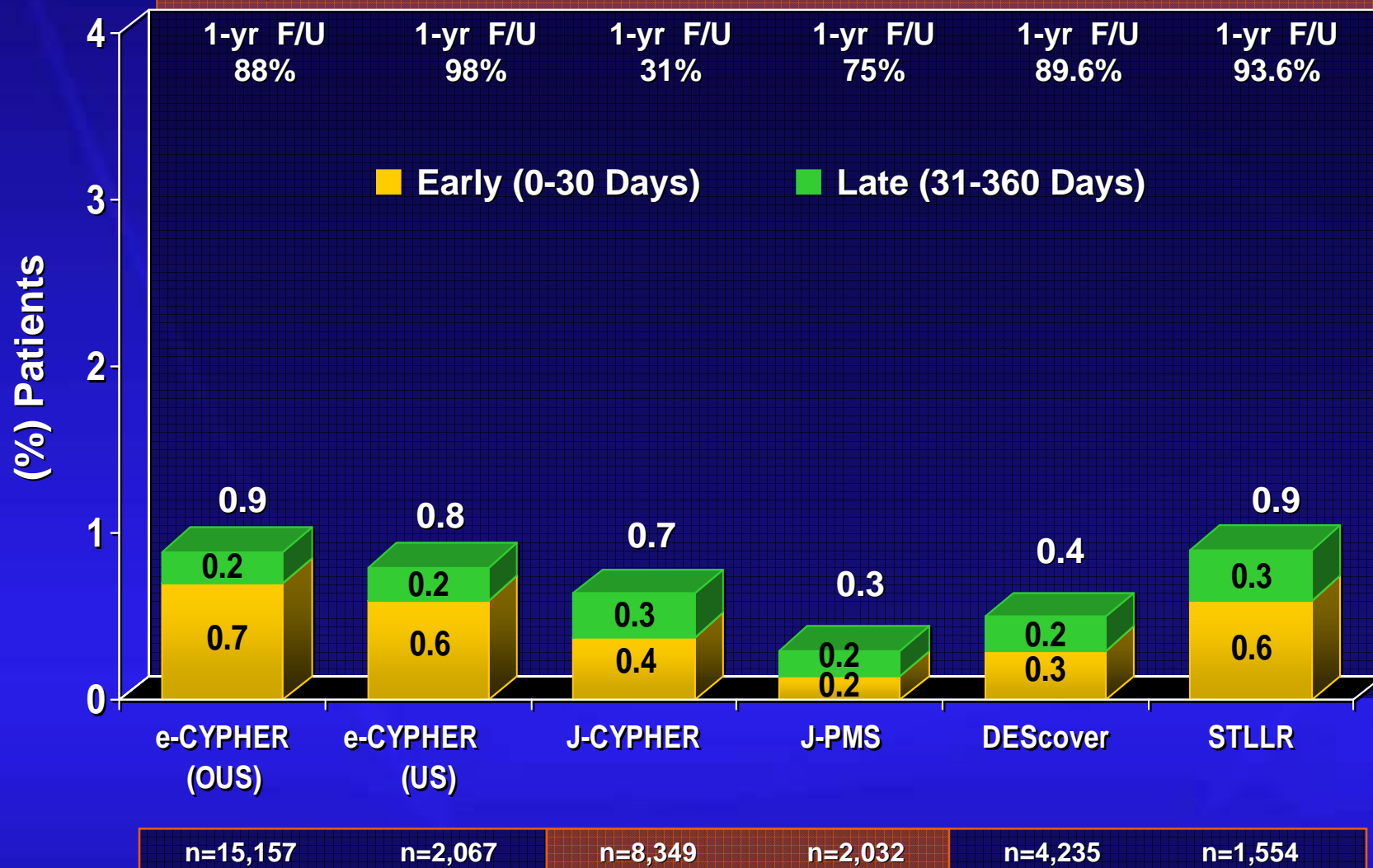
MI Rates Across 6 Registries



Stent Thrombosis Rates (Per Protocol) Across Six Registries



1-year F/U in 25,156 Patients - All Events CEC Adjudicated



n=15,157

n=2,067

n=8,349

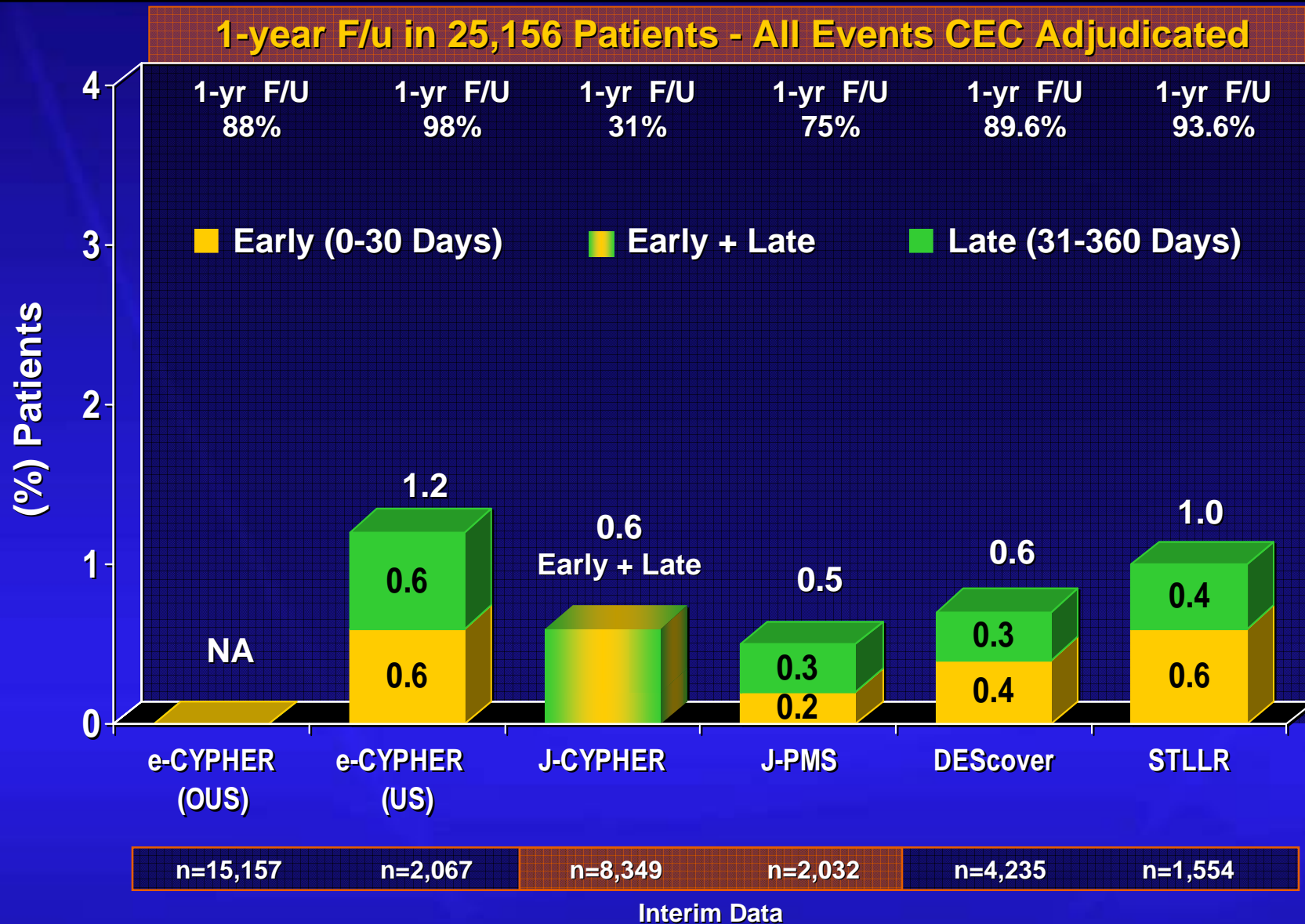
n=2,032

n=4,235

n=1,554

Interim Data

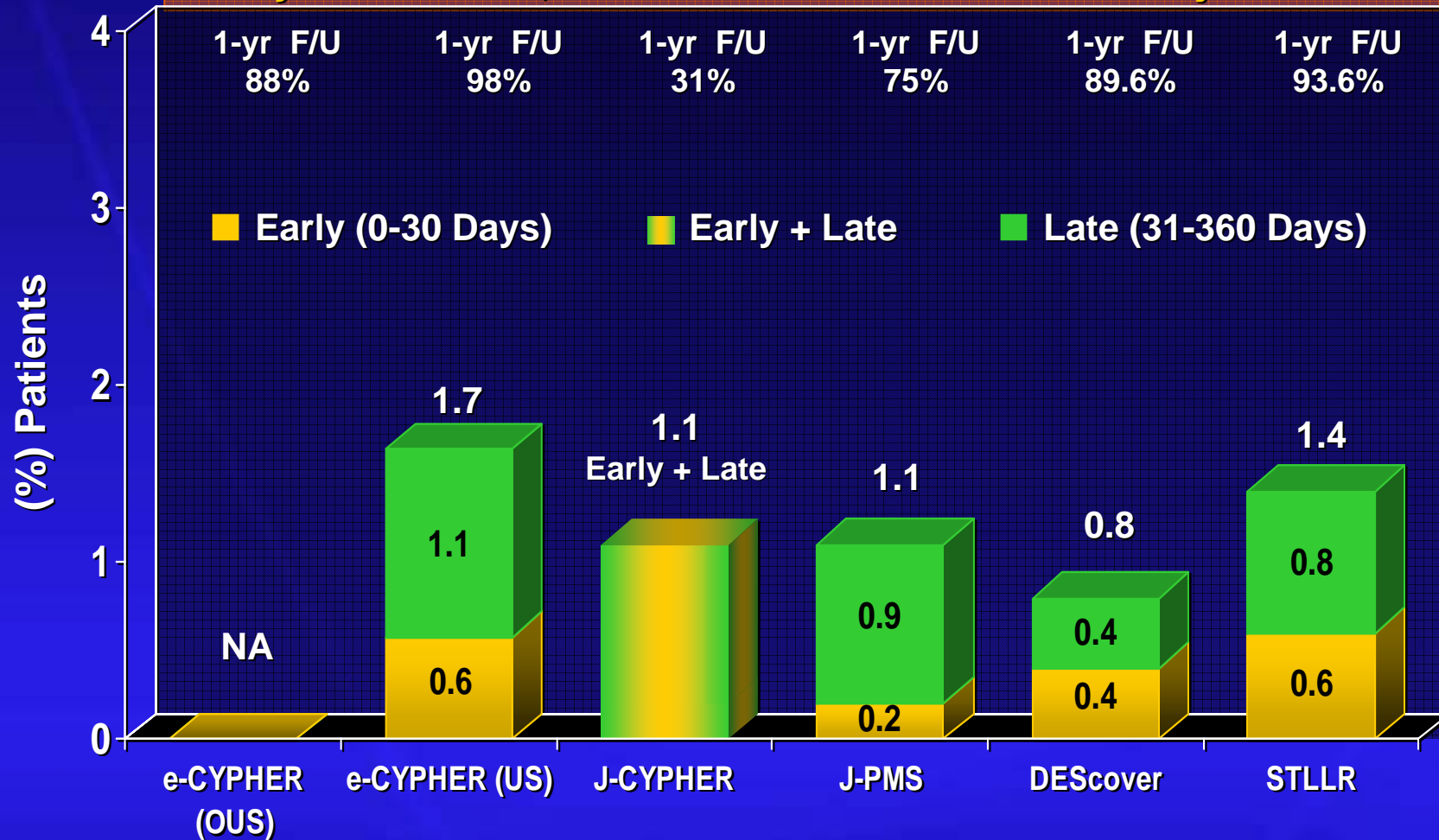
“Definite + Probable” ARC Stent Thrombosis Rates Across Six Registries



“Any” ARC Stent Thrombosis Rates Across Six Registries



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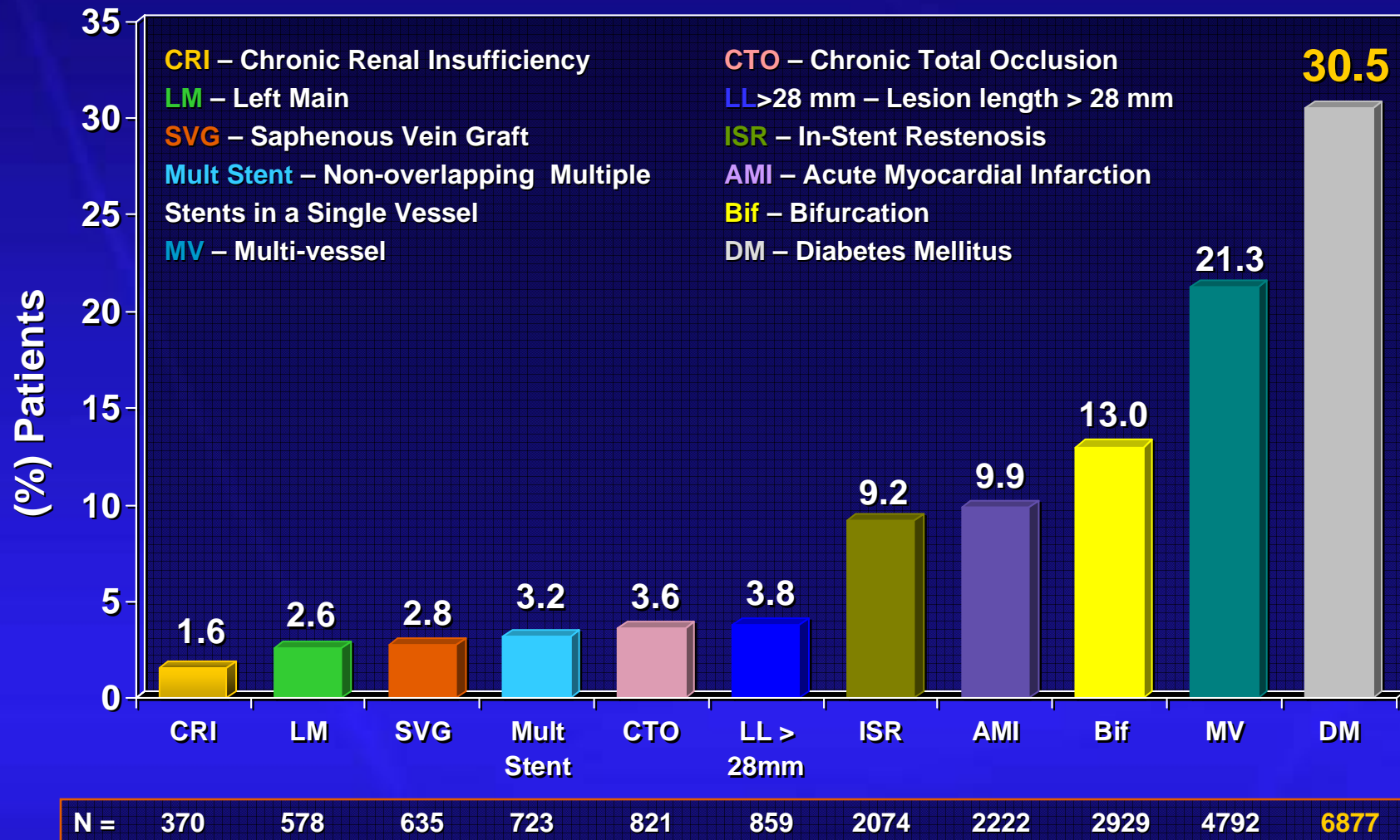
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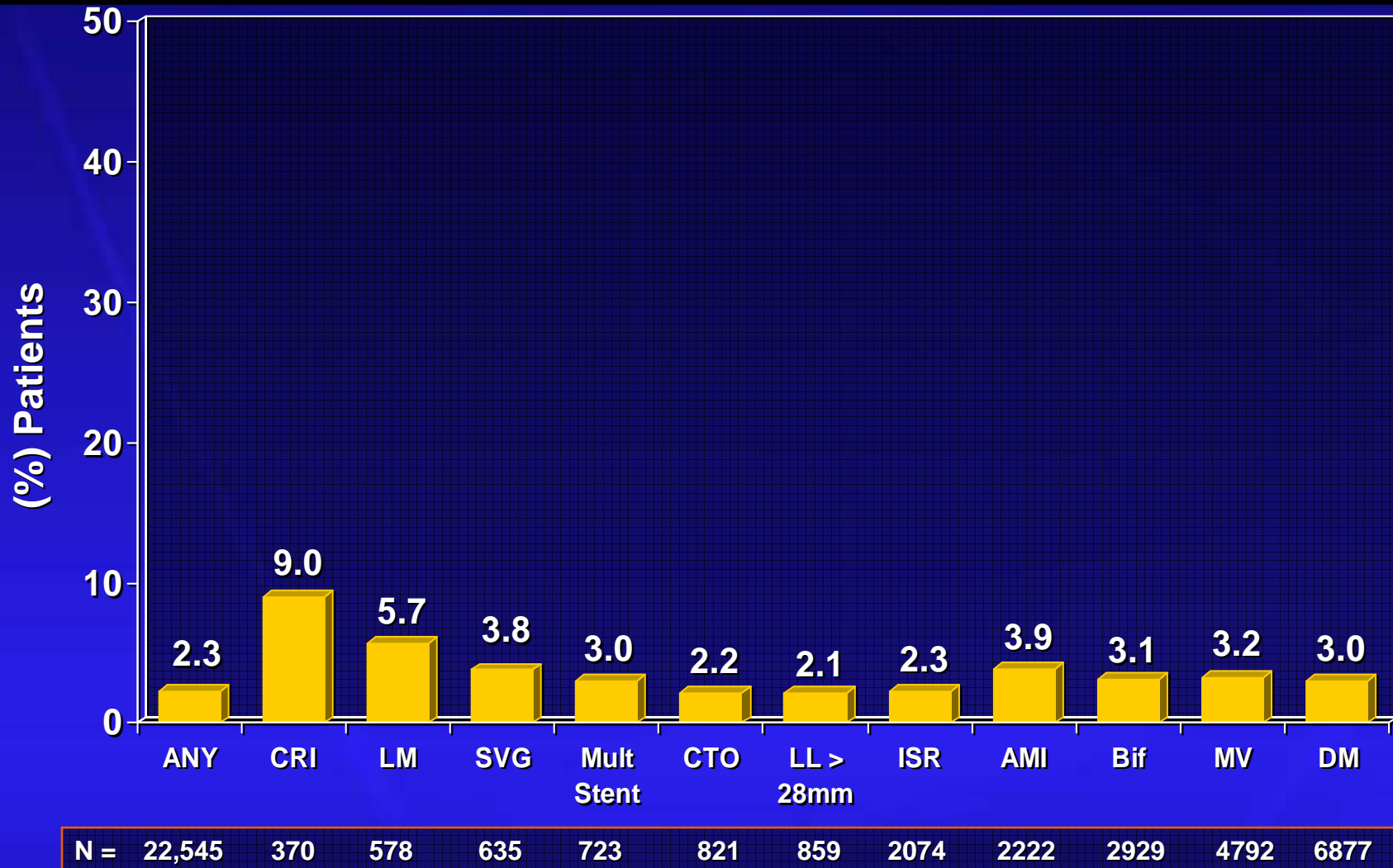
Interim Data

Distribution of Patients by Subgroups in 5 Registries*



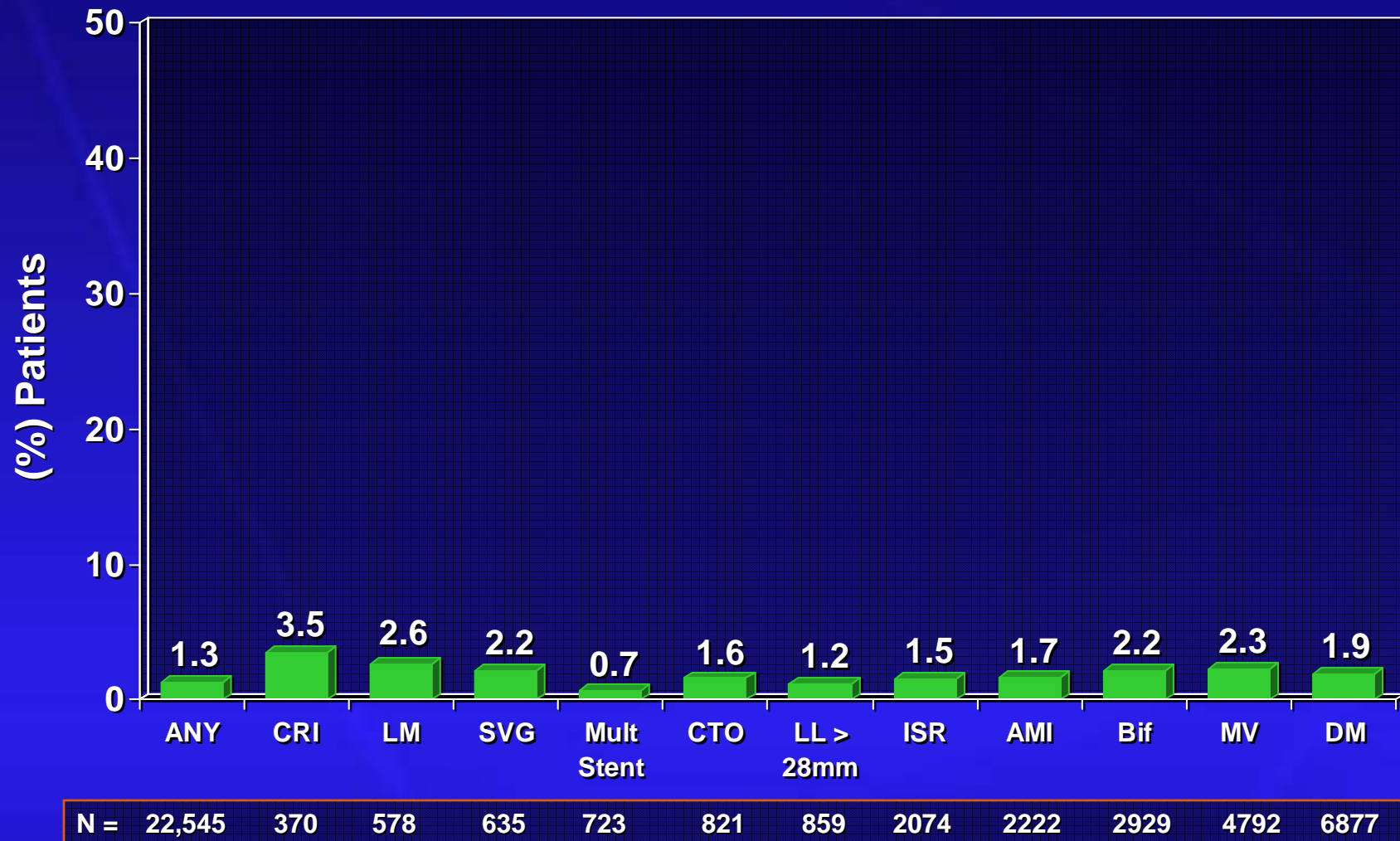
* Excludes J-CYPHER

Rates of Death: 1-Year Follow-up in Subgroups from 5 Registries*



* Excludes J-CYPHER

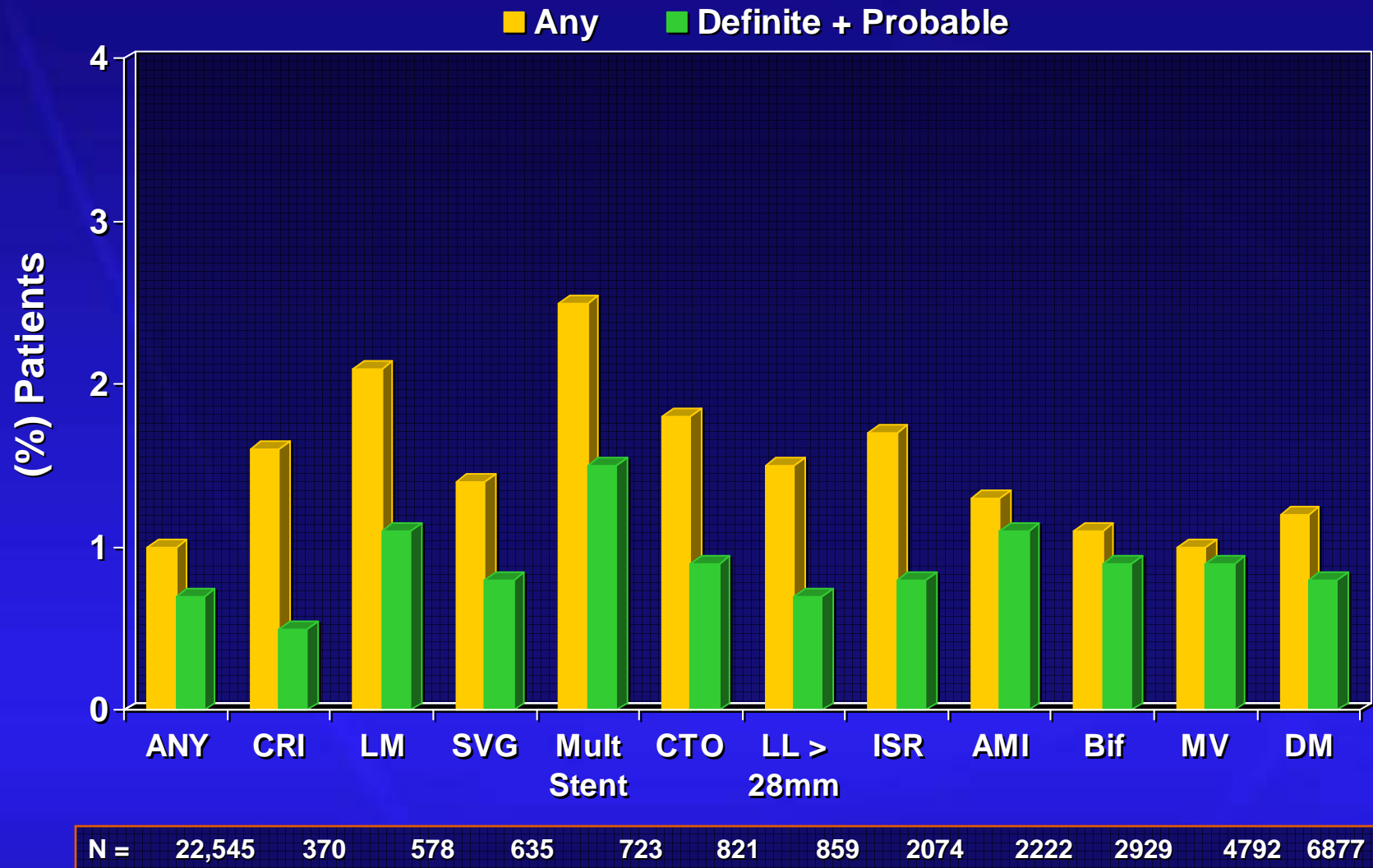
Rates of MI: 1-Year Follow-up in Subgroups from 5 Registries*



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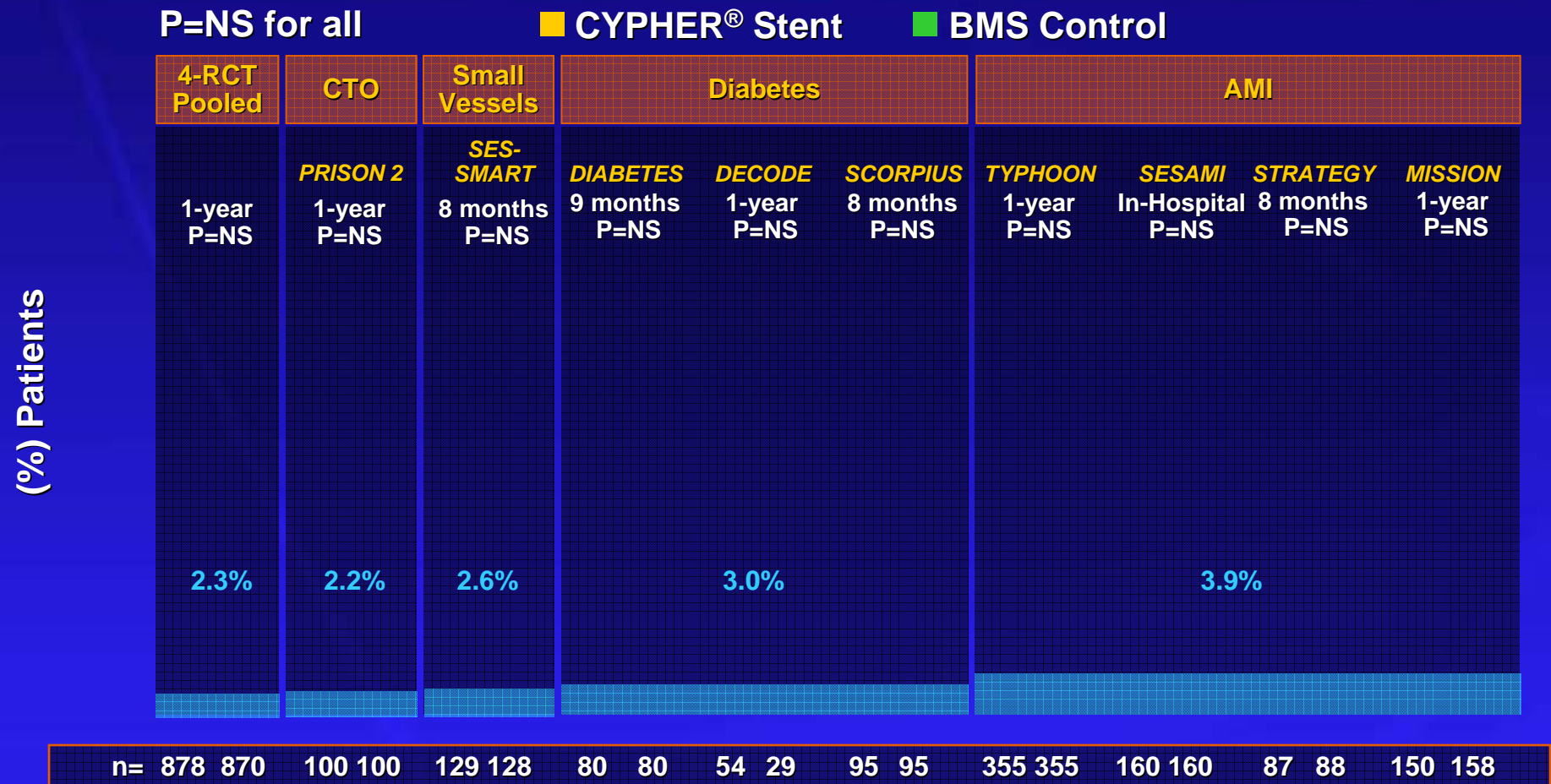
“Any” and “Definite + Probable” ARC Stent Thrombosis: 1-Year Follow-up in Subgroups from 5 Registries*

Cordis
a Johnson & Johnson company



* Excludes J-CYPHER

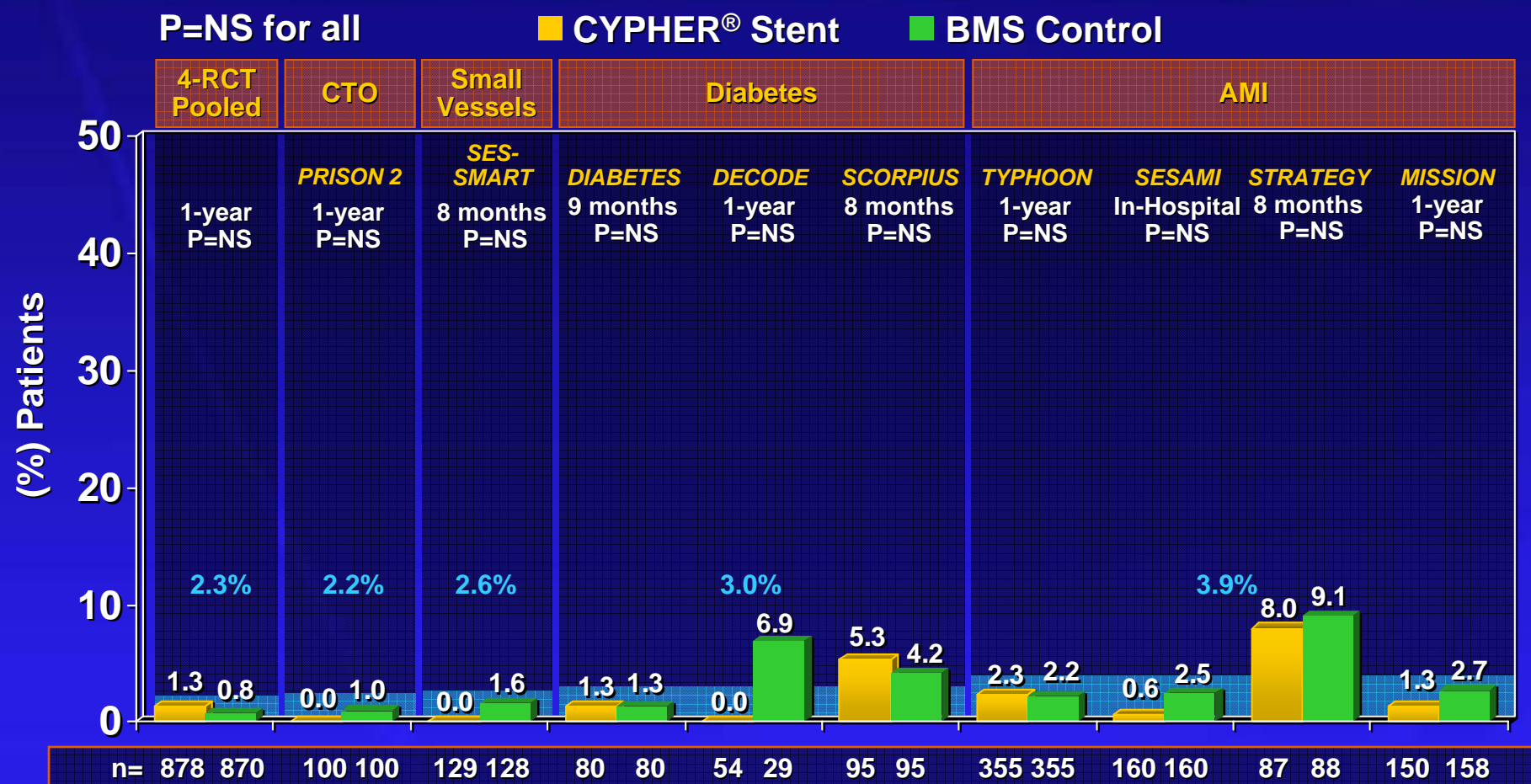
Death in CYPHER® Stent vs. BMS RCTs Compared with Death in Registries



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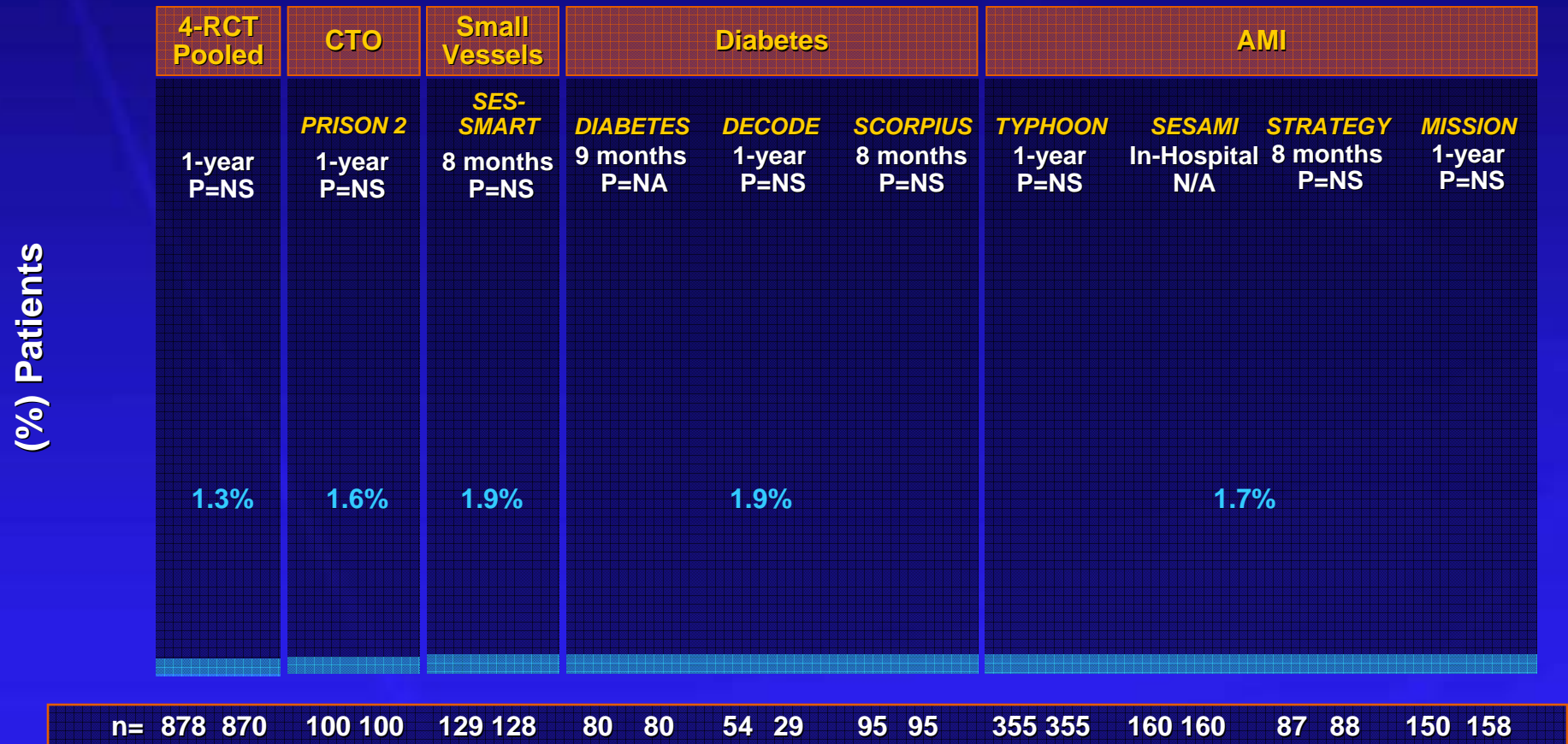
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MI in CYPHER® Stent vs. BMS Control Compared with MI's in Registries



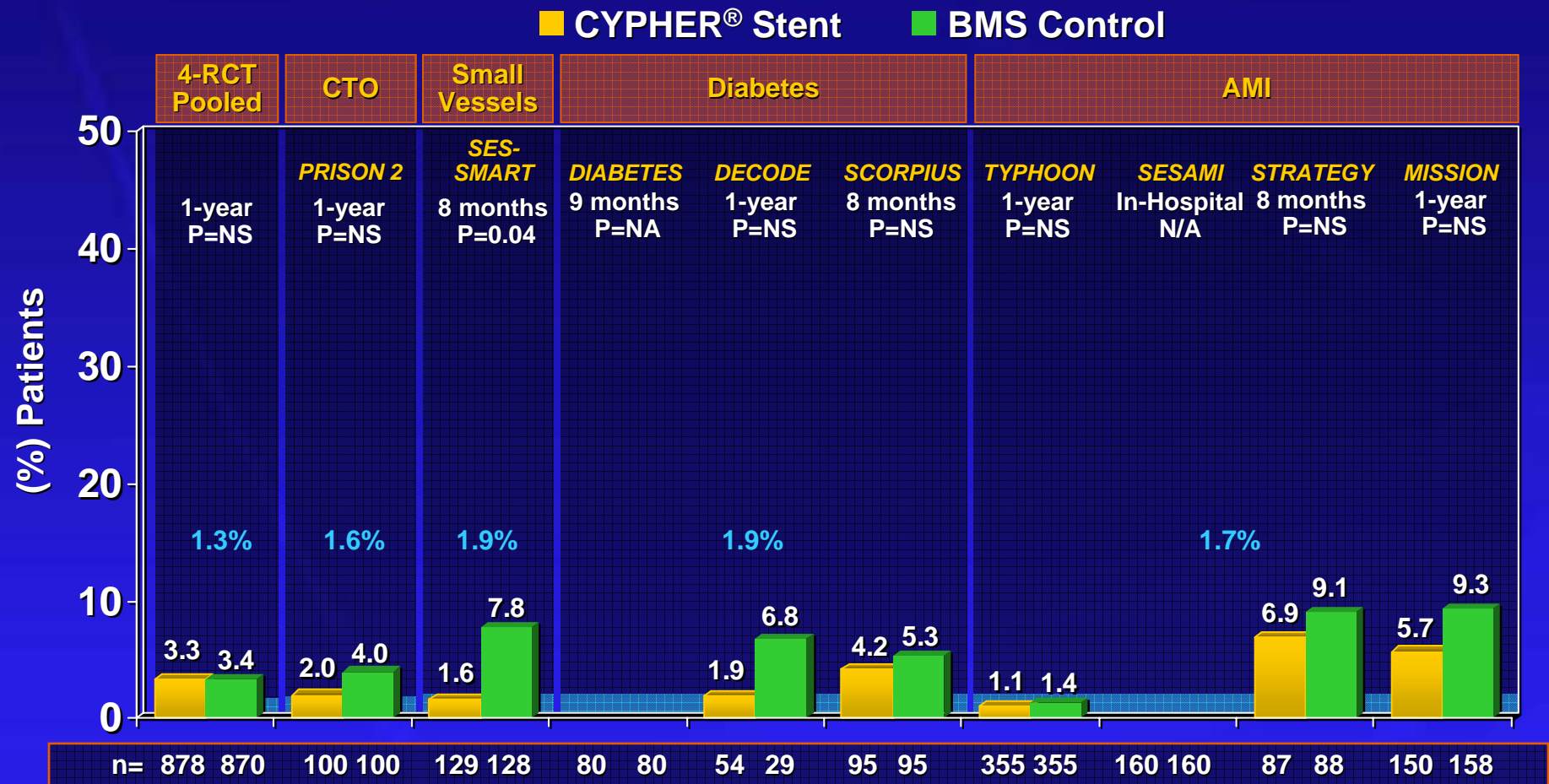
■ CYPHER® Stent ■ BMS Control



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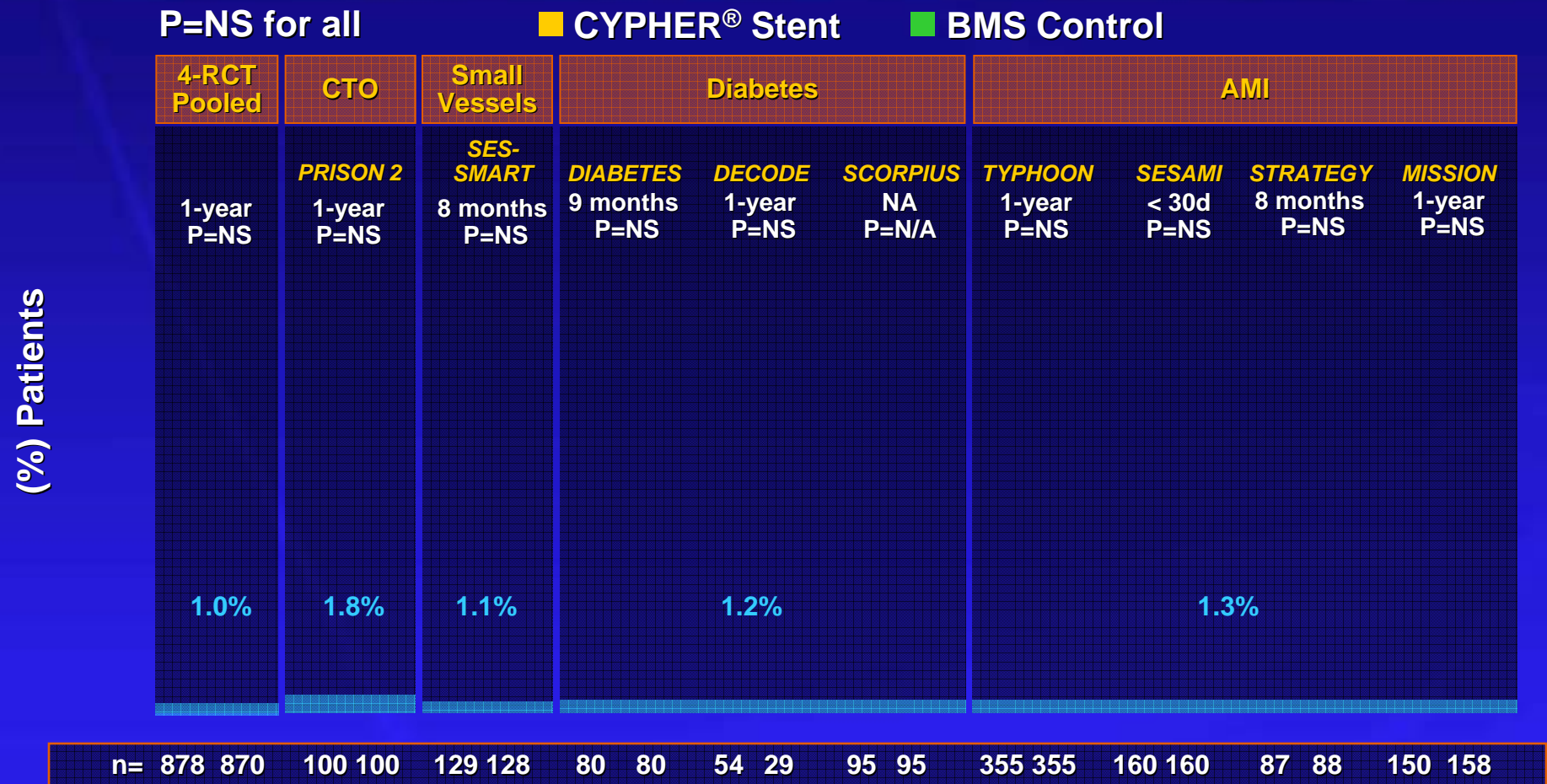
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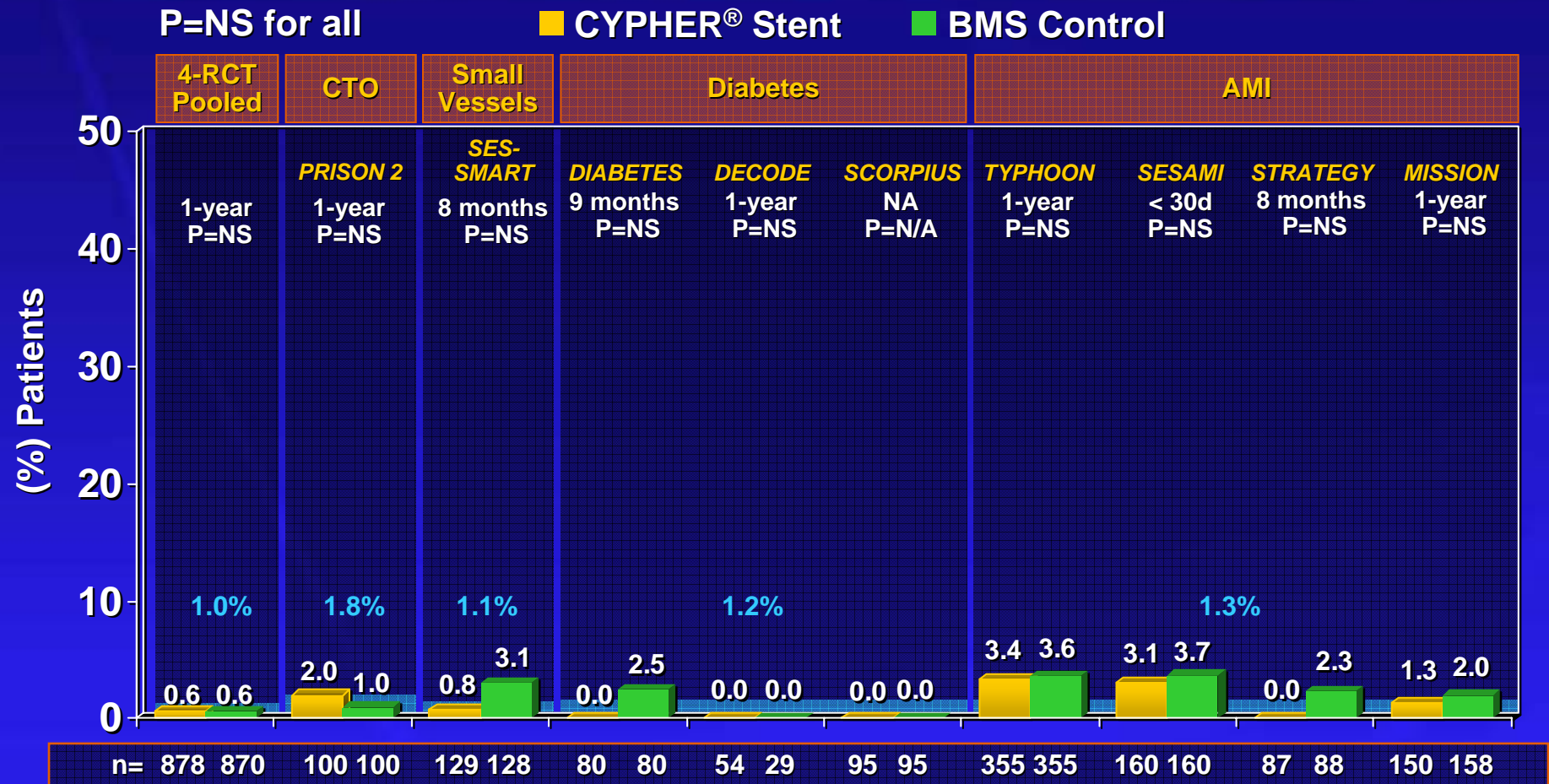
ST in CYPHER[®] Stent vs. BMS RCTs Compared with “Any” ARC Thrombosis in Registries



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Summary – Based on 1 Year Data



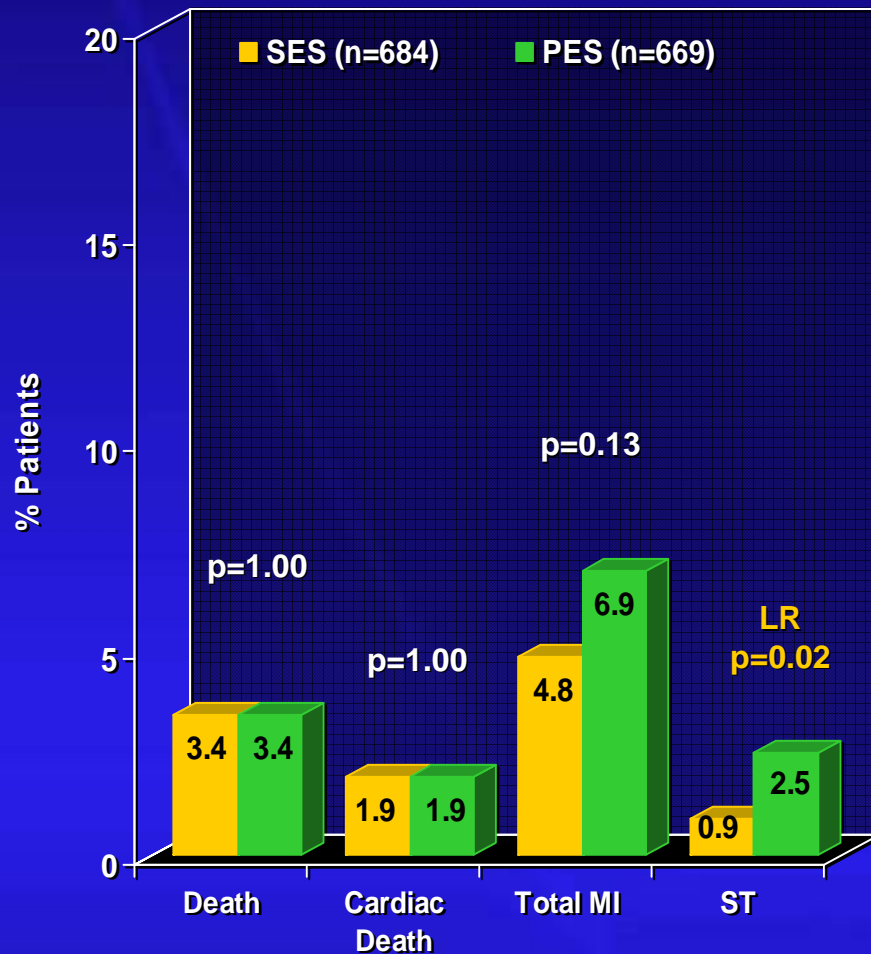
- No safety signals apparent from Meta-analysis of 12 RCTs
- No safety signals apparent from Registry data
 - Individual registries
 - In 12 different patient and lesion subsets
- In the subsets where randomized data is available, the registry data compares favorably with the randomized data
 - Except for lower rate of MIs in the registry
- Conclusion – no safety signal related to ST, death, or MI

Additional Safety Data: Meta-Analysis and RCT Data – CYPHER[®] Stent vs. TAXUS

2-Year Data: Head-to-Head CYPHER® Stent vs. TAXUS RCTs: Safety Outcomes

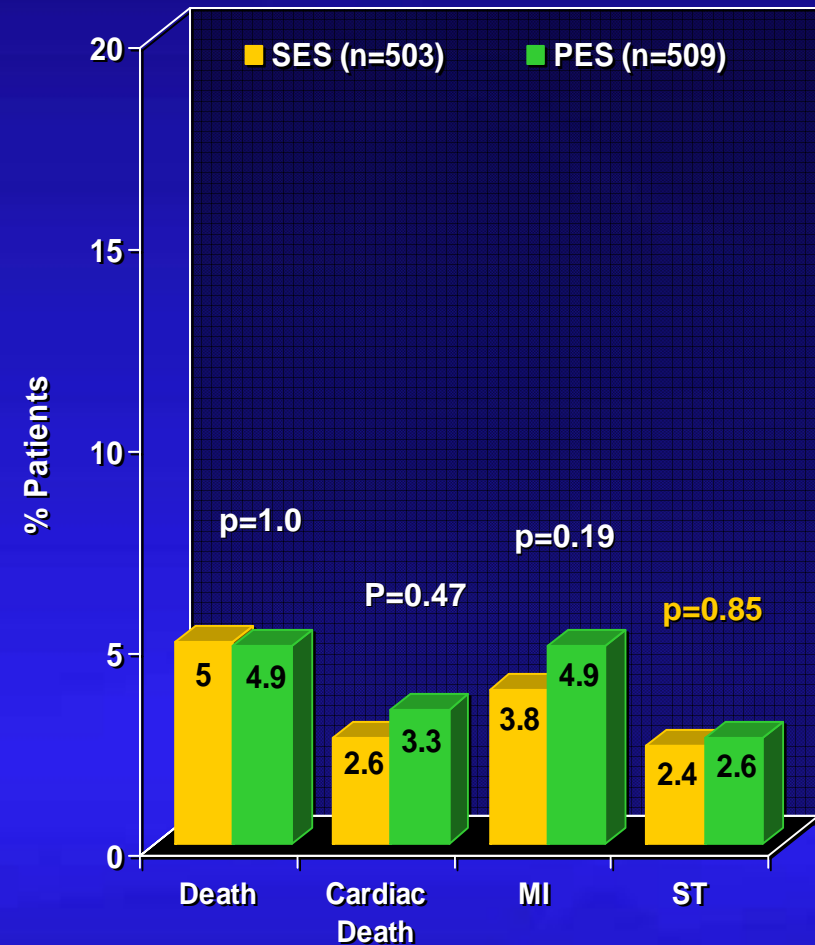


REALITY



Morice M.C. ESC 2006; Poster Presentation

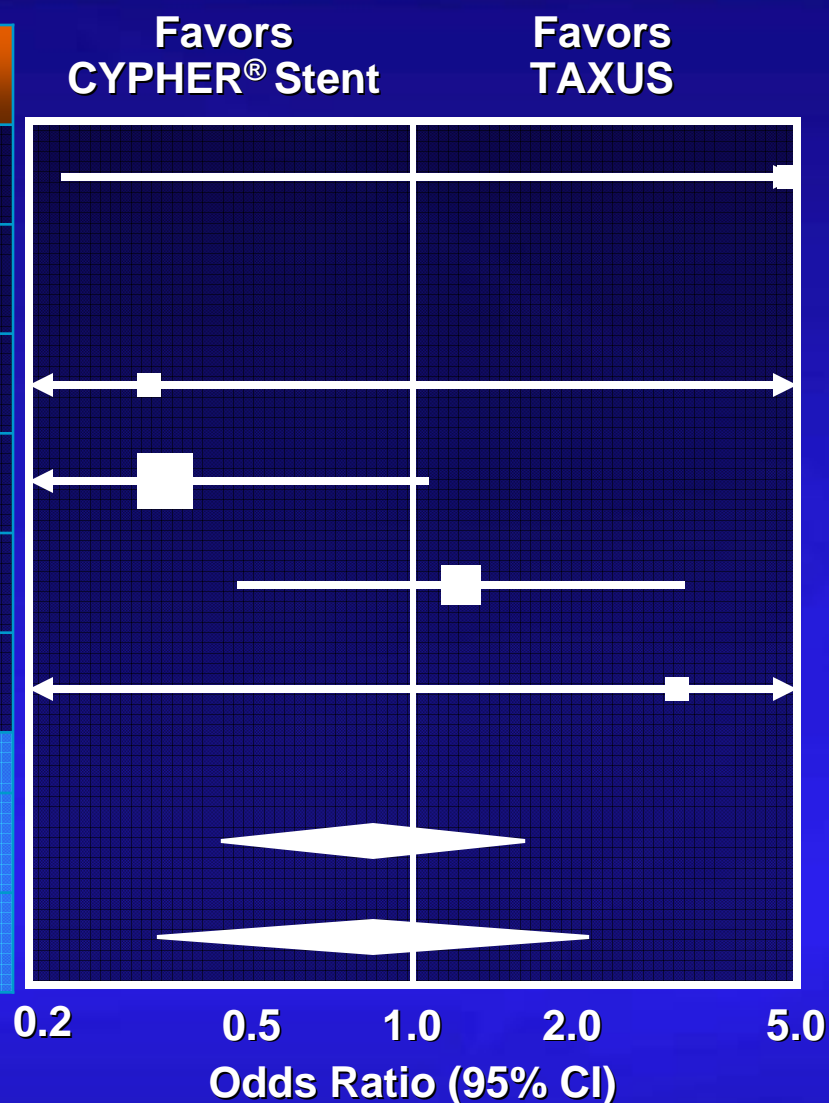
SIRTAX



Windecker S., et al., ESC 2005; Poster Presentation

Stent Thrombosis

	CYPHER® Stent	TAXUS	OR (95% CI)
CORPAL	2/331	0/321	4.88 (0.23-102.01)
ISAR-DESIRE	0/100	0/100	N/A
ISAR-Diabetes	0/125	1/125	0.33 (0.01-8.20)
REALITY	4/684	11/669	0.35 (0.11-1.11)
SIRTAX	10/503	8/509	1.27 (0.50-3.25)
TAXi	1/102	0/100	2.97 (0.12-73.79)
Overall	17/1,845	20/1,824	-
Fixed Effects			0.85 (0.46-1.59)
Random Effects			0.87 (0.36-2.08)



Test for Heterogeneity: $p=0.27$

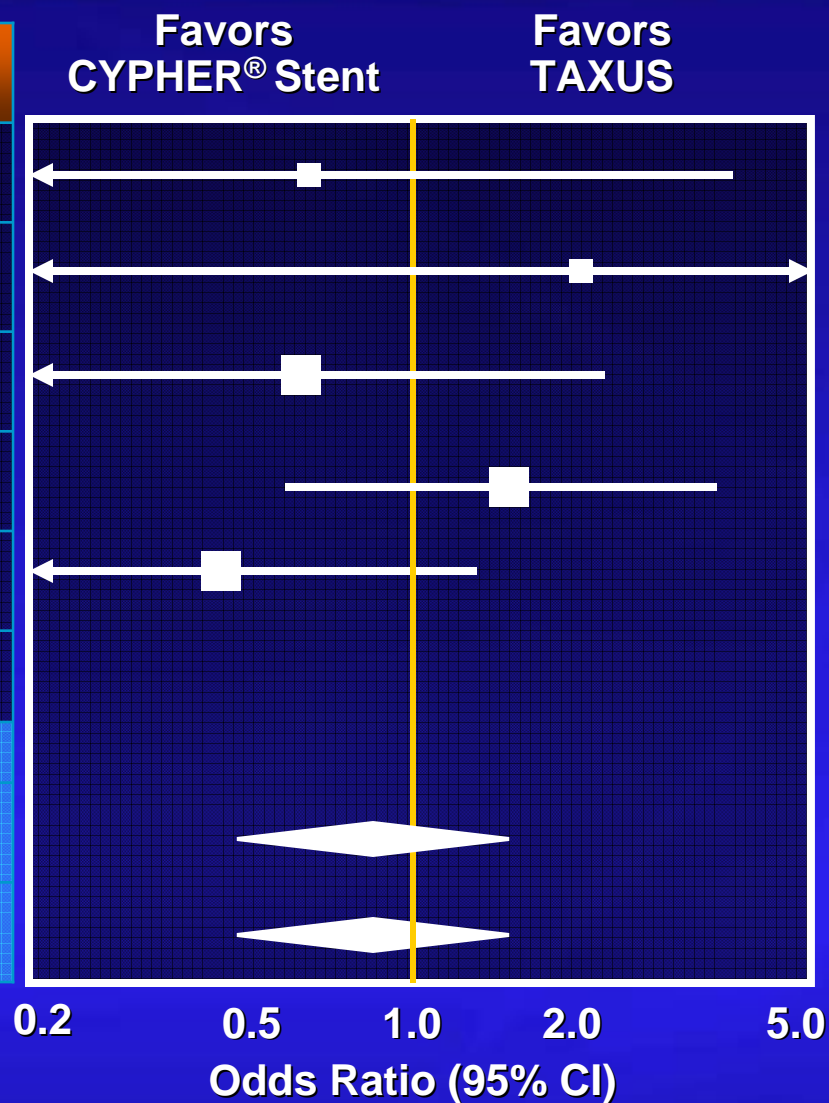
Test for Inconsistency: $I^2 = 22\%$ (95% CI, 0%-45%)

Test for Overall Effect: $p=0.62$

Death



	CYPHER® Stent	TAXUS	OR (95% CI)
CORPAL	2/331	3/321	0.64 (0.11-3.88)
ISAR-DESIRE	2/100	1/100	2.02 (0.18-22.65)
ISAR-Diabetes	4/125	6/125	0.66 (0.18-2.38)
REALITY	12/684	8/669	1.48 (0.60-3.63)
SIRTAX	5/503	11/509	0.45 (0.16-1.32)
TAXi	0/102	0/100	N/A
Overall	25/1,845	29/1,824	-
Fixed Effects			0.85 (0.50-1.46)
Random Effects			0.86 (0.49-1.50)



Test for Heterogeneity: $p=0.48$

Test for Inconsistency: $I^2 = 0\%$ (95% CI, 0%-54%)

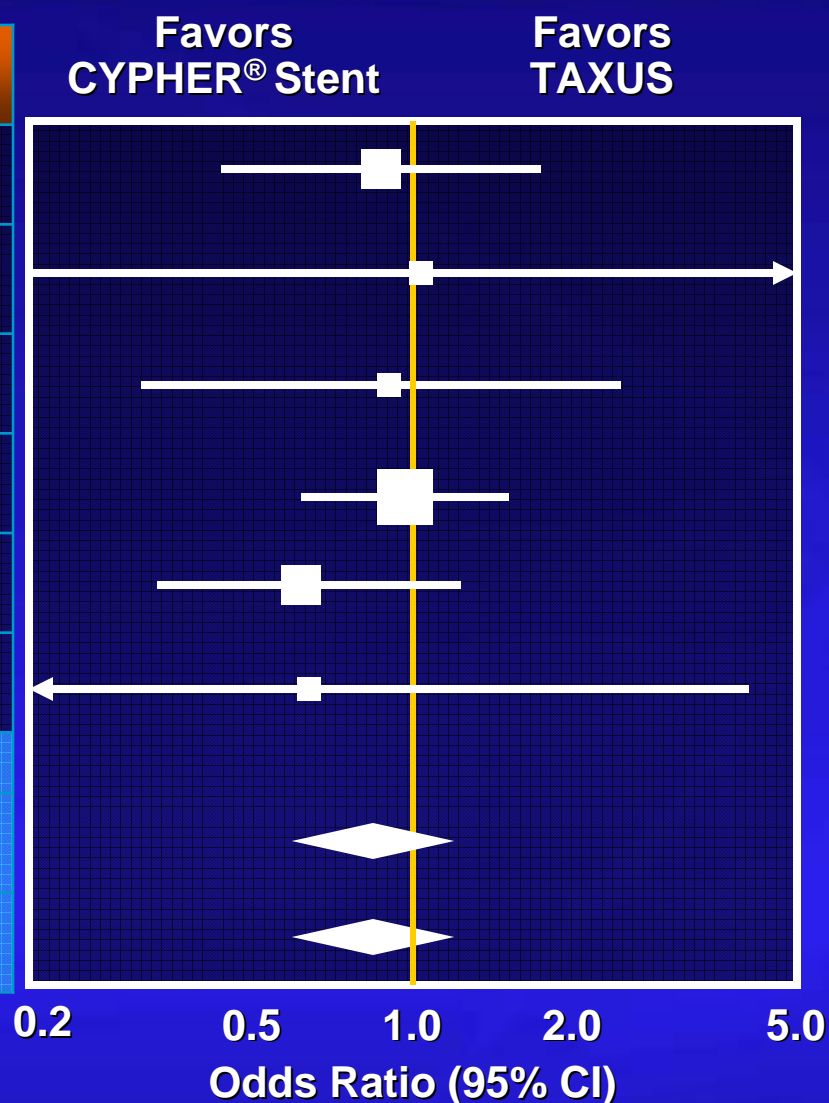
Test for Overall Effect: $p=0.56$

Meta-Analysis of Randomized, Head-to-Head Trials

Adapted from Kastrati, A., et al., *JAMA* 2005; 294:819-25.

Death or Myocardial Infarction

	CYPHER® Stent	TAXUS	OR (95% CI)
CORPAL	18/331	20/321	0.87 (0.45-1.67)
ISAR-DESIRE	3/100	3/100	1.00 (0.20-5.08)
ISAR-Diabetes	8/125	9/125	0.88 (0.33-2.36)
REALITY	42/684	43/669	0.95 (0.61-1.48)
SIRTAX	18/503	28/509	0.64 (0.35-1.17)
TAXi	2/102	3/100	0.65 (0.11-3.95)
Overall	91/1,845	106/1,824	-
Fixed Effects			0.84 (0.63-1.12)
Random Effects			0.84 (0.63-1.12)



Test for Heterogeneity: $p=0.94$

Test for Inconsistency: $I^2 = 0\%$ (95% CI, 0%-50%)

Test for Overall Effect: $p=0.23$

Meta-Analysis of Randomized, Head-to-Head Trials

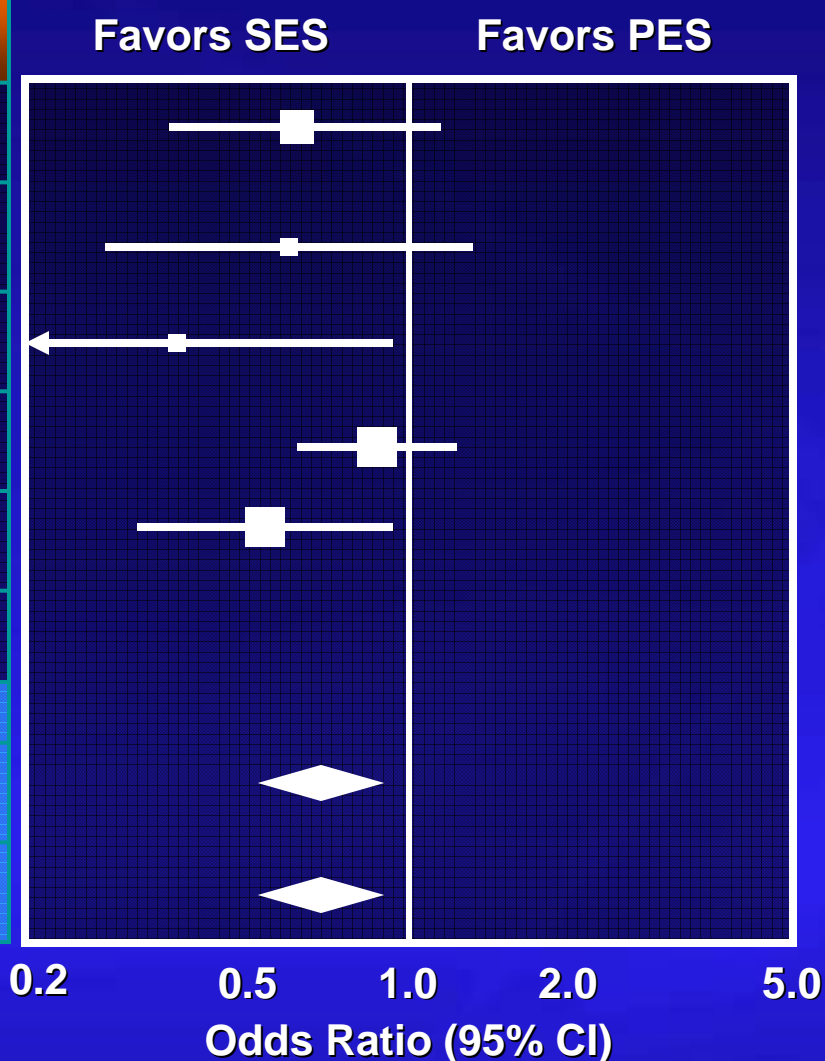
Adapted from Kastrati, A., et al., JAMA 2005; 294:819-25.

Meta-Analysis of Randomized, Head-to-Head Trials

Angiographic Restenosis



	SES	PES	OR (95% CI)
CORPAL	22/177	35/188	0.62 (0.35-1.11)
ISAR-DESIRE	13/91	20/92	0.60 (0.28-1.29)
ISAR-Diabetes	7/102	17/103	0.37 (0.15-0.94)
REALITY	88/898	95/855	0.85 (0.62-1.15)
SIRTAX	23/348	44/375	0.53 (0.31-0.90)
TAXi	-	-	-
Overall	151/1,616	211/1,613	-
Fixed Effects			0.68 (0.55-0.86)
Random Effects			0.67 (0.52-0.86)



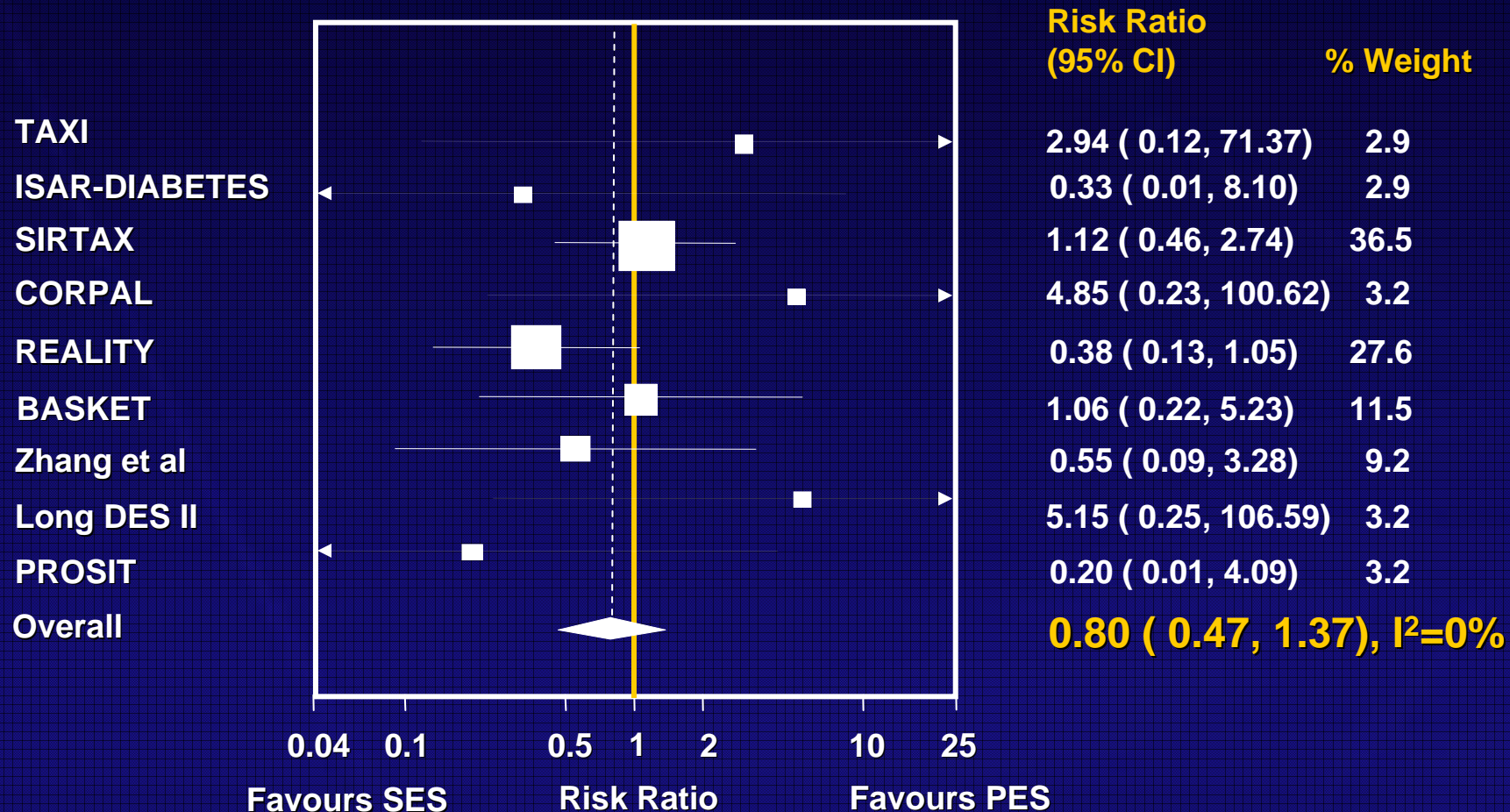
Test for Heterogeneity: $p=0.33$

Test for Inconsistency: $I^2 = 13\%$ (95% CI, 0%-57%)

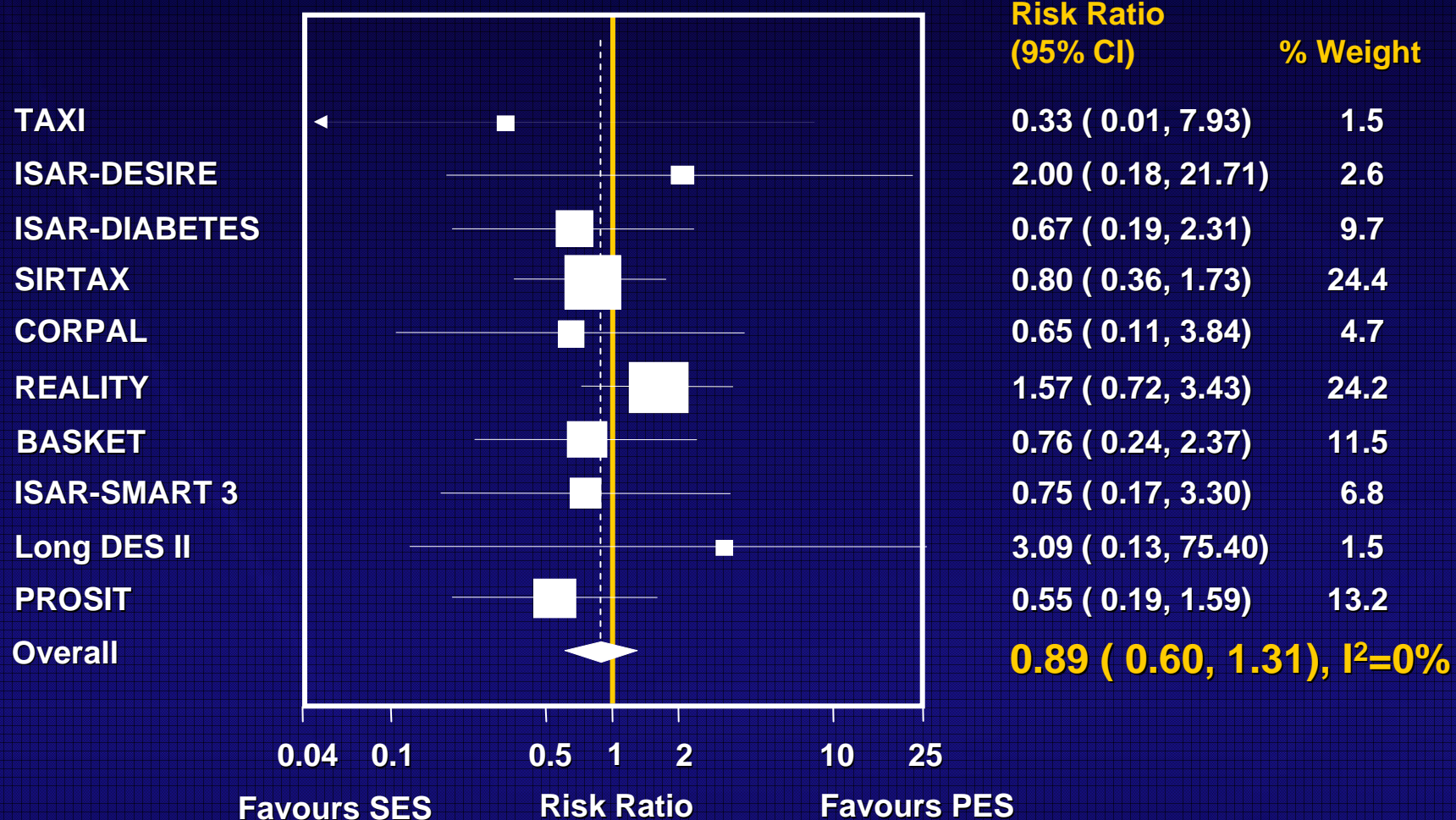
Test for Overall Effect: $p=0.001$

Adapted from Kastrati, A., et al., *JAMA* 2005; 294:819-25.

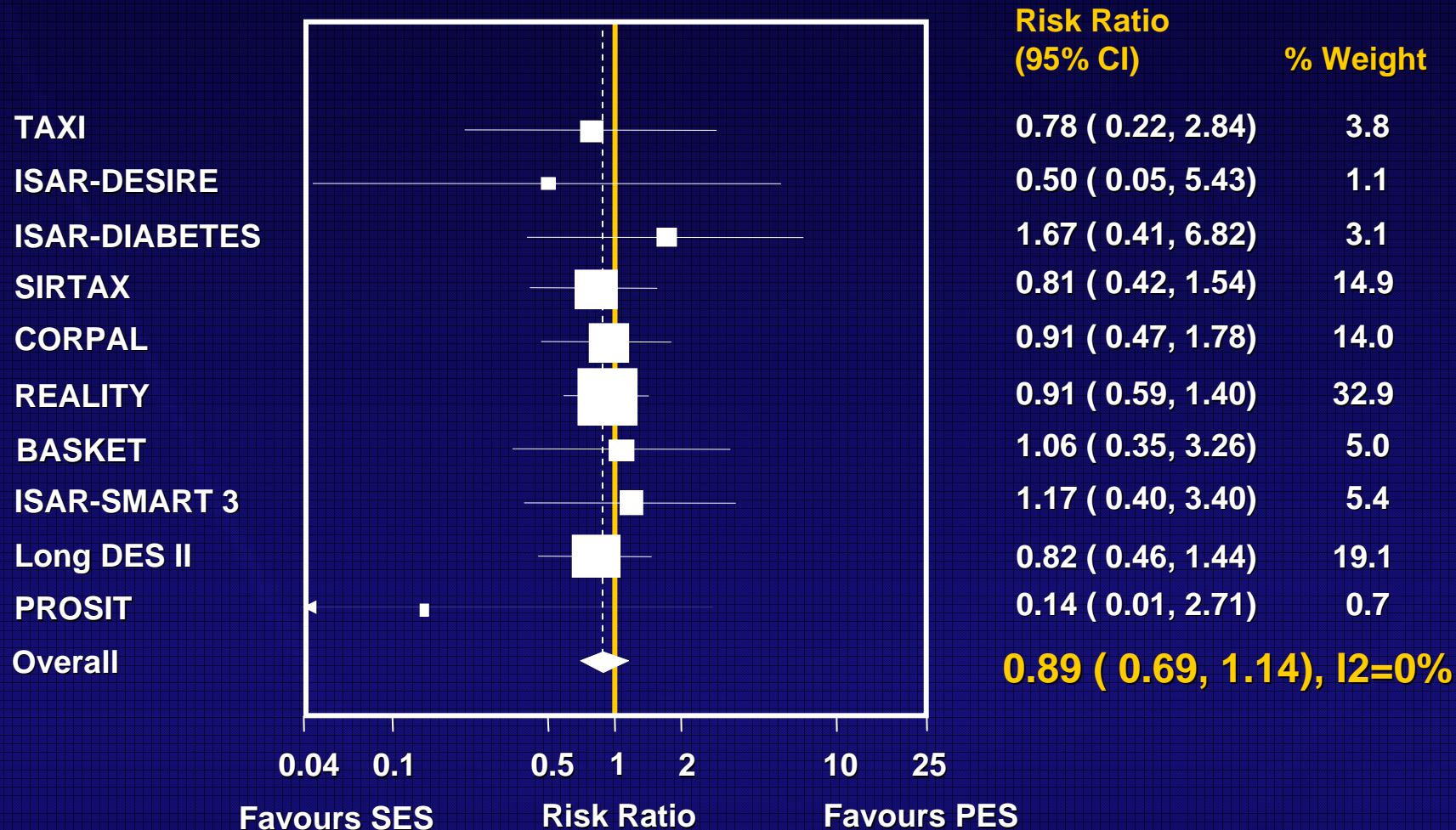
SIRPACT – Stent Thrombosis



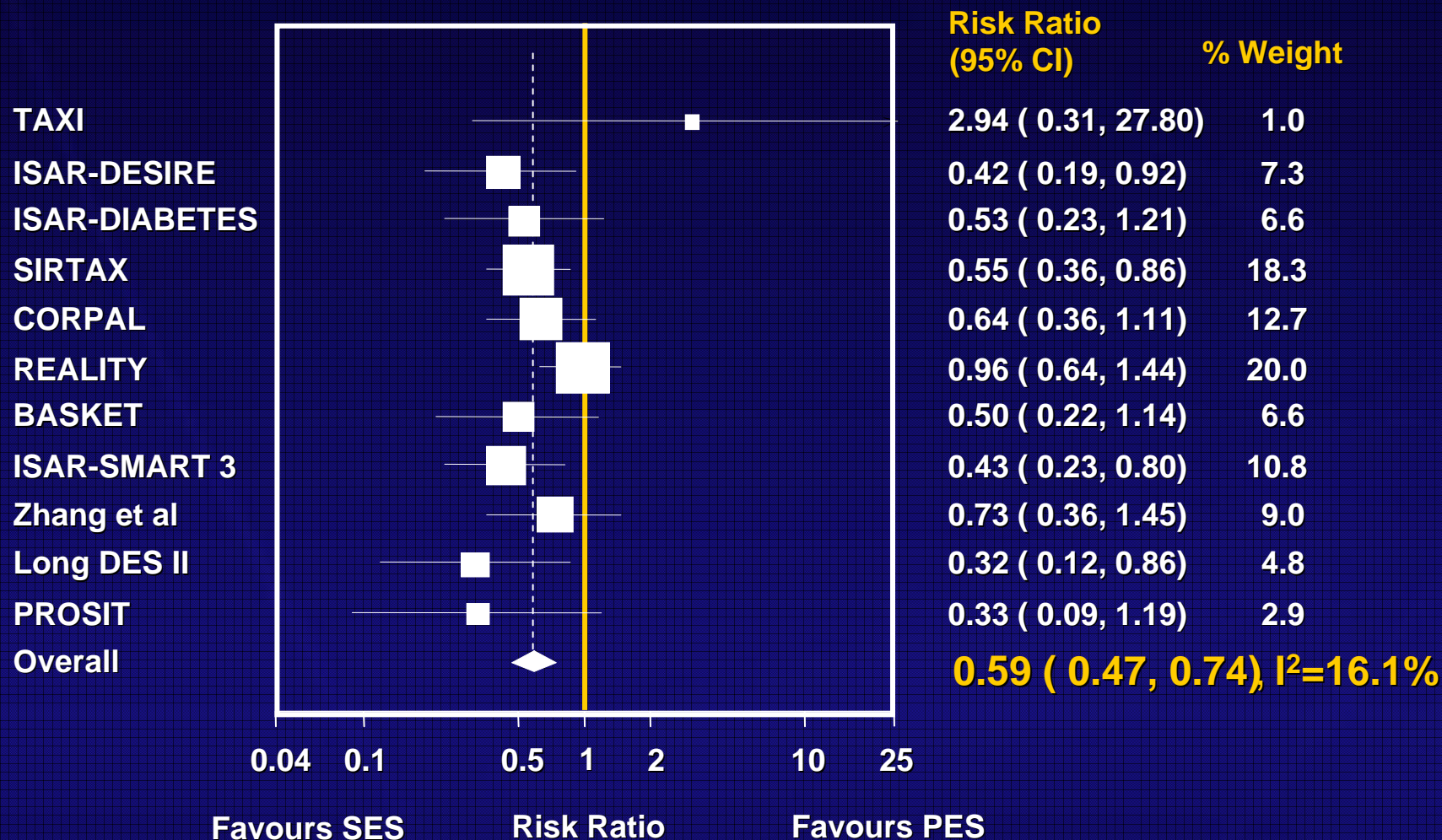
SIRPACT – Overall Mortality



SIRPACT – Myocardial Infarction



SIRPACT – Target Lesion Revascularization



Conclusions: Higher Risk Patient/Lesion Subsets



With Current Data Available to 1-year:

- CYPHER® Stent use beyond labeled indications due to unmet clinical need
- Benefit – similar to 4 RCTs
- Risk
 - higher than 4 RCTS
 - the same as with BMS
 - elevation related to higher-risk of these patient & lesion subsets
- Data on dual anti-platelet therapy insufficient to propose patient- or lesion-specific labeling in these subgroups

Plan:

- Obtain additional safety & efficacy data in these higher-risk patient/lesion subgroups including longer-term follow-up of patient outcomes

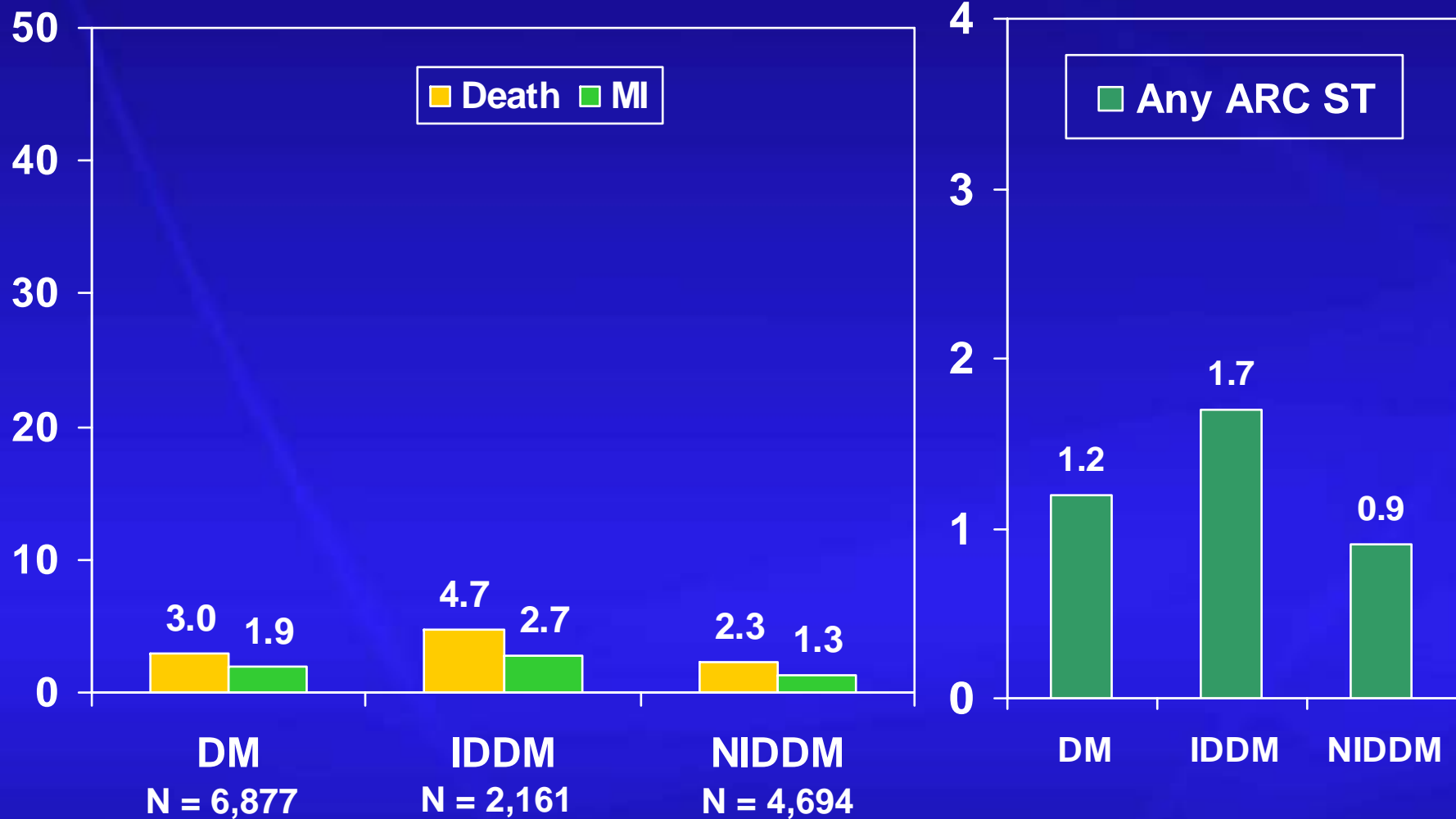
Thank You

Cordis
a Johnson & Johnson company

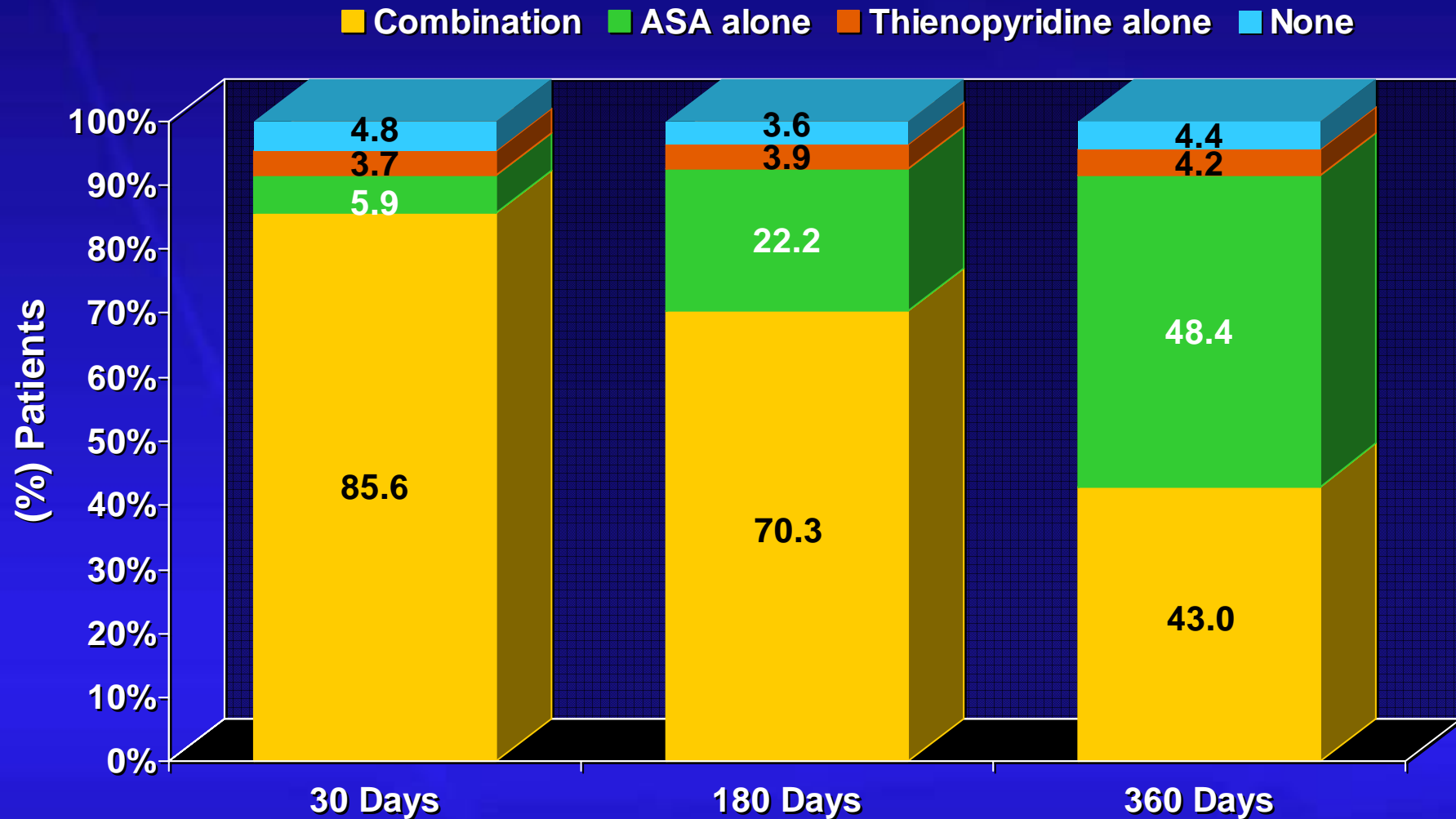
BACKUP

1-Year Follow-Up of the e-CYPHER US and OUS Registries

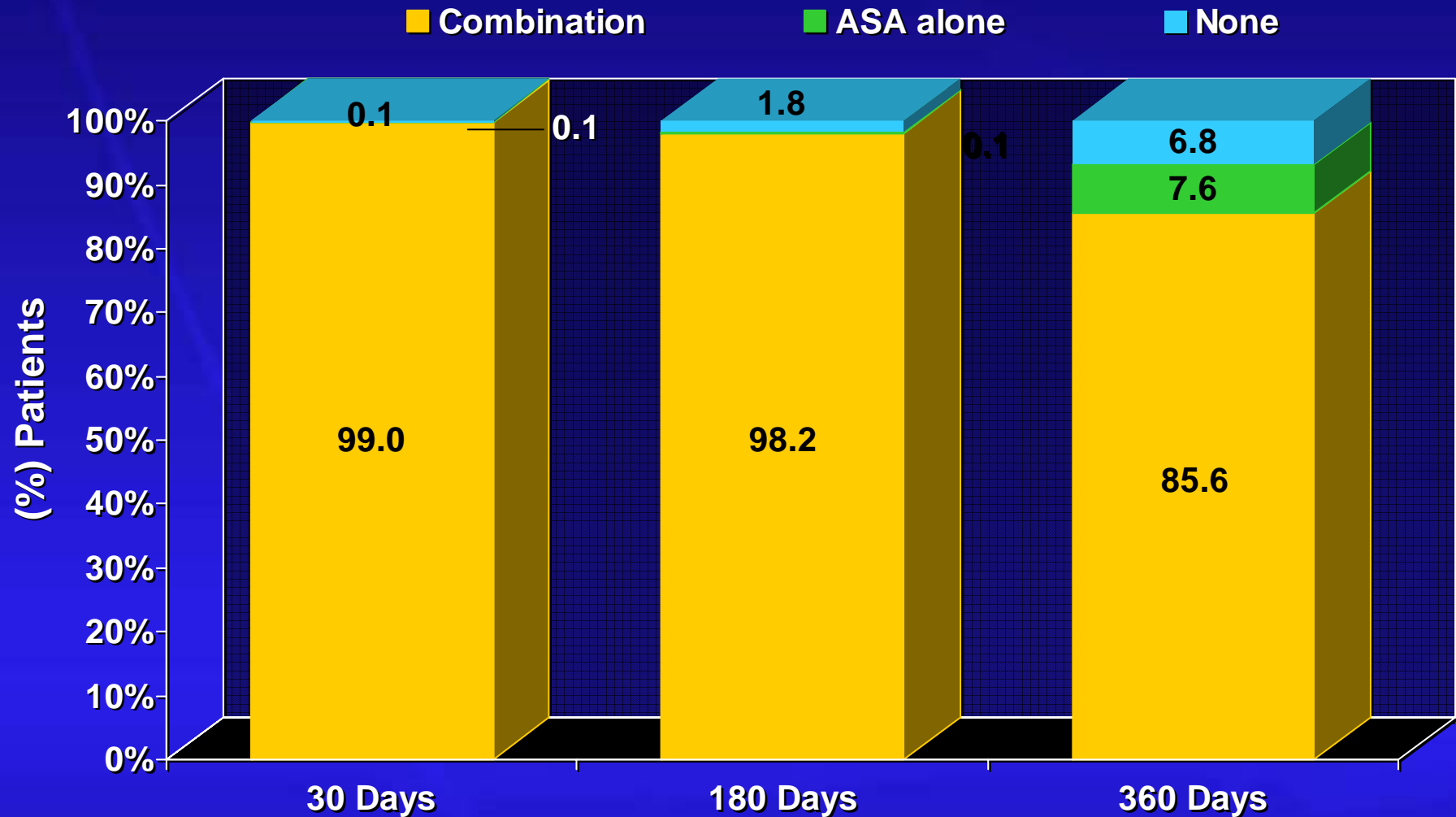
1-Year Safety Summary of Diabetic Patients Across 5 Registries



Antiplatelet Medications to 360-Day Follow-up in US e-CYPHER



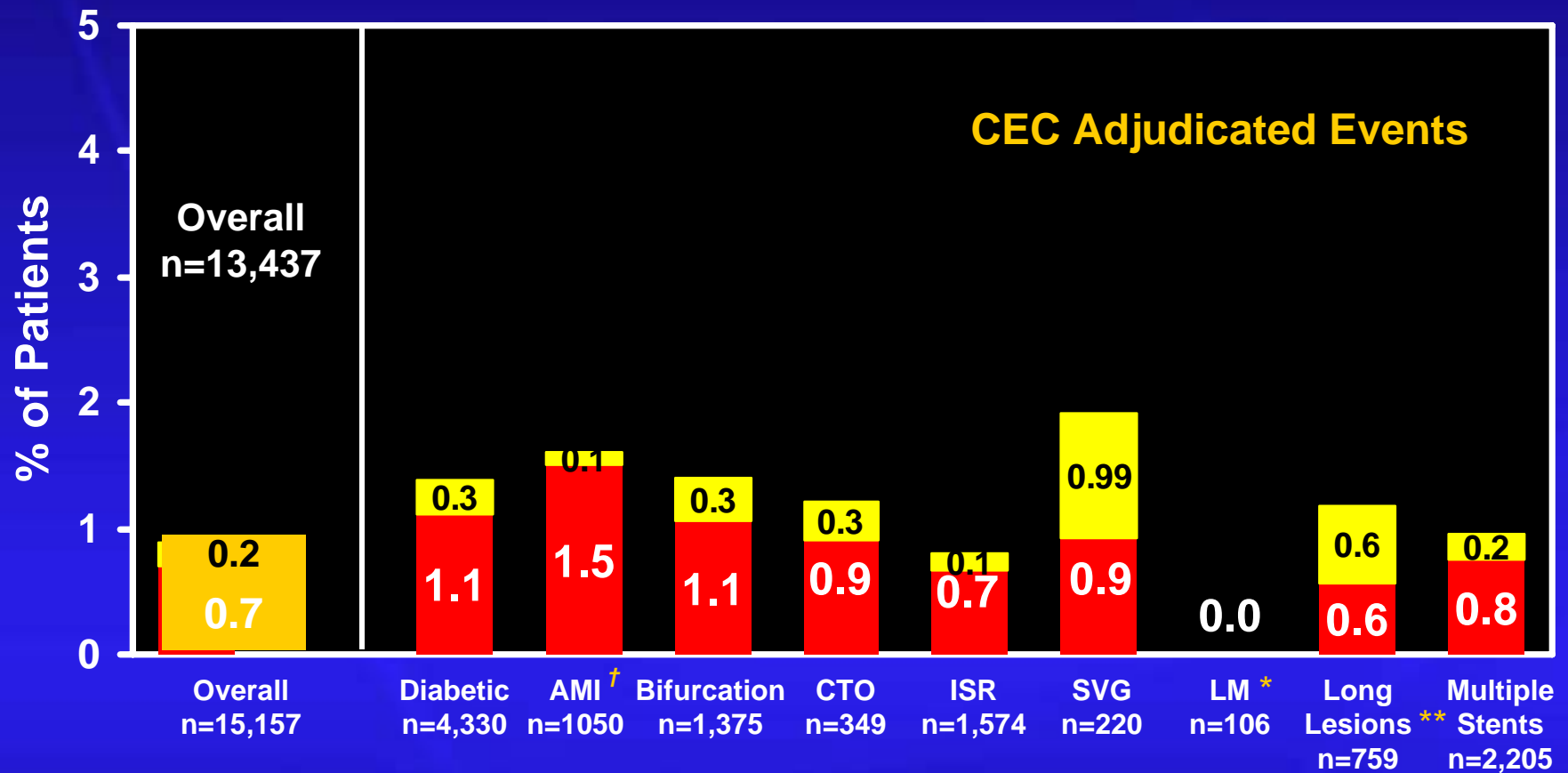
Antiplatelet Medications to 360-Day Follow-up in US e-CYPHER



Protocol Defined Stent Thrombosis: e-CYPHER-OUS Subgroup Analysis

e-CYPHER-OUS
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■ Early (<30 days) ■ Late (30 days - 1 year)



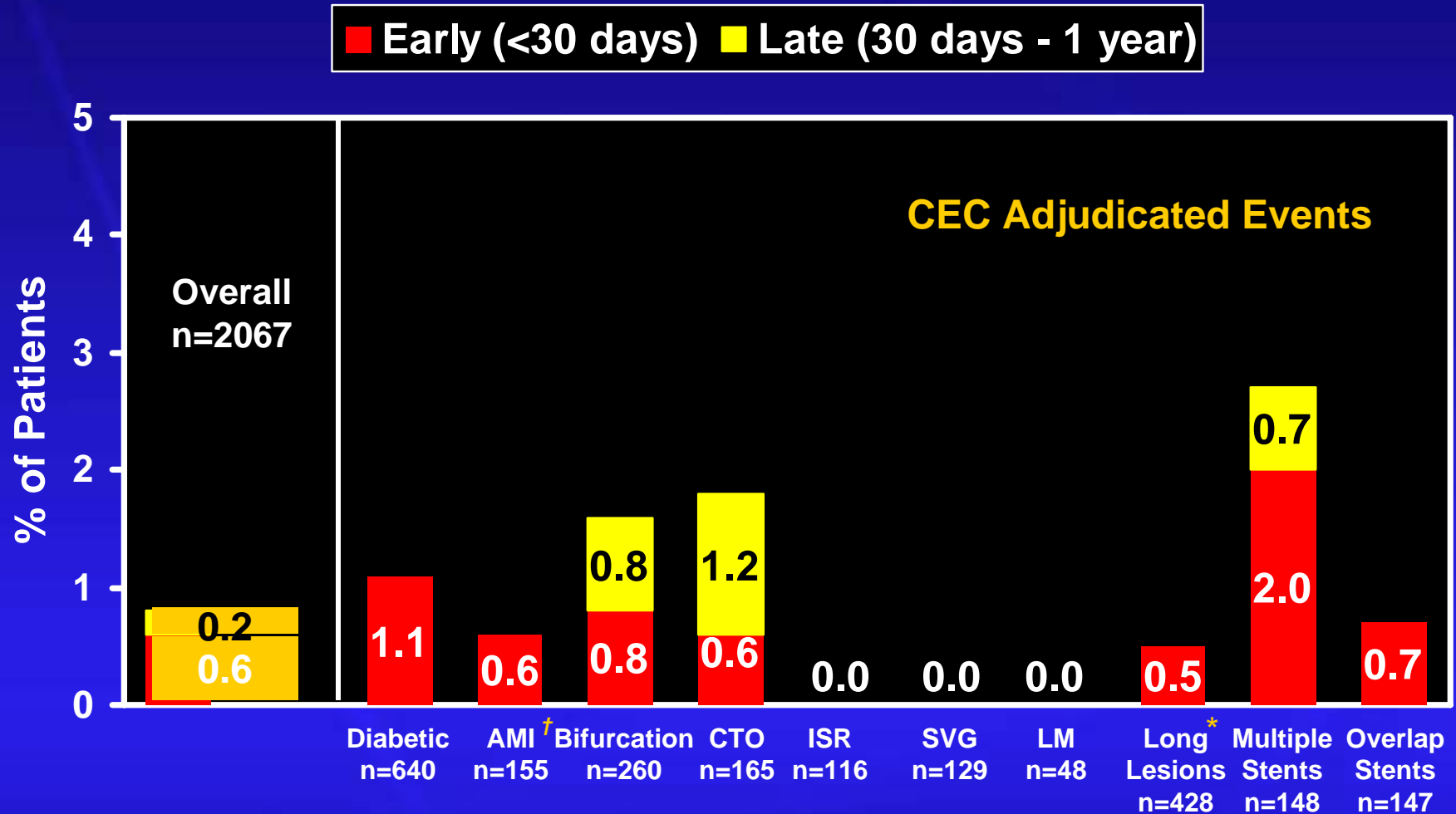
[†] AMI < 72 hours

^{*} Unprotected LM

^{**} Lesions > 30 mm

Protocol Defined Stent Thrombosis: e-CYPHER-US Subgroup Analysis

e-CYPHER-US
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[†] AMI < 24 hours

^{*} Lesions > 13.5 mm

Antiplatelet Therapy in SES vs. BMS Trials



RCTs	N-SES/N-BMS	APT	NRCTs	N-SES/ N-BMS	APT
RAVEL	120 / 118	C 2 m	Newell - AMI	156 / 150	C BMS > 1m, SES > 3m
SIRIUS	533 / 525	C 3 m	Marzocchi	872 / 3365	C/T BMS 1m, SES > 2 m
C-SIRIUS	50 / 50	C 2 m	Ge - CTO	122 / 259	C/T > 3m, BMS: 1 m
E-SIRIUS	175 / 177	C/T 2 m	Percoco - AMI	205 / 1412	C/T 3 m SES, BMS 1 m
DECODE	54/29	C \geq 3 m	Torre	100 / 100	C 3 m SES, 6 m PES
DIABETES	80 / 80	C 12 m	Iakovou (A-ostial)	32 / 50	C/T > 3m, BMS: 1 m
Pache - small	250 / 250	C \geq 6 m	Briguori - DM	100 / 122	C, SES > 2 m, BMS > 1 m
PRISON II	100/100	C \geq 6 m	Cheneau - AMI	103 / 504	C/T > 4 m
SES-SMART	129 / 128	C \geq 2 m	Chu - SVG	48 / 57	C > 6 m
BASKET	281/264	C 6 m	Devito - small	50 / 30	C/T 2 m
SCANDSTENT	163 / 159	C 12 m	Kim - Long	184 / 177	C 6 m
TYPHOON	355 / 357	C/T \geq 6 m	Kuchulakanti - CRI	76 / 153	C SES > 6 m, BMS 1 m
STRATEGY	87 / 88	C \geq 3 m	Lemos - AMI	186 / 183	C 3.7+2.1, BMS 2.1+1.5
SESAMI	160 / 160	Not Specified	Nakamura - CTO	60 / 120	T:Not specified
SCORPIUS	98 / 102	Not Specified	Park - LM	102 / 121	C SES 6m,BMS 1m, cilos SES 1m
MISSION	150/158	Not Specified	RESEARCH	112 / 118	C SES > 3 m unless complex > 6 m

Impact of Stent Deployment Techniques on Long-term Clinical Outcomes of Patients Treated with Sirolimus-eluting Stents:

Results of The Multicenter Prospective S.T.L.L.R. Trial*

Cordis

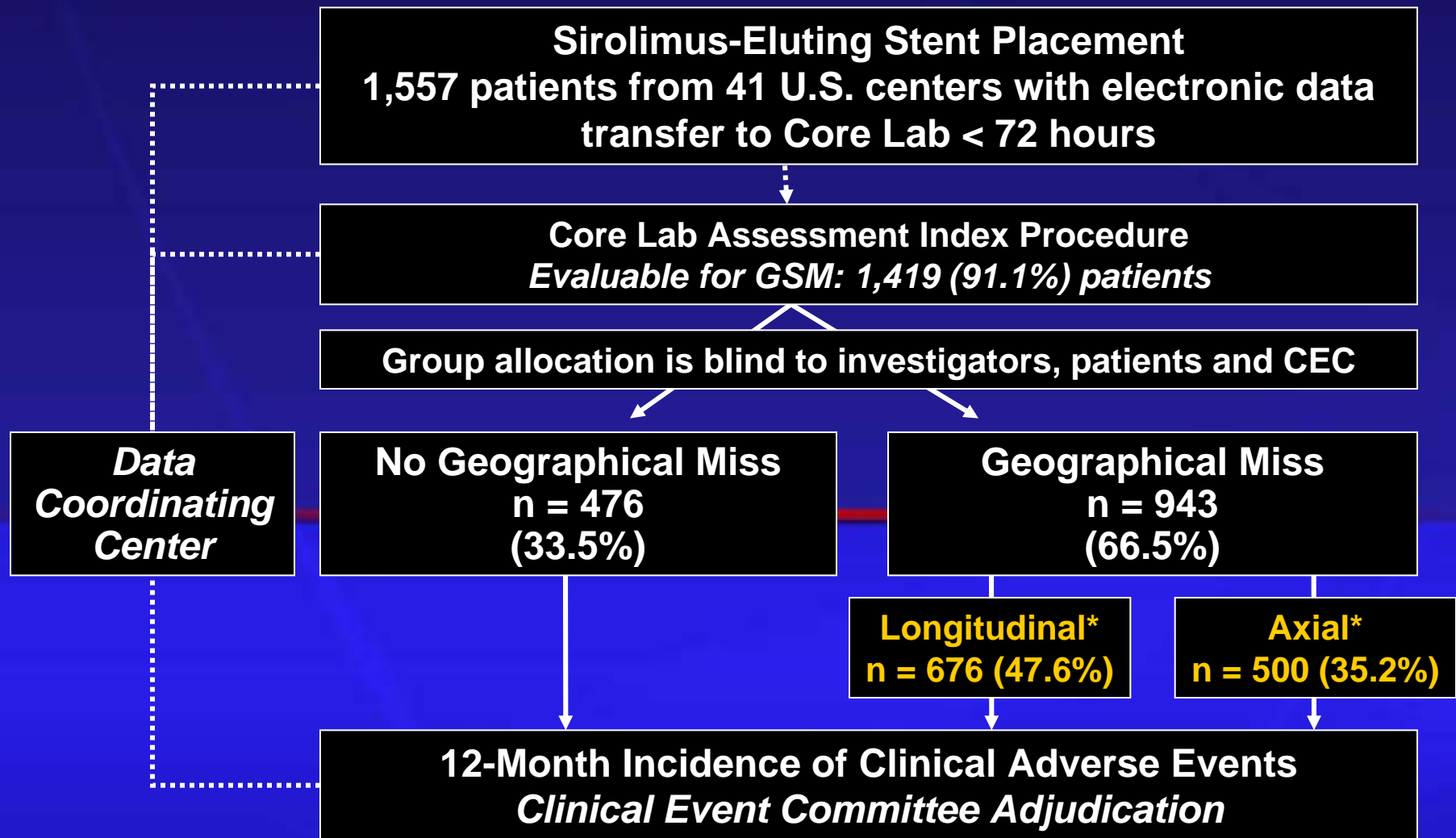
a Johnson & Johnson company

* Stent deployment Techniques on cLinical outcomes of patients treated with the cypher® stent

Hypothesis

- Patients with suboptimal SES deployment procedures, determined by the occurrence of geographic miss (GM), experience worse long-term clinical outcomes compared with patients who underwent procedures without GM

Study Flow

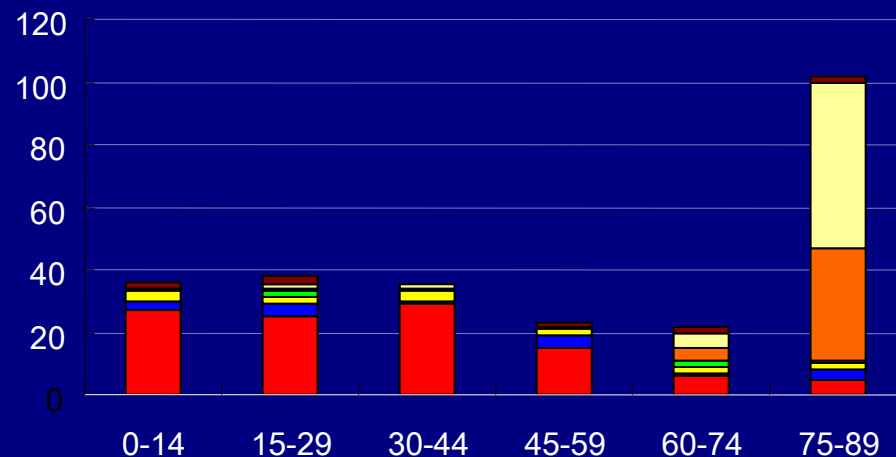


* 234 (16.5%) patients experience both types of GM

Ticlopidine Administration

Ticlopidine Discontinuation up to 3 M

■ Ticlopidine Side Effect	: 107 (8.1%)
■ Complications	: 16 (1.2%)
■ Surgical Operation	: 14 (1.1%)
■ Non-compliance/ Miss Description	6 (0.5%)
■ Judged full-term	: 40
■ Unknown/Others	: 63
■ Death	: 10

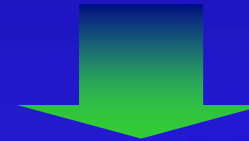


Tic. Administration Period

Ticlopidine Administration Period

Excluded: Unavoidable cases to discontinue Ticlopidine Administration

- Death/ Complications
- Side Effect by Ticlopidine
- Surgical Operation
- Non-Compliance/Miss Description



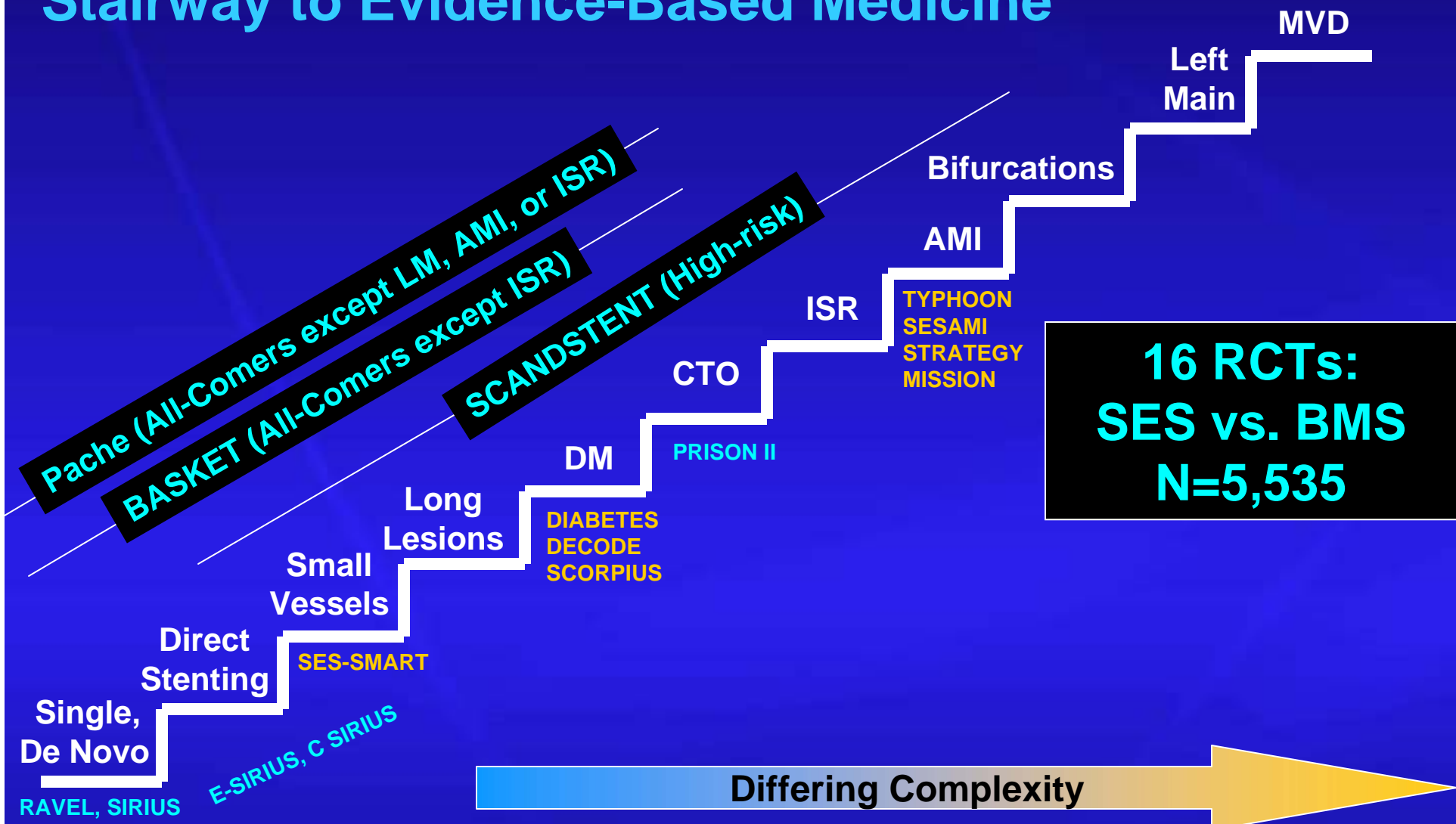
Tic. Administration	Ratio
Up to 3Months*	14.4%
Over 3Months*	85.6%

*: 90±10 days

Body of Evidence Comparing SES vs. BMS in a Randomized Fashion



Stairway to Evidence-Based Medicine



Ticlopidine Administration In J-PMS

Ticlopidine Discontinuation

Ticlopidine Administration	Tx Discontinued
Up to 3 Months*	14.4%
Over 3 Months*	85.6%

* 90±10 days

Ticlopidine Side Effect	107 (8.1%)
Complications	16 (1.2%)
Surgical Operation	14 (1.1%)
Non-compliance	6 (0.5%)

Subset Analysis From Registries

Patient types:

- Diabetic patients
- AMI Patients
- Patients with Renal Dysfunction

Lesions:

- Bifurcations (BIF)
- Chronic total occlusions (CTO)
- In-stent restenosis (ISR)
- Long lesions (>28mm, overlapping stents)
- Multiple stents – non-overlapping in a single vessel
- Multi-vessel stenting

Vessel types:

- Left main (LM)
- Saphenous vein grafts (SVG)

Multivariable Predictors

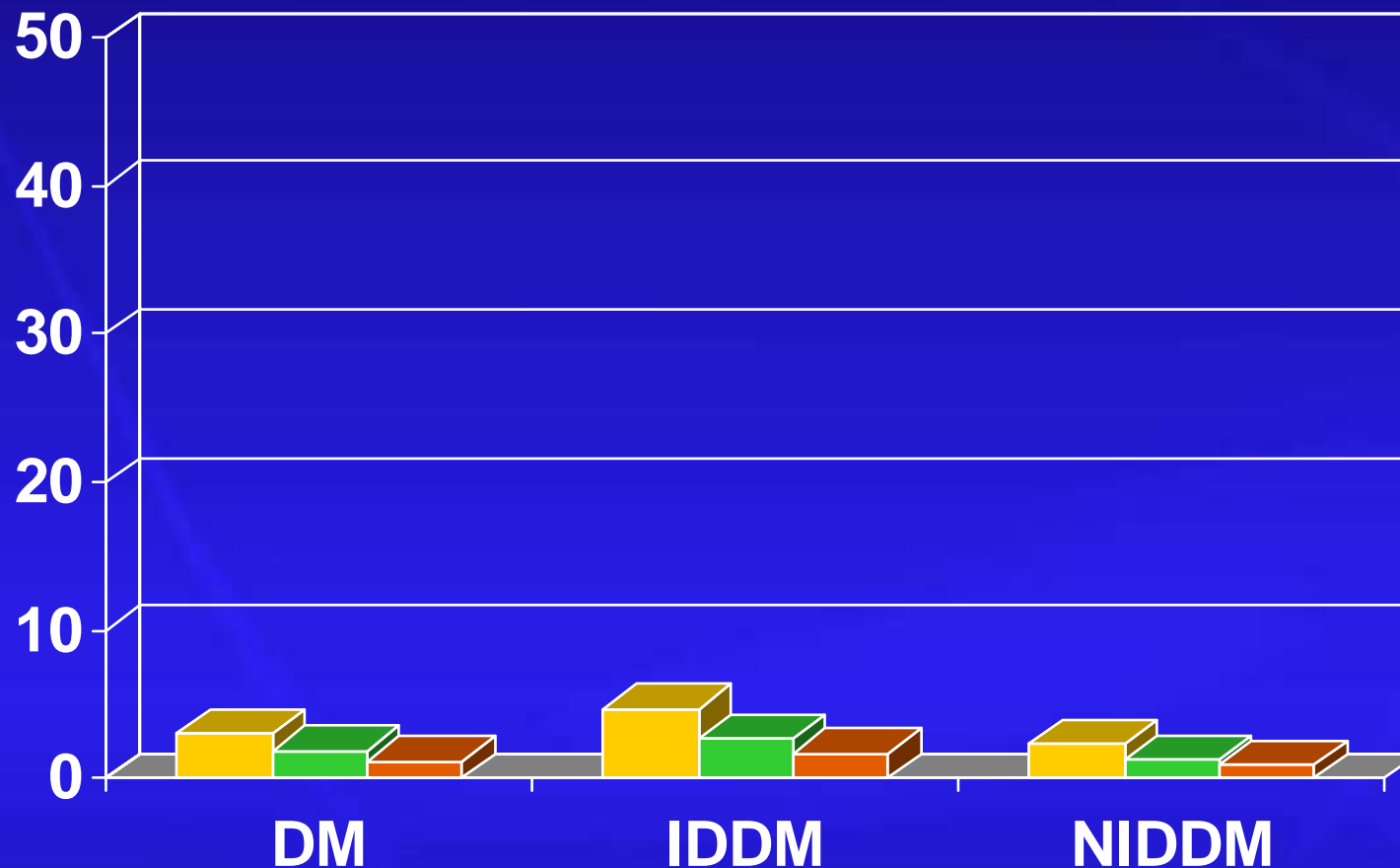
	Predictor	Coefficient	Standard Error	Odds Ratio	p-Value
ENDPOINT					
DEATH	Renal Insufficiency	1.6535	0.1591	5.23	<0.001
	Age (Years)	0.0399	0.0058	1.04	<0.001
	Acute MI	0.7228	0.1466	2.06	<0.001
	Diabetes	0.4013	0.1352	1.49	0.0030
	Male (vs. Female)	0.3393	0.1452	1.40	0.0194
ALL ARC Stent Thrombosis	Single vessel Tx with multiple non-overlapping stents	1.1771	0.3176	3.24	0.0002
	Acute MI	0.7449	0.2153	2.11	0.0005
Definite + Probable ARC Stent Thrombosis	Acute MI	0.8980	0.2287	2.45	<0.0001
	Single vessel Tx with multiple non-overlapping stents	1.1917	0.3510	3.29	0.0007
Protocol Stent Thrombosis	Acute MI	0.5544	0.1890	1.74	0.0033

Multivariable Predictors of Stent Thrombosis

	# of Pts	Type of ST	Predictor	OR (95% CI)	p-Value
ERASMUS	2,512	< 30 d	Bifurcation stenting	3.0 (1.3 to 6.8)	<0.001
Grube/ Colombo	2,229	< 9 m	Premature APT D/C	89.78 (29.90 – 269.60)	< 0.001
			Renal Failure	6.49 (2.60 – 16.15)	< 0.001
			Bifurcation	6.42 (2.93 – 14.07)	< 0.001
			Diabetes	3.71 (1.74 – 7.89)	0.001
			LVEF per 10% ↓	1.09 (1.05 – 1.13)	< 0.001
Moreno R.,	5,030	< 1 y	Stent Length	Correlation (R = 0.716)	0.031
E-CYPHER	15,157	< 1 y	IDDM	2.76 (1.71, 4.29)	< 0.0001
			ACS at PCI	1.75 (1.13, 2.67)	0.0105
			Age (per 10 yr)	1.25 (1.05, 1.50)	0.0122
			Post-PCI TIMI Flow < 3	4.42 (1.80, 9.26)	0.0003
			Moderate / Heavy Calc.	1.93 (1.29, 2.86)	0.0012
			Totally Occluded Target Artery	1.92 (1.14, 3.11)	0.0107
			No. Les. Treated	1.31 (1.01, 1.67)	0.0317
			> 1 Vessel Dis.	1.62 (1.04, 2.60)	0.0383
C/T REWARDS	2,974	< 1y	Age	0.97 (0.94 – 1.0)	0.06
			Male	0.66 (0.31-10.4)	0.27
			History of CABG	0.15 (0.01-1.2)	0.07
			Acute Renal Failure	3.75 (1.2-11.3)	0.0183
			IDDM	2.0 (0.84-4.9)	0.12
			Bifurcation	4.4 (1.96-10.0)	0.0004
			ISR	4.5 (1.8-11.4)	0.0013
			Clopidogrel D/C	0.21 (0.09-0.49)	0.0003
ASAN	1,911	< 2 y	Premature APT D/C	19.21 (5.63 – 63.51)	< 0.001
			1° Stenting for AMI	12.24 (1.67-89.71)	0.014
			Total Stent Length	1.02 (1.001-1.04)	0.037

Diabetic Patients Across 6 Registries

■ Death ■ MI ■ Any ARC Stent Thrombosis



Diabetic Patients Across 6 Registries

