

LESSON - I

Long-term comparison of Everolimus-eluting and Sirolimus-eluting Stents for cOronary revascularization

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Conflicts of Interest

- Lecture and Consultant Fees
 - Abbott
 - Astra Zeneca
 - Biosensors
 - Boston Scientific
 - Cordis
 - Edwards Lifesciences
 - Eli Lilly
 - Medtronic
 - Sanofi Aventis

Everolimus-Eluting Stent

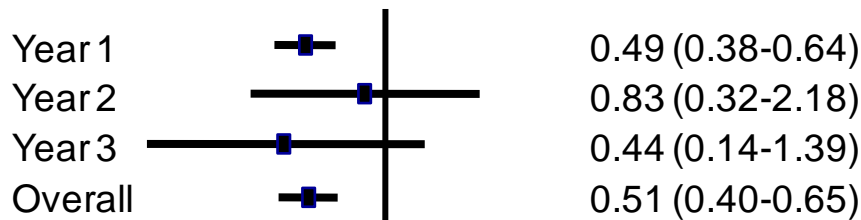
- Stent
 - Material: L605 cobalt chromium alloy
 - Strut thickness: 81 μm
- Polymer
 - Durable polymer consisting of acrylic and fluoro polymers
 - \approx 6-8 μm thick
- Drug
 - Everolimus $\text{C}_{53}\text{H}_{83}\text{NO}_{14}$, MW 958 Da
 - C40 position of sirolimus alkylated with a 2-hydroxyethyl group
 - Drug concentration: 100 $\mu\text{g}/\text{cm}^2$
 - IC 50 for FKBP 12 = 1.8-2.6 (nmol/l)(3x higher than for sirolimus)
 - Drug release
 - 80% of Everolimus during first 30 days

Comparison of Everolimus-Eluting and Paclitaxel-Eluting Stents

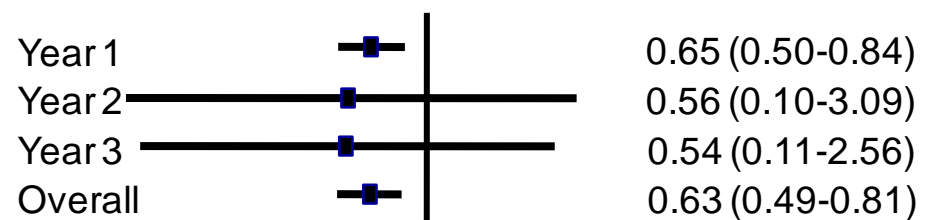
Meta-Analysis of SPIRIT II, III, IV and COMPARE

Clinical Outcomes Up to 3 Years

TLR



Cardiac Death or MI



Favors EES **Favors PES**

Favors EES **Favors PES**

6,789
Patients

LESSON I - Objective

- The therapeutic benefit of everolimus-eluting stents compared to other limus-analogues - namely sirolimus-eluting stents - in terms of safety and efficacy remains to be established
- The purpose of the present study was to compare the safety and efficacy of the unrestricted use of everolimus-eluting stents (XIENCE™) with sirolimus-eluting stents (CYPHER™) in a large, consecutively enrolled patient population followed up to 3 years in a propensity-score matched analysis

LESSON I - Patient Population

Inclusion Criteria

All consecutive patients treated with SES and EES in the setting of stable angina and acute coronary syndromes (UA, NSTEMI and STEMI) at Bern University Hospital were eligible

Diameter stenosis $\geq 50\%$

Number of lesions: no limitation

Number of vessels: no limitation

Lesion length: no limitation

Written informed consent


Exclusion Criteria

Patients with SES implanted prior to April 2003 due to clopidogrel prescription of 3 instead of 12 months

Patients with SES included into the SIRTAX trial in view of mandatory angiographic follow-up

LESSON I - Sample Size Calculation

Primary Endpoint

- Composite of death, MI and TVR through 3 years
- Relative risk assumption of 0.75 in favour of **EES** compared with **SES** based on
 - Meta-analysis comparing **EES** vs **PES** (RR=0.60)
 - Network meta-analysis comparing **SES** vs **PES** (RR=0.80)
- Expected event rate = 18% @ median f/u 1.5 years
- 1400 matched patients  90% power

Secondary Endpoints

- Death, MI, TLR, TVR
- Cardiac death or MI
- Stent thrombosis according to ARC

LESSON I – Patient Flow

3133 Patients Undergoing PCI

Everolimus Eluting Stent
1601 Consecutive Patients
Nov 2006 – March 2009

Sirolimus Eluting Stent
1532 Consecutive Patients
May 2004 – Jan 2006

After Propensity Score Matching
2684 Patients Undergoing PCI

Everolimus Eluting Stent
1342 Matched Patients

Sirolimus Eluting Stent
1342 Matched Patients

2221 Patient-Years

Clinical Follow-up
Median 1.3 Years
(1.0 - 2.2 Years)

2238 Patient-Years

LESSON I – Antithrombotic Drug Regimen

Pre or during procedure

Acetylsalicylic acid: ≥ 100 mg

Clopidogrel: 300-600 mg loading dose

Unfractionated heparin

– Bolus of at least 5000 IU i.v. or 70 IU/kg

Glycoprotein IIb/IIIa antagonists

– Operator discretion

Post procedure

Acetylsalicylic acid: 100 mg/d indefinitely

Clopidogrel 75 mg/d for 12 months

LESSON I – Patient Characteristics

Before Propensity Score Matching (N=3133)

	Everolimus Stent 1601 Patients	Sirolimus Stent 1532 Patients	P
Age	65±12	63±11	<0.001
Male sex, %	76	78	0.16
Body mass index	27±5	27±4	0.66
Diabetes mellitus, %	18	18	0.76
Hypertension, %	60	54	<0.01
Hypercholesterolemia, %	54	50	0.02
Current smoking, %	28	32	0.01
Family History of CAD, %	29	27	0.30
Indication			<0.001
stable angina	44	45	
unstable angina	7	4	
NSTEMI	33	30	
STEMI	16	21	
Cardiogenic shock	2	1	<0.01

LESSON I – Patient Characteristics

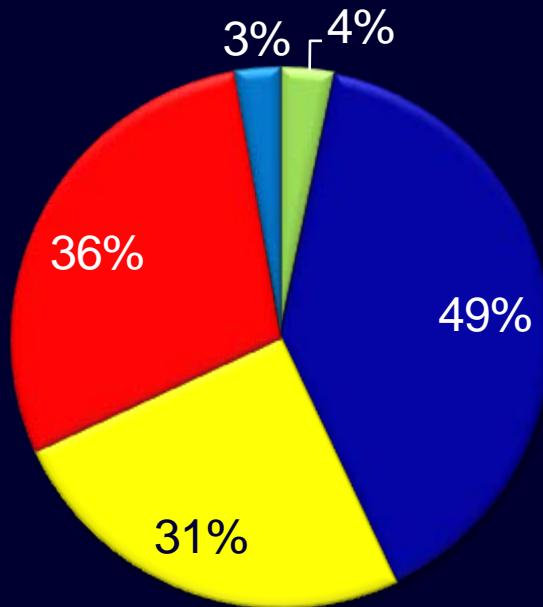
After Propensity Score Matching (N=2684)

	Everolimus Stent 1342 Patients	Sirolimus Stent 1342 Patients	P
Age	64±12	64±11	0.62
Male sex, %	78	78	0.72
Body mass index	27±5	27±4	0.72
Diabetes mellitus, %	17	18	0.72
Hypertension, %	56	55	0.94
Hypercholesterolemia, %	51	53	0.33
Current smoking, %	30	32	0.48
Family History of CAD, %	29	27	0.25
Indication			0.009
stable angina	48	45	
unstable angina	3	5	
NSTEMI	30	31	
STEMI	19	20	
Cardiogenic shock	2	1	0.08

LESSON I – Target Lesion Distribution

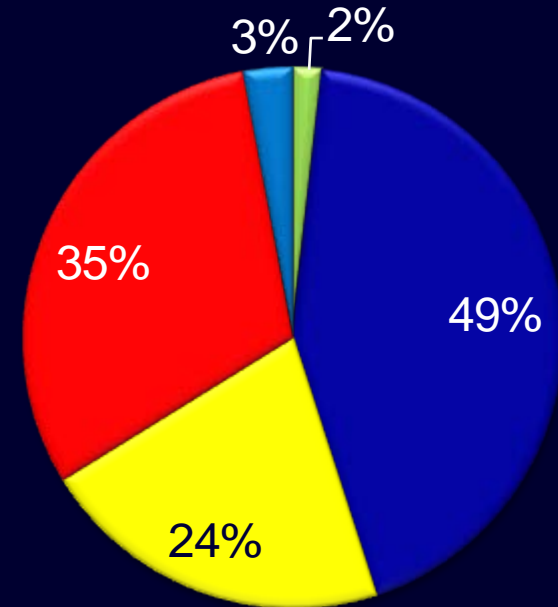
After Propensity Score Matching (N=2684)

Everolimus Eluting Stent
N=1342



■ LM
■ LAD
■ LCX
■ RCA

Sirolimus Eluting Stent
N=1342



■ LM
■ LAD
■ LCX
■ RCA

LESSON I – Procedural Characteristics

After Propensity Score Matching (N=2684)

	Everolimus Stent 1342 Patients	Sirolimus Stent 1342 Patients	P
Multivessel treatment, %	24	16	<0.001
Number of vessels per patient	1.3 ± 0.5	1.2 ± 0.4	<0.001
Number of lesions per patient	1.8 ± 1.0	1.5 ± 0.7	<0.001
1 lesion, %	52	63	
2 lesions, %	29	27	
3 lesions, %	13	9	
4 lesions, %	6	2	
Number of stents per patient	2.0 ± 1.1	1.8 ± 0.9	<0.001
Stent diameter (mm)	2.9 ± 0.4	2.9 ± 0.4	0.001
Stent length per patient (mm)	31.4 ± 19.4	32.7 ± 19.0	0.07
Maximal inflation pressure (atm)	14.7±4.0	14.9±4.2	0.28

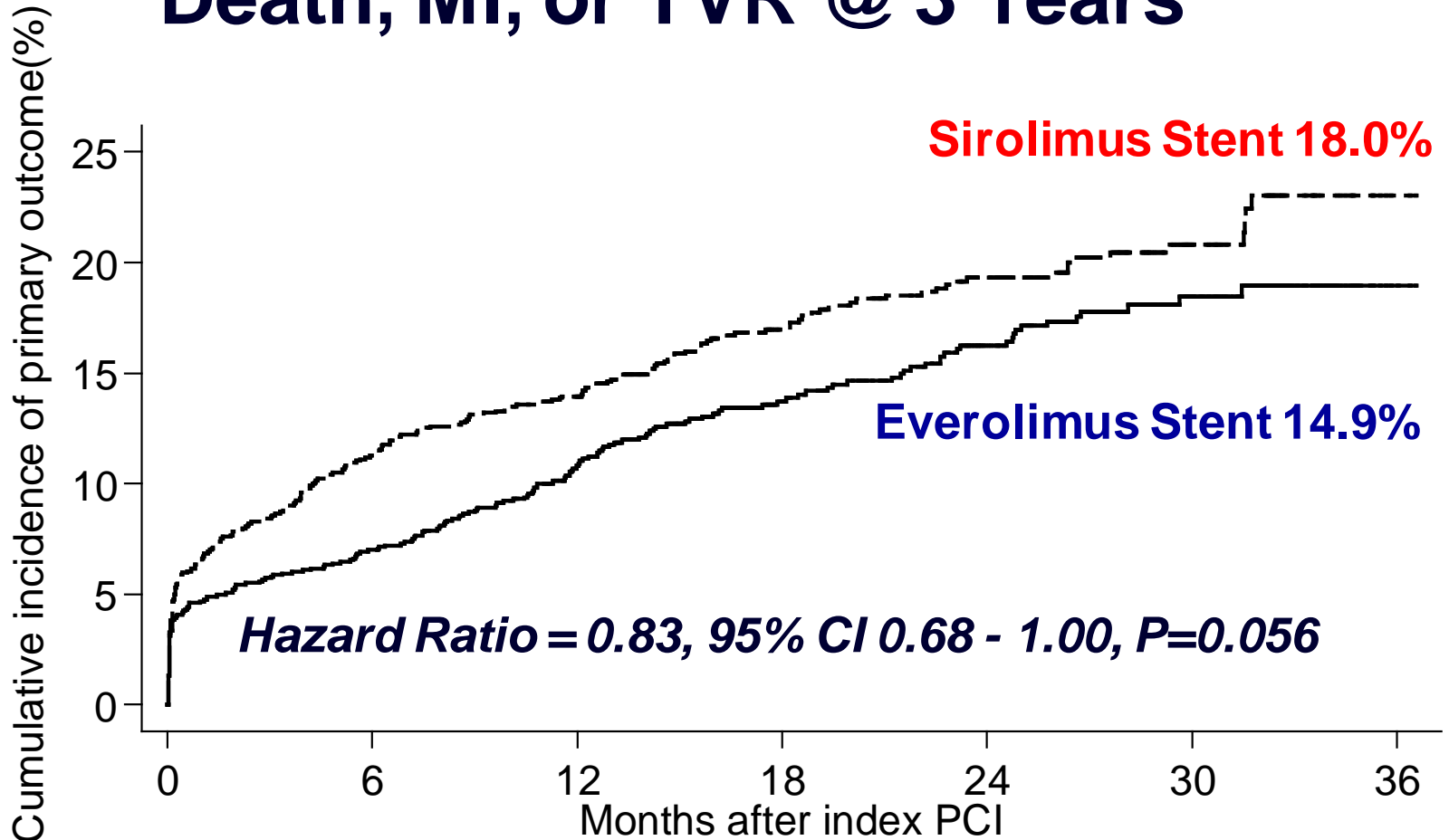
LESSON I – Medication at Discharge

After Propensity Score Matching (N=2684)

	Everolimus Stent 1342 Patients	Sirolimus Stent 1342 Patients	P
Acetylsalicylic Acid, %	98	97	0.06
Clopidogrel, %	98	96	0.07
Oral Anticoagulation, %	1.4	2.0	0.23
Betablocker, %	64	61	0.14
ACE Inhibitor, %	52	54	0.20
AT II Inhibitor, %	14	16	0.23
Calcium Antagonist, %	8.8	9.9	0.32
Statin, %	83	86	0.06
Oral Antidiabetics, %	10	10	0.84
Insulin, %	6.1	6.0	0.91
Diuretics, %	18	19	0.43
Proton Pump Inhibitor, %	20	19	0.33

Lesson I - Primary Endpoint

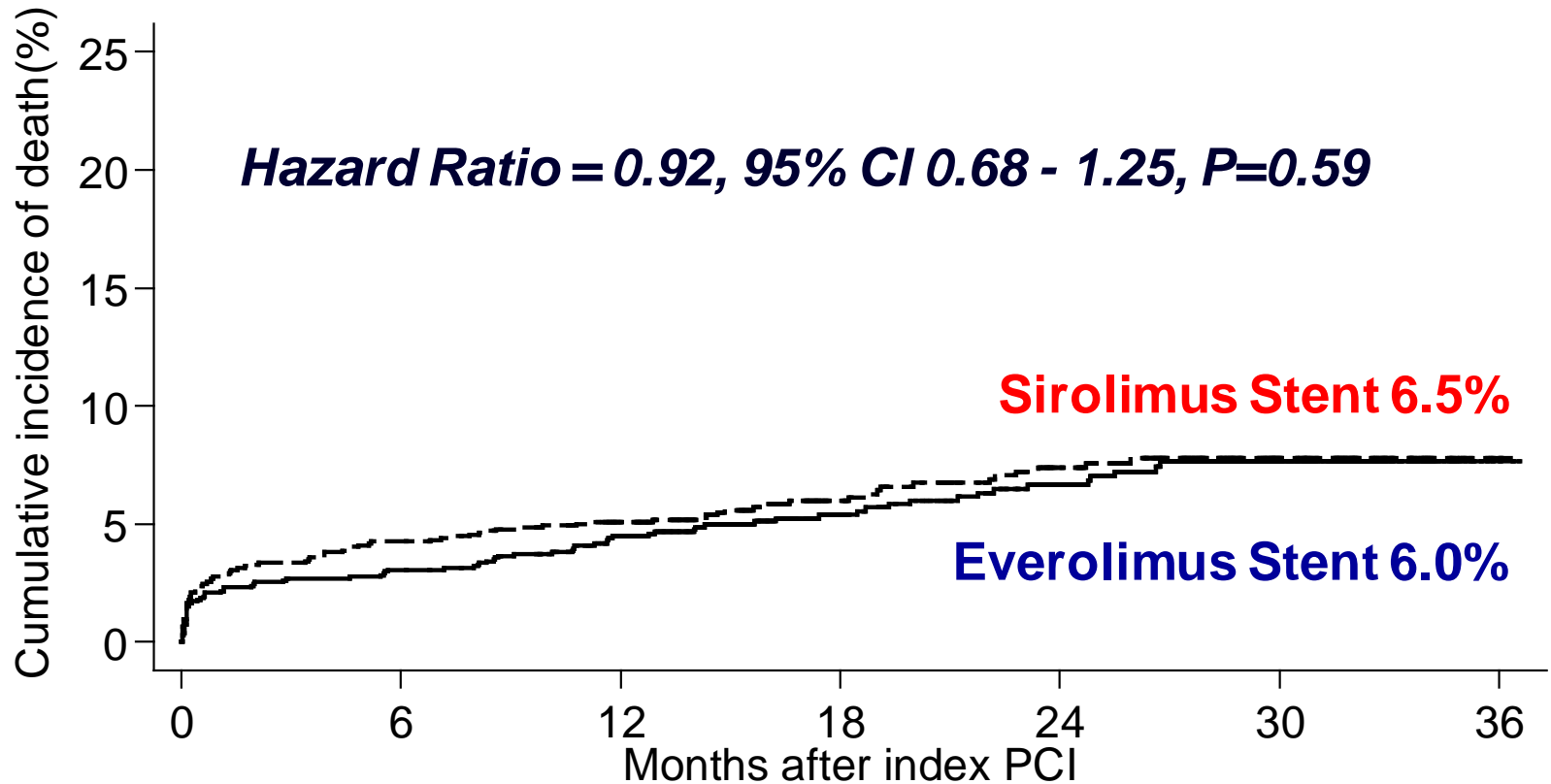
Death, MI, or TVR @ 3 Years



No. at risk

EES	1342	1247	1156	571	492	209	27
SES	1342	1188	1112	555	469	198	24

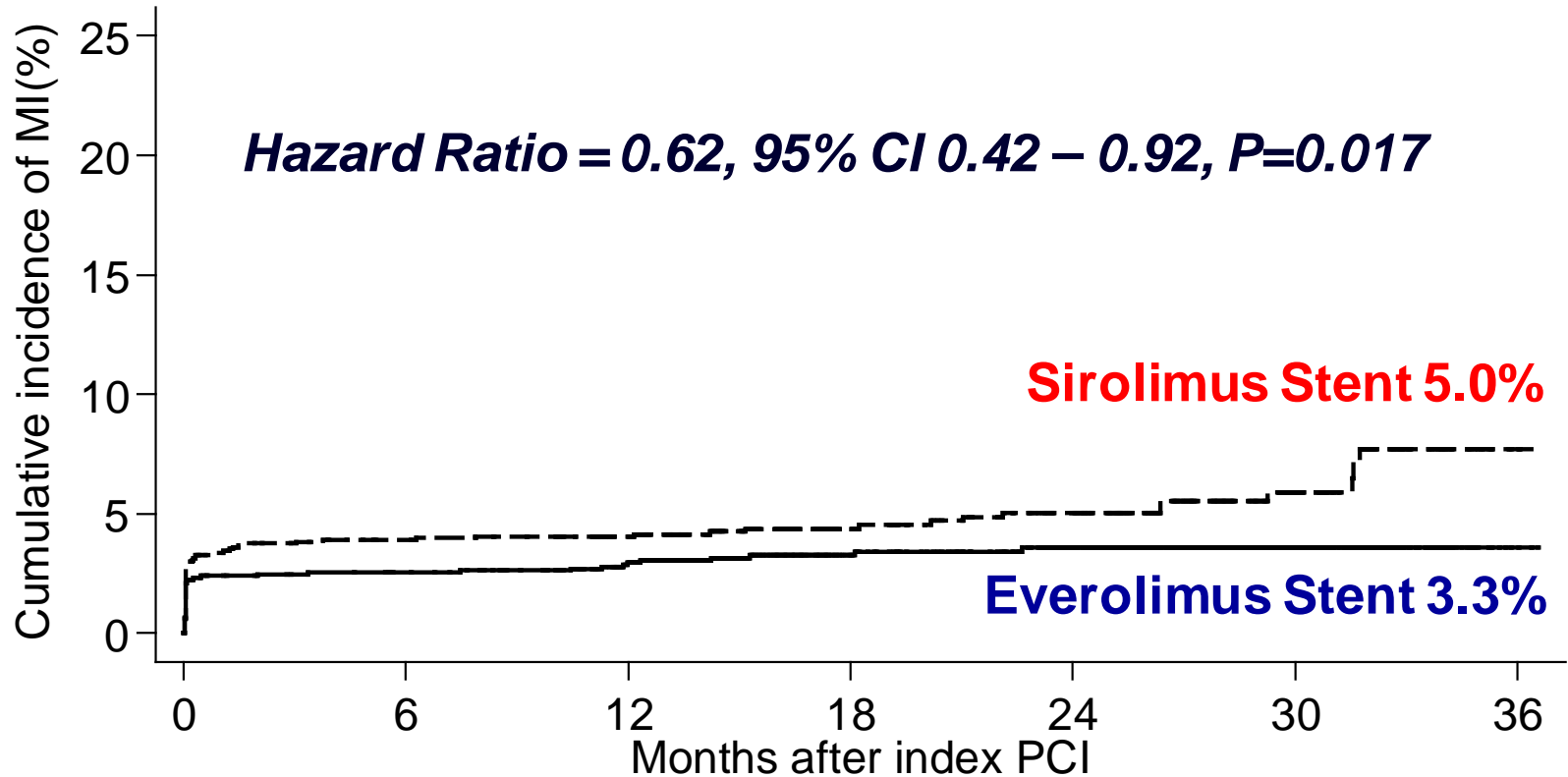
Lesson I – All Cause Mortality @ 3 Years



No. at risk

EES	1342	1299	1237	621	544	227	29
SES	1342	1283	1226	626	537	229	28

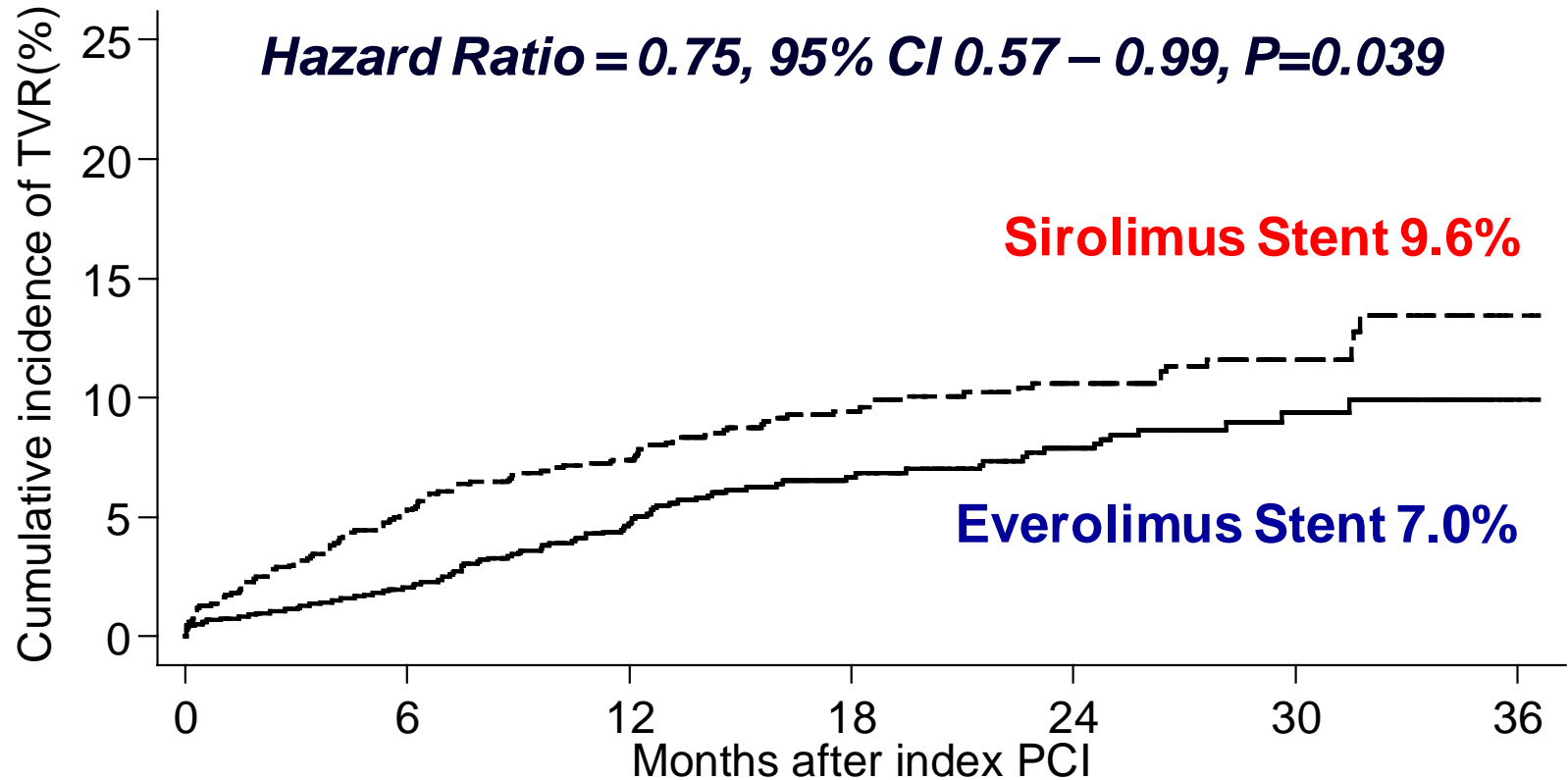
Lesson I – Myocardial Infarction @ 3 Years



No. at risk

EES	1342	1271	1205	603	525	221	29
SES	1342	1235	1182	599	509	217	26

Lesson I – Target Vessel Revascularization



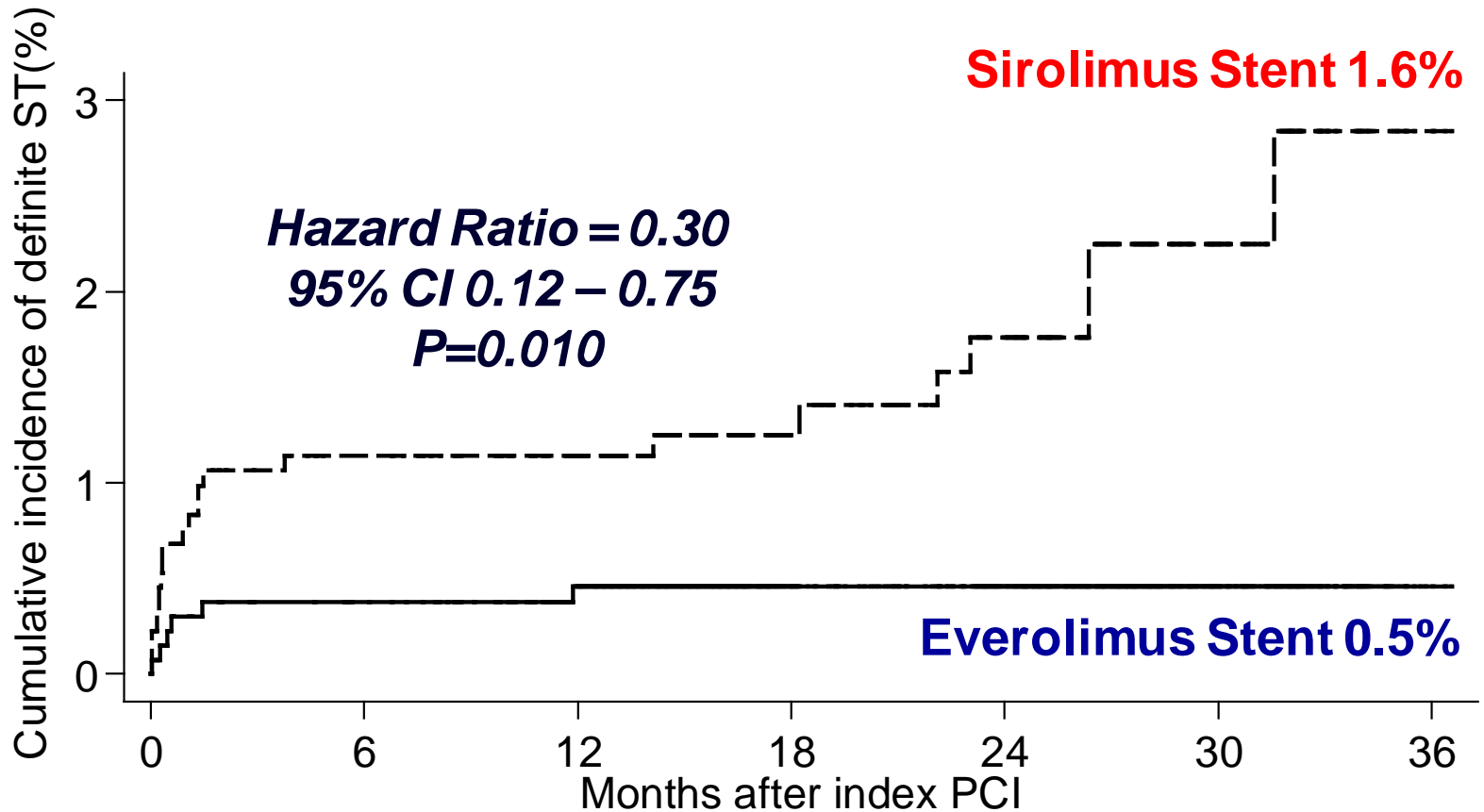
No. at risk

EES	1342	1273	1181	583	504	211	27
SES	1342	1219	1140	571	483	203	25

LESSON I – Clinical Outcome @ 3 Years

	Everolimus Stent 1342 Patients	Sirolimus Stent 1342 Patients	P
Death	6.0%	6.5%	0.59
Cardiac death	3.9%	4.4%	0.51
Myocardial infarction	3.3%	5.0%	0.017
NQWMI	2.8%	3.1%	0.43
QWMI	0.5%	1.6%	0.010
Cardiac death or MI	6.8%	8.9%	0.030
Death or MI	8.9%	10.8%	0.08
Cardiac death, MI or TVR	12.7%	16.2%	0.025
Death, MI, or TVR	14.9%	18.0%	0.056

Lesson I – Definite Stent Thrombosis @ 3 Years



No. at risk

EES	1342	1296	1234	620	543	226	29
SES	1342	1271	1216	619	527	223	28

LESSON I - Stent Thrombosis Through 3 Years

	Everolimus Stent 1342 Patients	Sirolimus Stent 1342 Patients	P
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Definite Stent Thrombosis

Early	0.3%	0.8%	0.12
Late	0.2%	0.4%	0.42
Very late	0%	0.7%	0.007
Overall	0.5%	1.6%	0.010

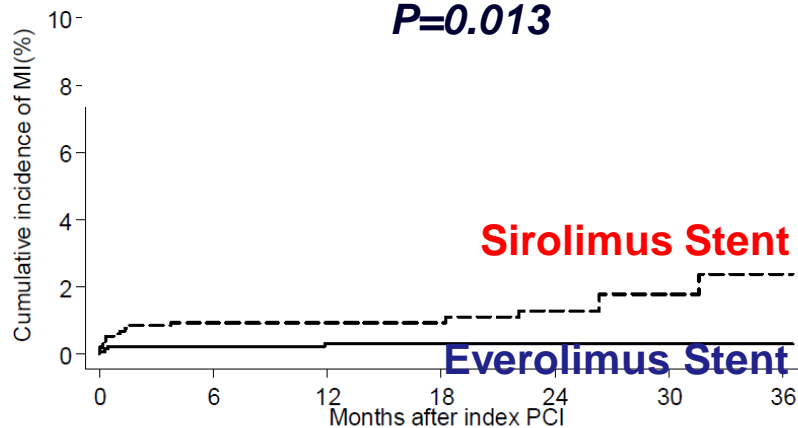
Definite or Probable Stent Thrombosis

Early	2.3%	3.1%	0.20
Late	0.2%	0.4%	0.42
Very late	0%	0.7%	0.007
Overall	2.5%	4.0%	0.041

Association of Myocardial Infarction With Definite Stent Thrombosis

MI associated with ST

Hazard Ratio = 0.25
95% CI 0.08 – 0.75
P=0.013

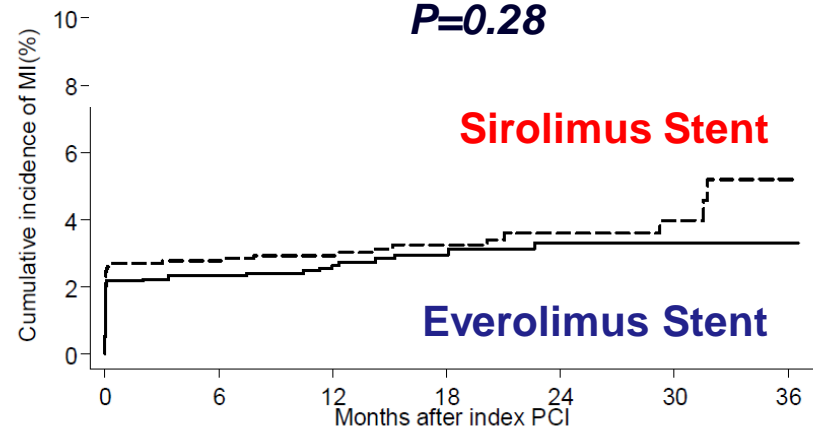


No. at risk

EES	1342	1271	1205	603	525	221	29
SES	1342	1235	1182	599	509	217	26

MI not associated with ST

Hazard Ratio = 0.79
95% CI 0.51 – 1.21
P=0.28



No. at risk

EES	1342	1271	1205	603	525	221	29
SES	1342	1235	1182	599	509	217	26

Limitations

- *Non-randomized observational study*
 - Propensity score matching to minimize bias
- *Patients treated with EES were more complex as compared to patients treated with SES*
 - Sensitivity analysis adjusted for procedural characteristics showed robust results
 - Death, MI, or TVR: HR=0.78, 95% CI 0.63-0.97, P=0.029
- *Sequential enrolment period for patients treated with SES and EES*
 - Treatment protocols and medication regimen at a single institution did not change significantly
 - Minimizes the potential of confounding by indication

Conclusions

- In this observational, propensity-score matched study, the unrestricted use of EES was associated with a lower risk of myocardial infarction, target vessel revascularization and stent thrombosis compared with SES during long-term follow-up to three years.
- Differences in rates of myocardial infarction were driven by a 70% lower risk of QWMI and were observed early and continued to increase during long-term follow-up.
- The lower risk of myocardial infarction in favour of EES was explained in part by the lower risk of definite stent thrombosis.
- These results require confirmation in large scale randomized clinical trials.

Clinical Implications

- DES efficacy can be further advanced beyond the level of the previous gold-standard of SES without compromising, but even improving their safety profile.
- The phenomenon of very late ST - the principal limitation of early generation DES - may be less frequent with EES.
- Our results suggest that the lower rate of MI was driven at least in part by a lower risk of ST. This has important implications for the duration of dual antiplatelet therapy.