Four-Year Follow-up of Sirolimus-eluting Stents in Comparison with Bare Metal Stents: A Pooled Safety Analysis of the RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS Trials in 1,748 Patients

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On behalf of

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No conflict of interest to declare

Independent physician-directed meta-analysis

Camenzind

RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS N = 1748	Camenzind		
	Cypher	Control	P-value
Death total	4.7%	3.3%	0.18
Q-MI	1.6%	0.6%	0.06
Non-Q-MI	-	-	-
Death total and Q-MI	6.3%	3.9%	0.03
Death total and all MI	-	-	-

New era of awareness:

Independent physician-directed meta-analysis

versus

Independent physician-assessed patient level meta-analysis

- Pooled analysis performed by Cordis at the request of 2 trialists (CS and PWS)
  Data management performed by 2 independent central research organizations (Cardialysis, Rotterdam, NL, for RAVEL trial, and by Harvard Clinical Research Institute, Boston, MA, USA for the SIRIUS, E-SIRIUS and C-SIRIUS studies)
- Clinical events adjudicated by independent clinical event committees.
- Patient based data transferred to two independent academic statisticians for verification (Drs J. Massaro, Harvard Clinical Research Institute, Boston, MA and H. Boersma, Erasmus University Medical Center, Rotterdam, NL).
- Re-adjudication of stent thromboses by HCRI according to (Washington/Dublin) ARC definitions

MACE rates indi al d ooled data
H & Card men d

RAVEL, S			40 days
E-SIRIUS,			
SIRIUS			
			0.22
			0.26
			0.57
		6.1%	0.13
		11.4%	10.1%	0.40
MI			

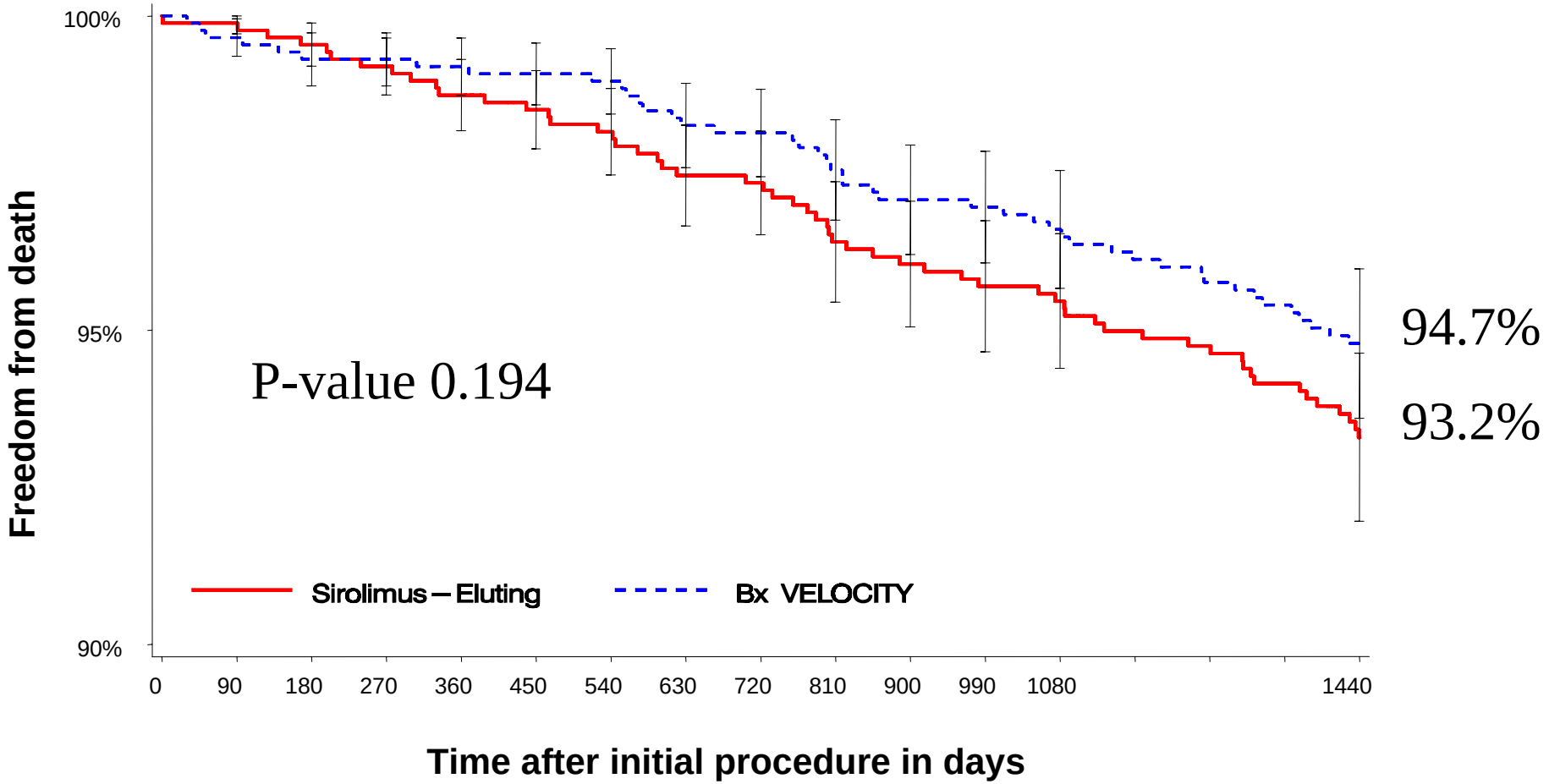
Although not completely correct from a methodological point of view, the Camenzind's report at ESC became a wake up call for everybody (device industry, PI's, CRO's, EMEA and FDA)

ependent physician-directed meta-analysis

versus

Ind pendent physician-assessed patient level meta-analysis

KM all-cause mortality

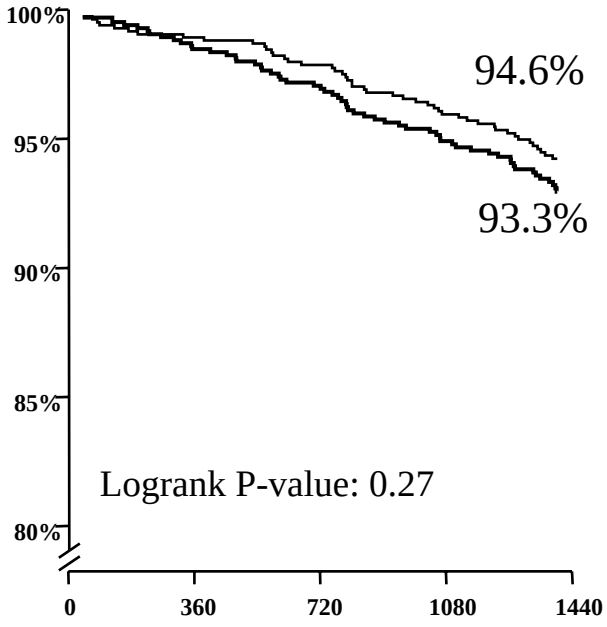


- Subsequent exploratory analyses were performed to evaluate possible heterogeneities in treatment effects on mortality according to the trial-of-enrolment and the following clinically relevant characteristics : age ,gender, diabetes, dyslipidemia,hypertension,prior MI,heart failure,CCS angina,number of diseased vessels and left ventricular ejection fraction.
  Treatment effect were evaluated by Cox'PH regressions that included a characteristic times allocated treatment interaction term with adjustment for between-trial outcome difference.
  Extensive regression models were applied to estimate adjusted treatment effects.

All-cause death

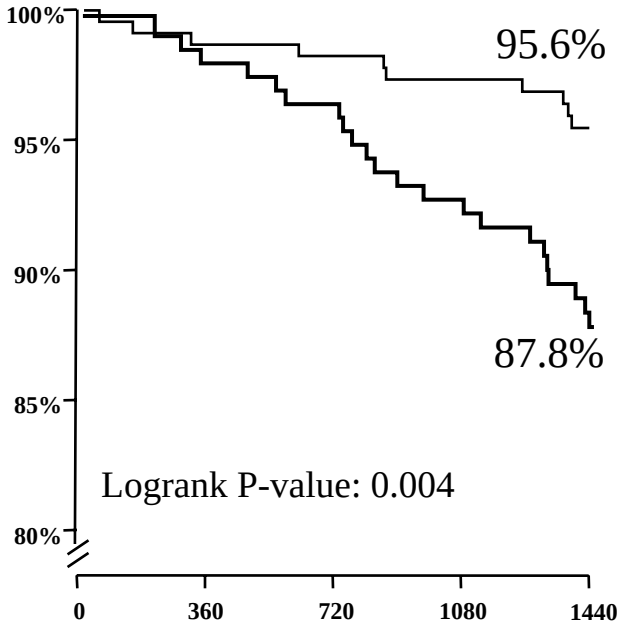
Total population

N=1748



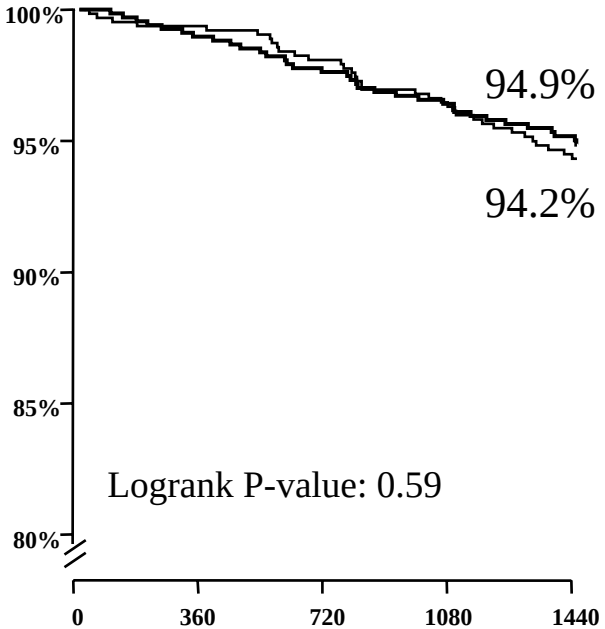
Diabetic patients

N=428



Non-diabetic patients

N=1318



	Patients at risk					Patients at risk					Patients at risk				
BMS	869	855	838	816	763	232	230	227	221	197	634	623	608	593	545
SES	877	860	835	809	740	194	188	185	175	158	682	672	650	634	579

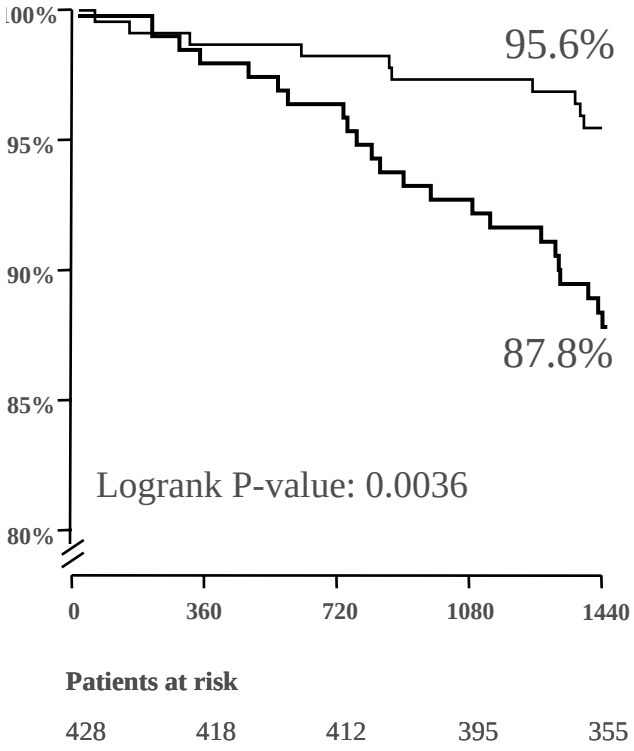
Sirolimus-eluting stent group

Bare metal stent group

All-cause death

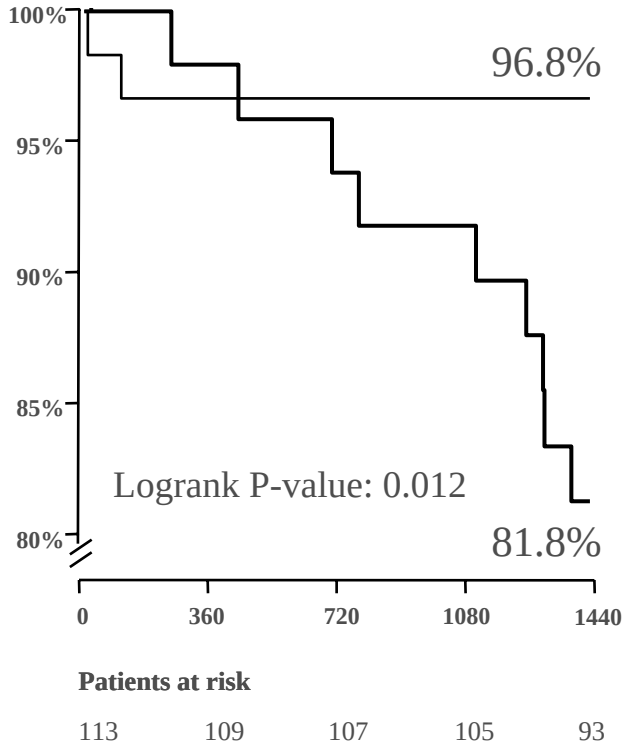
Diabetic patients

N=428



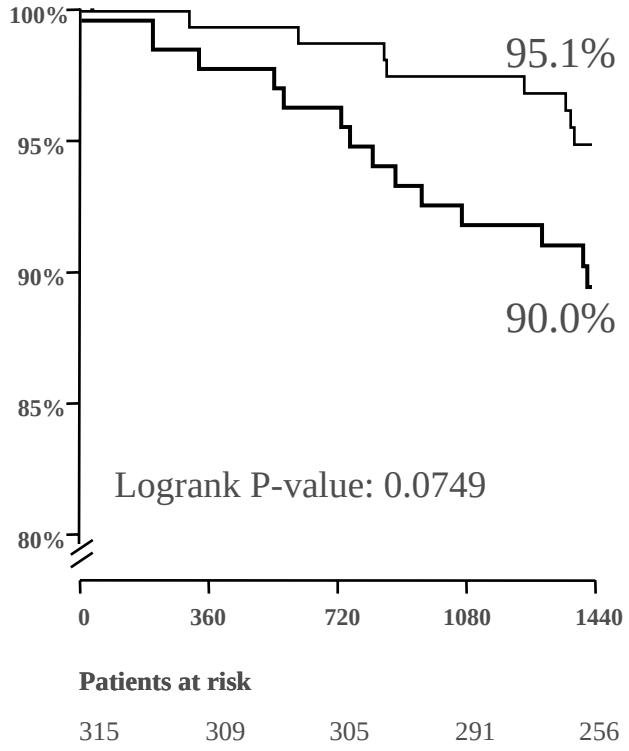
IDDM patients

N=113



NIDDM patients

N=315



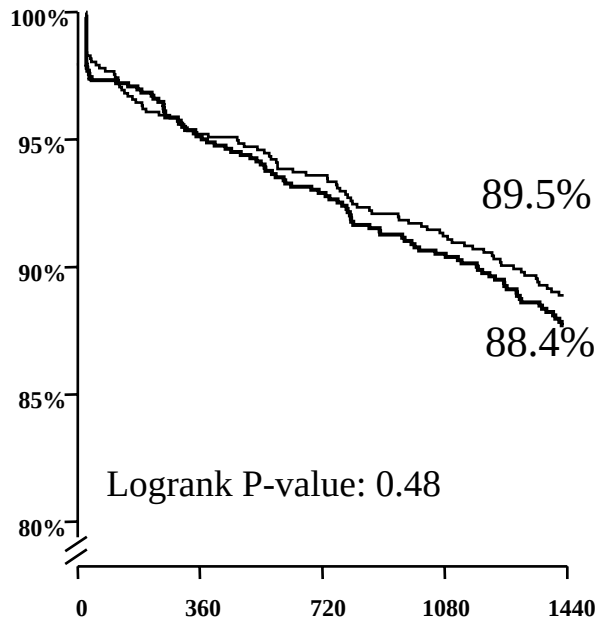
Sirolimus-eluting stent group

Bare metal stent group

All-cause death or all MI

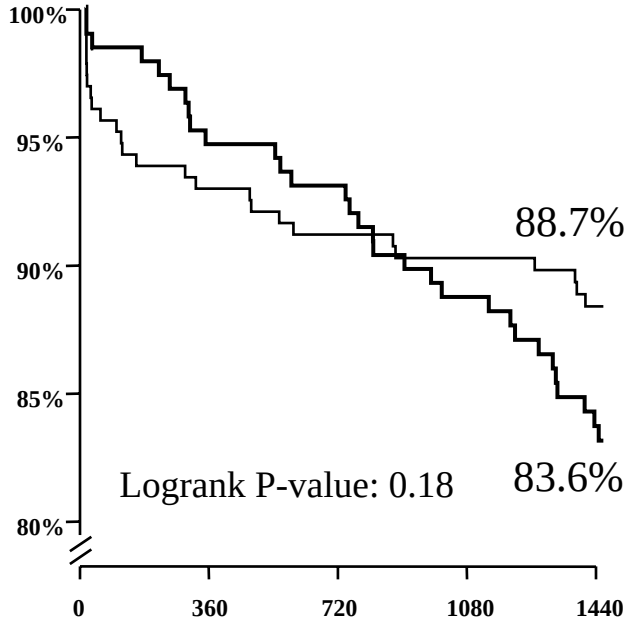
Total population

N=1748



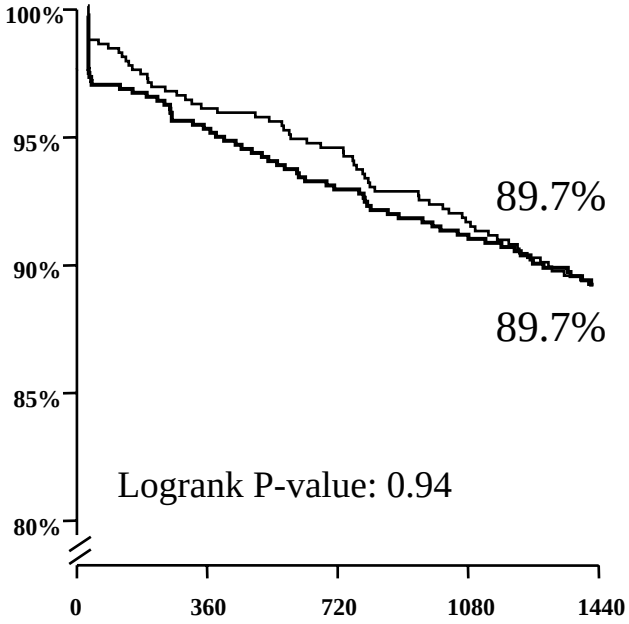
Diabetic patients

N=428



Non-diabetic patients

N=1318



	Patients at risk					Patients at risk					Patients at risk				
BMS	869	823	802	775	706	232	217	211	205	182	634	604	589	568	522
SES	877	829	800	771	704	194	182	179	169	152	682	647	621	602	552

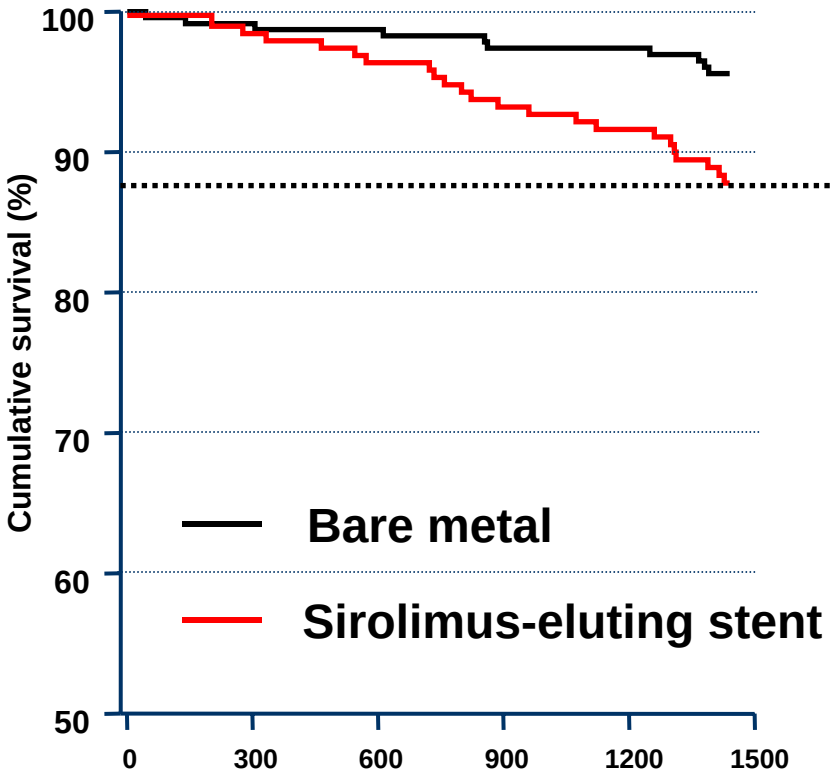
Sirolimus-eluting stent group

Bare metal stent group

Mortality in pooled analyses

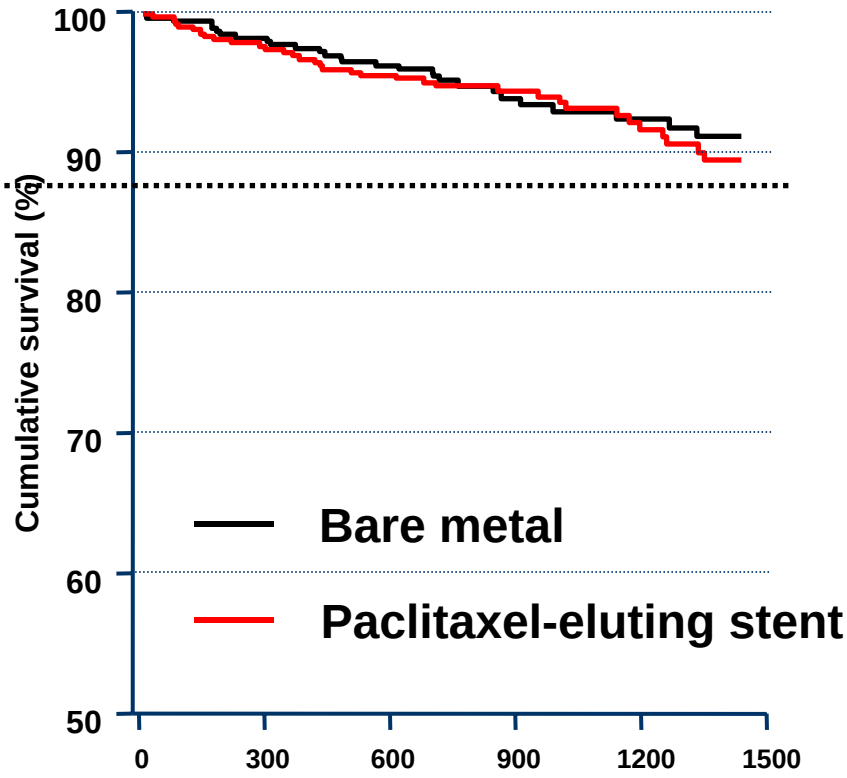
Diabetic subset

Cypher trials (n=428)



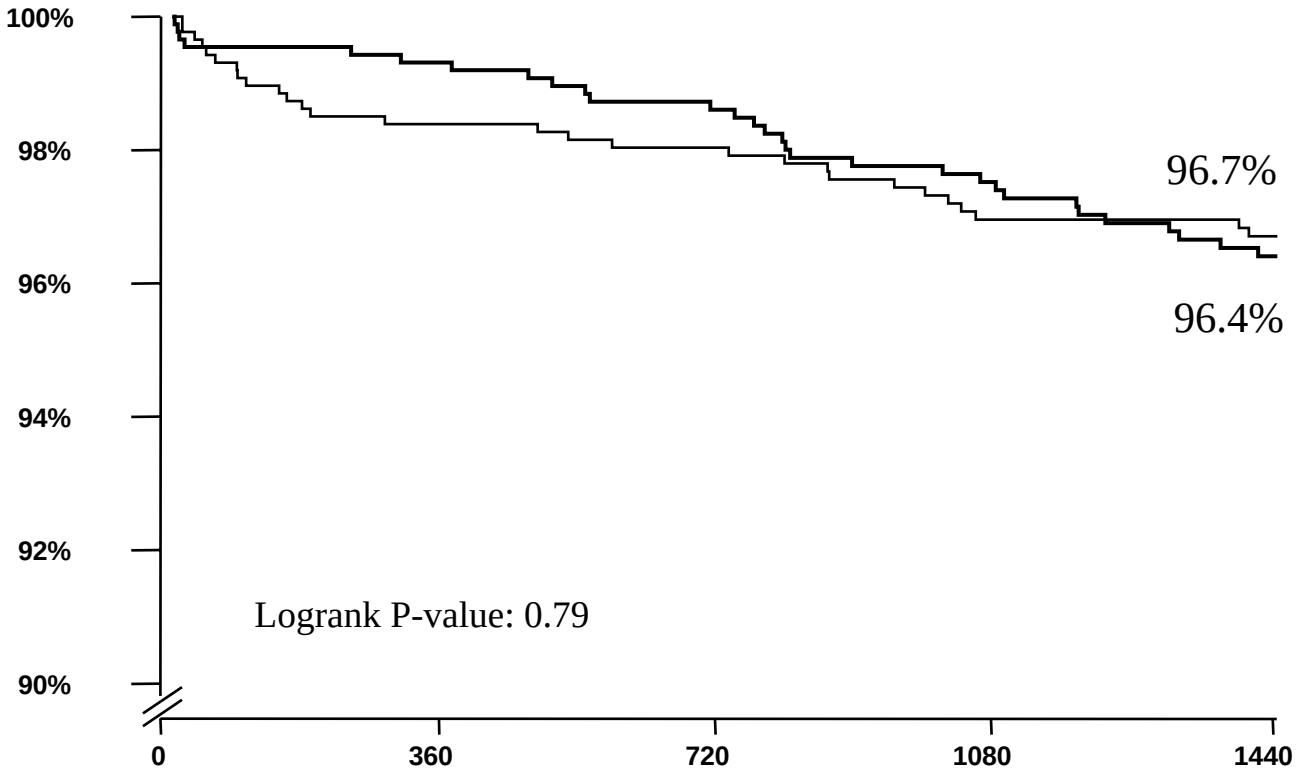
Pooled patient level based analysis of 4-year f/u of RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS

TAXUS trials (n=814)



Pooled patient level based analysis of TAXUS II (4 yr) , IV (4 yr), V (2yr), VI (3 yr)

Any ST Dublin definitions
Total population



Mortality and ST Dublin/ARC definitions

	Cypher (n=195)	Control (n=233)
Total mortality	11.8% (23/195)	4.3% (10/233)
Cardiac	7.7% (15/195)	2.6% (6/233)
Non-Cardiac	4.1% (8/195)	1.7% (4/233)
Total (Dublin definitions)	6.1% (12/195)	3.9% (9/233)
Definite Thrombosis	1.0% (2/195)	0.4% (1/233)
Probable thrombosis	0.0% (0/195)	1.7% (4/233)
Possible thrombosis	5.6% (10/195)	1.7% (4/233)

Non cardiac deaths

Patient ID	Age	Days post proc.	Narrative	Dublin ST
Sirolimus group (n=8)				
517/204	79	203	Septicemia	No ST
261/108	54	277	Osteomyelitis post amputation	No ST
25/104	65	572	Respiratory failure	No ST
155/113	77	1309	Respiratory failure	No ST
17/1204	56	333	Subarachnoidal hemorrhage	No ST
105/122	54	723	Car accident	No ST
18/1264	74	1261	Pancreatic cancer	No ST
111/114	74	1122	Lymphoma	No ST
Control group (n=4)				
4/104	53	306	Lung carcinoma	No ST
533/208	67	862	CVA	No ST
108/118	77	1250	Lung collapse in hospital	No ST
68/116	71	1367	Urinary tract infection - sepsis	No ST

Cardiac deaths

Patient ID	Age	Days	Narrative	Dublin ST
Sirolimus group (n=15)				
8/110	53	1	Intracerebral hemorrhage post procedure	No ST
1/1063	68	1389	Heart Failure	No ST
15/1168	67	1428	Heart failure – bilateral pneumonia	No ST
106/112	75	823	Myocardial infarction in non-TVR region, 3 weeks post non-TVR	No ST
15/1299	71	961	Acute dyspnea and arrhythmia – Kidney failure and septicemia	No ST
11/1146	70	465	Acute shortage of breath - unexplained	Possible ST
266/122	64	1416	Difficulty breathing	Possible ST
3/110	65	545	Sudden death	Possible ST
11/107	80	800	In her sleep	Possible ST
509/202	80	887	Unexplained – thus cardiac	Possible ST
124/105	73	734	Unexplained – thus cardiac	Possible ST
108/103	68	759	Unexplained – thus cardiac	Possible ST
607/401	73	1074	Unexplained with post mortem ?	Possible ST
270/121	53	1313	Unexplained – thus cardiac	Possible ST
206/155	80	1300	Unexplained – thus cardiac	Possible ST
Control group (n=6)				
502/203	54	140	Unexplained – thus cardiac	Possible ST
6/117	50	855	Unexplained – thus cardiac	Possible ST
11/1148	62	45	Unexplained – thus cardiac	Possible ST
10/104	66	1391	Unexplained – thus cardiac	Possible ST
206/120	73	613	MI	Probable ST
11/1098	81	85 / 1381	MI target area / Unknown – thus cardiac	Probable/Possible ST

Unexplained deaths (all cardiac)

Bare		
11/1148	45 days	…the patient died on 11 March 2002. She had an acute shortage of breath. No autopsy was performed. The event was adjudicated by the CEC as non-cardiac death due to pulmonary embolism.
502/203	140 days	…on 1/17/2002 the site reported the patient was found dead at home. No attempts were made at resuscitation. An autopsy was not performed. The categorical cause of death is unknown. The official cause of death was "internal cause."
10/104	1391 days	…A subsequent review of the The Social Security Death Index revealed that the patient had expired on 03/14/2005. The exact cause of death was unknown, and the site confirmed that no further information would be forthcoming…
6/117	855 days	…the patient was discharged on 5/28/2003. The patient's referring physician contacted the site and reported the patient had expired at home on 8/27/2003 as reported by his wife. Further information will not be available.
Cypher		
509/202	887 days	…on 05/01/2004 the patient expired at home. No examinations were performed at the time of death.
124/105	734 days	…the site reported that when the patient's referring physician was contacted for 3 year follow-up, the physician reported the patient had expired in 2003. The site reported no autopsy was performed and the death certificate or further information regarding death was unobtainable.
108/103	759 days	…on 3/29/2003 the patient was found expired in her motor vehicle. A Death Certificate revealed the immediate cause of death was an acute myocardial infarction.
607/401	1074 days	…the patient was discovered unresponsive in his home and resuscitation attempts were unsuccessful. A post-mortem examination revealed "evidence of recent medical intervention, but significant recent injuries." The immediate cause of death was atherosclerotic cardiovascular disease. Diabetes mellitus and prostate cancer were reported as other significant contributing conditions.
270/121	1313 days	…at the time of the four year follow-up contact, the investigational site discovered via the Social Security Death Index, that the patient expired on 03/07/2005. The site indicated that no further information would be forthcoming.
206/155	1300 days	…the patient expired at home on 02/27/2005. The Death Form and Death Certificate revealed the cause of death was an acute myocardial infarction.

- Subgroup analyses,including diabetes, were not pre-specified and the number of fatal events in this subgroup was numerically small so that the findings of our statistical assessment may still be the play of chance.
  In this pooled analysis of four randomized trials,slightly higher rates of all-cause death at four years were found in patients receiving SES. This observation was explained by a significantly higher mortality rate in the diabetic patient

- This clearly shows that there is a need for large-scale studies in diabetics using death,MI or ST as primary endpoints. In the near future long term safety of the SES in diabetics should be re-evaluated by pooled analyses incorporating the long-term results of the most recently completed randomized studies comparing SES vs.BMS such as theTYPHOON,DIABETES,the PRISON-II trials and the results of Pache et al.