

*Rome Cardiology Forum 2014*

# **Coronary Stent Choice in Patients With Diabetes Mellitus**



**Stephan Windecker**



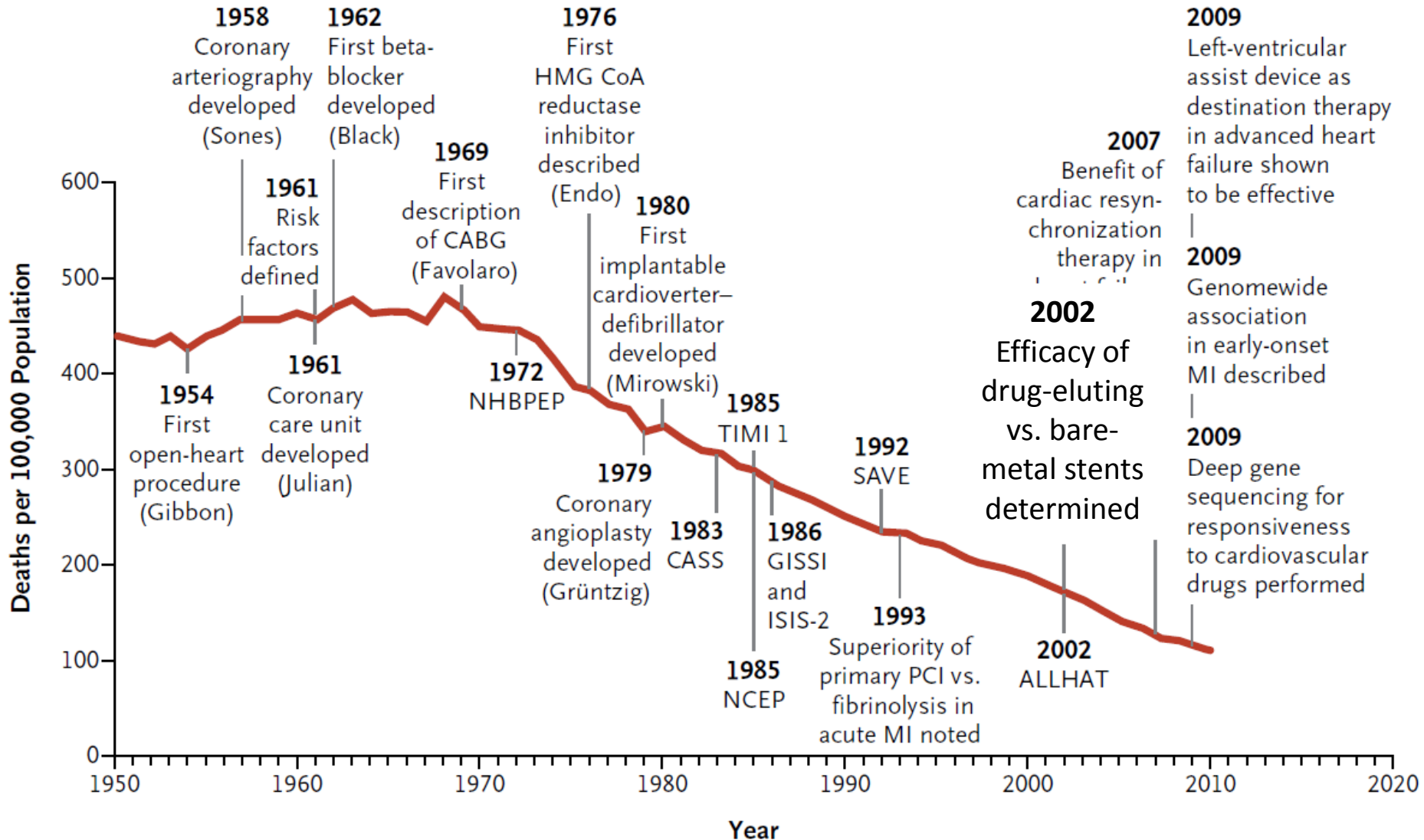
*Department of Cardiology*

*Swiss Cardiovascular Center and Clinical Trials Unit Bern*

*Bern University Hospital, Switzerland*

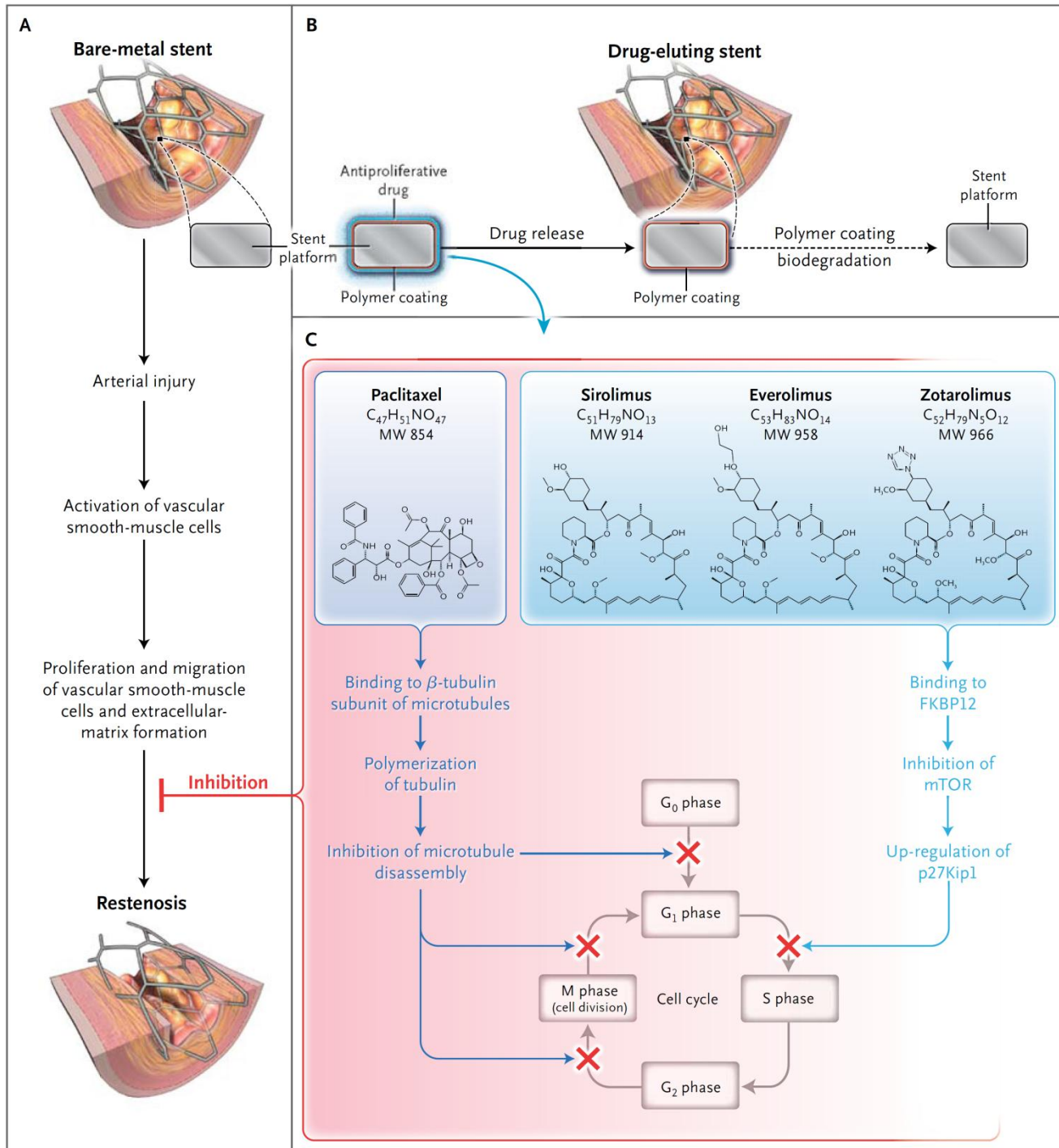
# Scientific Advances and Cardiovascular Mortality

Nabel and Braunwald. *N Engl J Med* 2012;366:54-63



# Drug-Eluting Stents

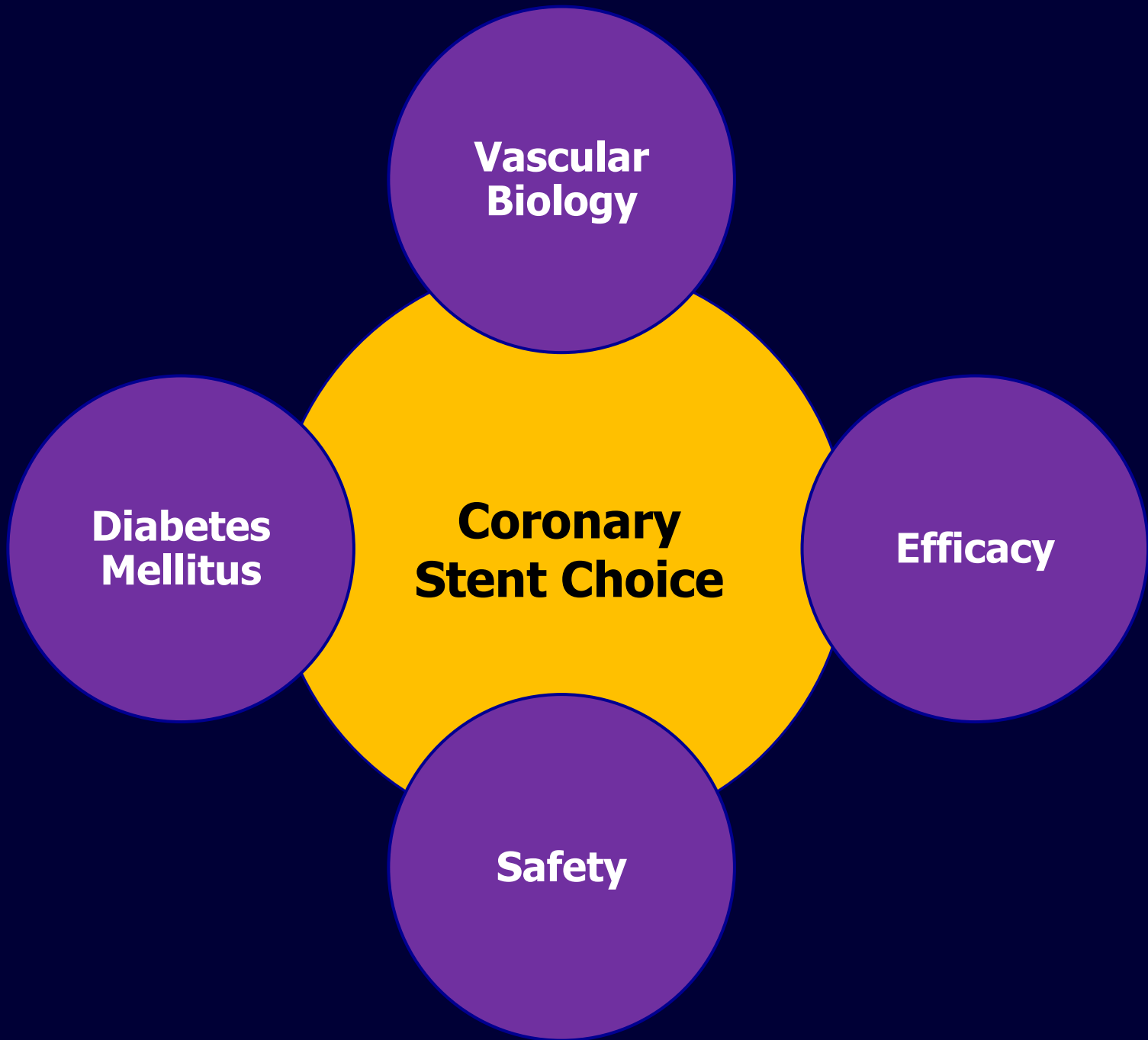
Stefanini G, Holmes D.  
*N Engl J Med* 2013; 368:254-65



# Progress in Metallic DES Technology

Stefanini, Taniwaki, Windecker. *Heart* 2013, online ahead of print

	Taxus	Cypher	BioMatrix Nobori	Endeavor	Yukon PC	Xience Promus	Resolute	Synergy	Orsiro
Platform material	SS	SS	SS	CoCr	SS	CoCr PtCr	CoCr	PtCr	CoCr
Strut thickness (μm)	132	140	120	91	87	81	91	74	60
Polymer type	Durable	Durable	Biodegradable	Durable	Biodegradable	Durable	Durable	Biodegradable	Biodegradable
Polymer material	SIBS	PEVA/PBMA	PDLLA	MPC/LMA/HPMA/ 3-MPMA	PDLLA	PBMA/PVDF-HFP	PBMA/PHMA/ PVP/PVA	PLGA	PLLA
Coating distribution	Circumferential	Circumferential	Abluminal	Circumferential	Circumferential	Circumferential	Circumferential	Abluminal	Circumferential
Polymer thickness (μm)	22	13	10	6	5	8	6	4	7
Additional coating	-	-	-	-	-	-	-	-	Silicon carbide
Drug released	Paclitaxel	Sirolimus	Biolimus	Zotarolimus	Sirolimus	Everolimus	Zotarolimus	Everolimus	Sirolimus



**Vascular  
Biology**

**Diabetes  
Mellitus**

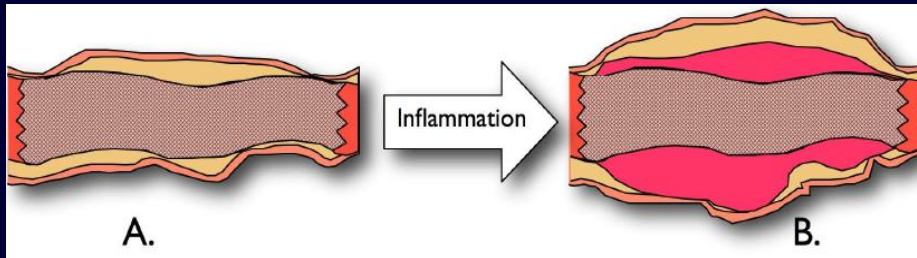
**Coronary  
Stent Choice**

**Efficacy**

**Safety**

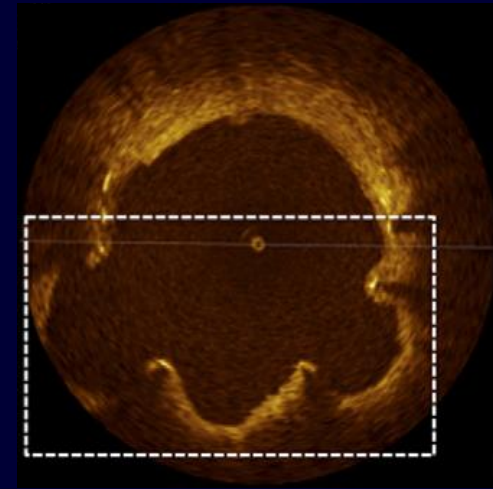
# Pathological Healing Response to Implantation of Early Generation DES

## Inflammation and Vessel Remodeling



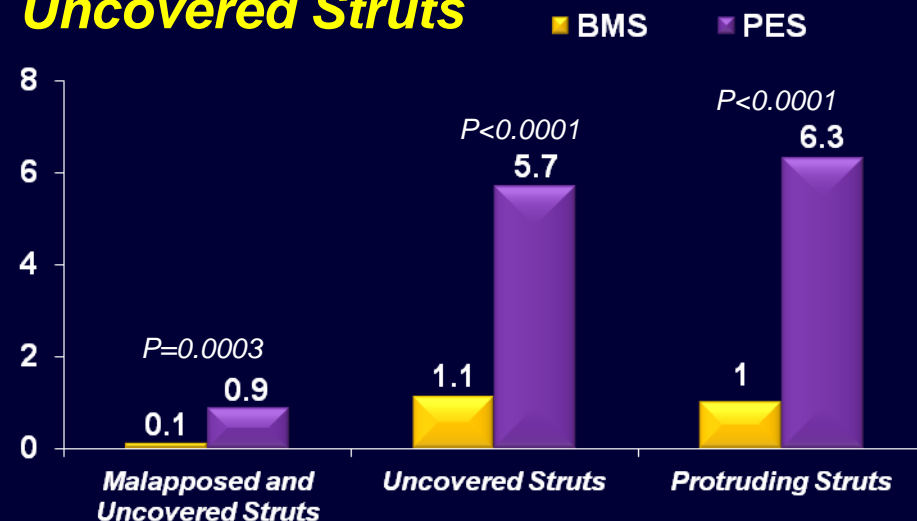
Cook et al. *Circulation* 2007  
Cook et al. *Circulation* 2009

## Coronary Evaginations



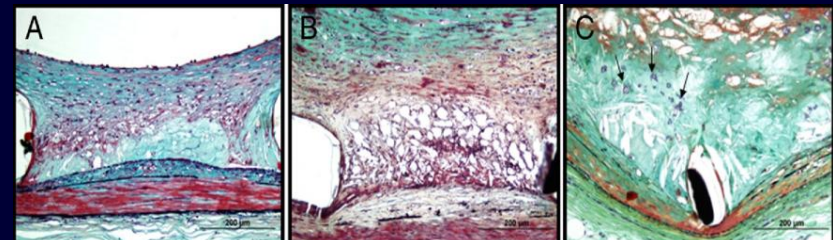
Räber et al. *J Am Coll Card Intv* 2012

## Uncovered Struts



Guagliumi et al. *Circulation* 2011

## Neoatherosclerosis



Nakazawa et al. *J Am Coll Card* 2011

# Human Pathology of New Generation EES Compared With Early Generation SES and PES

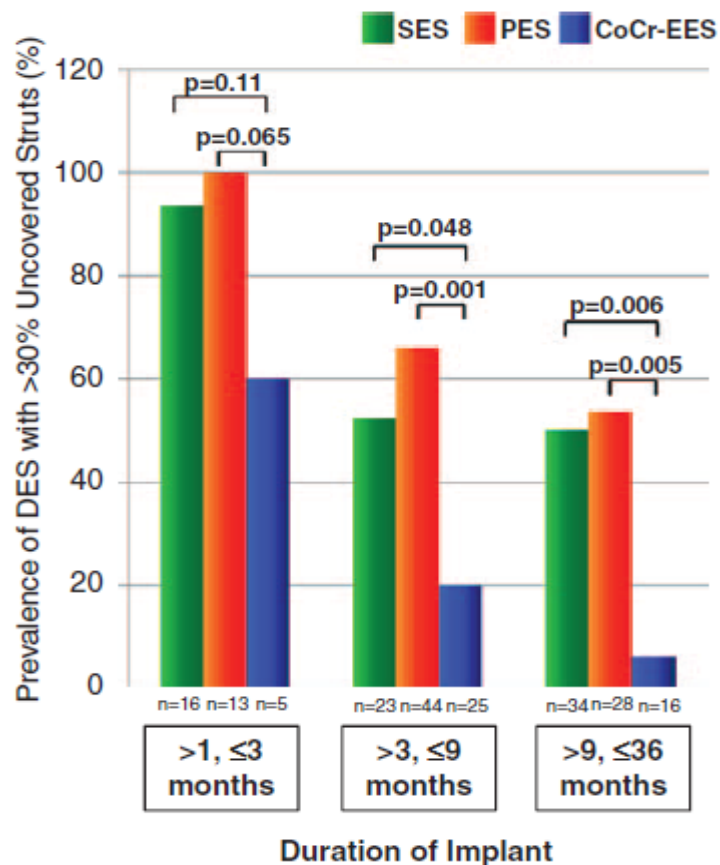
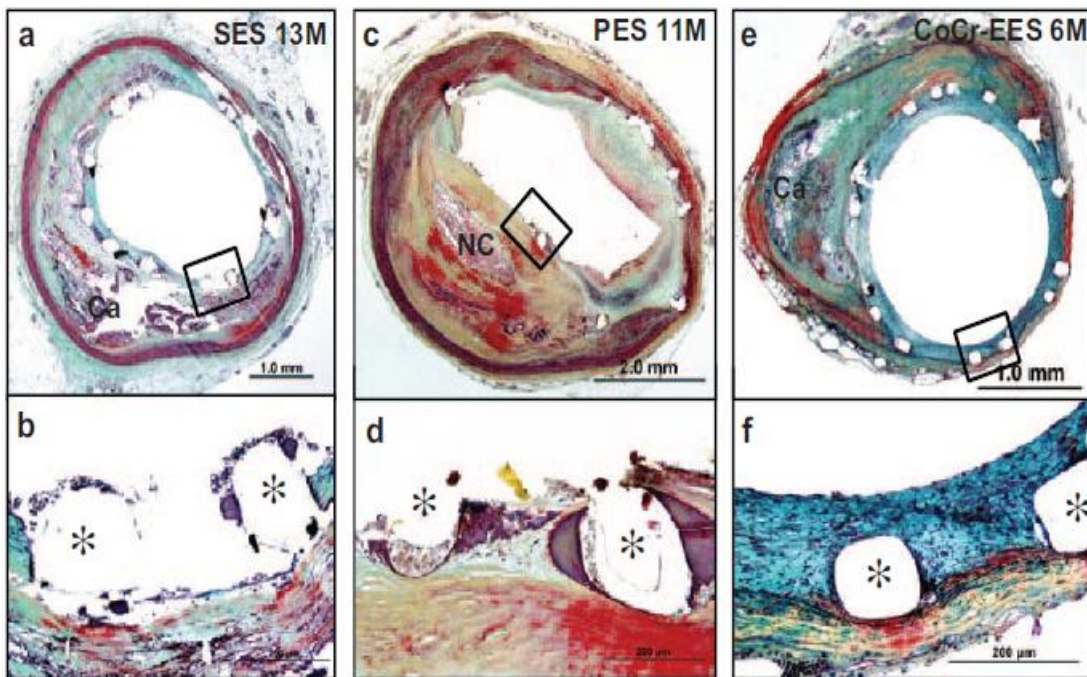
Otsuka F et al. *Circulation* 2014; 129:211-223.

**>30% Uncovered Struts**

**SES**

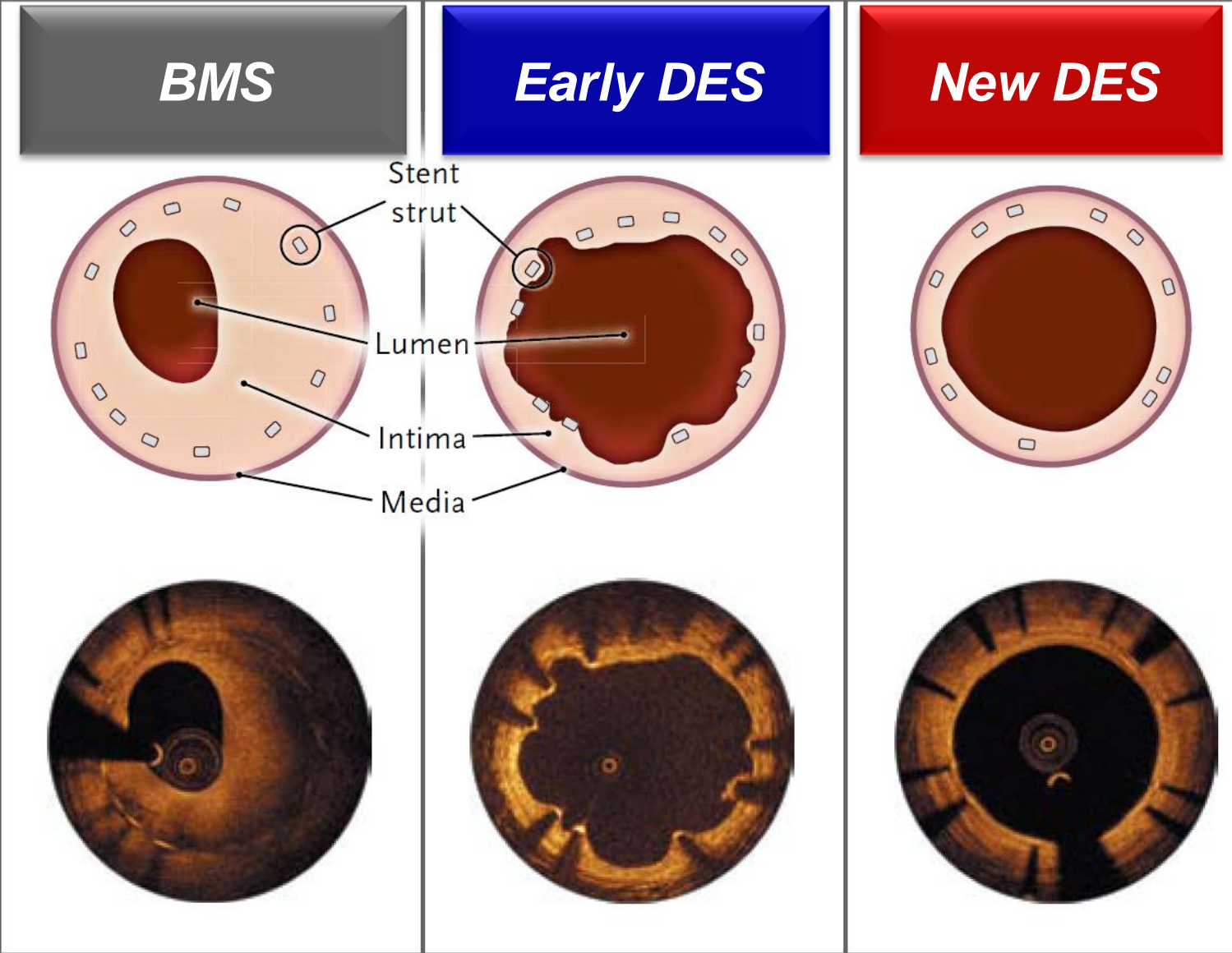
**PES**

**EES**

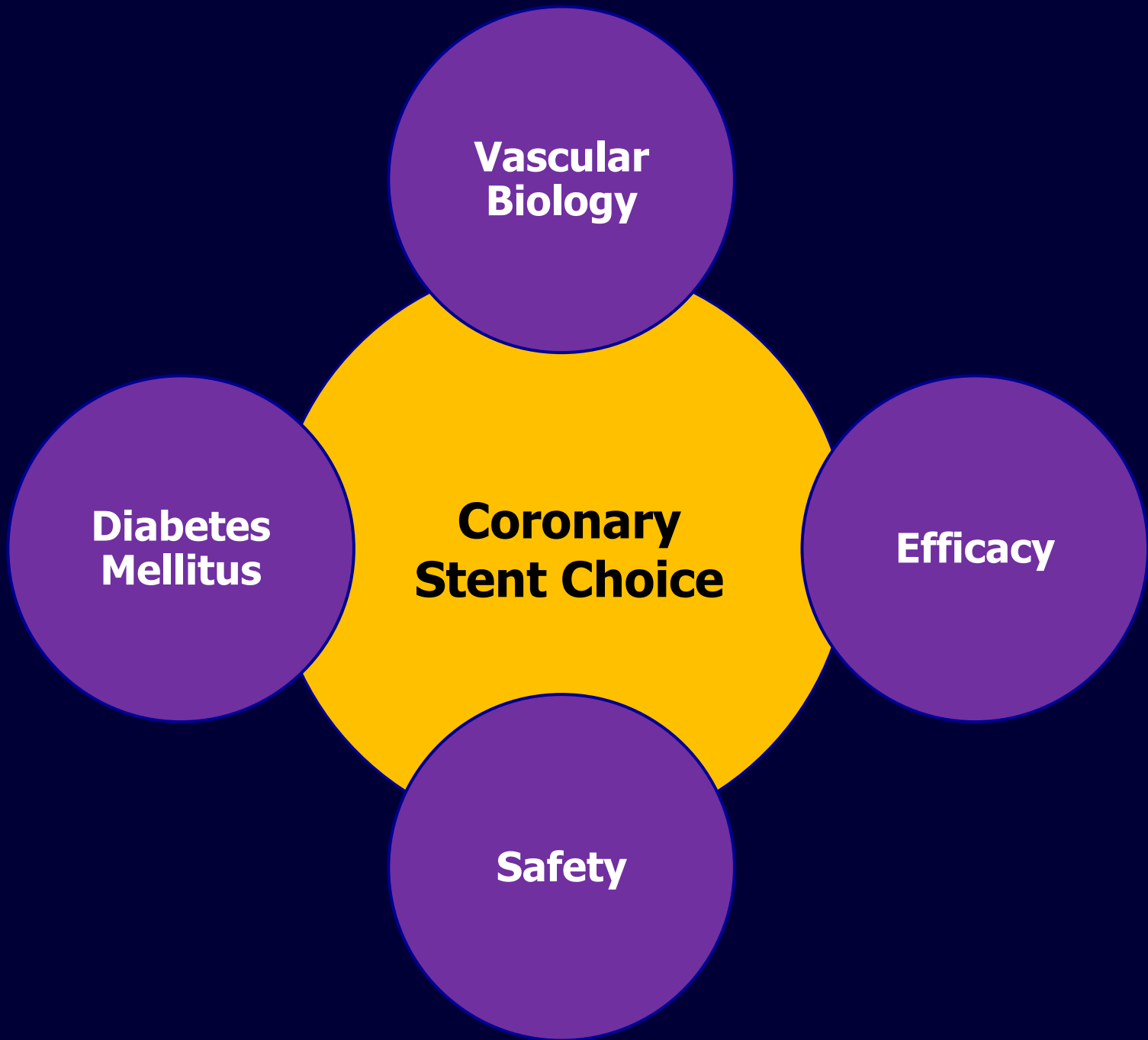


# Arterial Healing After Coronary Stents Implantation

Stefanini G, Holmes D. *N Eng J Med* 2013;368:254-65







**Vascular  
Biology**

**Diabetes  
Mellitus**

**Coronary  
Stent Choice**

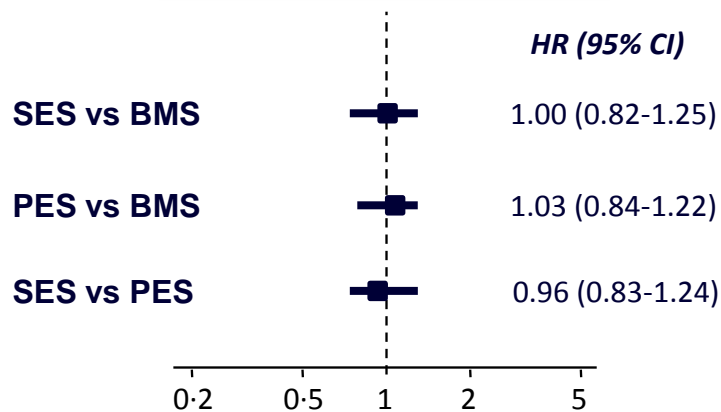
**Efficacy**

**Safety**

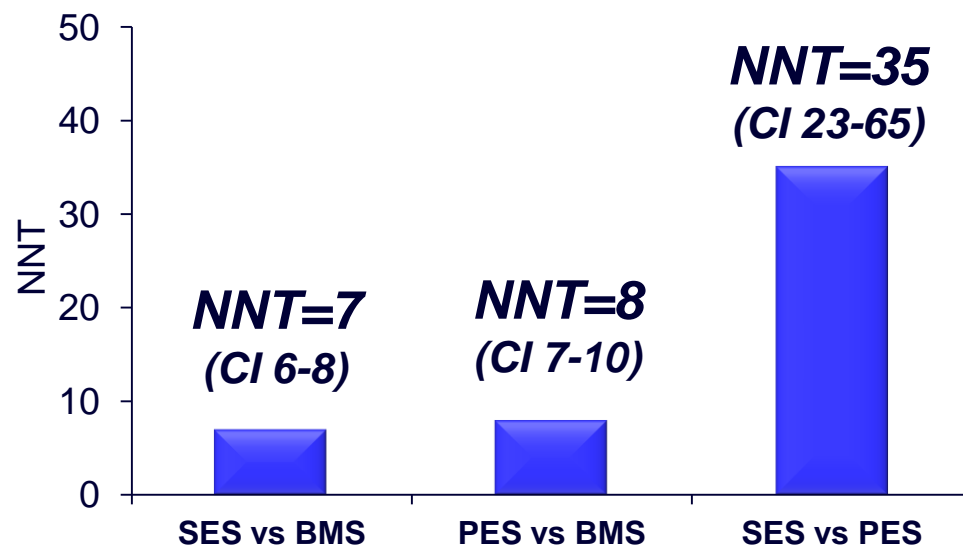
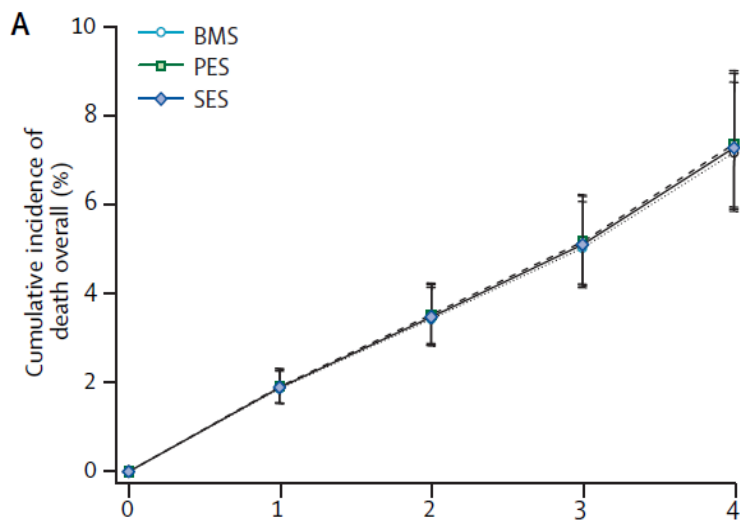
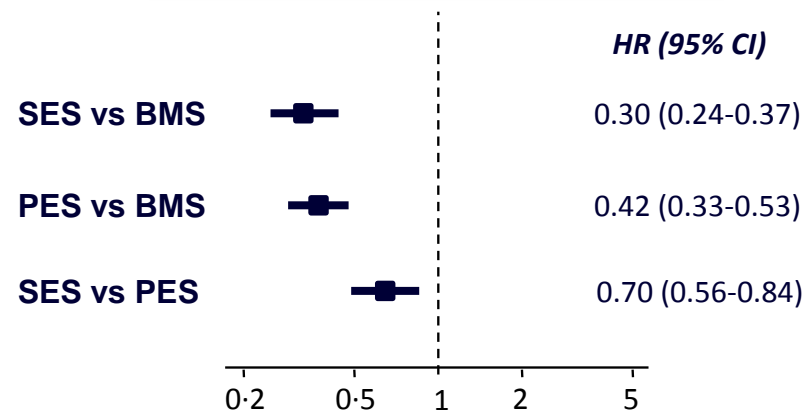
# Mortality and Repeat Revascularization with Early Generation DES versus Bare Metal Stents

Stettler C et al. *Lancet* 2007;370:937-48

## Mortality



## Repeat Revasc

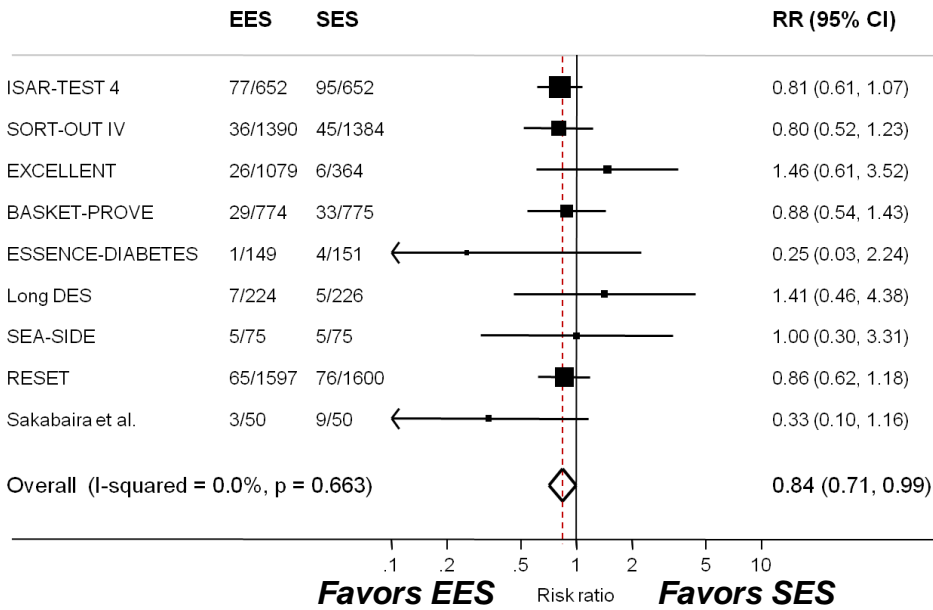


# New Generation DES Improved Efficacy

## Target Lesion Revascularization

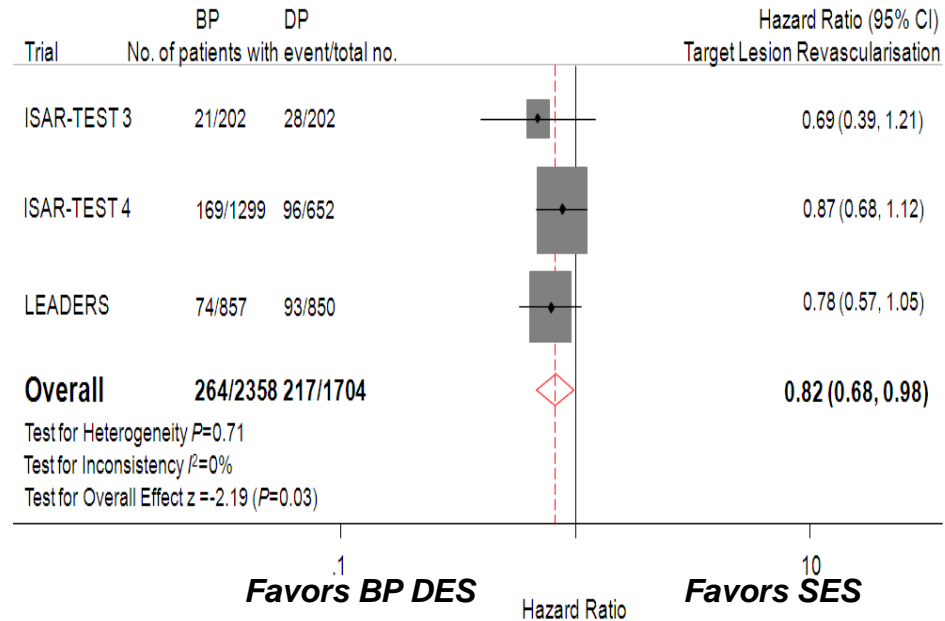
### Everolimus-Eluting Stents vs. Sirolimus-Eluting Stents

Stefanini, Windecker



### Biodegradable Polymer DES vs. Sirolimus-Eluting Stents

Stefanini G et al. *Eur Heart J* 2012; 33, 1214–1222



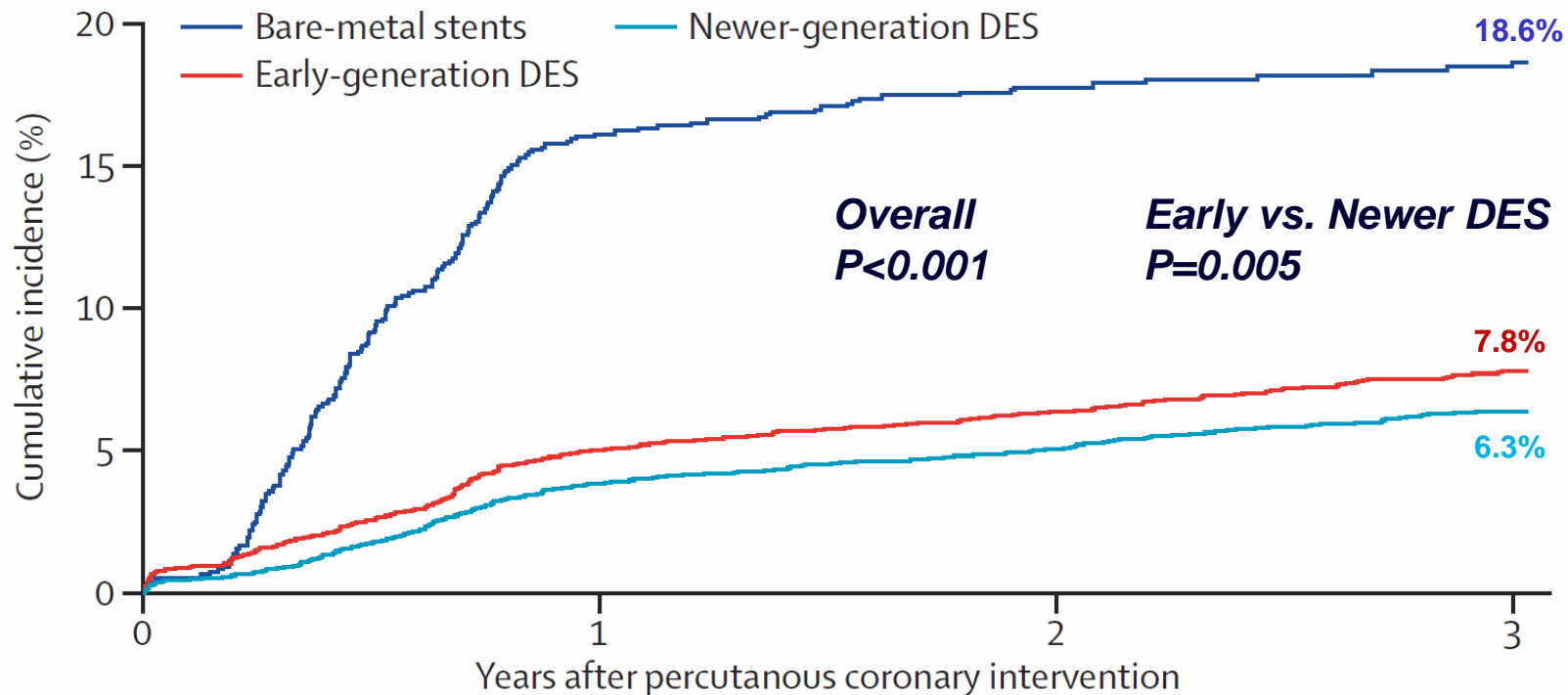
**N = 11,167 – Updated Metaanalysis**

**N = 4,062 – IPD Pooled Analysis**

# Safety and Efficacy of DES vs BMS

Stefanini G et al. *Lancet* 2013; 382(9908):1879-88

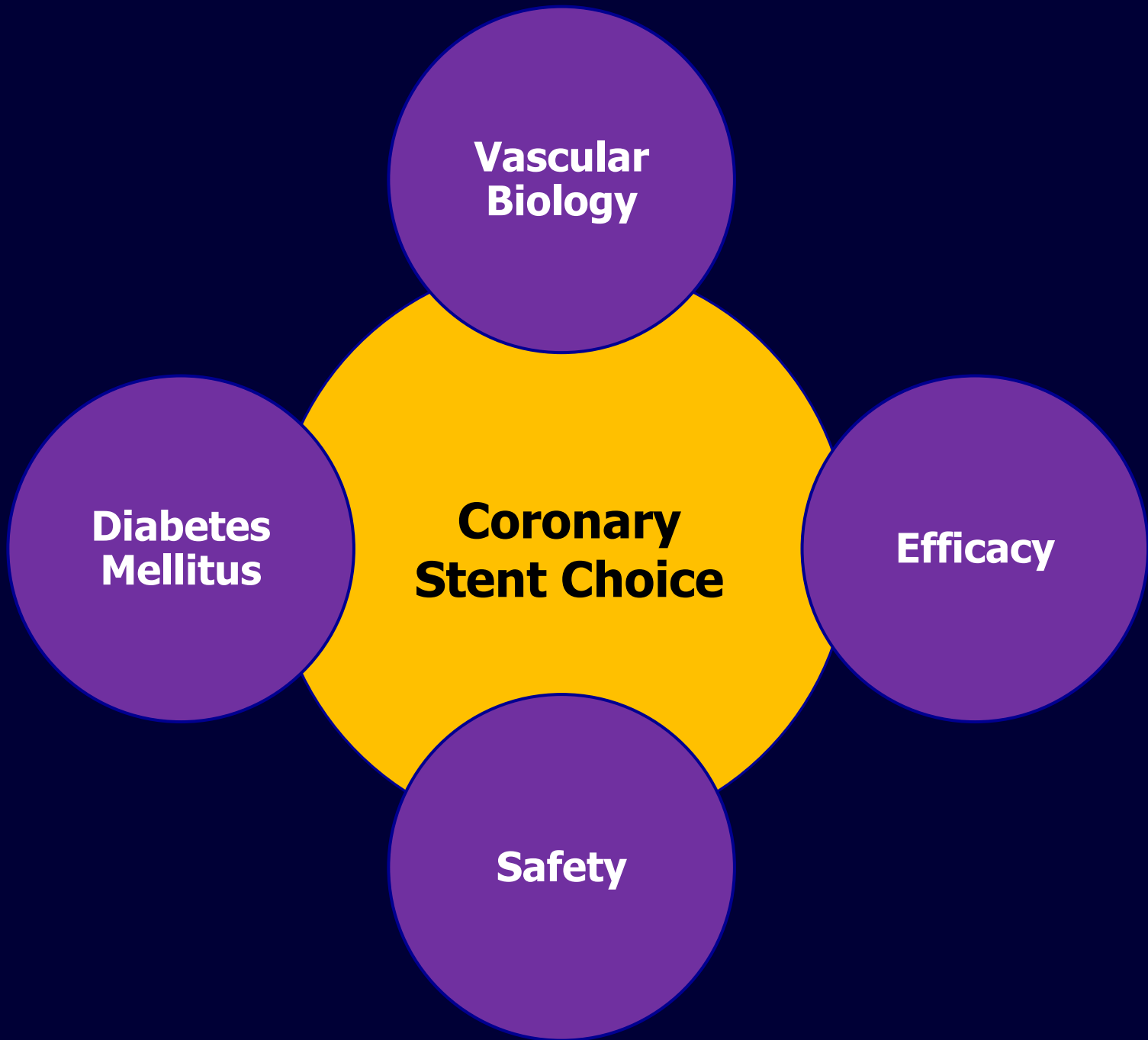
## Target Lesion Revascularization



### Number at risk

Bare-metal stents	1108	898	710	457
Early-generation DES	4171	3764	3113	1955
Newer-generation DES	6278	5217	3307	1951

**11,557 Women enrolled into 26 Randomized Trials between 2000 and 2013**



**Vascular  
Biology**

**Diabetes  
Mellitus**

**Coronary  
Stent Choice**

**Efficacy**

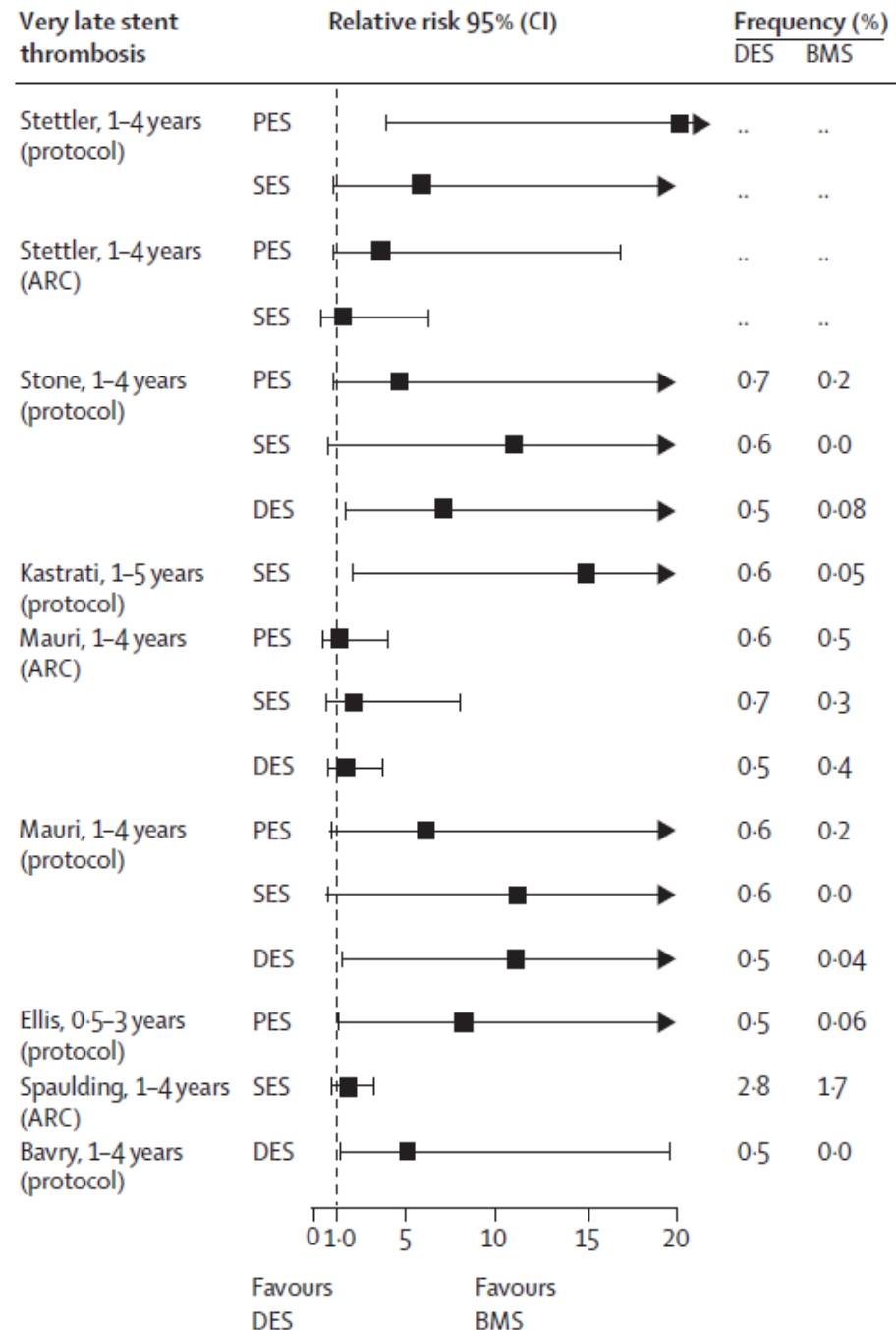
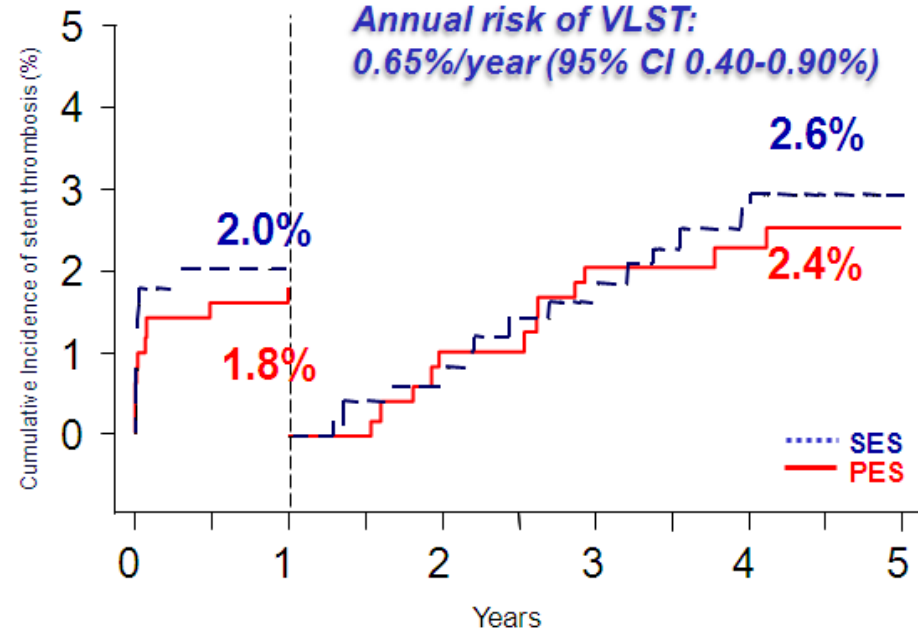
**Safety**

# Early DES and Very Late ST

## SIRTAX LATE

Räber L et al. *Circulation* 2011

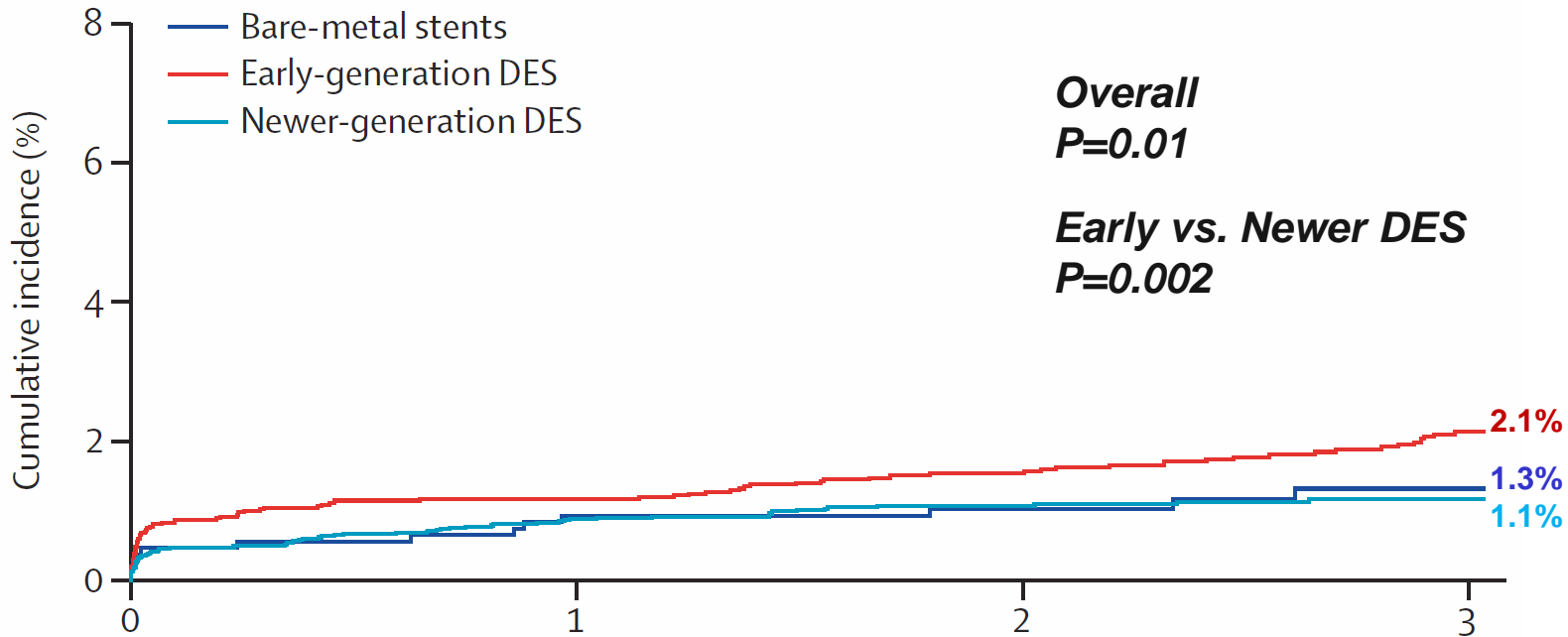
Annual risk of VLST:  
0.65%/year (95% CI 0.40-0.90%)



# Safety and Efficacy of DES vs BMS in Women

Stefanini G et al. *Lancet* 2013; 382(9908):1879-88

## Definite/Probable Stent Thrombosis



Number at risk					
Bare-metal stents	1108	1056	859	574	
Early-generation DES	4171	3919	3297	2099	
Newer-generation DES	6278	5382	3476	2074	

**11,557 Women enrolled into 26 Randomized Trials between 2000 and 2013**

# Stent Thrombosis With Everolimus-Eluting Stents and Bare Metal Stents

## A Network Meta-Analysis

Palmerini T et al. *Lancet* 2012; 379:1393-402

	log (odds ratio)	SE	Weight	Odds ratio IV, random, 95% CI
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### (A) Definite thrombosis

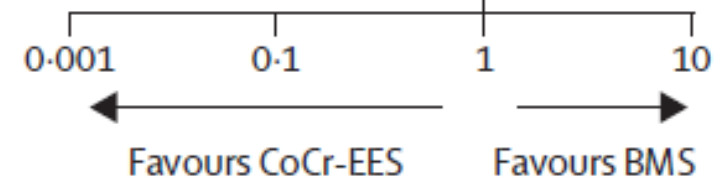
Direct estimate	-1.427	0.519	32.4%	0.24 (0.09-0.66)
Indirect estimate	-1.421	0.359	67.6%	0.24 (0.12-0.49)
<b>Total (95% CI)</b>			<b>100.00%</b>	<b>0.24 (0.14-0.43)</b>

Test for overall effect  $Z=4.82$  ( $p<0.00001$ )

### (B) Definite or probable thrombosis

Direct estimate	-0.968	0.377	39.4%	0.38 (0.18-0.80)
Indirect estimate	-1.122	0.304	60.6%	0.33 (0.18-0.59)
<b>Total (95% CI)</b>			<b>100.00%</b>	<b>0.35 (0.22-0.55)</b>

Test for overall effect  $Z=4.48$  ( $p<0.00001$ )





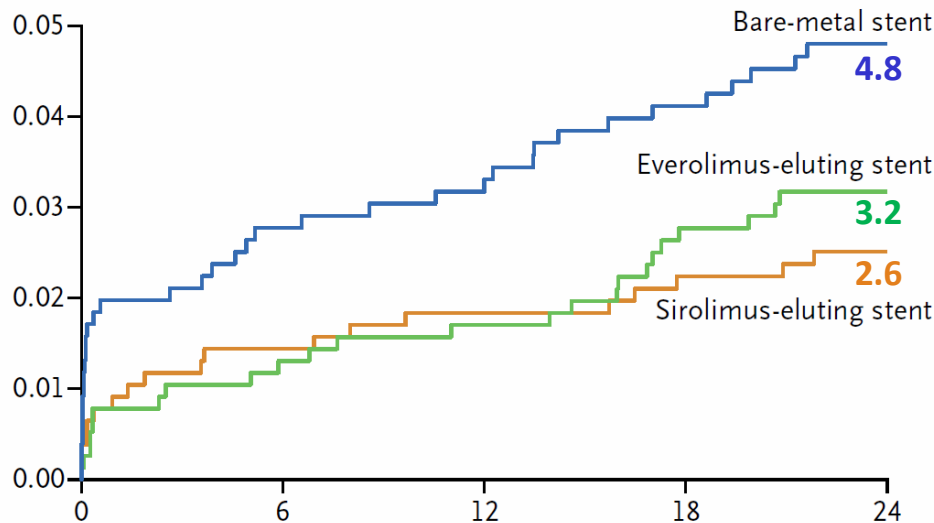
# DES vs. BMS in Large Coronary Arteries

Kaiser C et al. *N Eng J Med* 2010; 363:2310-9

## Large Investigator-Driven Trial: BASKET-PROVE

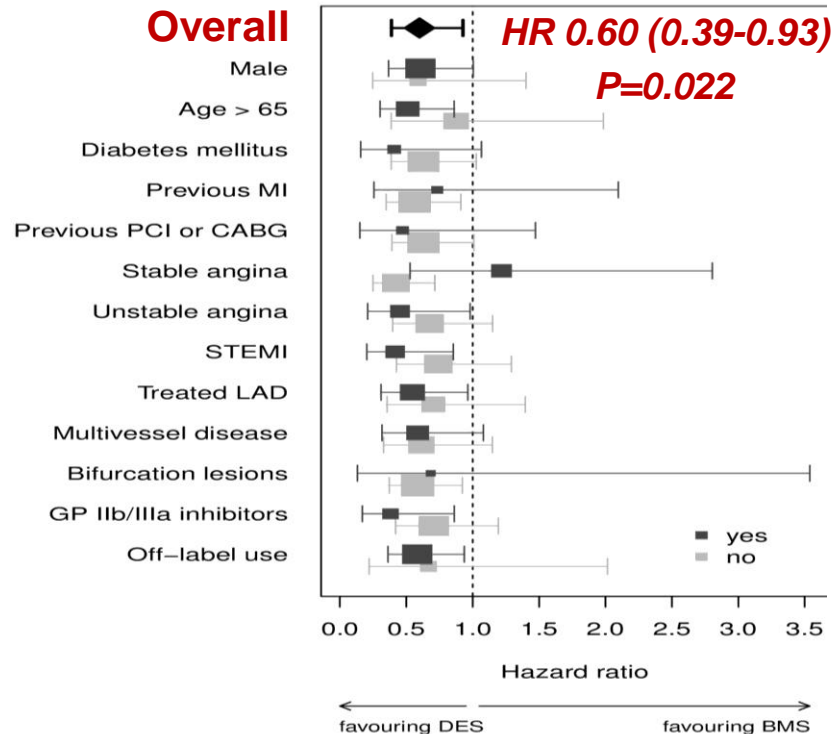
### EES vs. SES vs. BMS

### DES Pooled vs. BMS



No. at Risk

	0	6	12	18	24
Sirolimus-eluting stent	775	746	742	728	567
Everolimus-eluting stent	774	753	745	729	546
Bare-metal stent	765	734	724	707	541

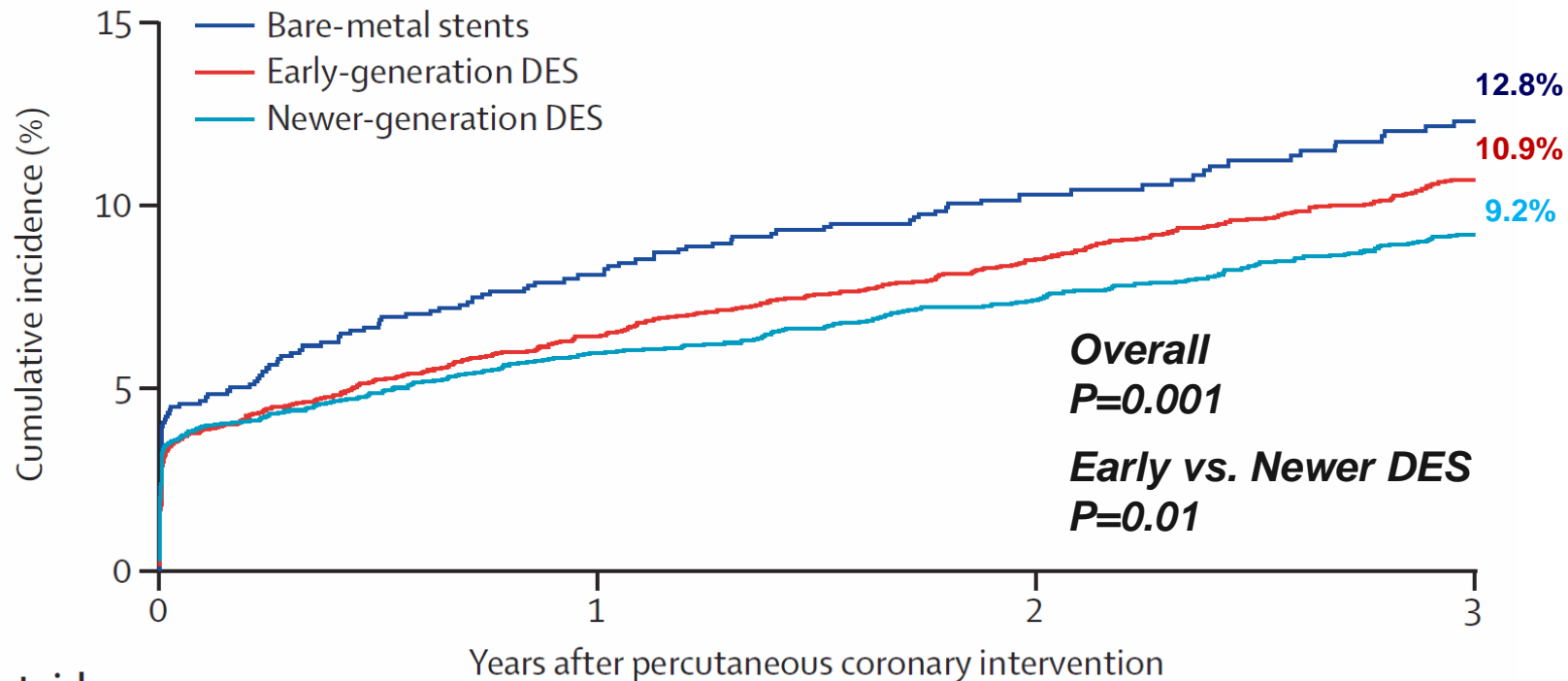


Courtesy: C Kaiser for the BASKET-PROVE Investigators

# Safety and Efficacy of DES vs BMS in Women

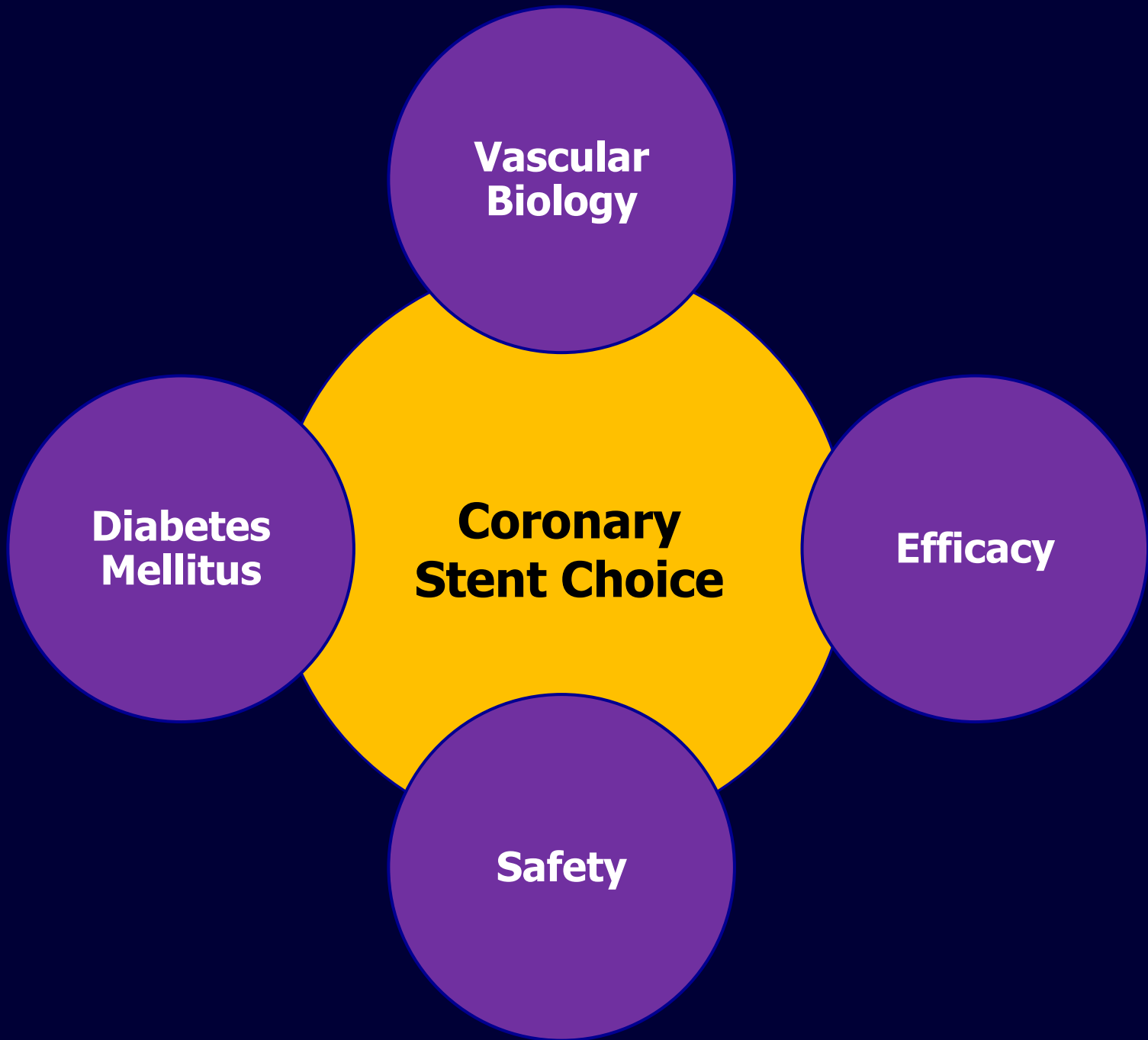
Stefanini G et al. *Lancet* 2013

## Death or Myocardial Infarction



Number at risk		Years after percutaneous coronary intervention			
	0	1	2	3	
Bare-metal stents	1108	998	822	544	
Early-generation DES	4171	3788	3191	2019	
Newer-generation DES	6278	5210	3379	2008	

**11,557 Women enrolled into 26 Randomized Trials between 2000 and 2013**



**Vascular  
Biology**

**Diabetes  
Mellitus**

**Coronary  
Stent Choice**

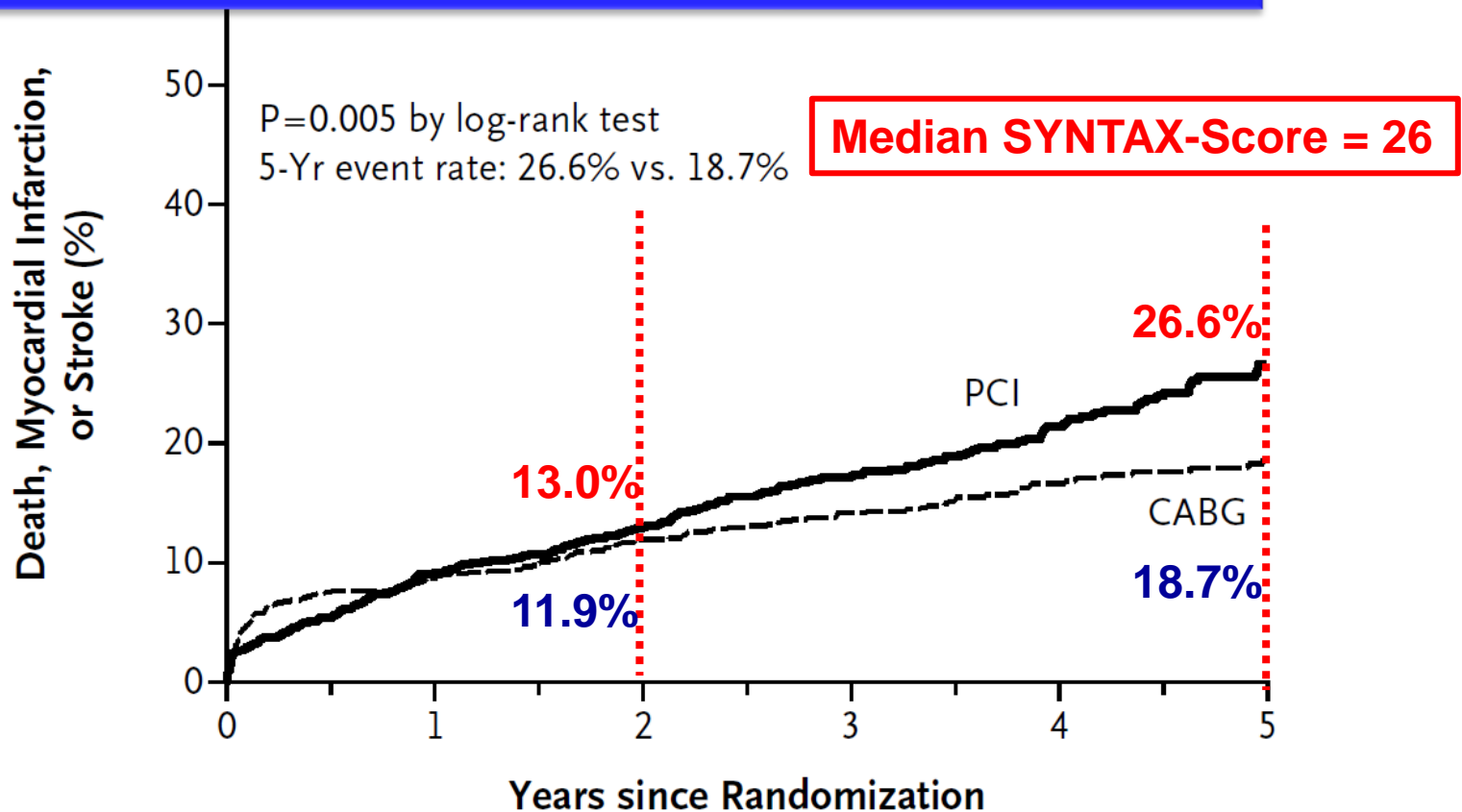
**Efficacy**

**Safety**

# Strategies for Multivessel Revascularization in Patients with Diabetes – the FREEDOM Trial

Farkouh ME et al. *N Engl J Med* 2012; 367:2375-84.

## Death, MI, or Stroke Through 5 Years



### No. at Risk

	0	1	2	3	4	5
PCI	953	848	788	625	416	219
CABG	947	814	758	613	422	221

# FREEDOM TRIAL

Farkouh ME et al.  
*N Engl J Med* 2012

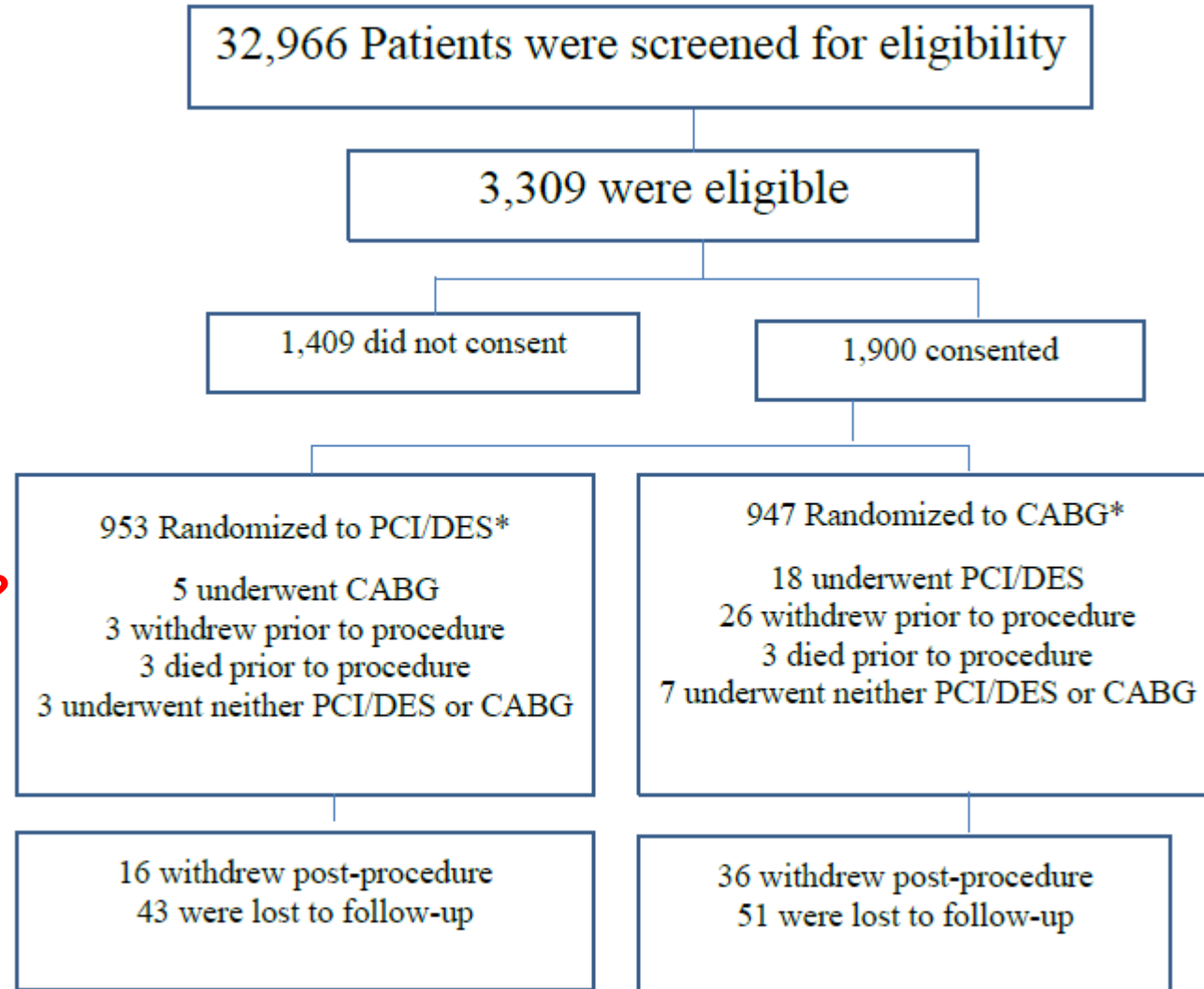
32,966 patients assessed  
1,900 patients randomized

= 5.6% **Generalisability?**

Anticipated difference in outcome between PCI and CABG

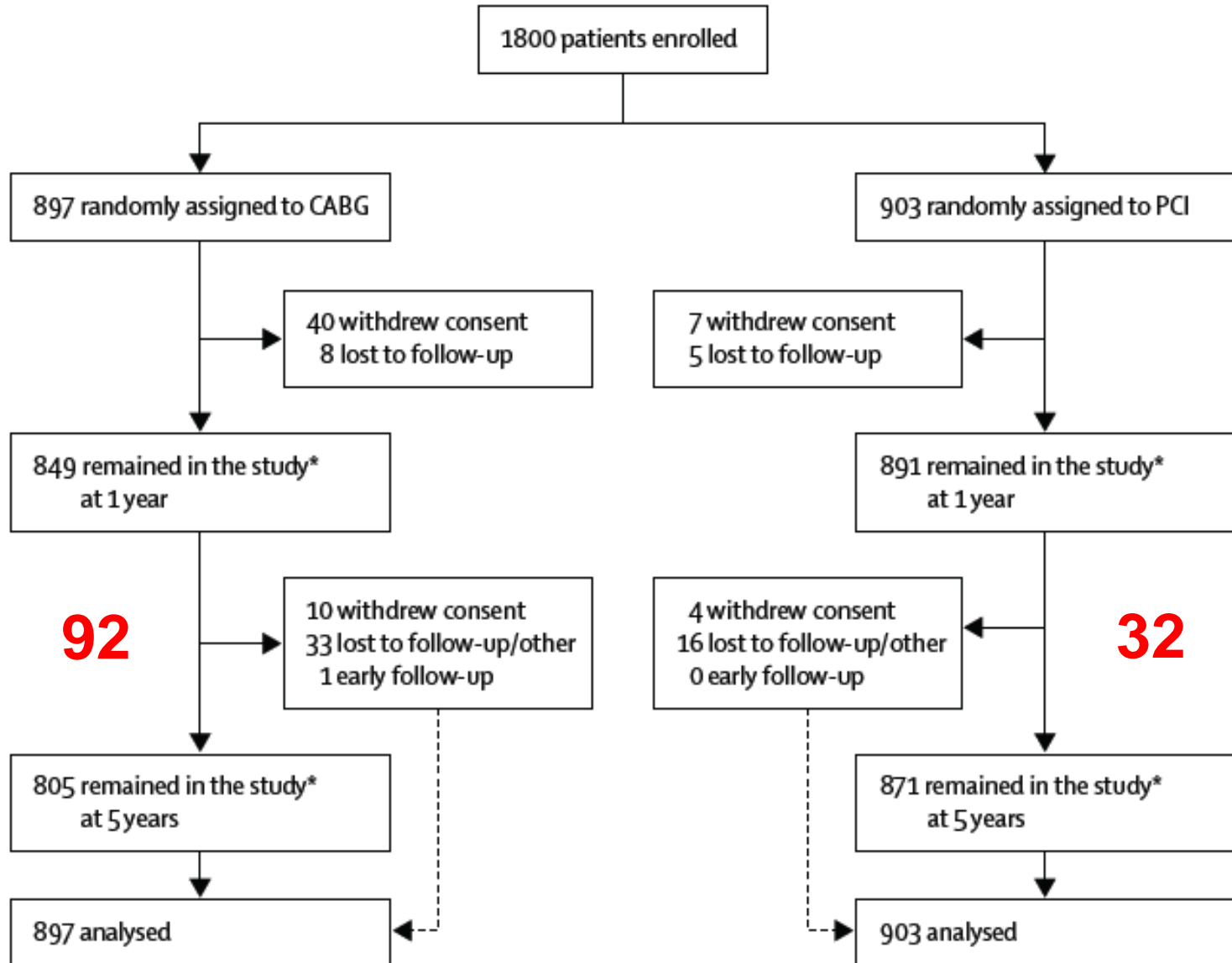
- RR 23%

146 patients lost to follow-up/withdrew  
= 4.4%



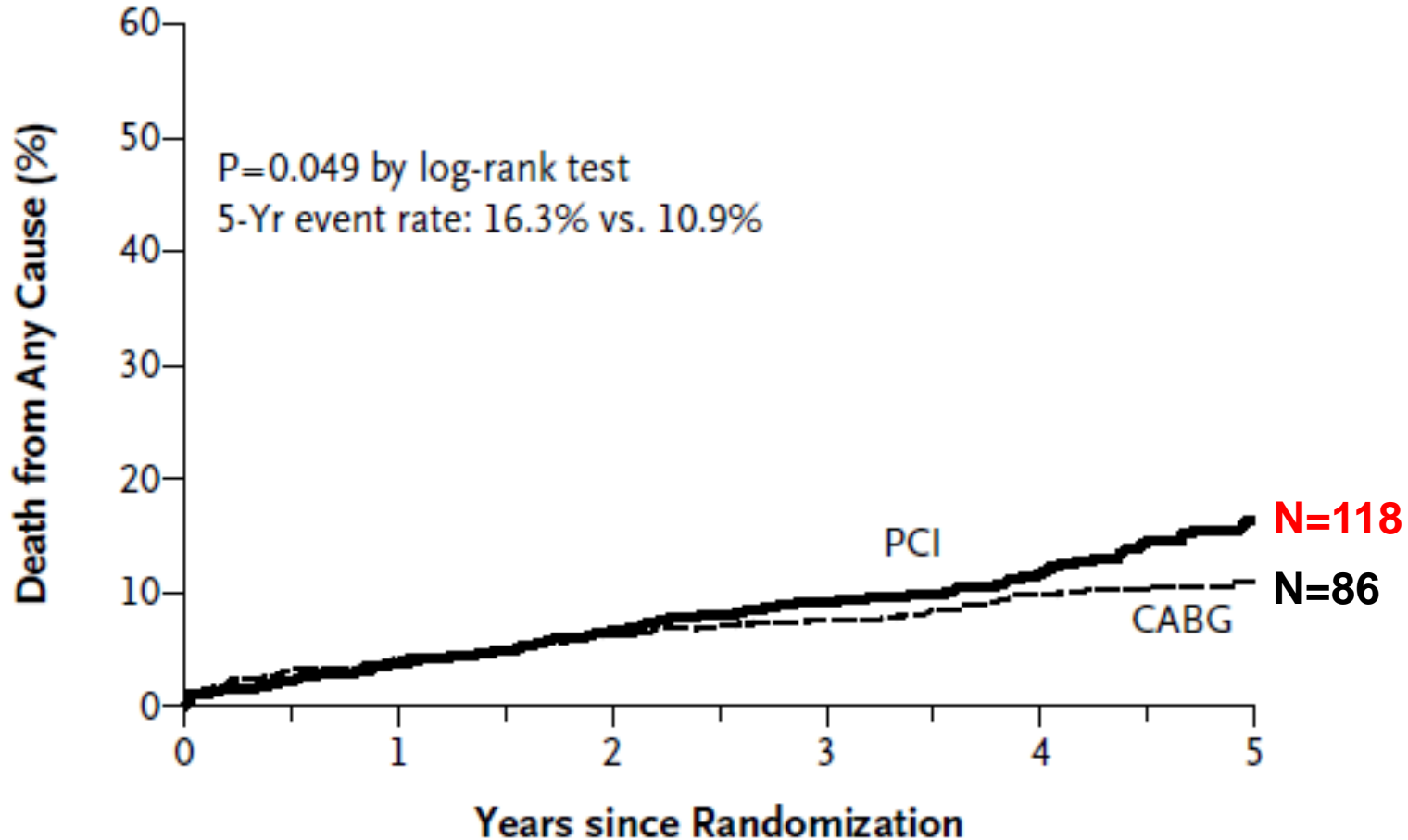
# FREEDOM TRIAL – PATIENT FLOW

Farkouh ME et al. *N Engl J Med* 2012; 367:2375-84



# FREEDOM TRIAL – MORTALITY

Farkouh ME et al. *N Engl J Med* 2012; 367:2375-84



## No. at Risk

PCI	953	897	845	685	466	243
CABG	947	855	806	655	449	238

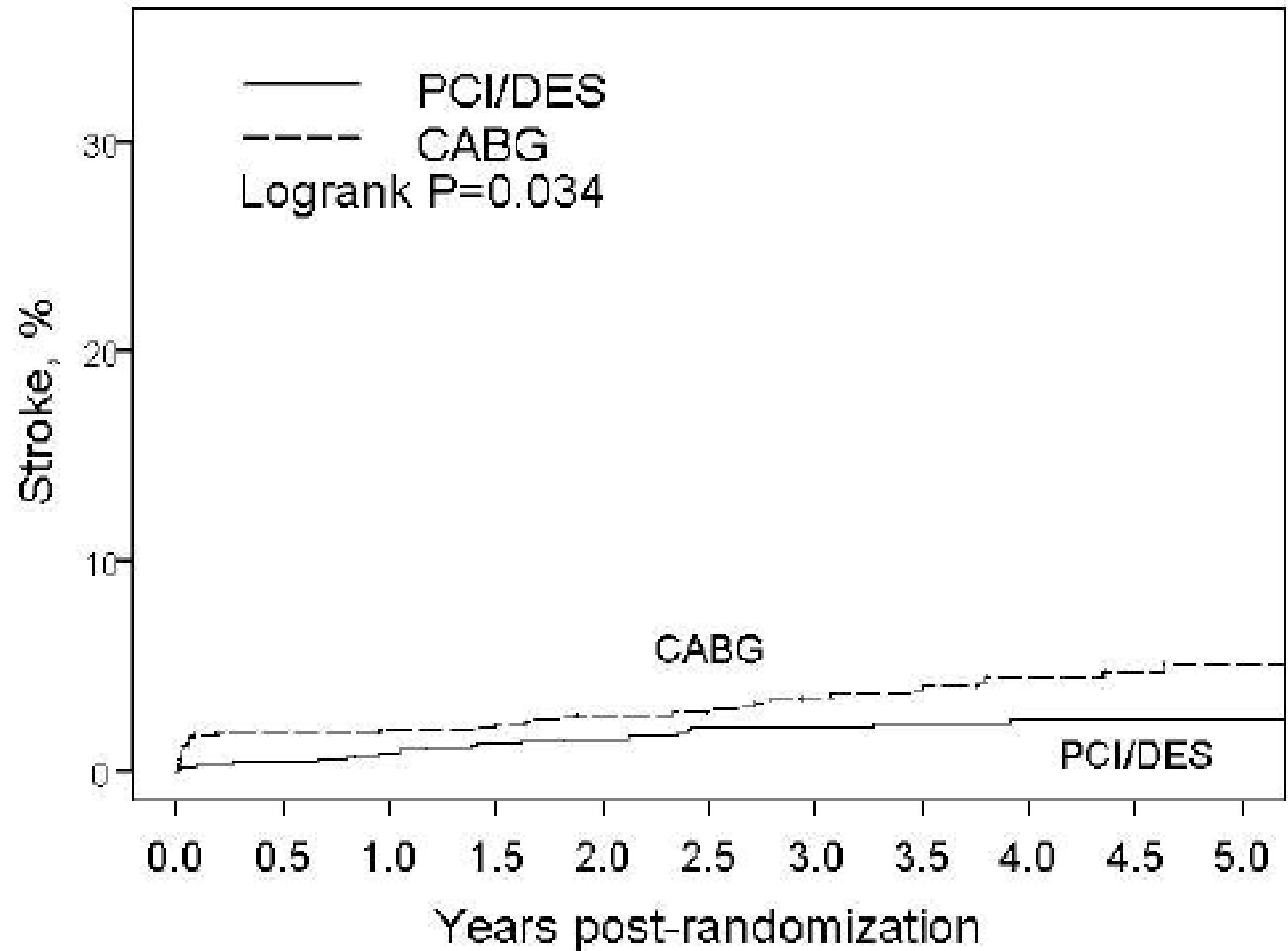
# Sensitivity Analysis - Mortality

	All non-evaluable patients having survived	All non-evaluable patients having died
PCI	118	177
CABG	86	173



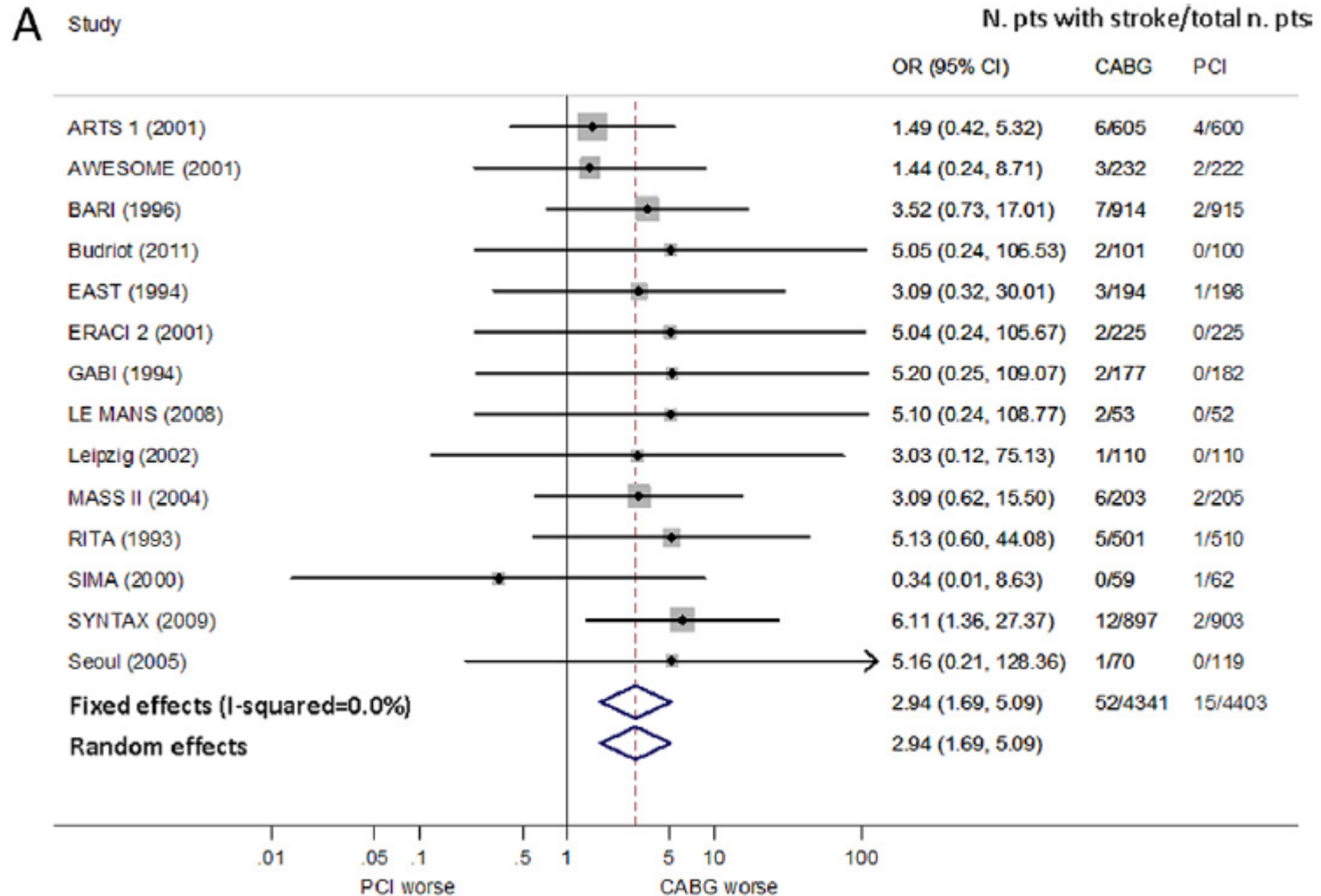
# FREEDOM TRIAL – STROKE OVER TIME

Farkouh ME et al. *N Engl J Med* 2012; 367:2375-84



# CABG vs PCI – RISK OF STROKE

Palmerini T et al. *J Am Coll Cardiol* 2012

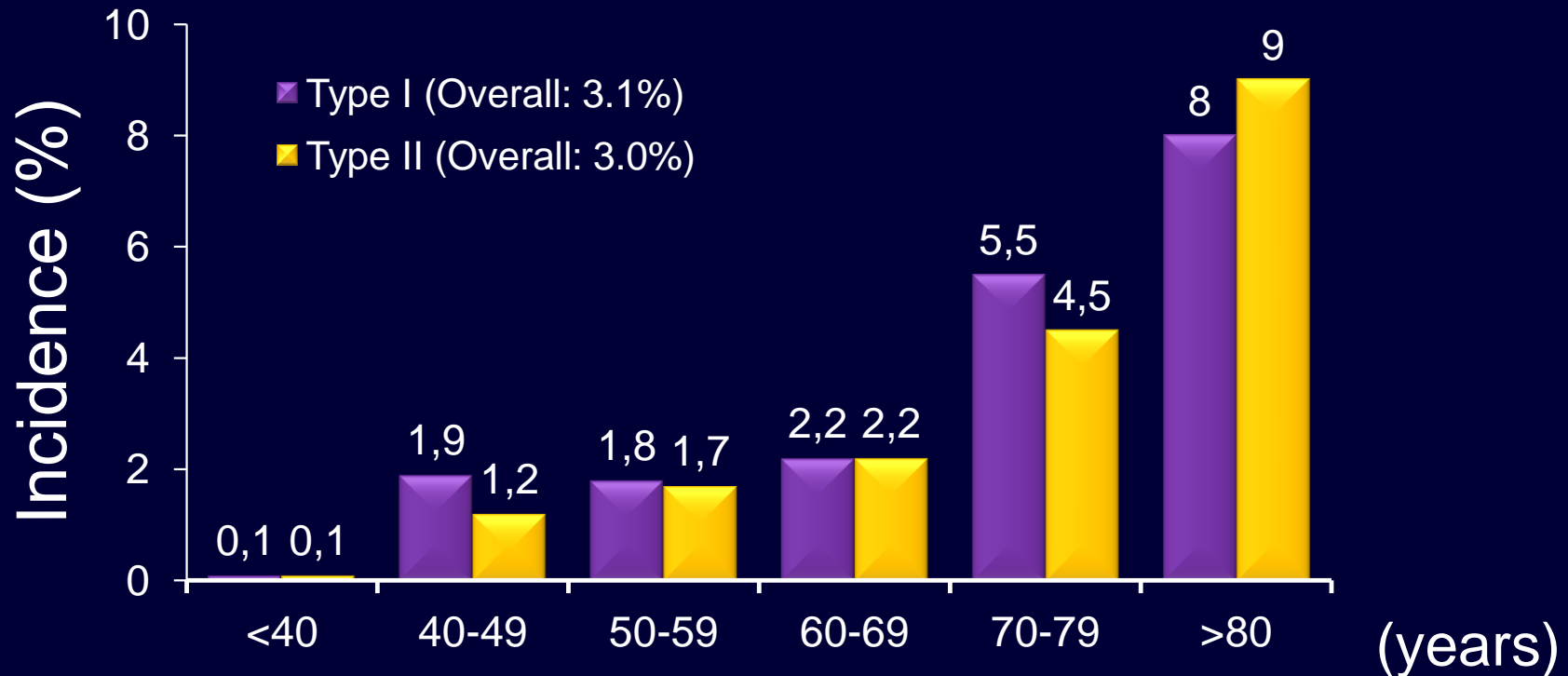


# Adverse Cerebral Outcomes After Coronary Artery Bypass Surgery

Roach et al. *N Engl J Med* 1996;335:1857-63

**Type I neurologic deficit: stroke, TIA, coma**

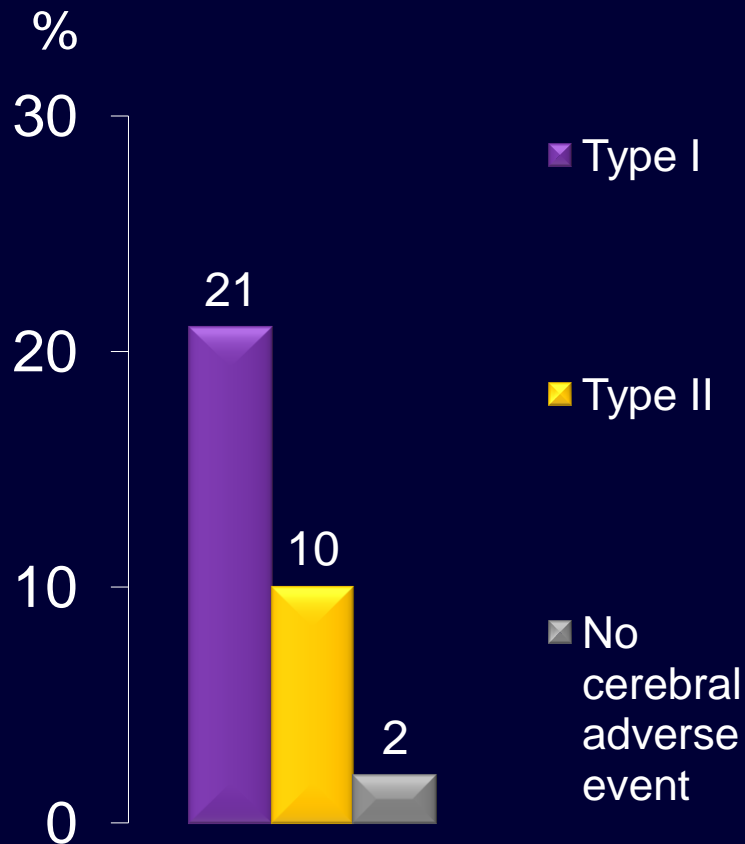
**Type II neurologic deficit: deterioration of intellect or seizures**



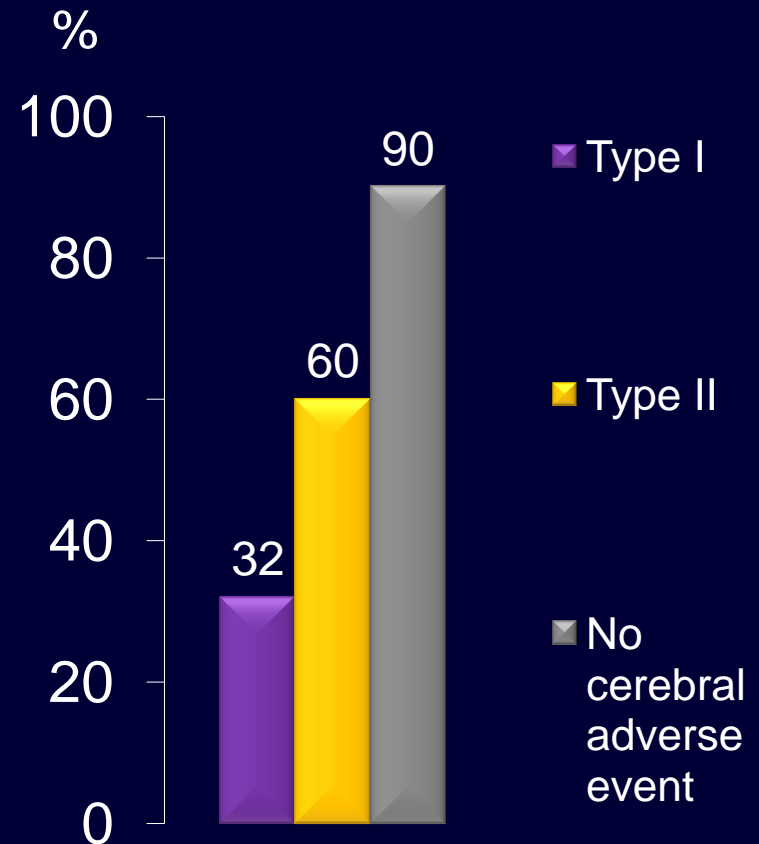
# Adverse Cerebral Outcomes After Coronary Artery Bypass Surgery

Roach et al. *N Engl J Med* 1996;335:1857-63

### In-hospital Mortality



### Discharge to Home



# Target Lesion Revascularization Network Meta-Analysis: DES vs BMS

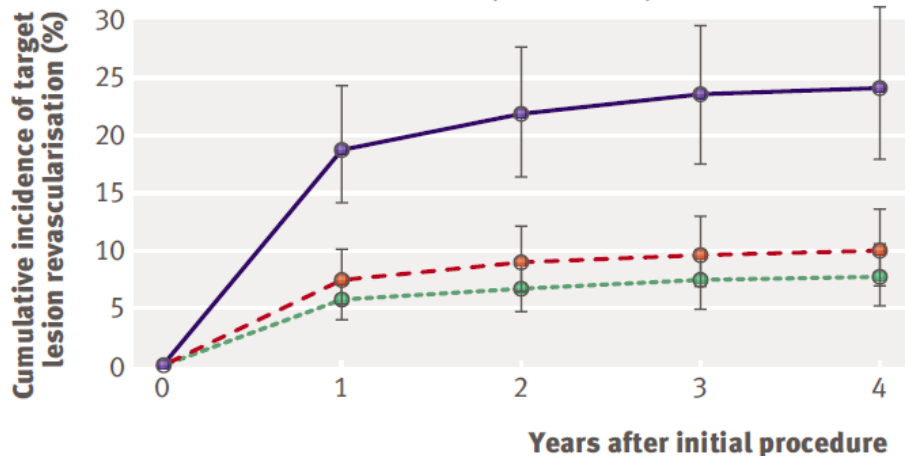
Stettler C et al. *BMJ* 2008; 337:a1331

**Diabetic Patients**  
**N=3,852**

**Non-Diabetic Patients**  
**N=10,947**

## People with diabetes mellitus

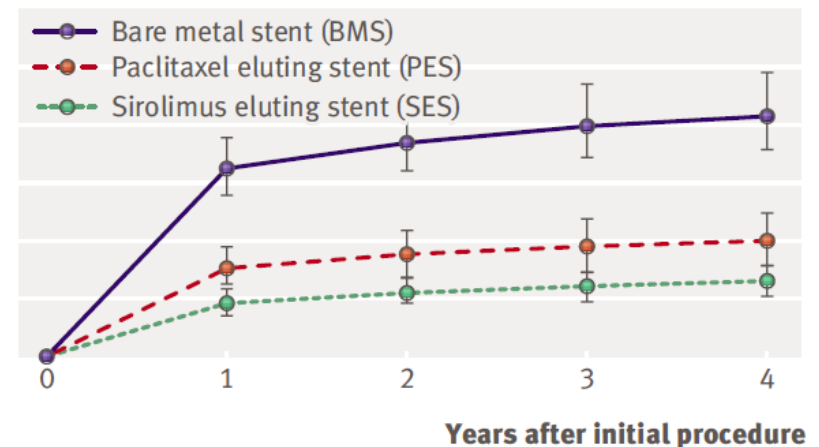
SES v BMS: hazard ratio 0.29 (0.19 to 0.45)  
PES v BMS: hazard ratio 0.38 (0.26 to 0.56)  
SES v PES: hazard ratio 0.78 (0.50 to 1.14)



	No of events/No of patients				
BMS	935	193/935	10/496	4/282	2/185
PES	1171	99/1171	21/946	3/487	3/146
SES	1122	80/1122	14/780	1/446	2/66

## People without diabetes mellitus

SES v BMS: hazard ratio 0.29 (0.19 to 0.42)  
PES v BMS: hazard ratio 0.46 (0.32 to 0.60)  
SES v PES: hazard ratio 0.64 (0.49 to 0.84)



	No of events/No of patients				
BMS	2851	423/2851	35/1619	6/916	3/711
PES	3582	278/3582	66/2844	13/1509	3/691
SES	2857	161/2857	34/1963	6/906	1/164

# Mortality in Diabetic vs Non-Diabetic Patients in Trials With At Least 6 Months Clopidogrel

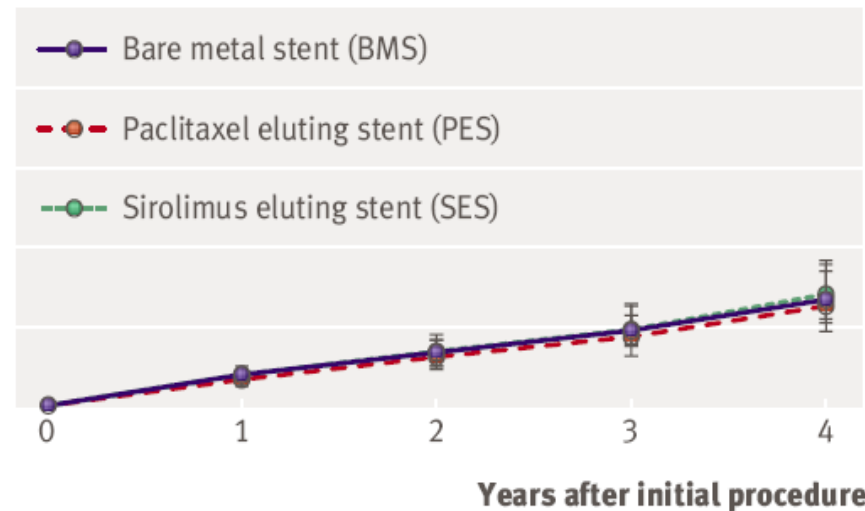
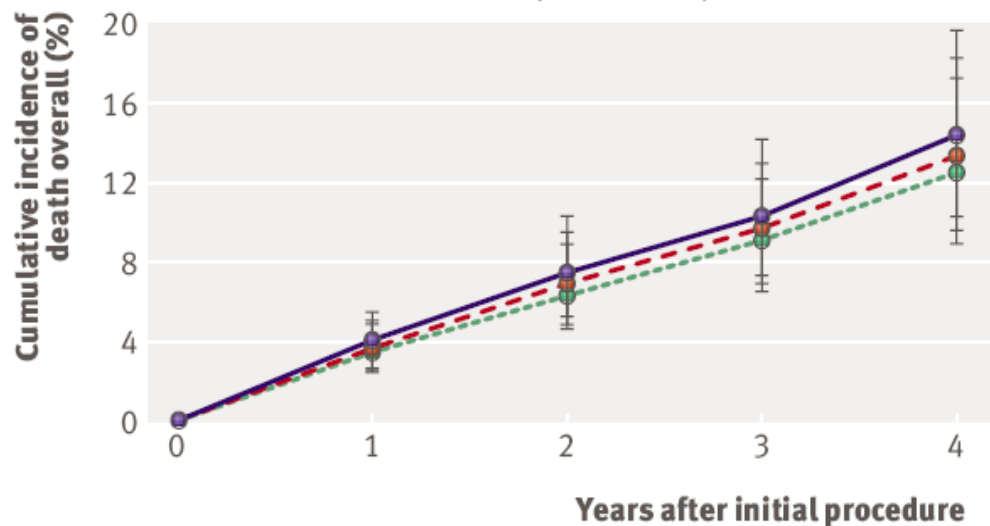
Stettler C et al. *BMJ* 2008; 337:1331

**Diabetic Patients**  
**N=3,852**

**Non-Diabetic Patients**  
**N=10,947**

SES v BMS: hazard ratio 0.88 (0.55 to 1.30)  
PES v BMS: hazard ratio 0.91 (0.60 to 1.38)  
SES v PES: hazard ratio 0.95 (0.63 to 1.43)

SES v BMS: hazard ratio 1.05 (0.69 to 1.73)  
PES v BMS: hazard ratio 0.89 (0.66 to 1.18)  
SES v PES: hazard ratio 1.23 (0.82 to 1.69)



No of events/No of patients

No of events/No of patients

BMS	904	37/904	15/632	7/358	10/224
PES	1162	35/1162	40/1020	11/535	3/158
SES	1078	39/1078	26/830	12/497	1/73

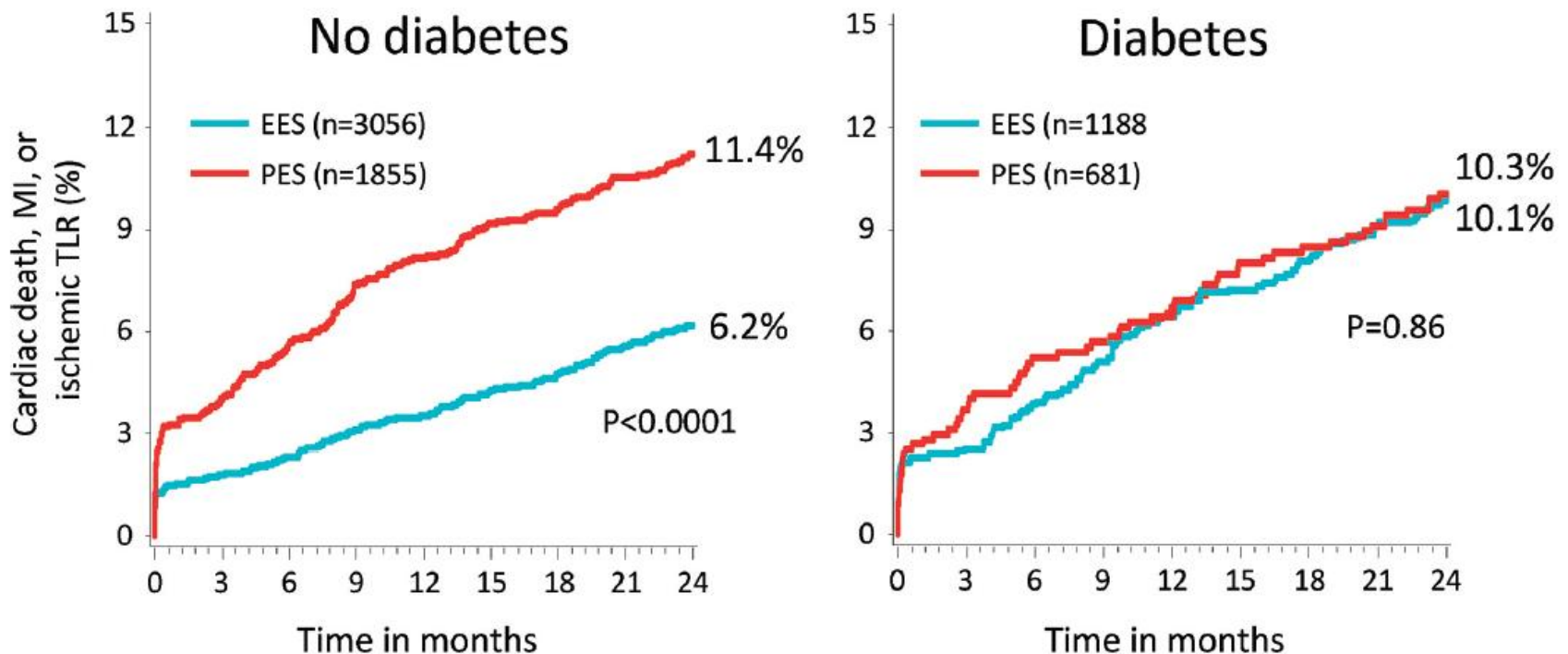
BMS	2851	60/2851	26/1845	10/1052	18/811
PES	3585	63/3585	35/3080	21/1655	12/722
SES	2857	52/2857	25/2091	10/995	6/182

# Everolimus- Versus Paclitaxel-Eluting Stents Among Diabetic and Nondiabetic Patients

Stone G et al. *Circulation* 2011; 124:893-900

**MACE @ 2 Years**

***P-inter = 0.0009***

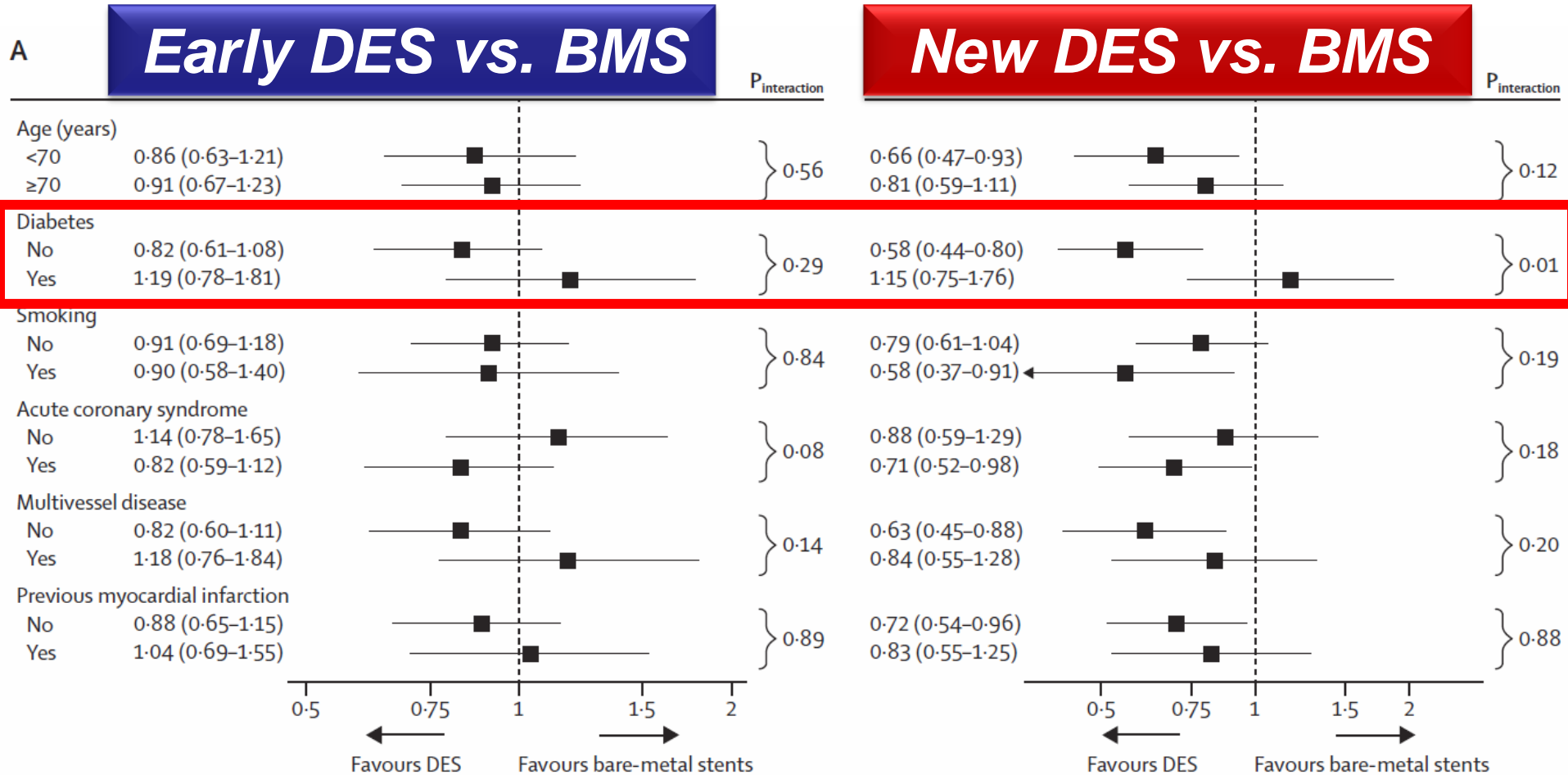


***IPD of SPIRIT II, III, IV, and COMPARE Trials (N=6,789)***

# Drug-Eluting vs. Bare-Metal Stents in Women

Stefanini G et al. *Lancet* 2013; 382(9908):1879-88

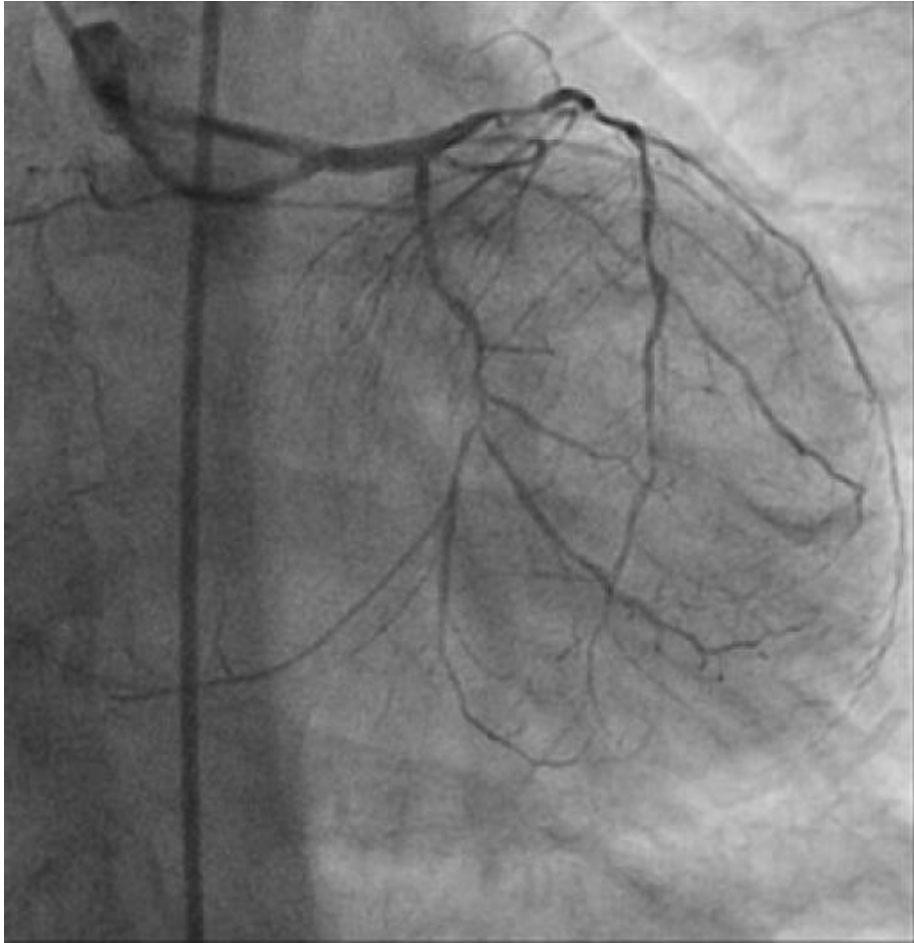
## Death or MI in Major Subgroups



**11,557 Women enrolled into 26 Randomized Trials between 2000 and 2013**

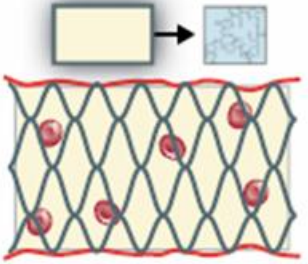
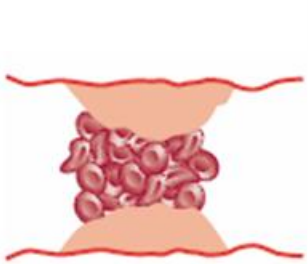


# DIFFUSE MULTIVESSEL CAD

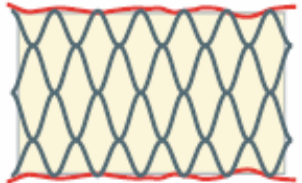


# Coronary Scaffolds Compared With Coronary Stents

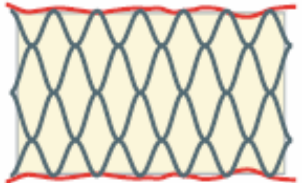
## Stents



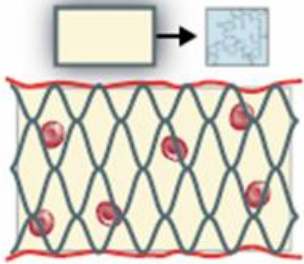
*Scaffolding function and drug release*



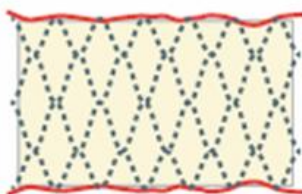
*Caged Vessel*



## Scaffolds



*Scaffolding function and drug release*



*Bioresorption*



*Restoration of vascular physiology and lumen enlargement*

# Efficacy and Safety of DES, BMS, and CABG According to Clinical Indication

Stefanini G, Holmes D. *N Eng J Med* 2013;368:254-65

Outcome and Intervention	Stable Coronary Artery Disease	Acute Myocardial Infarction	Diabetes	Multivessel Disease	Left Main Coronary Artery Disease
<b>Restenosis</b>					
Implantation of bare-metal stent	+	+	+	+	+
Implantation of drug-eluting stent					
Early-generation	++	++	++	++	++
New-generation	+++	+++	++	++ [+]	++ [+]
CABG	+++	-	+++	+++	+++
<b>Cardiac death, myocardial infarction, or stent thrombosis</b>					
Implantation of bare-metal stent	+	+	+	+	+
Implantation of drug-eluting stent					
Early-generation	+	+/-	+	+	+
New-generation	+ [+]	+ [+]	+	+ [+]	++ [+]
CABG	+	-	++	++	++

# Conclusions

- Advanced stent platforms with excellent deliverability, less arterial injury and improved biocompatibility
- The risk of repeat revascularization is further reduced
- The risk of ST is extremely low
- Diabetes remains the Achilles heel of current DES, particularly in patients with complex multivessel disease