

Left Main Clinical Trials

MAIN COMPARE Registry, AMC MAIN registry, SYNTAX LM, Pre-COMBAT, Pre-COMBAT-2, and IRIS-MAIN

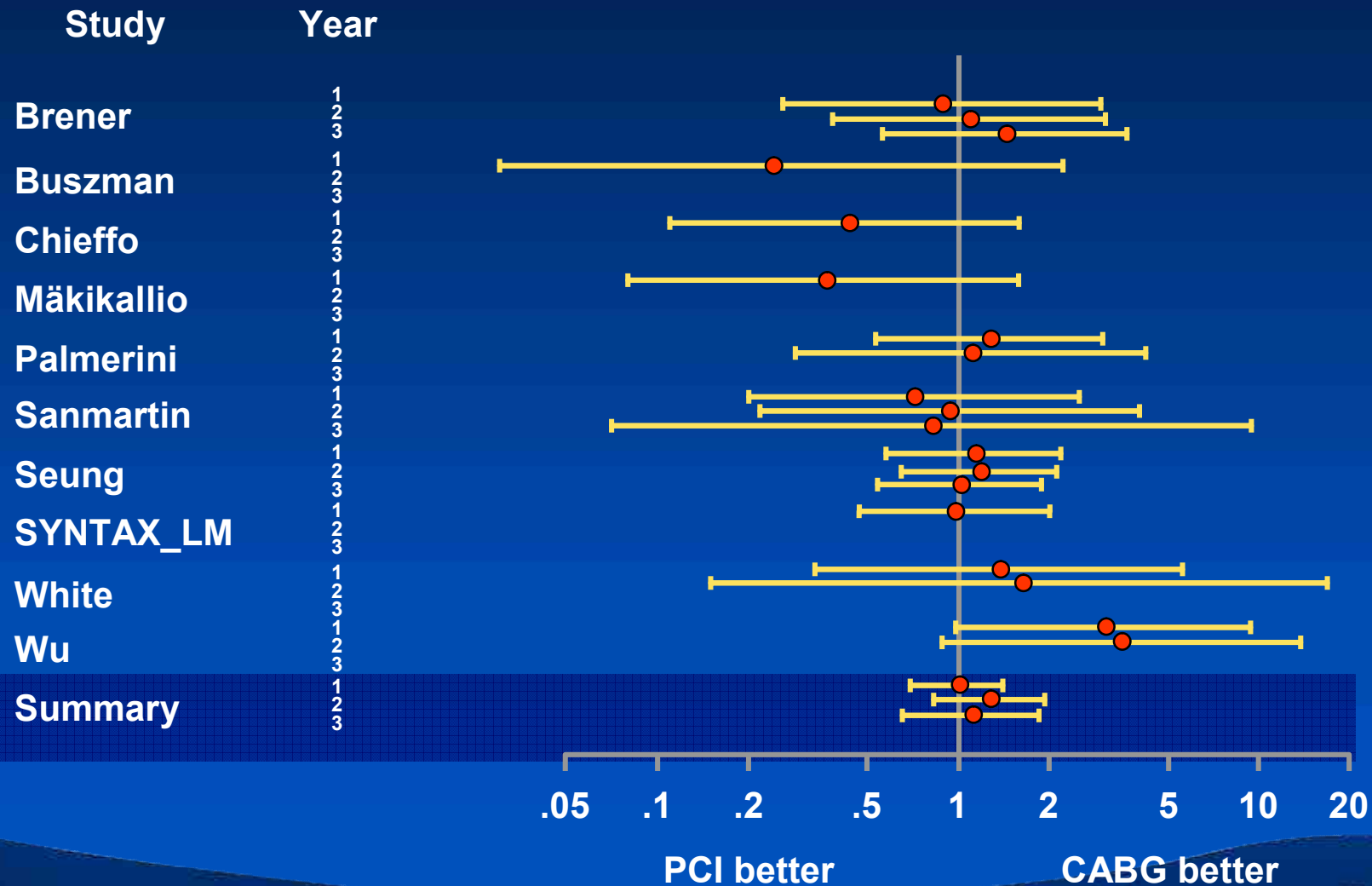
Seung-Jung Park, MD, PhD

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Heart Institute, Asan Medical Center,
Seoul, Korea

Unprotected LMCA - PCI vs CABG

Meta-analysis of 3,773 patients in 10 studies (CABG: 2,114 patients, PCI: 1,659 patients)

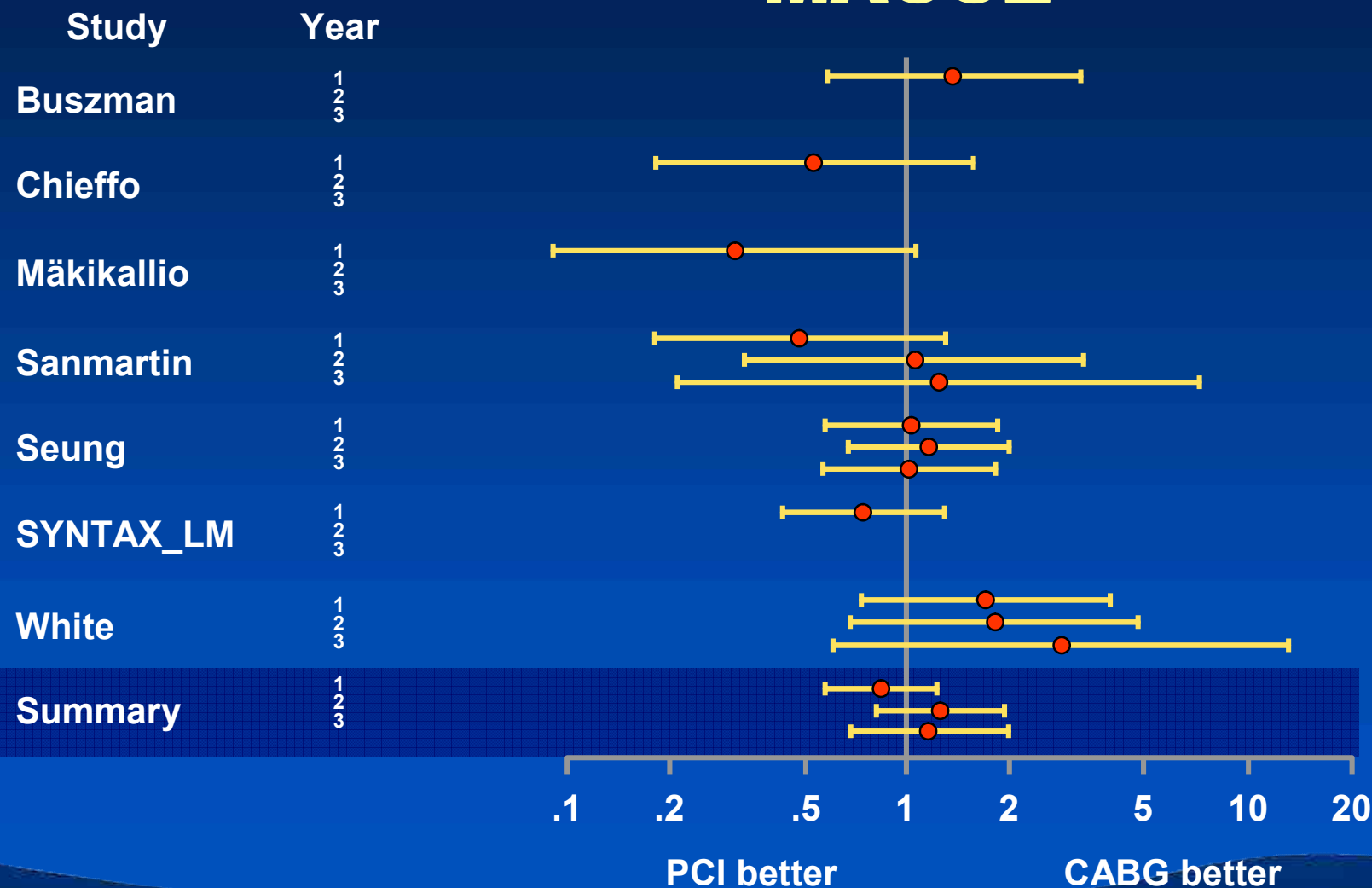
Mortality



Unprotected LMCA - PCI vs CABG

Meta-analysis of 3,773 patients in 10 studies (CABG: 2,114 patients, PCI: 1,659 patients)

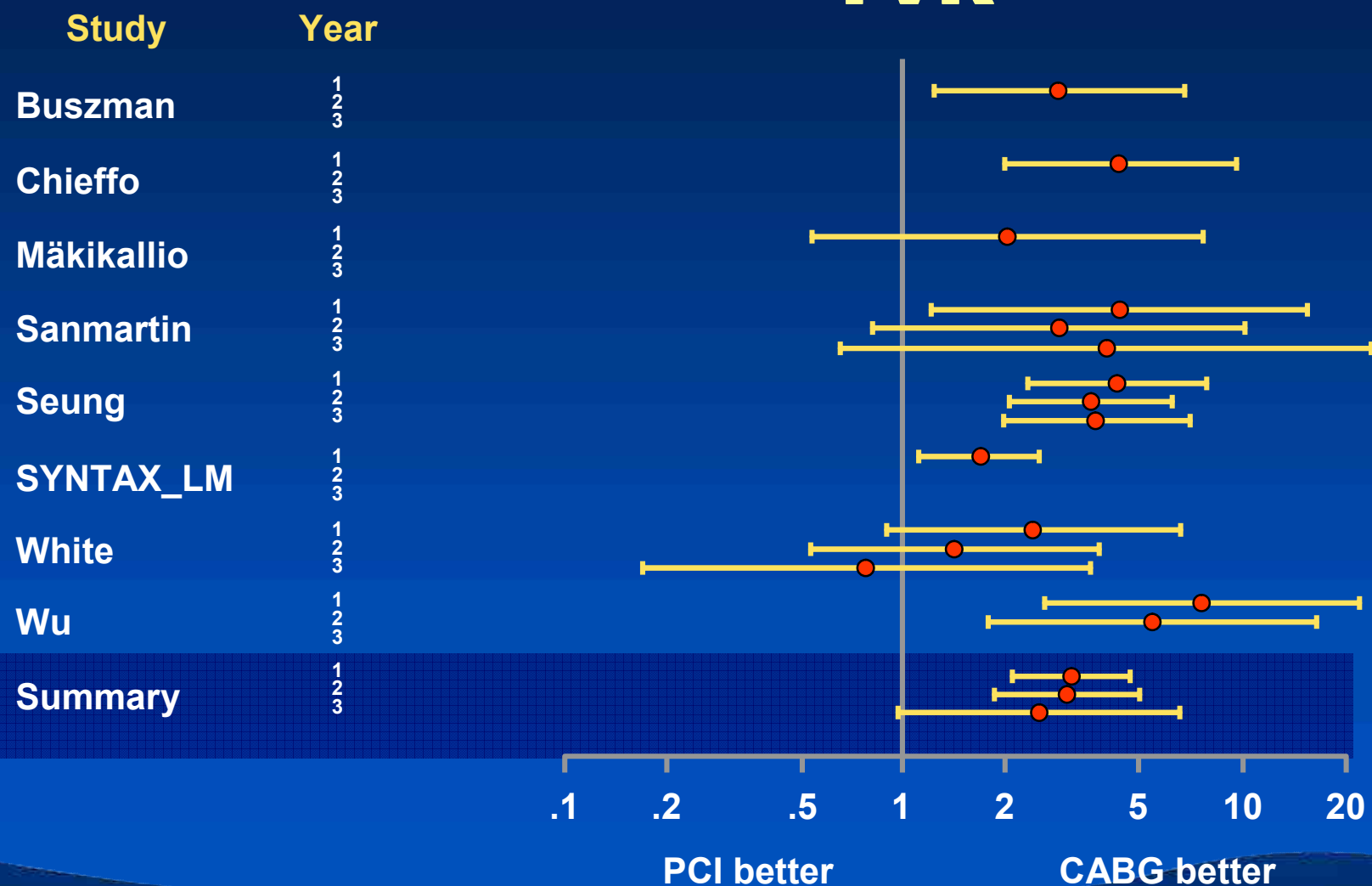
MACCE



Unprotected LMCA - PCI vs CABG

Meta-analysis of 3,773 patients in 10 studies (CABG: 2,114 patients, PCI: 1,659 patients)

TVR



MAIN COMPARE Registry

STENT vs CABG follow-up at 3 year

The MAIN-COMPARE Study

Crucial Points

- Total 2,240 patients with either PCI or CABG were included
- 97% of 1,102 patients suitable for either PCI or CABG
- DES used in 71%
- Propensity matched patients
- Central adjudication of events

Seung KB, Park DW, Park SJ, NEJM 2008;358:1781-92

MAIN COMPARE registry

Wave 1 (BMS)

LM disease treated
with BMS (n=318)
and CABG (n=448)

Wave 2 (DES)

LM disease treated
with DES (n=784)
and CABG (n=690)

Total
2240

Stent (N=1102)

CABG (N=1138)



From January 2000 through June 2006

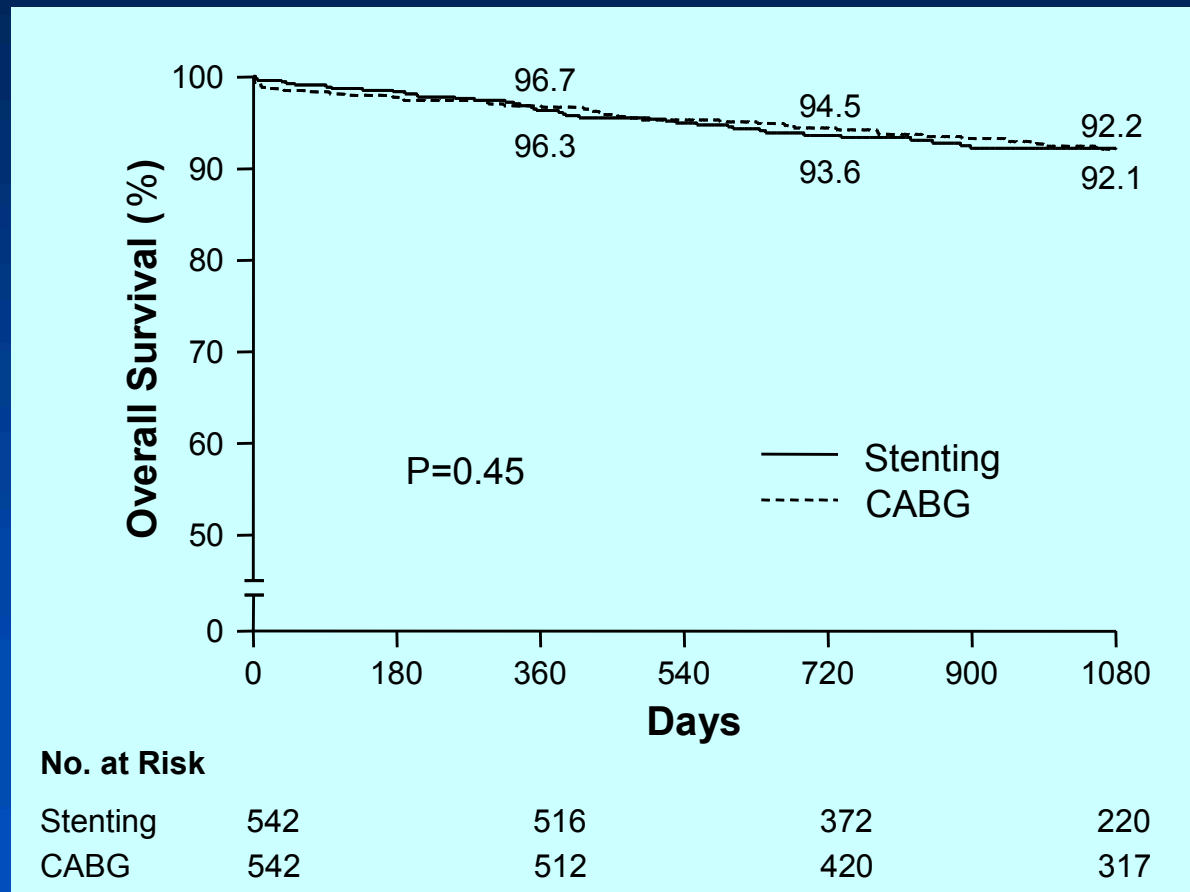
Clinical follow-up every 12 months
Death, Composite of Death/MI/Stoke, TVR

After Propensity-Matching

Overall matched cohort (n=542 pairs)
PCI vs CABG

Death

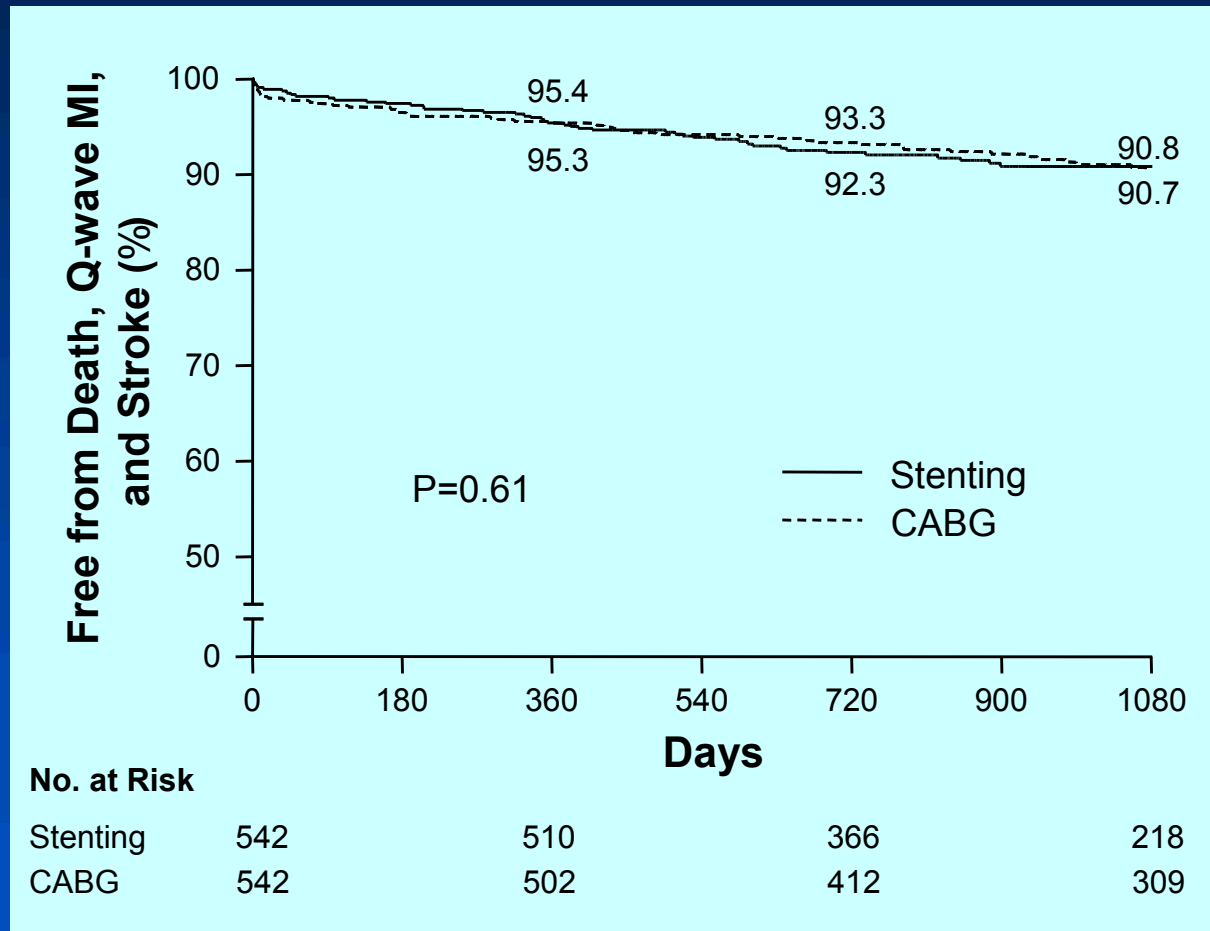
(Overall PCI and CABG matched cohort: 542 pairs)



Seung KB, Park DW, Park SJ, NEJM 2008;358:1781-92

Death, Q-MI, or Stroke

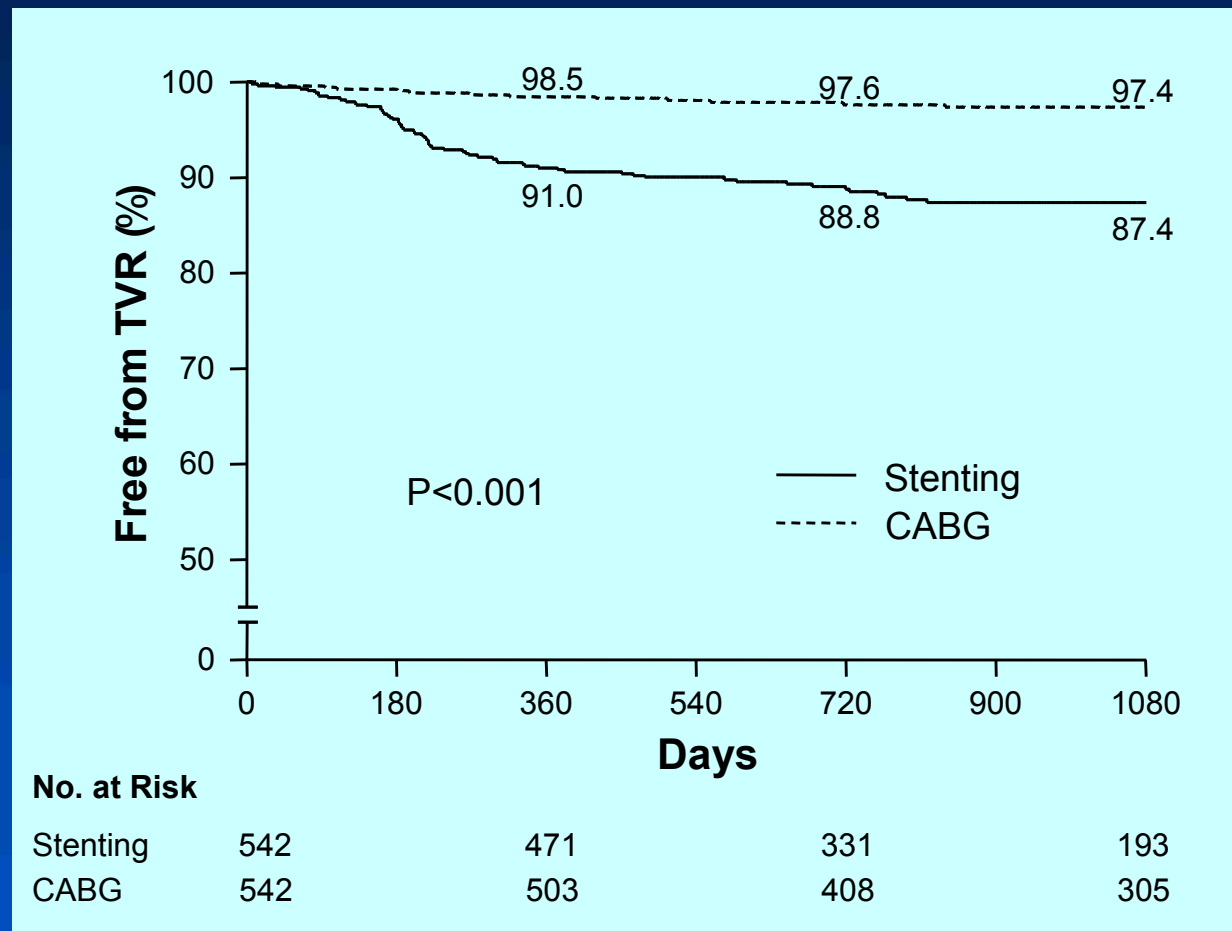
(Overall PCI and CABG matched cohort: 542 pairs)



Seung KB, Park DW, Park SJ, NEJM 2008;358:1781-92

Target-vessel revascularization

(Overall PCI and CABG matched cohort: 542 pairs)



Seung KB, Park DW, Park SJ, NEJM 2008;358:1781-92

Hazard Ratios for Clinical Outcomes : Median 3-Year Outcomes

- All PCI patients (n=542 pairs)
- Bare-metal stents (n=207 pairs)
- Drug-eluting stents (n=542 pairs)

P<0.001

P=NS

P=NS

HR 1.0 to
concurrent CABG

1.18 1.04 1.36

1.10 0.86 1.40

4.76 10.70 5.96

Death

Composite of death,
Q-wave MI, or stroke

Target-vessel
revascularization

Key Subgroup Analysis in **MAIN-COMPARE Registry**

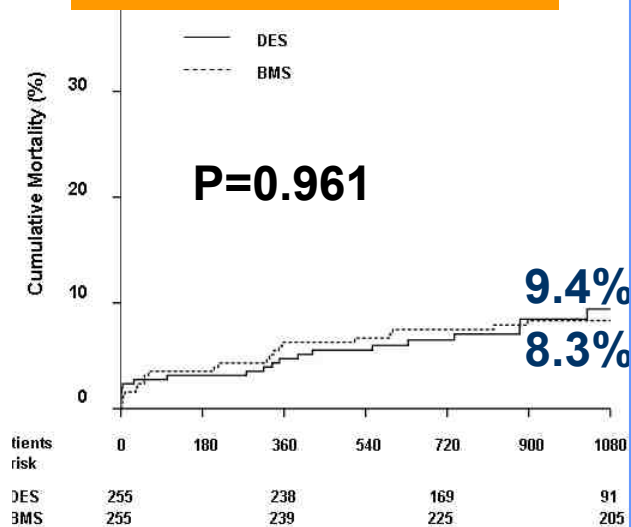
- BMS vs. DES
- IVUS guided vs. Angio-guided
- Cypher vs. TAXUS
- Non-distal vs. Distal
- 1 stent vs. 2 stents for distal LM
- Isolated LM disease
- Impact of disease extent
- Impact of DM
- Predictor analysis

BMS vs. DES

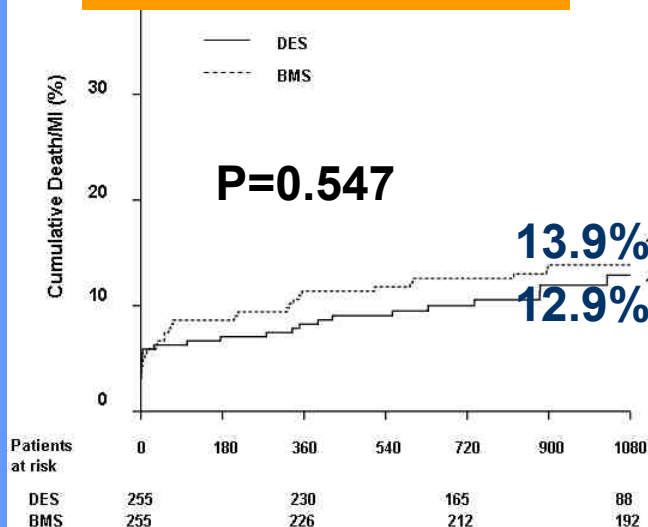
255 Propensity Matched-Pairs

Clinical Outcomes at 3 year F/U

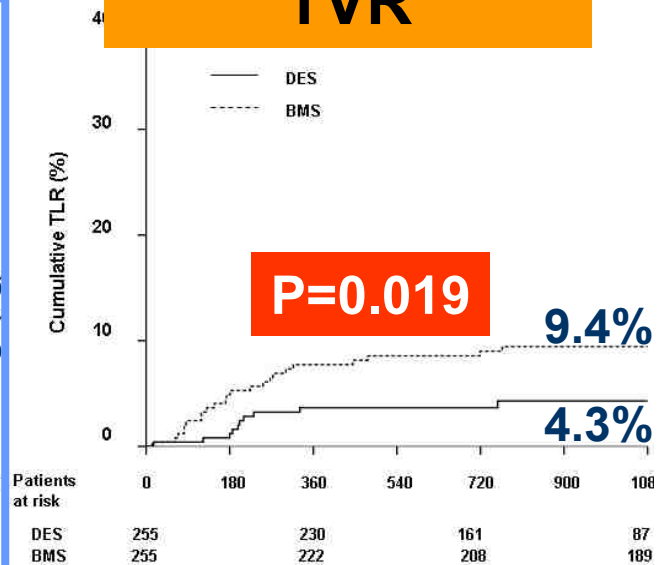
Death



Death or MI



TVR

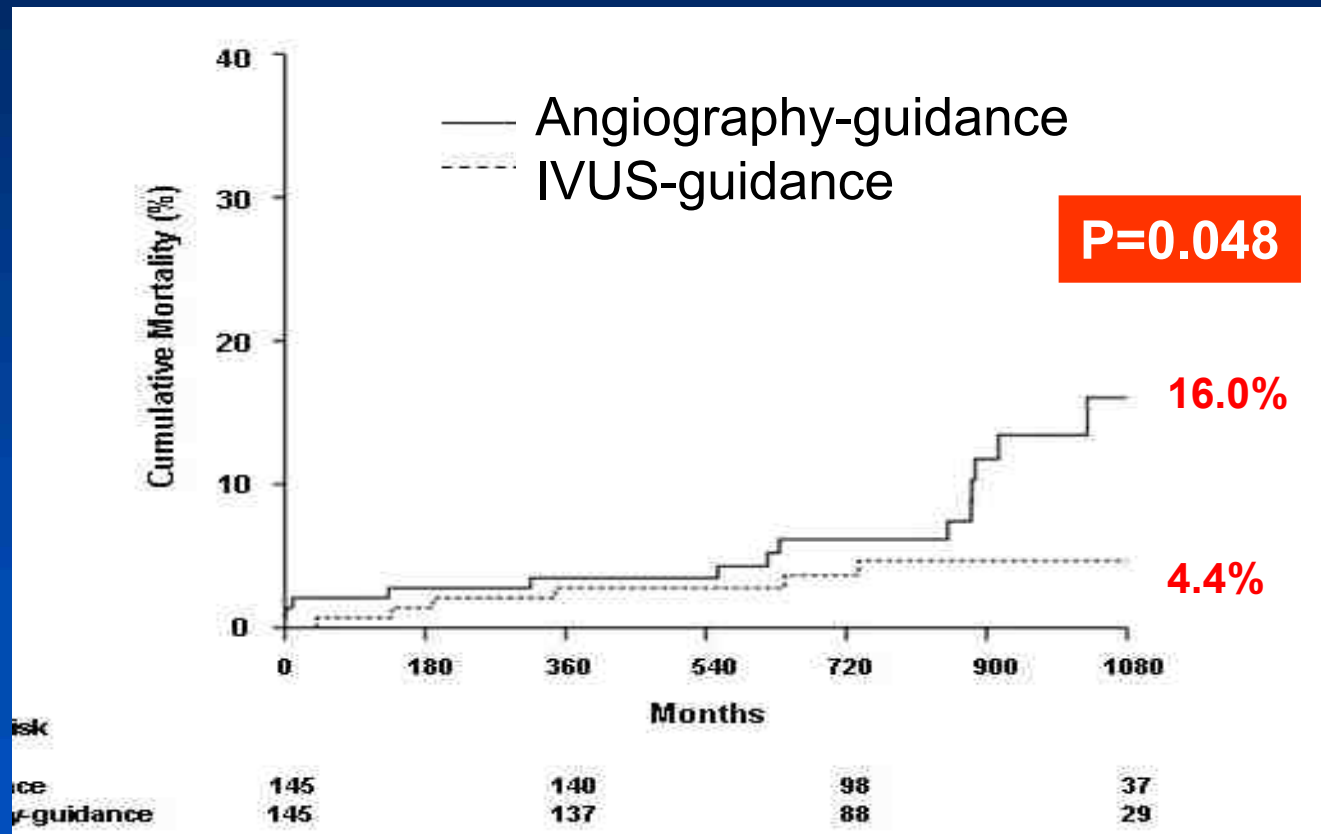


Kim YH, Park SJ, et al. Circulation 2009

IVUS guided in DES

201 Propensity Matched-Pairs

All cause Mortality at 3 year F/U



Park SJ et al, Circulation Cardiovasc Intervent 2009

Cypher vs. TAXUS

Crude and Adjusted HRs of Clinical Outcomes According to DES Type

Outcome	Crude		Multivariable adjusted†		Adjusted for propensity	
	Hazard Ratio (95% CI)	<i>P</i>	Hazard Ratio (95% CI)	<i>P</i>	Hazard Ratio (95% CI)	<i>P</i>
Death	0.88 (0.49-1.56)	0.66	0.92 (0.47-1.80)	0.82	0.93 (0.50-1.71)	0.81
MI	0.95 (0.54-1.70)	0.87	0.80 (0.43-1.48)	0.47	0.87 (0.48-1.59)	0.66
TVR	1.27 (0.64-2.51)	0.49	1.10 (0.53-2.29)	0.81	1.11 (0.55-2.26)	0.77
Death, MI, or TVR	1.02 (0.71-1.49)	0.90	0.95 (0.64-1.41)	0.79	0.99 (0.67-1.46)	0.95

*HR for cypher with reference to taxus.

Lee JY, Park SJ, et al. JACC 2009

Non-distal vs. Distal LM

Crude and Multivariable-Adjusted Cox Regression Analysis ;

**Non-Distal lesions :
DES (N=363) vs. CABG (N=355)**

**Distal Bifurcation lesions :
DES (N=467) vs. CABG (N=566)**

Hazard Ratios of Clinical outcomes DES in Non-Distal Lesions

Outcome	Crude		Multivariable adjusted	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Death	0.97 (0.59-1.59)	0.90	1.001 (0.50-1.99)	0.99
Stroke	2.0 (0.61-6.67)	0.25	1.42 (0.37-5.45)	0.61
TVR	3.83(1.43-10.25)	0.004	7.71 (1.78-33.38)	0.006
Death, Q-MI, or Stroke	0.97 (0.61-1.55)	0.90	1.06 (0.57-1.99)	0.852
Death, Q-MI, Stroke, or TVR	1.23 (0.82-1.85)	0.31	1.51 (0.91-2.49)	0.111

***HR for stents with reference to CABG.**

Hazard Ratios of Clinical outcomes DES in Distal Bifurcation Lesions

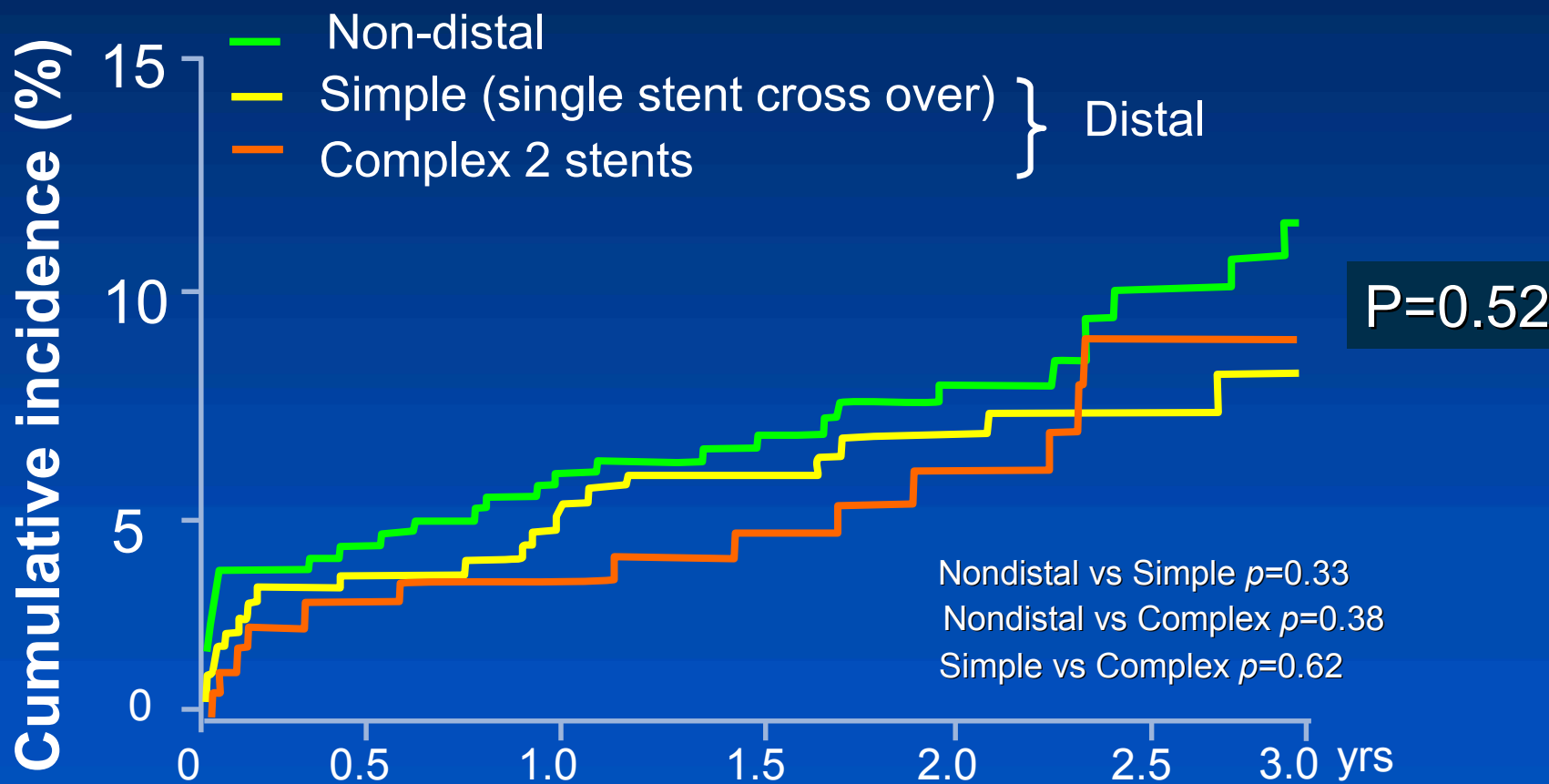
Outcome	Multivariable adjusted	
	Hazard Ratio (95% CI)	P
Death	0.66 (0.35-1.26)	0.21
Stroke	0.72 (0.23-2.23)	0.57
TVR	6.23 (3.12-12.44)	<0.001
Death, Q-MI, or Stroke	0.95 (0.56-1.82)	0.62
Death, Q-MI, Stroke, or TVR	1.42 (1.02-1.97)	0.04

***HR for stents with reference to CABG.**

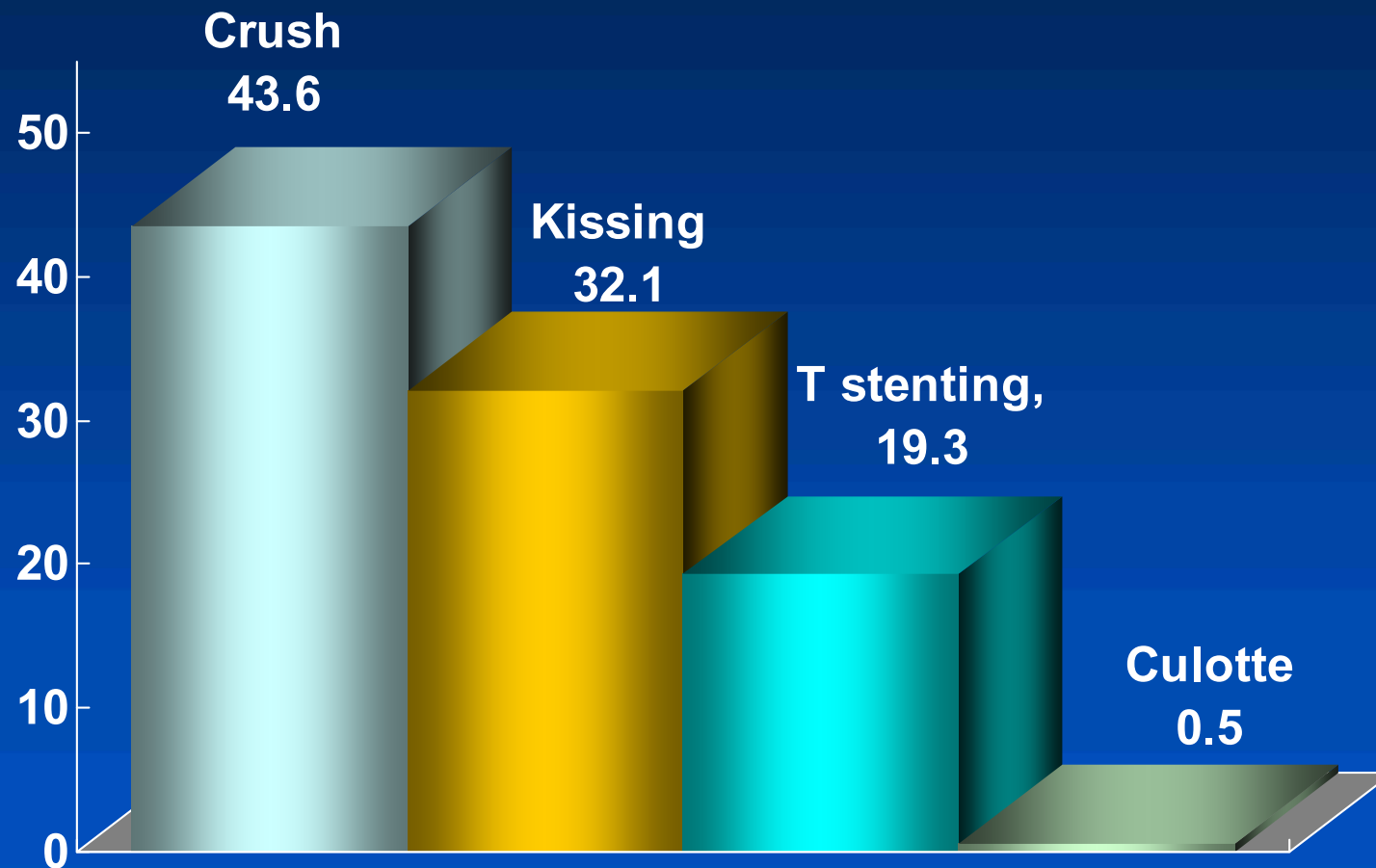
1 stent vs 2 stents

For Distal LM disease

Death at 3 year F/U



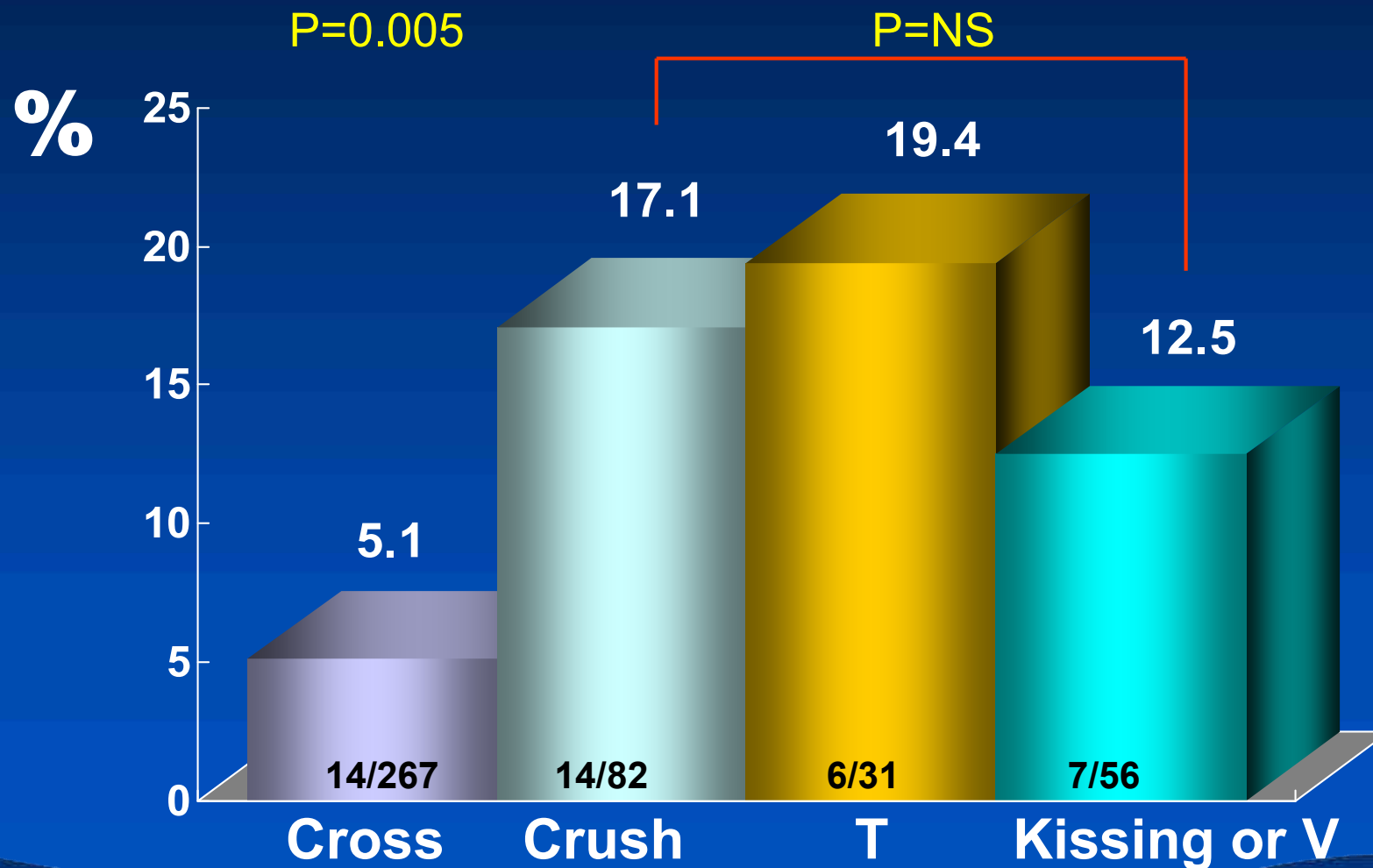
2 Stenting Techniques for LM bifurcation (DES, N=503 patients)



Data from MAIN COMPARE Registry

TLR at 4 year

According to LM Bifurcation Stenting Technique

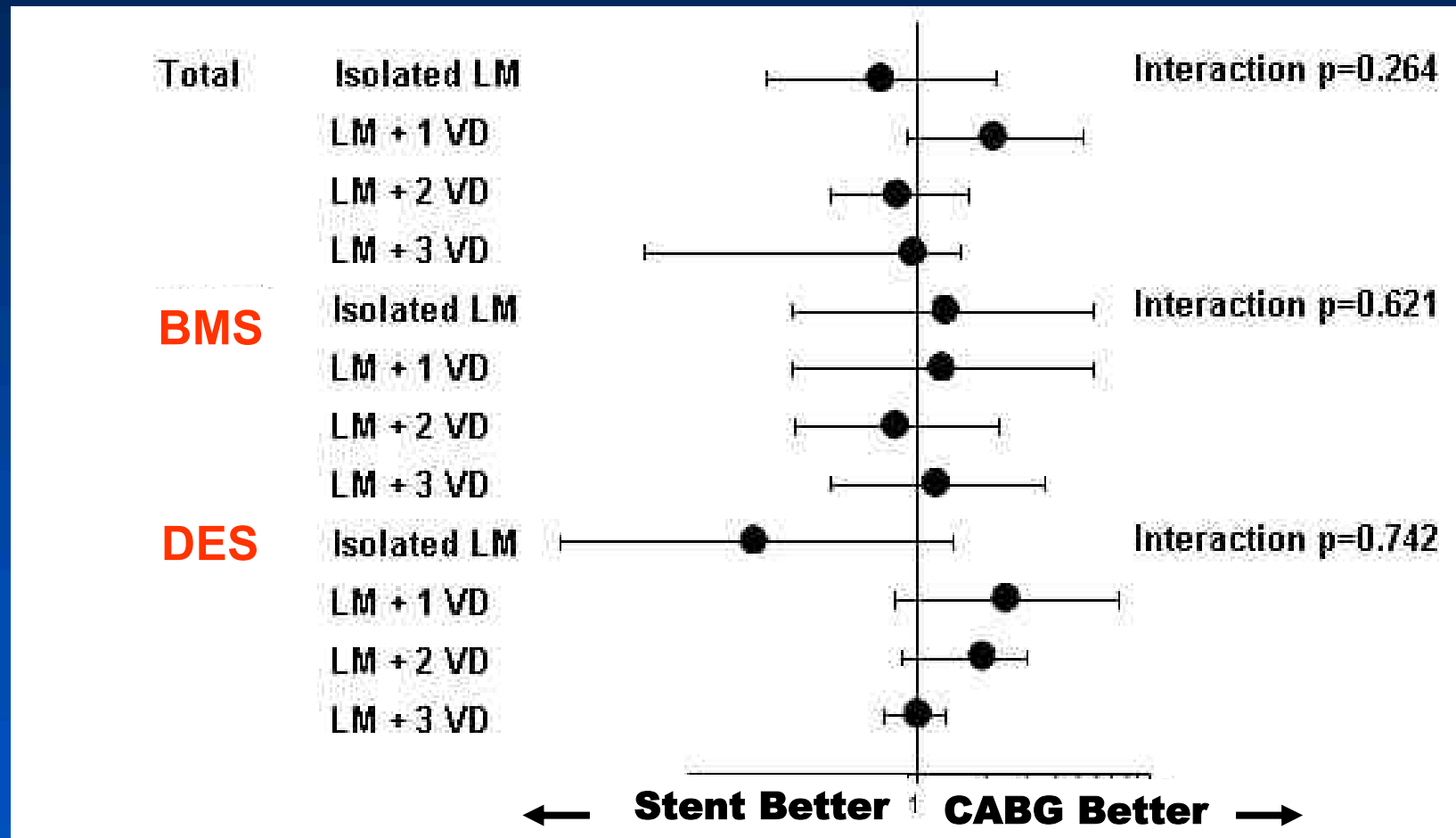


Impact of Disease Extents

Kim YH, Park SJ, et al. JACC 2009

Adjusted HR: Treatment effect of Stents to CABG

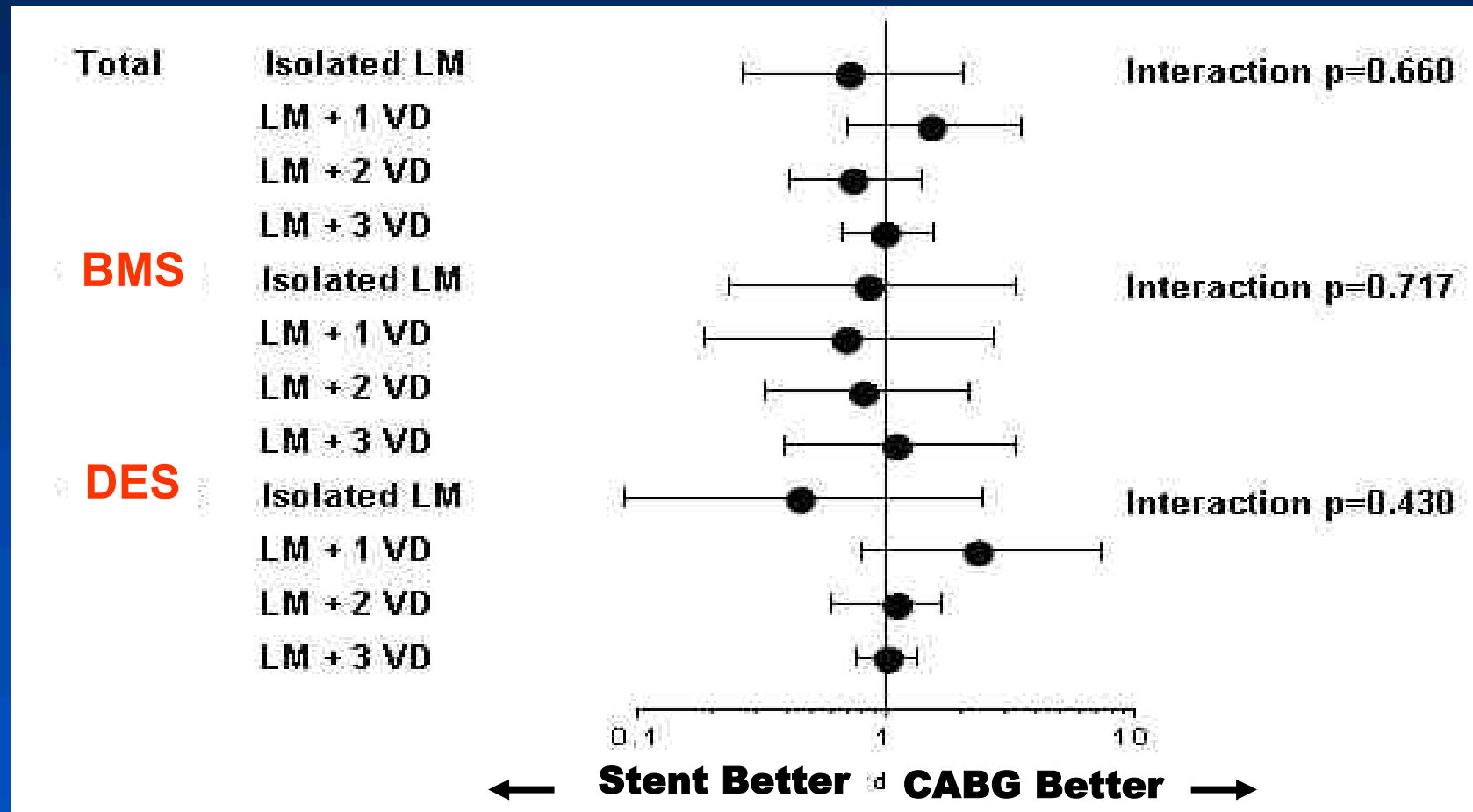
Death



Kim YH, Park SJ, et al. JACC 2009

Adjusted HR: Treatment effect of Stents to CABG

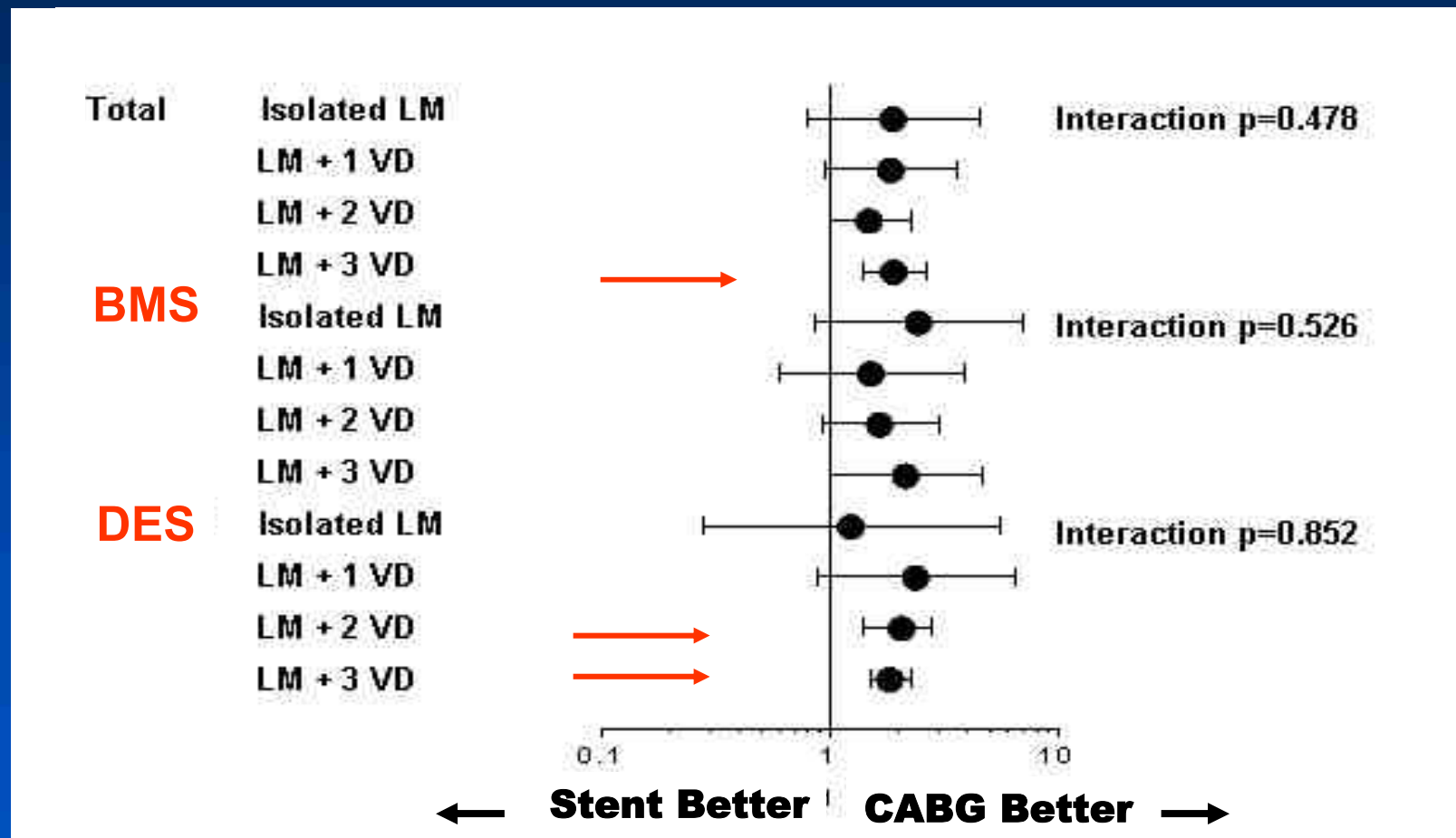
Death, Q-MI, or Stroke



Kim YH, Park SJ, et al. JACC 2009

Adjusted HR: Treatment effect of Stents to CABG

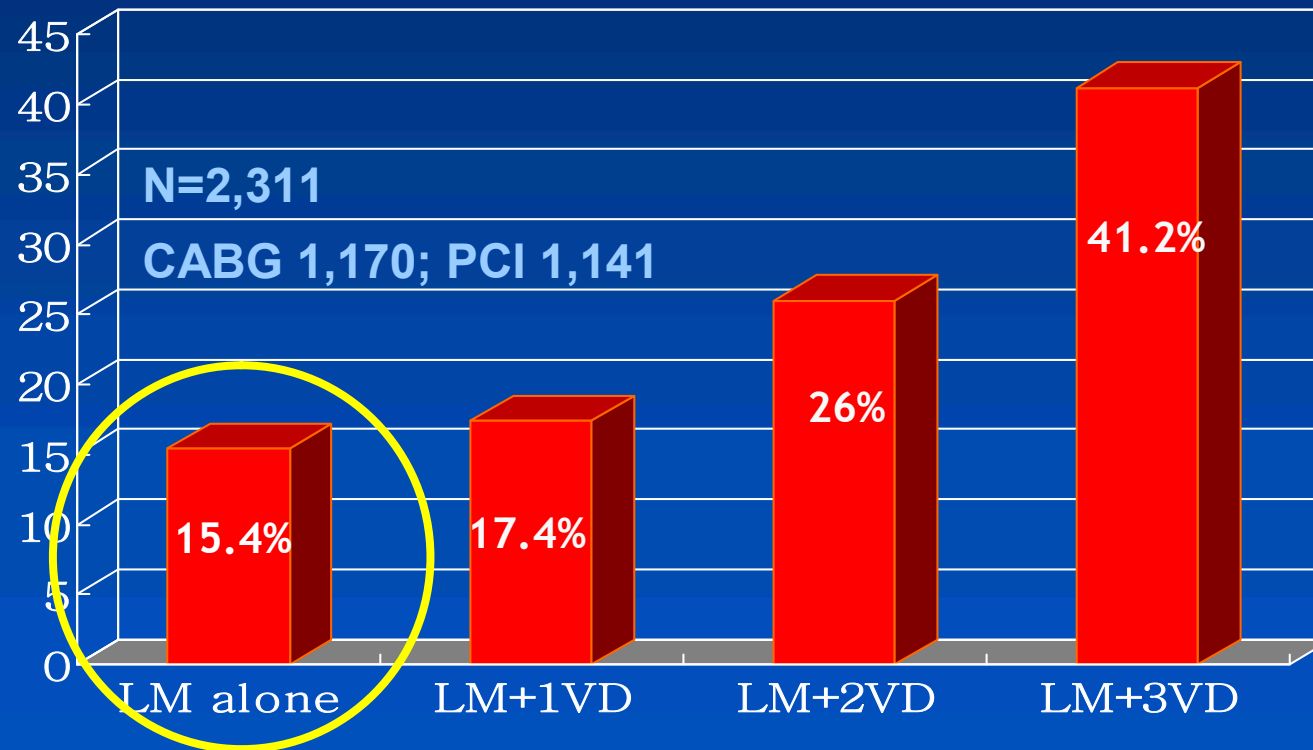
Death, QMI, Stroke, or TVR



Kim YH, Park SJ, et al. JACC 2009

Isolated Left Main Stenosis

Supportive data from MAIN COMPARE registry about **Isolated LM disease**

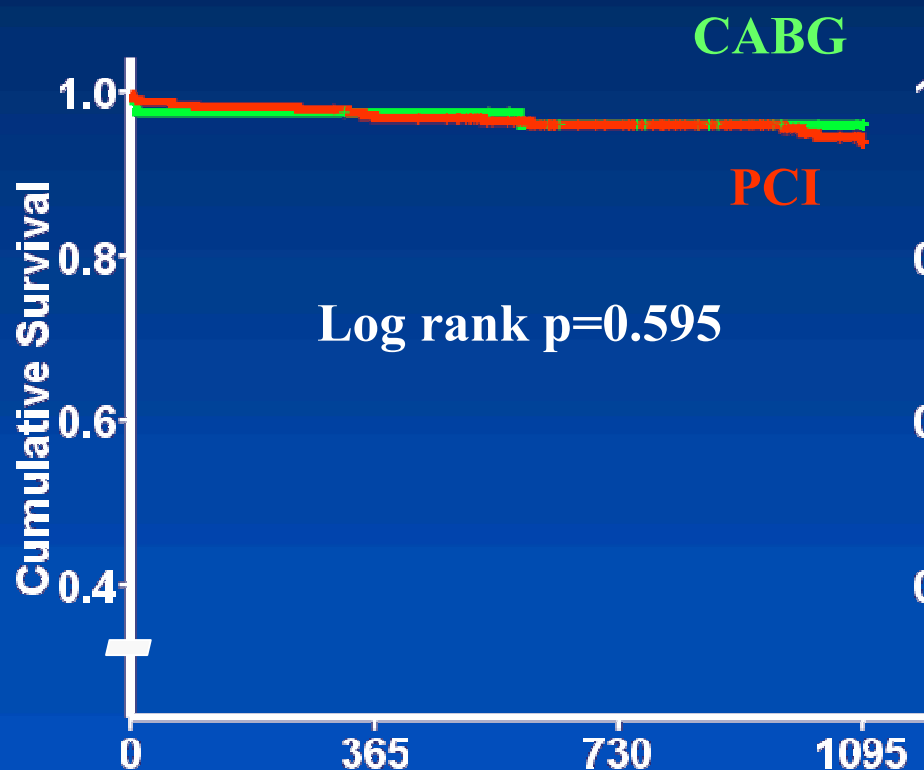


LM Involved Site

	CABG (n=73)	PCI (n=291)
Ostium	18 (25.7%)	122 (41.9%)
Shaft	27 (38.6%)	103 (35.4%)
Bifurcation	25 (35.7%)	63 (21.6%)

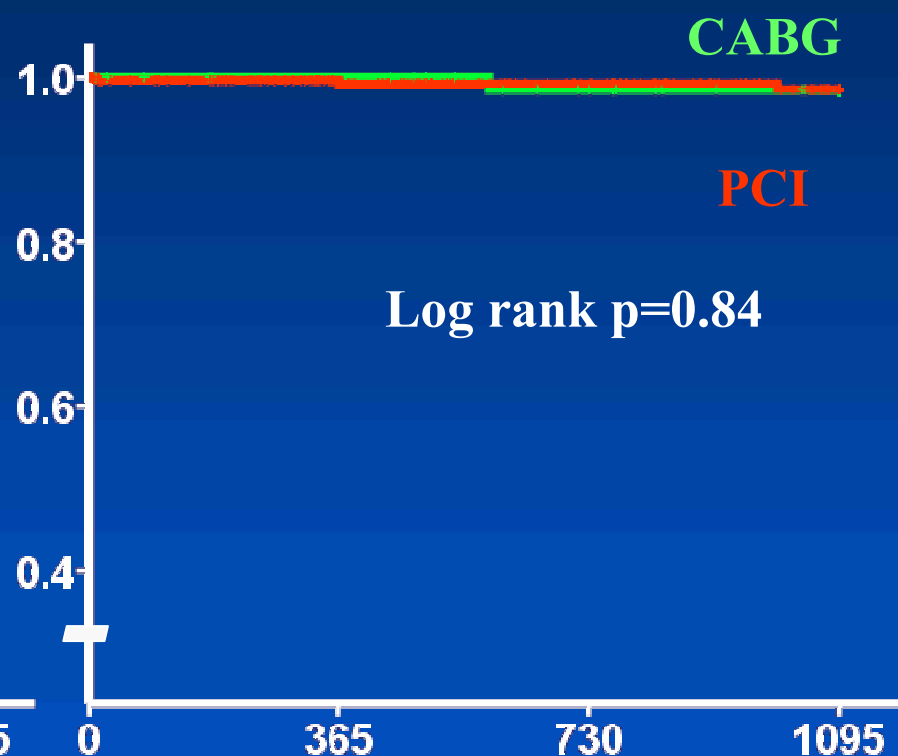
Clinical Outcomes in Isolated LM disease at 3 years

Death



CABG	73	70	65	55
PCI	291	281	236	179

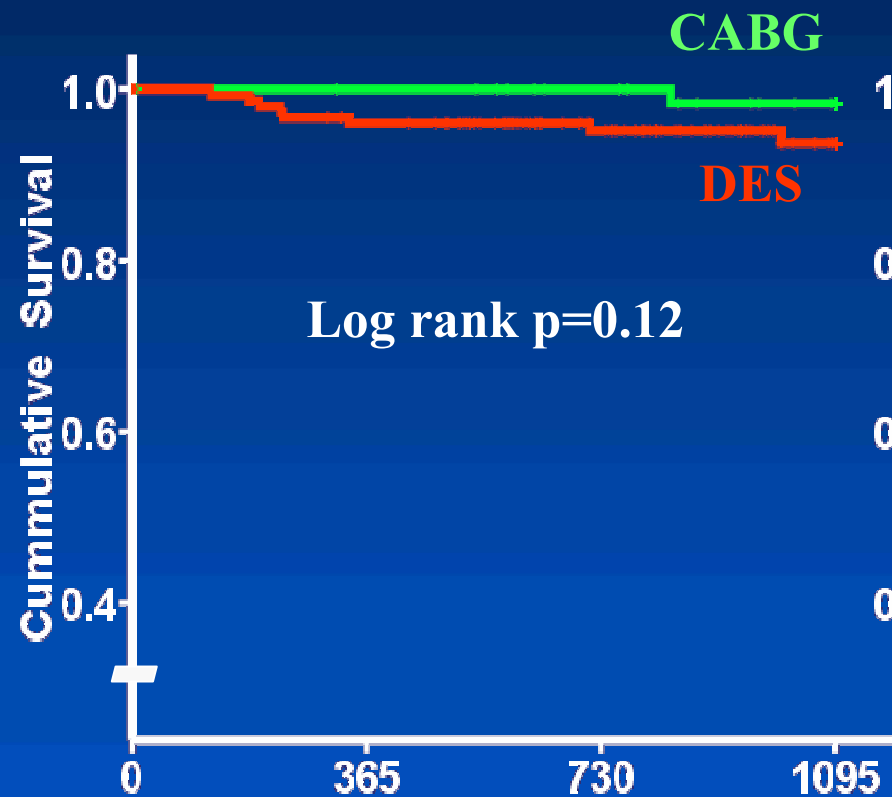
Q- MI



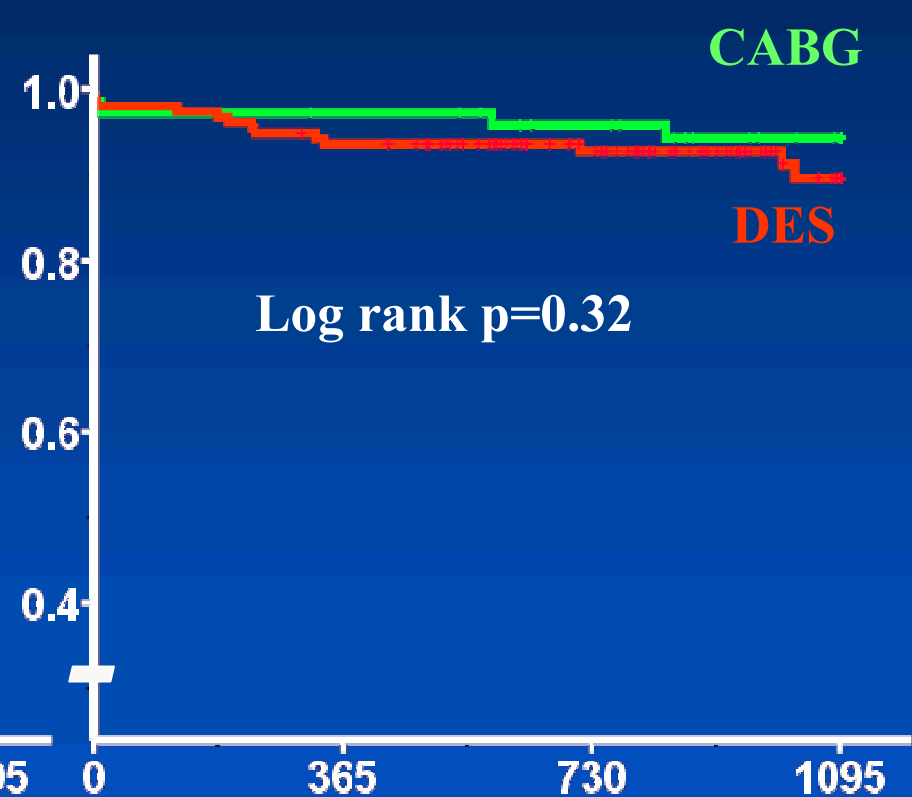
73	67	59	49
291	231	172	116

Clinical Outcomes in Isolated LM disease at 3 years

TVR



MACE



CABG	73	70	65	54
PCI	155	144	105	54

73	70	65	54
155	144	105	54

Isolated LM disease may be unique disease entity and has comparable clinical outcomes (all-cause mortality, Q-MI, TVR and composite MACE) with surgery.

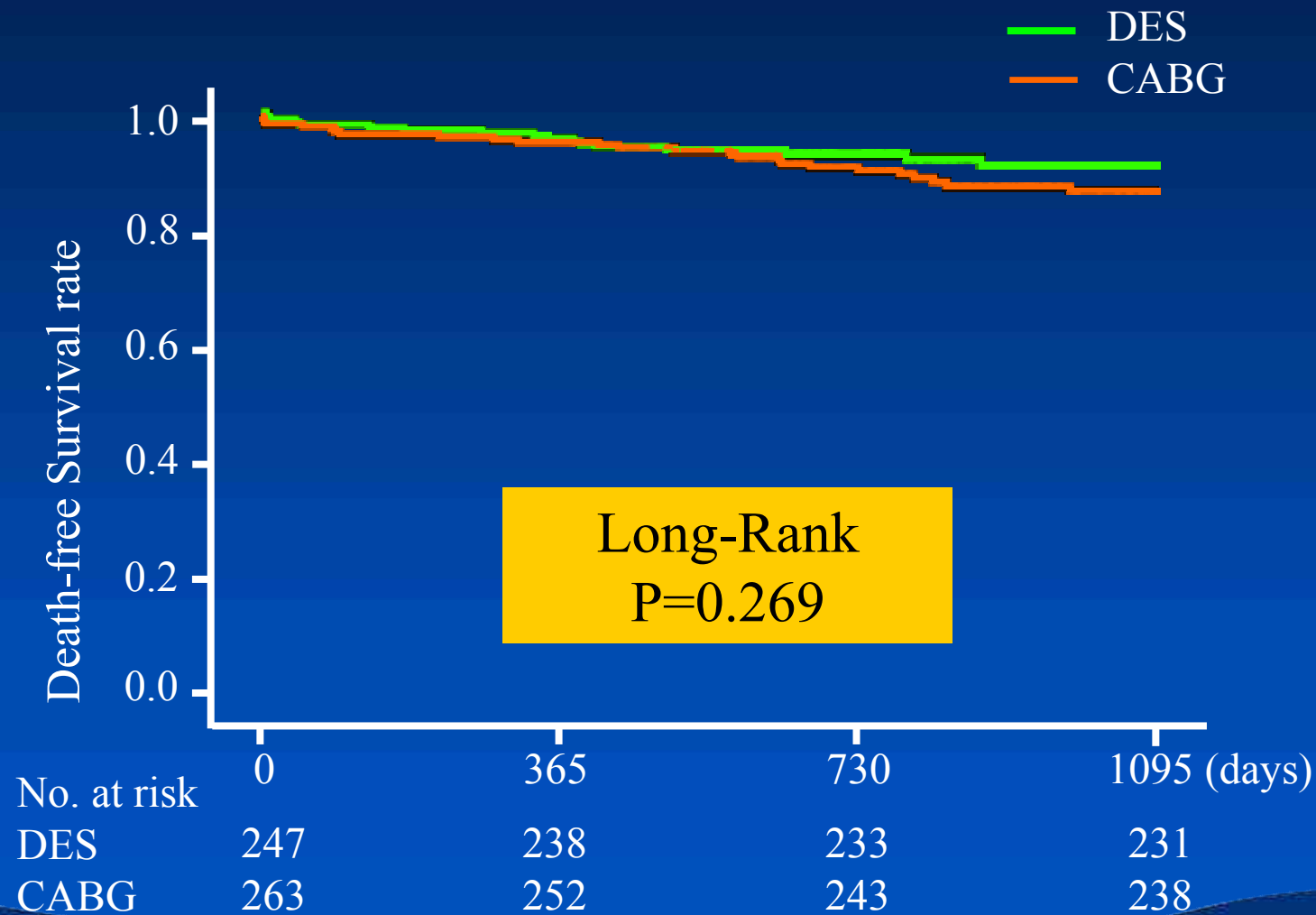
Based on the data from MAIN COMPARE Registry and Syntax trial

Impact of DM

Kim WJ et al, JACC Intv, 2009; 2: 956 – 963

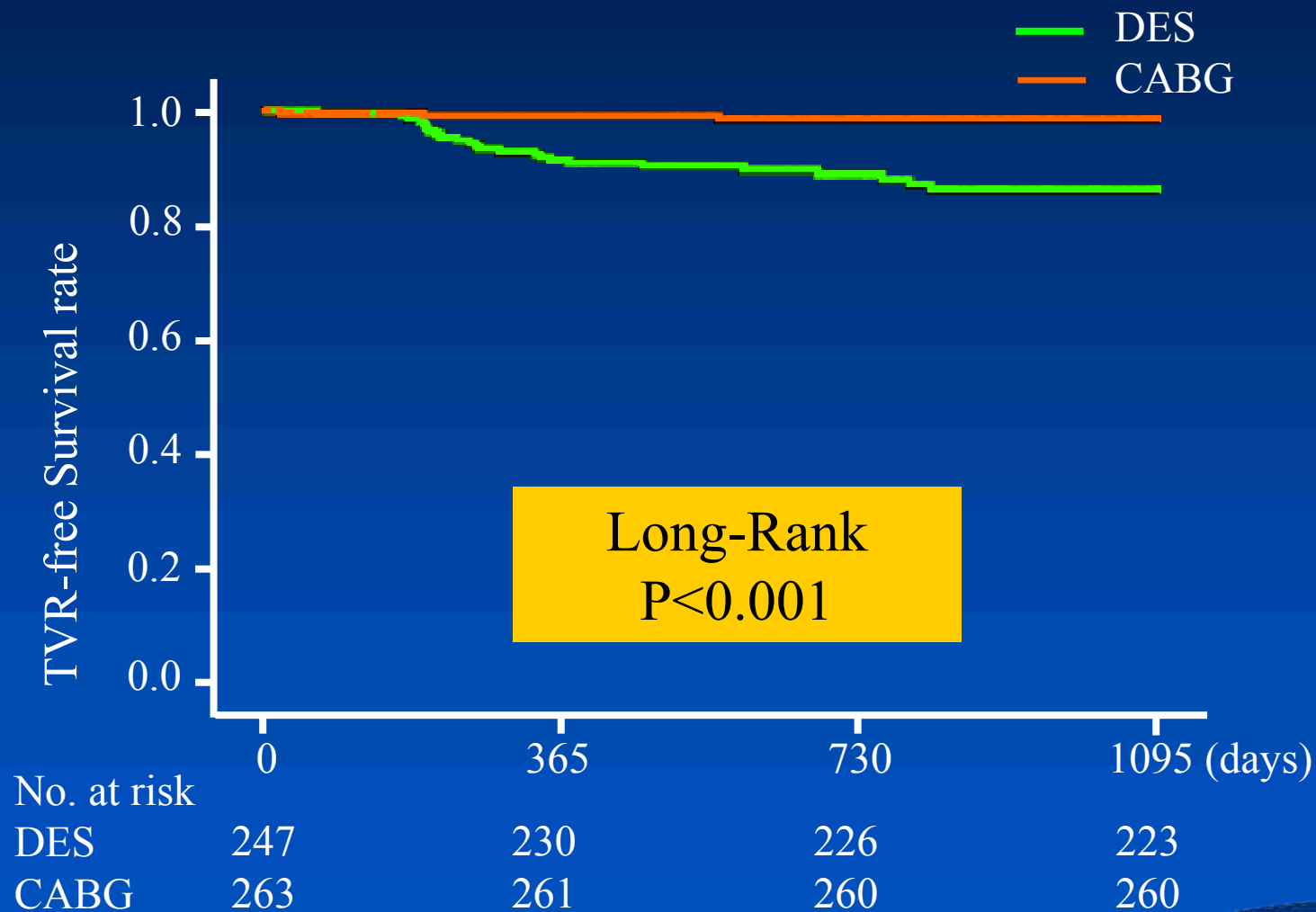
Unadjusted Kaplan-Meier Curves

Death in Diabetics



Unadjusted Kaplan-Meier Curves

TVR in Diabetics



Hazard Ratios of Clinical outcomes : DES vs. CABG for Diabetic Patients

	Crude		Multivariable adjusted*	
	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Death	0.70 (0.38-1.32)	0.27	0.78 (0.38-1.60)	0.50
Q-MI	0.38 (0.04-3.67)	0.39	0.30 (0.02-4.81)	0.39
TVR	9.00 (2.71-29.90)	<0.001	13.14 (3.09-55.92)	<0.001
Stroke	1.29 (0.39-4.22)	0.68	1.72 (0.49-6.02)	0.39
Death/Q-MI/TVR	1.53 (0.95-2.48)	0.08	1.64 (0.96-2.82)	0.07
Death/Q-MI/TVR/CVA	1.41 (0.91-2.20)	0.12	1.95 (1.19-3.22)	0.01

*HR for stents with reference to CABG.

Kim WJ et al, JACC Interv, 2009; 2: 956 – 963

Predictors

MACE : Death /MI /Stroke

MACCE : Death /MI /Stroke and *TVR*

Subgroup Analysis in
MAIN-COMPARE Study

Multivariate Predictors by Cox Model

For MACE (Death/ MI/ Stroke)

Outcomes	Hazard Ratio	95% CI	P value
Overall patients			
EuroSCORE	1.25	1.16, 1.34	<0.001
Chronic lung disease	2.14	1.07, 4.29	0.032
Chronic renal failure	2.67	1.54, 4.63	<0.001
Atrial fibrillation	2.21	1.11, 4.42	0.024
PCI patients			
EuroSCORE	1.17	1.05, 1.31	0.004
Prior congestive heart failure	3.86	1.58, 9.44	0.003
Chronic renal failure	6.15	2.90, 13.01	<0.001
CABG patients			
EuroSCORE	1.27	1.16, 1.39	<0.001
Diabetes mellitus	1.76	1.13, 2.75	0.013
Chronic lung disease	4.03	1.79, 9.05	<0.001
Prior cerebrovascular disease	2.36	1.29, 4.31	0.005
Hyperlipidemia	0.60	0.36, 0.99	0.043

Multivariate Predictors by Cox Model

For MACCE (Death/ MI/ Stroke and TVR)

Outcomes	Hazard Ratio	95% CI	P value
Overall patients			
EuroSCORE	1.10	1.04, 1.16	<0.001
CABG	0.71	0.54, 0.92	0.010
Chronic renal failure	2.32	1.40, 3.85	0.001
Prior cerebrovascular disease	1.58	1.08, 2.33	0.020
Use of intra-aortic balloon pump	2.00	1.09, 3.64	0.024
PCI patients			
Prior congestive heart failure	2.98	1.44, 6.16	0.003
Use of intra-aortic balloon pump	2.25	1.23, 4.10	0.008
Chronic renal failure	4.17	2.27, 7.64	<0.001
CABG patients			
EuroSCORE	1.22	1.12, 1.33	<0.001
Chronic lung disease	2.52	1.15, 5.49	0.021
Prior MI	1.76	1.06, 2.94	0.030
Prior cerebrovascular disease	2.32	1.36, 3.99	0.002

MAIN COMPARE Registry 5 year Follow-Up

5 Year Long-term Outcomes

Complete follow-up for major clinical events was obtained in 97.9% of the overall cohort (98.1% for the PCI group and 97.6% for the CABG group; $P=0.45$).

The median follow-up was 62.0 months (IQR range, 48.0 to 78.3 months) in the overall patients.

After Propensity-Matching

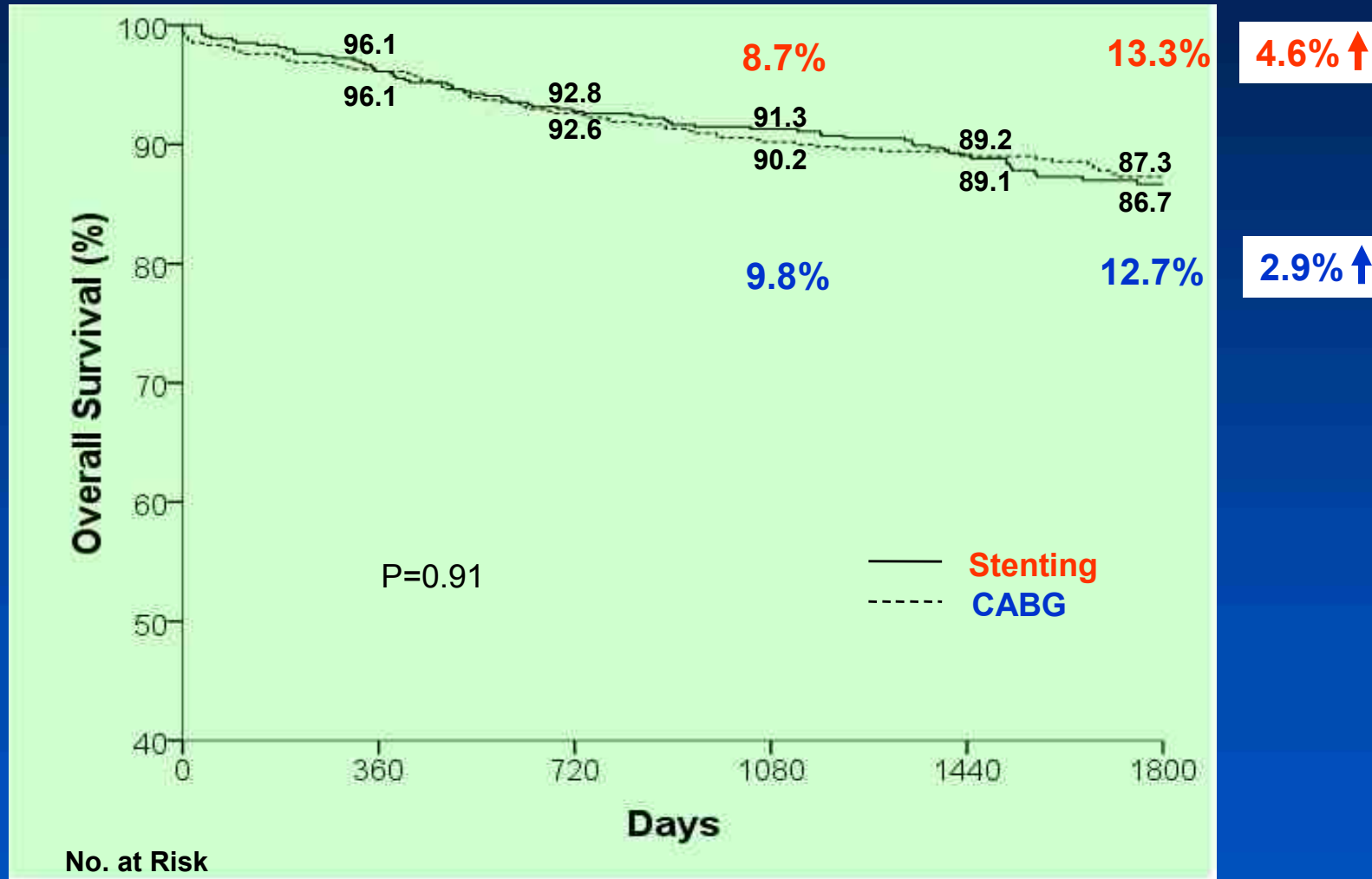
Overall matched cohort (n=542 pairs)

Wave 1; BMS vs. contemporary CABG (n=207 pairs)

Wave 2; DES vs. contemporary CABG (n=396 pairs)

5-Year: Death

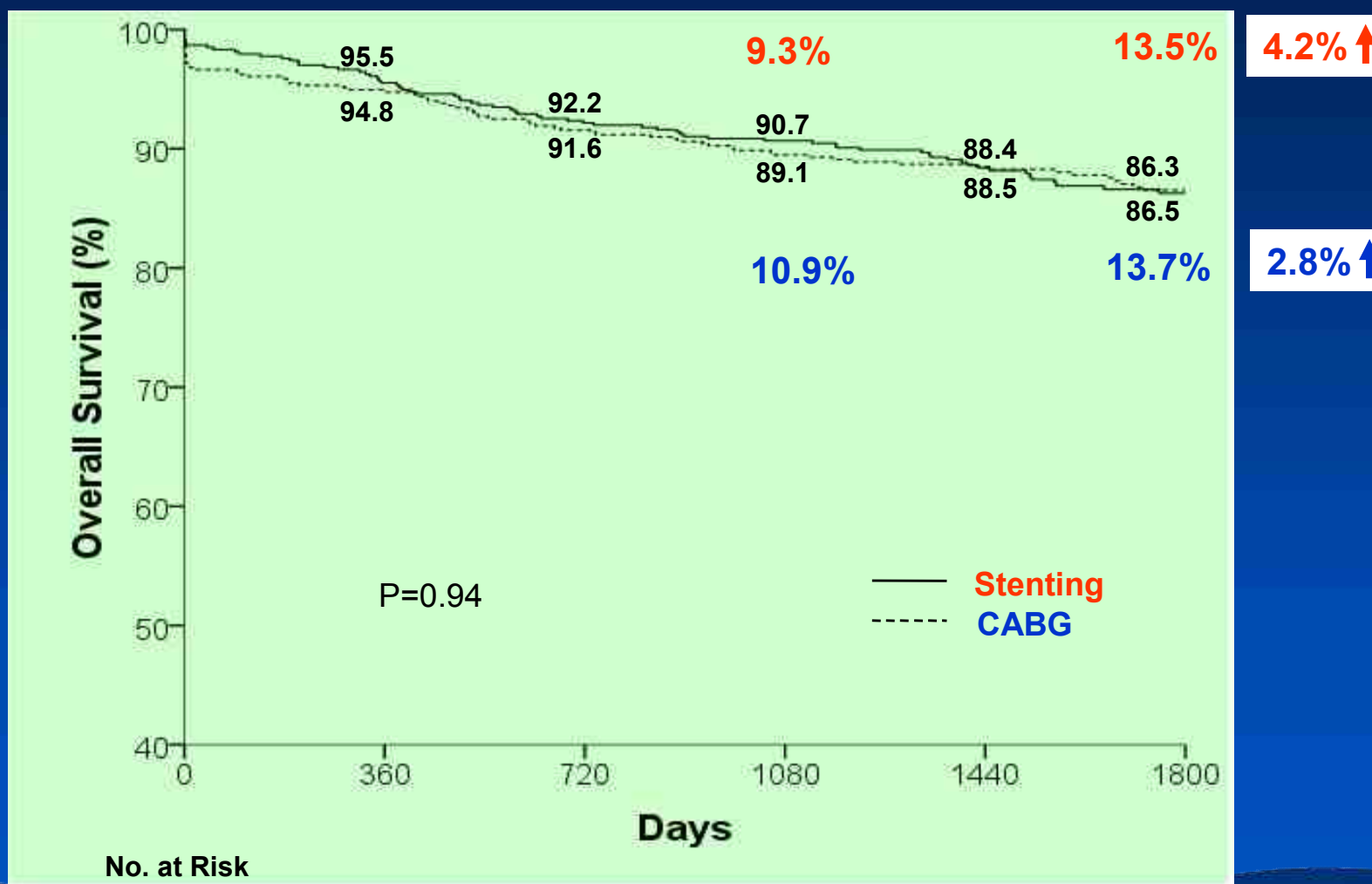
(Overall : 542 pairs)



Stenting	542	519	499	486	388	241
CABG	542	521	499	478	421	320

5-Year: Death, Q-MI, or Stroke

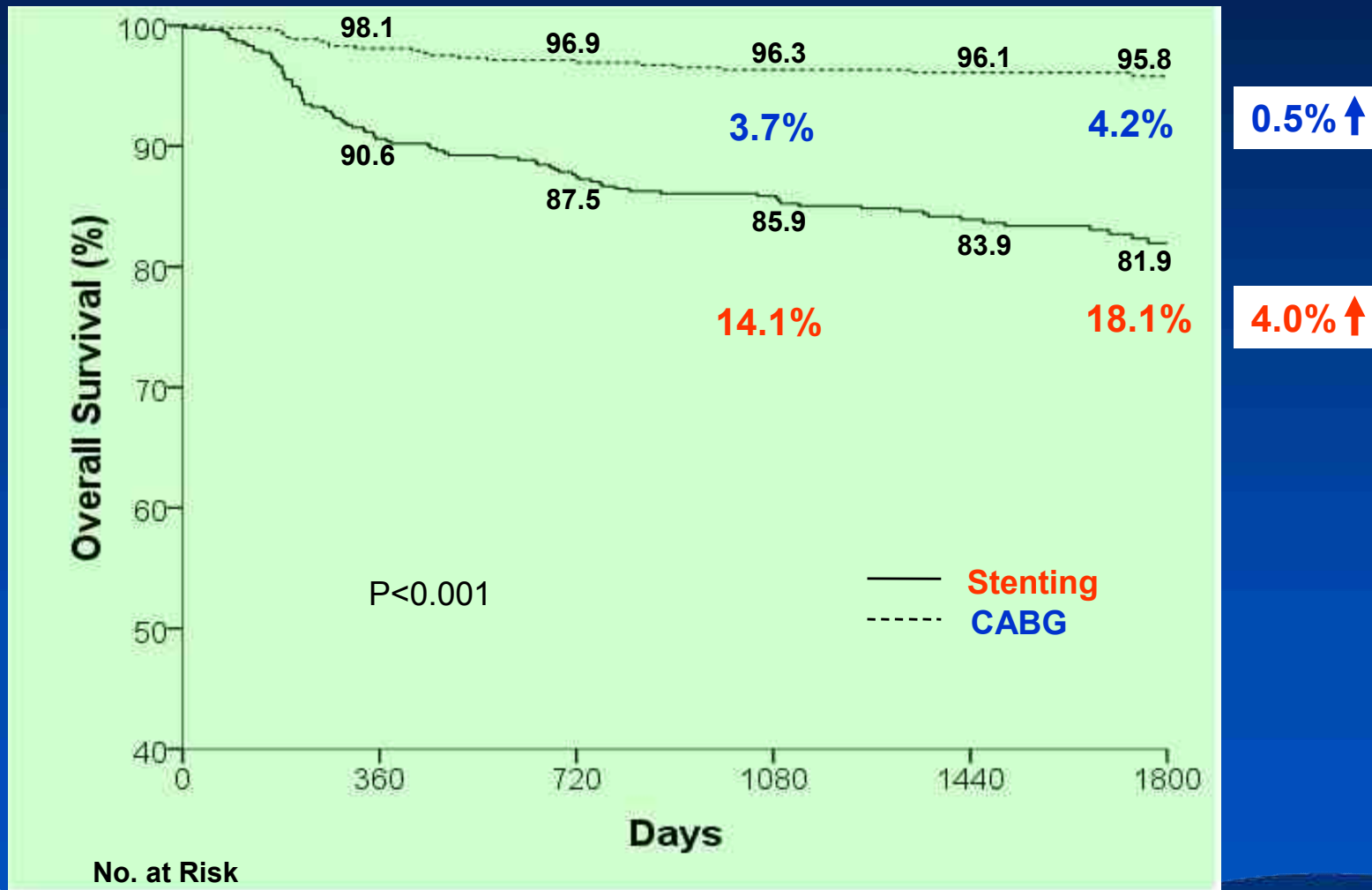
(Overall 542 pairs)



Stenting	542	512	492	479	383	239
CABG	542	506	487	467	411	311

5-Year: TVR

(Overall : 542 pairs)



HR for Clinical Outcomes after Stenting as Compared with after CABG among Propensity

	Overall Patients (N=542 pairs)		Wave 1* (N=207 pairs)		Wave 2* (N=396 pairs)	
Outcome	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Death	1.02 (0.74-1.39)	0.91	1.04 (0.66-1.64)	0.86	1.26 (0.85-1.87)	0.24
Composite outcome	1.10 (0.74-1.38)	0.94	0.94 (0.60-1.47)	0.79	1.27 (0.86-1.87)	0.24
TVR	4.55 (2.88-7.20)	<0.001	7.97 (3.34-19.00)	<0.001	6.69 (3.44-13.03)	<0.001

Hazard Ratios for Clinical Outcomes

: Median 3-Year Outcomes

- All PCI patients (n=542 pairs)
- Bare-metal stents (n=207 pairs)
- Drug-eluting stents (n=542 pairs)

P<0.001

P=NS

P=NS

HR 1.0 to
concurrent CABG

1.18 1.04 1.36

1.10 0.86 1.40

4.76 10.70 5.96

Death

Composite of death,
Q-wave MI, or stroke

Target-vessel
revascularization

Hazard Ratios for Clinical Outcomes

: Median 5-Year Outcomes

- All PCI patients (n=542 pairs)
- Bare-metal stents (n=207 pairs)
- Drug-eluting stents (n=542 pairs)

P<0.001

P=NS

P=NS

HR 1.0 to
concurrent CABG

1.02 1.04 1.26

1.10 0.94 1.27

4.55 7.97 6.69

Death

Composite of death,
Q-wave MI, or stroke

Target-vessel
revascularization

ASAN MAIN Registry 5 – 10 year Follow-Up

AMC Works since 1998

- 1997** J Am Coll Cardiol 1998;31:37-42 : Early experience
- 1998** Am J Cardiol 1998;82:670-3 : IVUS analysis
- 1999** J Am Coll Cardiol 2001;38:1054-60 : Role of debulking
- 2000** Circulation 2001;104:1609-1614 : ULTIMA registry

More than 1,200 patients have been preformed unprotected left main stenting in AMC

- 2003** Int J Cardiol 2004;97:75-8 : Acute MI
- 2004** JACC 2005;45:351-6 : SES stenting.
- 2005** Am J Cardiol 2006;98:1567-1570 : EuroSore evaluation
- 2005** Int Jour of Cardiology 2007. 208-213 : 5 year F/U data
- 2007** Cathter Cardio Interv 70:840-846, 2007: Kissing stent technique longterm
- 2008** NEJM. 2008 Apr 24;358(17):1781-92. MAIN COMPARE registry

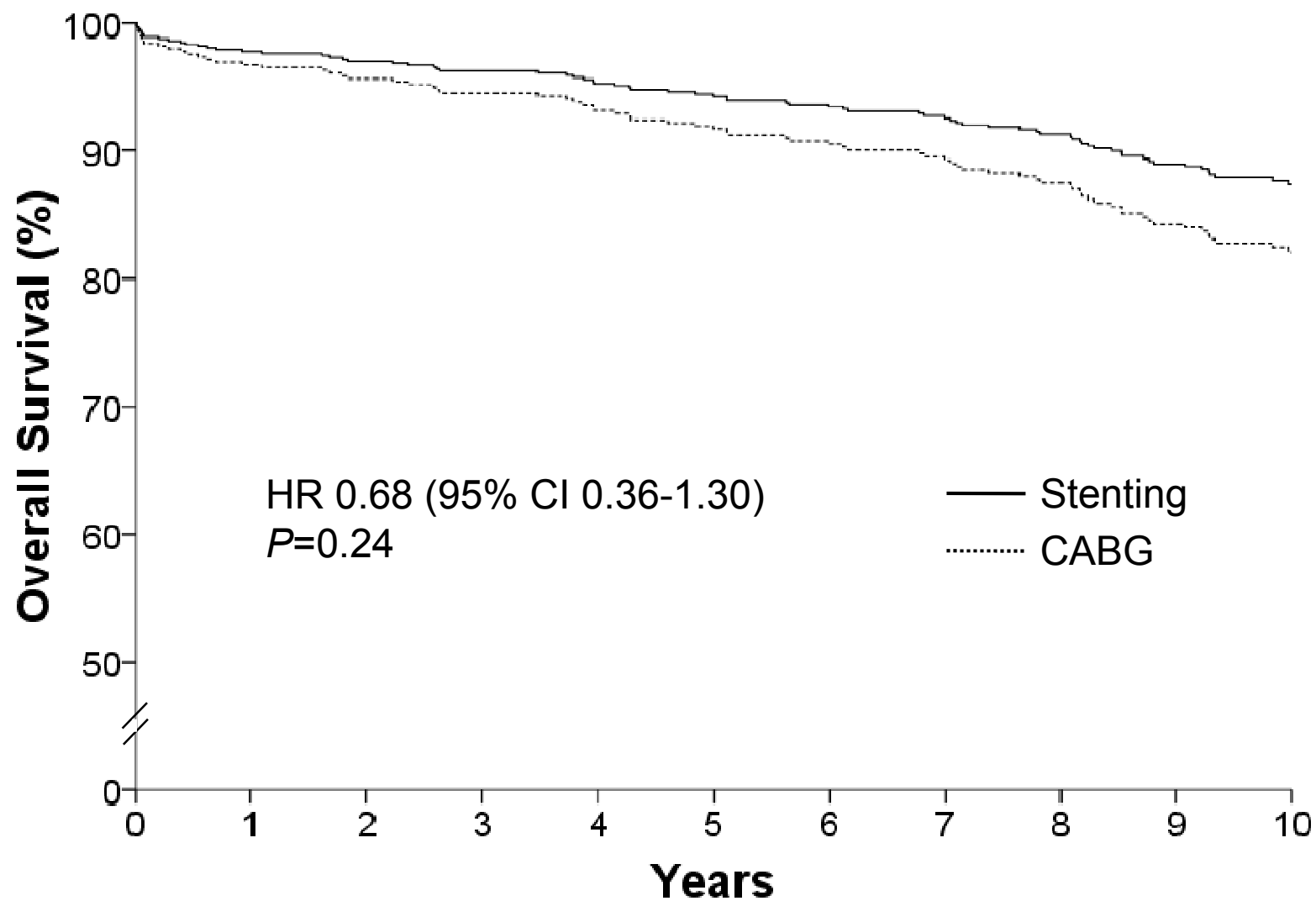
10 Year Clinical Outcomes

BMS vs. CABG

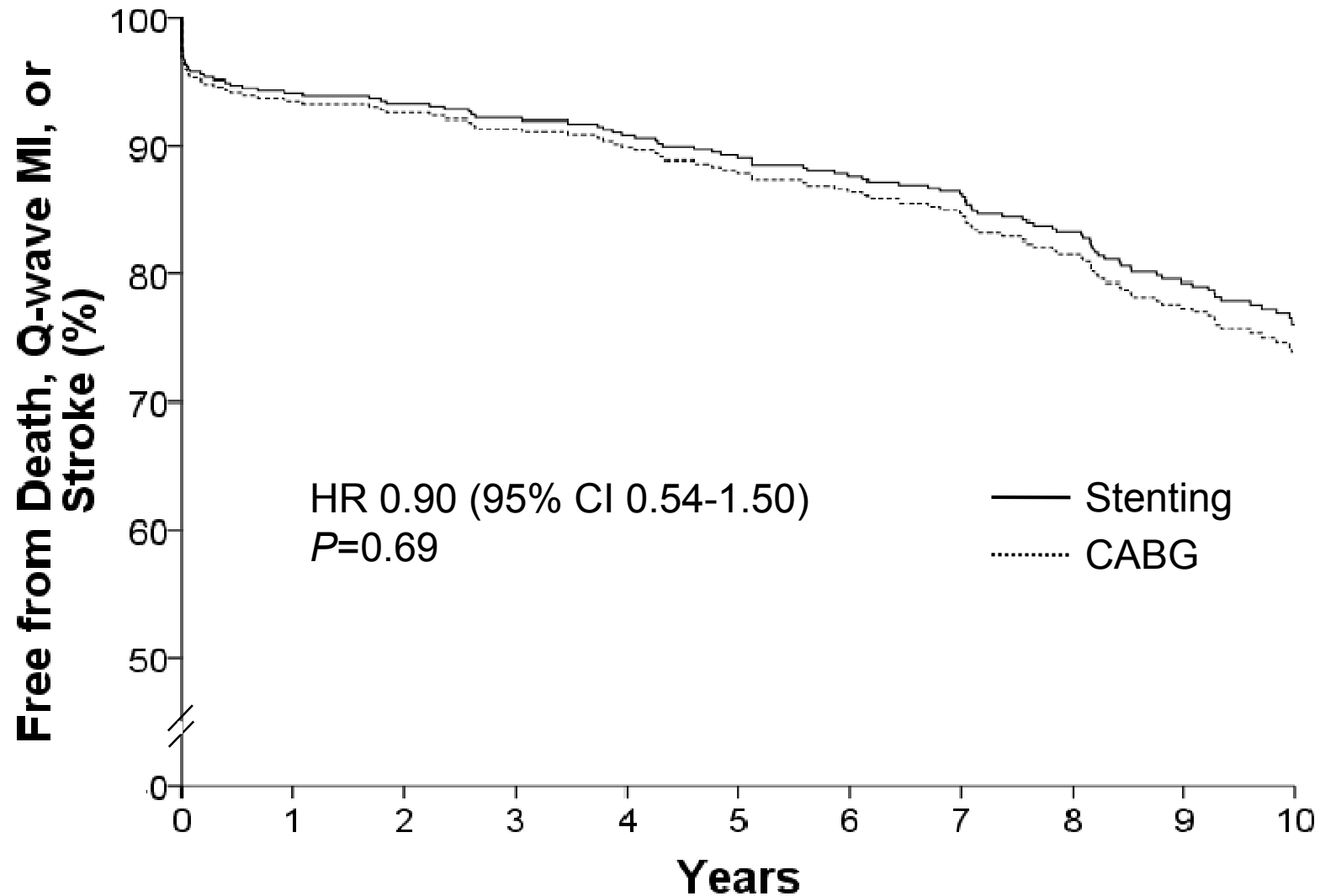
(100 : 250 pts)

for Unprotected LMCA Disease

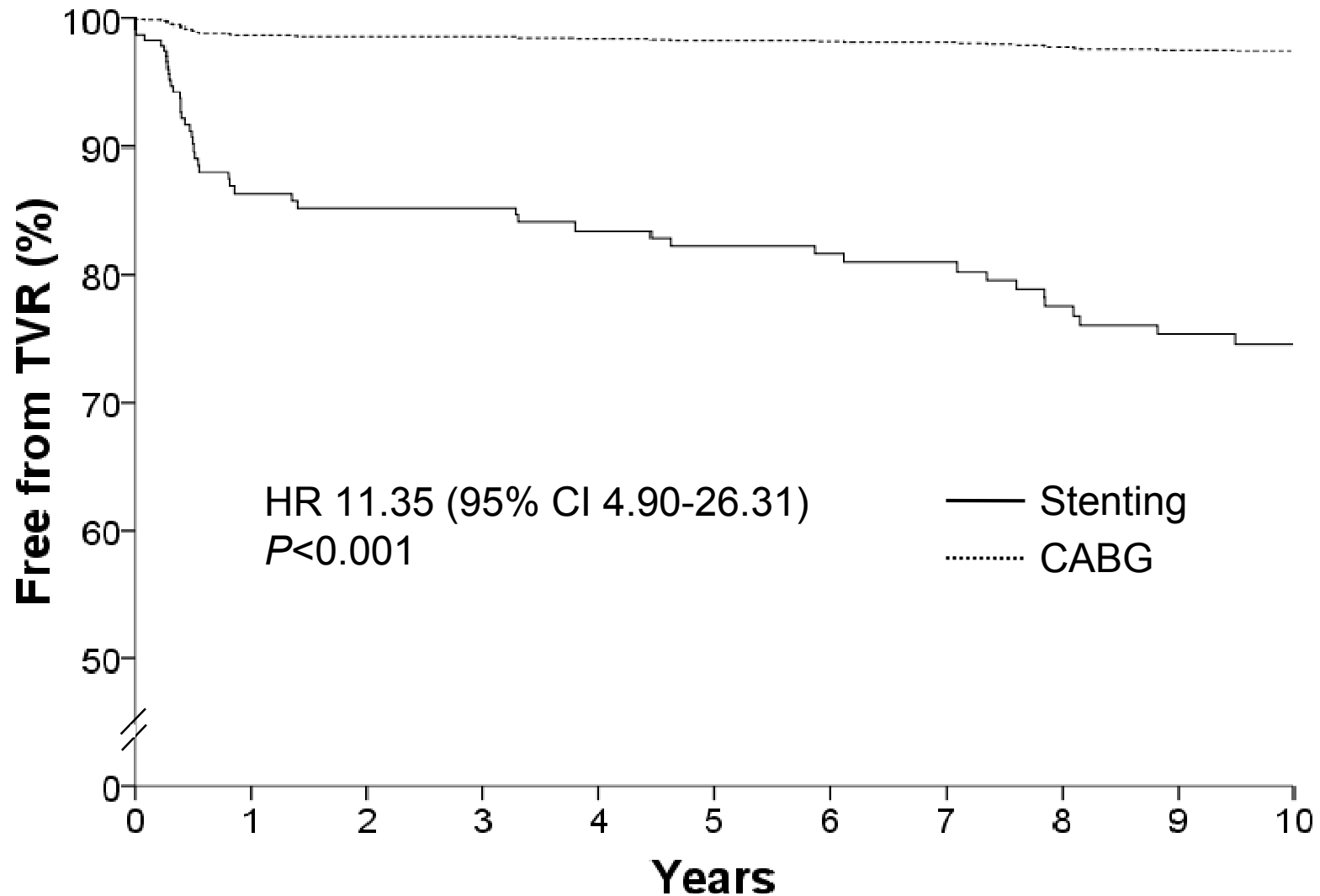
Adjusted Outcomes: **Death**



Adjusted Outcomes: **Death, Q-MI, Stroke**



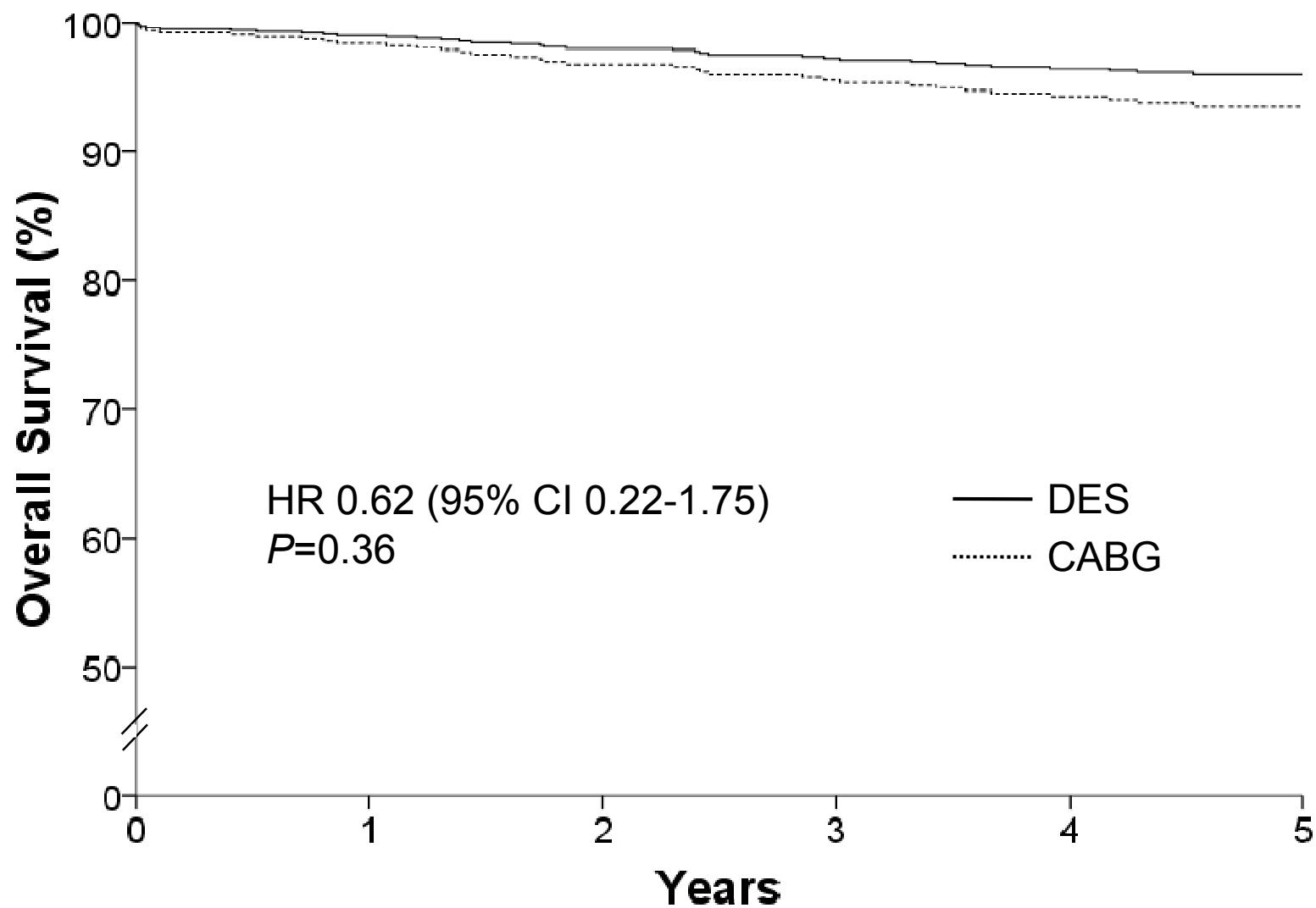
Adjusted Outcomes: TVR



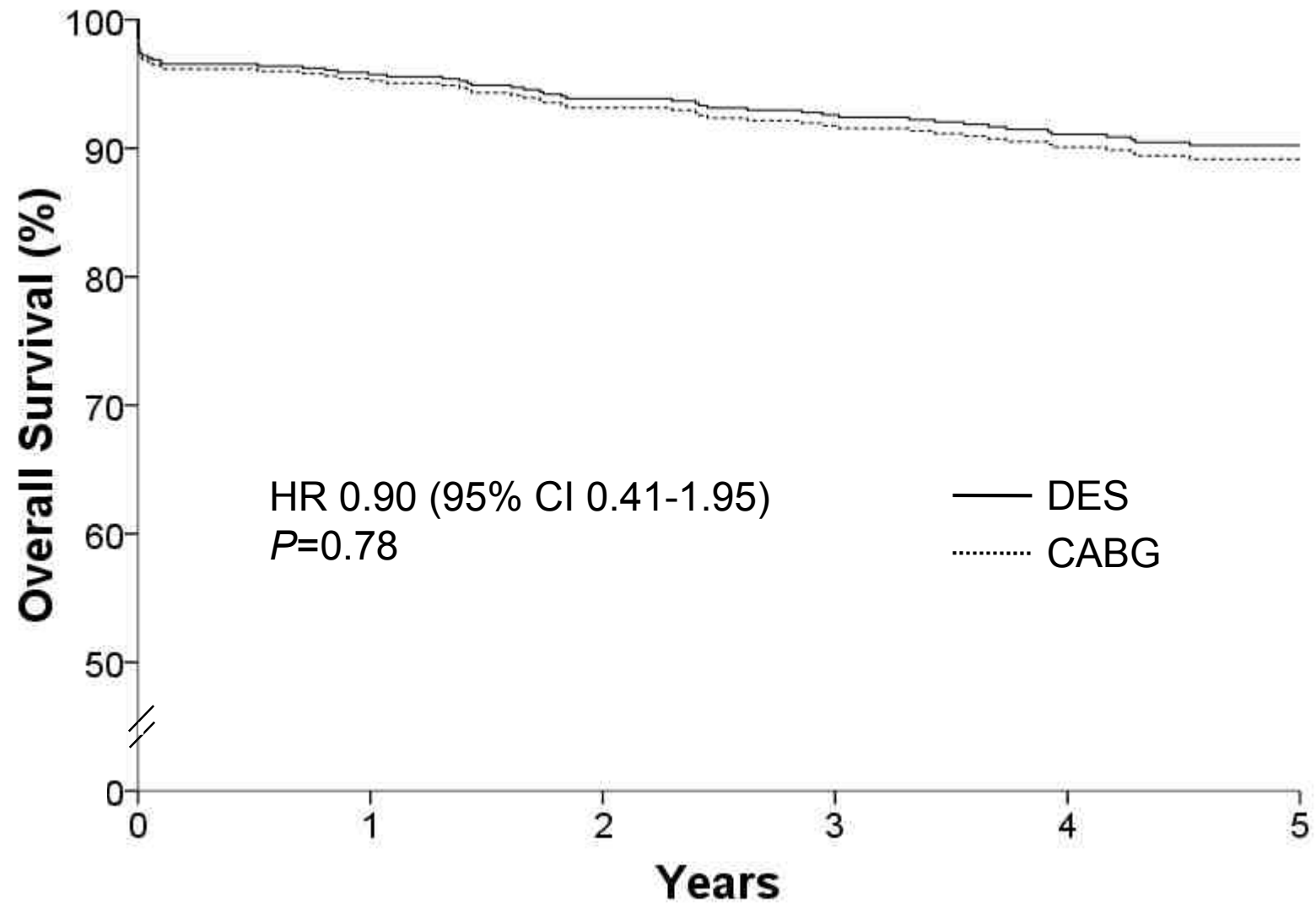
5 Year Clinical Outcomes

DES vs. CABG
(176 : 219 pts)
for Unprotected LMCA Disease

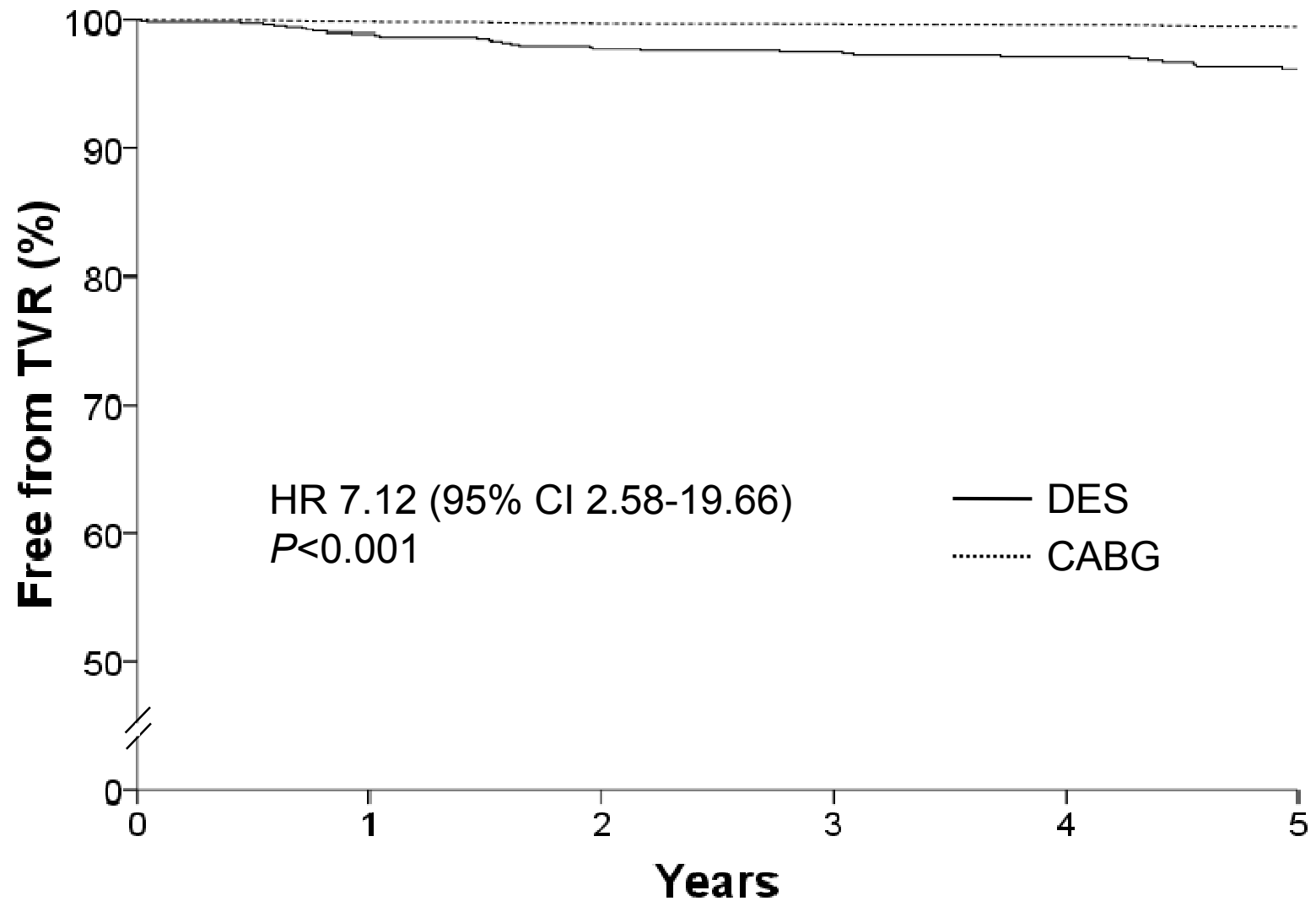
Adjusted Outcomes: **Death**



Adjusted Outcomes: **Death, Q-MI, Stroke**



Adjusted Outcomes: TVR



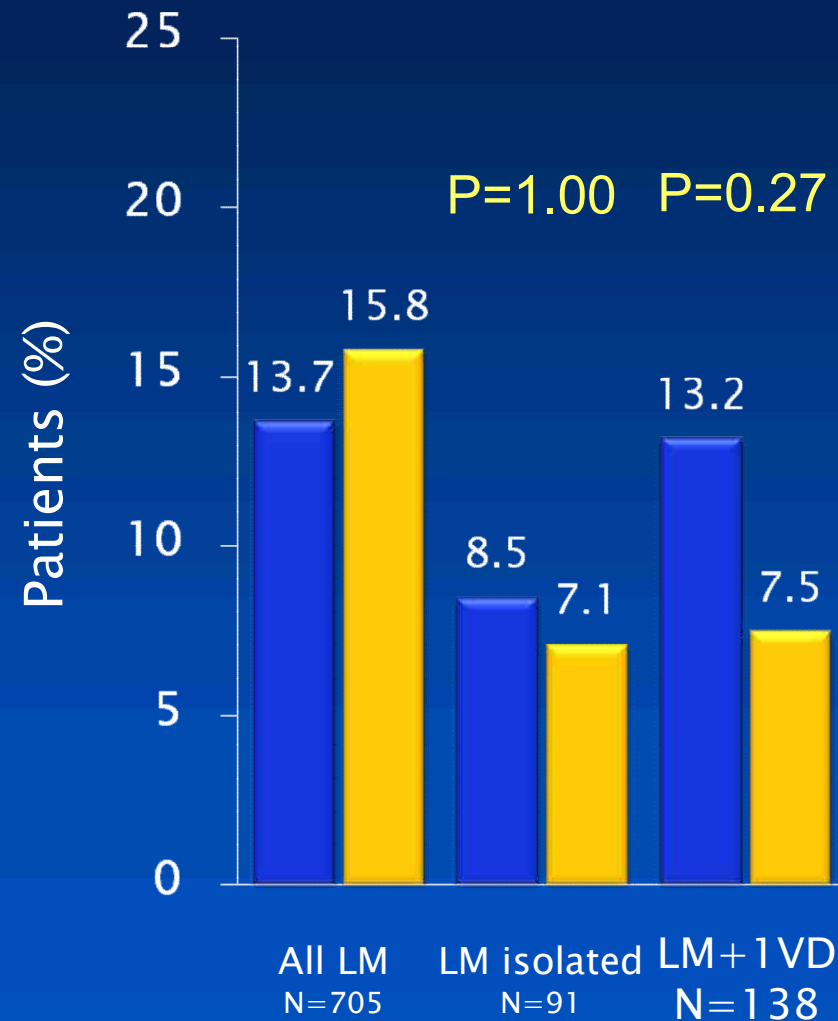
SYNTAX

LM subgroup

Left Main and Three Vessel Disease

Subgroup MACCE Rates at 12 Months

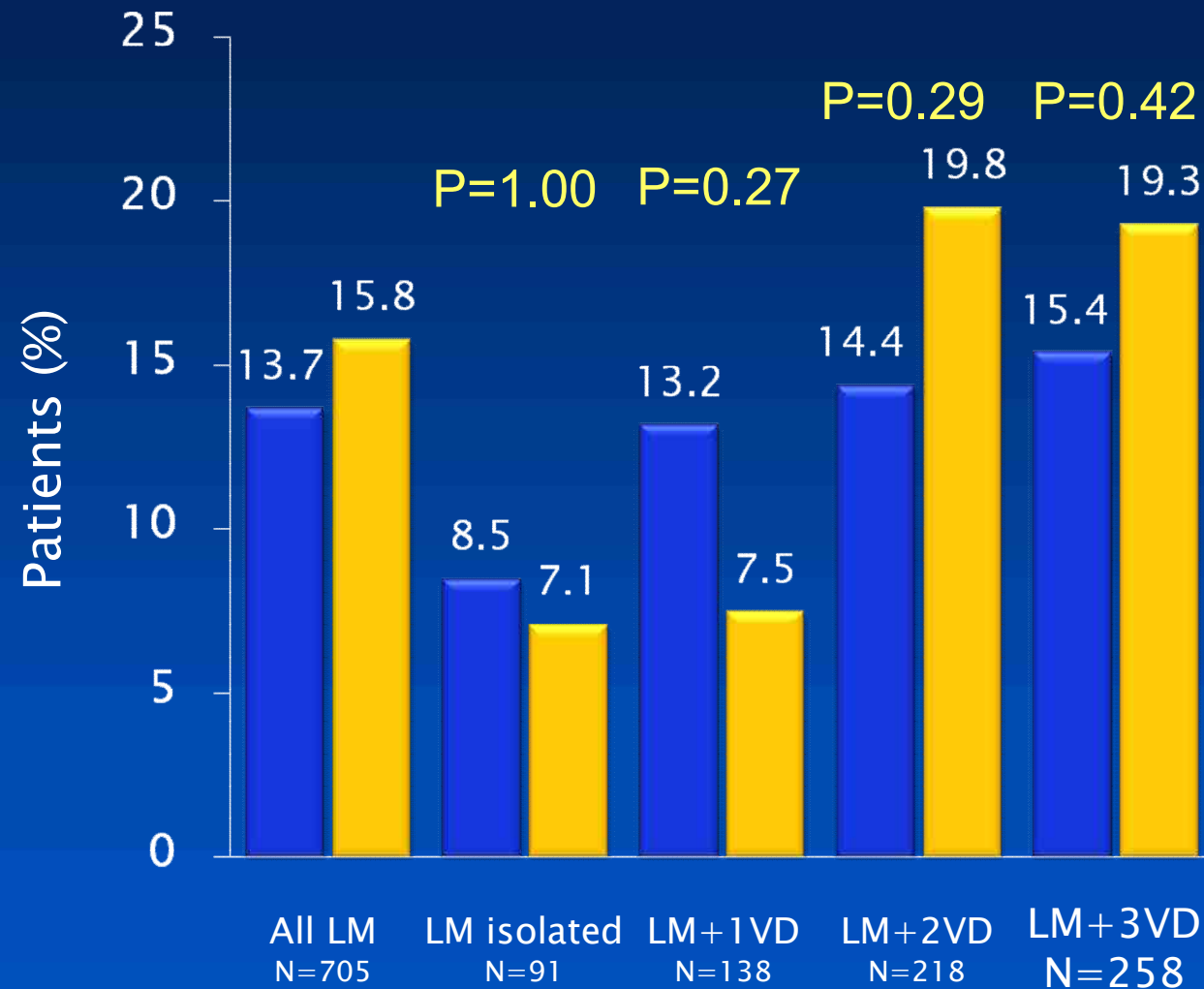
■ CABG ■ TAXUS



Left Main and Three Vessel Disease

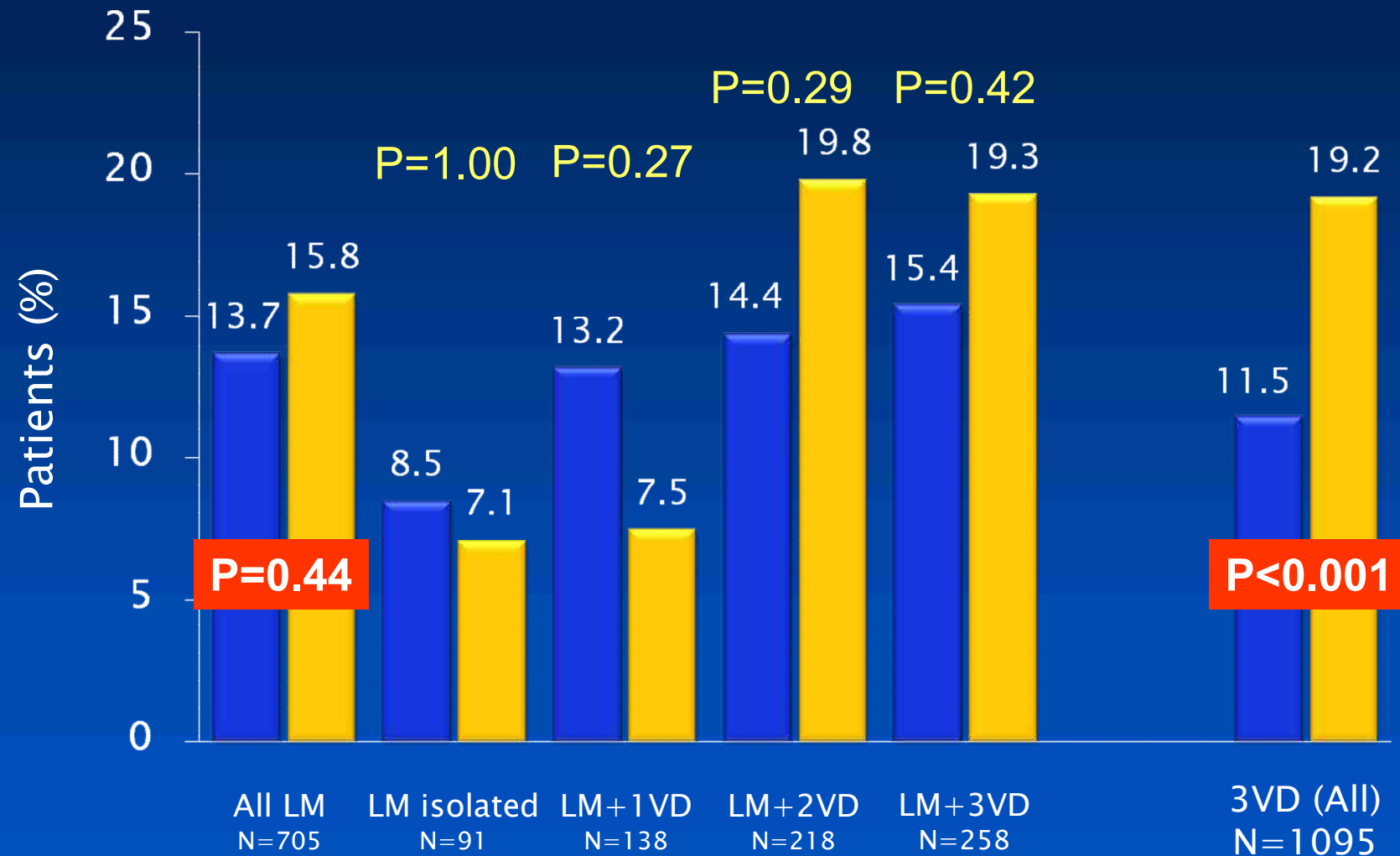
Subgroup MACCE Rates at 12 Months

■ CABG ■ TAXUS



Left Main and Three Vessel Disease Subgroup MACCE Rates at 12 Months

CABG TAXUS



SYNTAX trial end points in 3VD subset

End point	CABG (%)	Taxus (%)	p
Death	2.9	4.4	0.18
Stroke	1.9	0.8	0.09
MI	2.6	5.2	0.04
Revascularization	5.4	14.7	<0.001
Death/stroke/MI	6.4	7.9	0.39
MACCE	11.2	19.1	<0.001

SYNTAX trial end points in left main subset

End point	CABG (%)	Taxus (%)	p
Death	4.4	4.2	0.88
Stroke	2.7	0.3	0.009
MI	4.1	4.3	0.97
Revascularization	6.7	12.0	0.02
Death/stroke/MI	9.1	7.0	0.29
MACCE	13.6	15.8	0.44

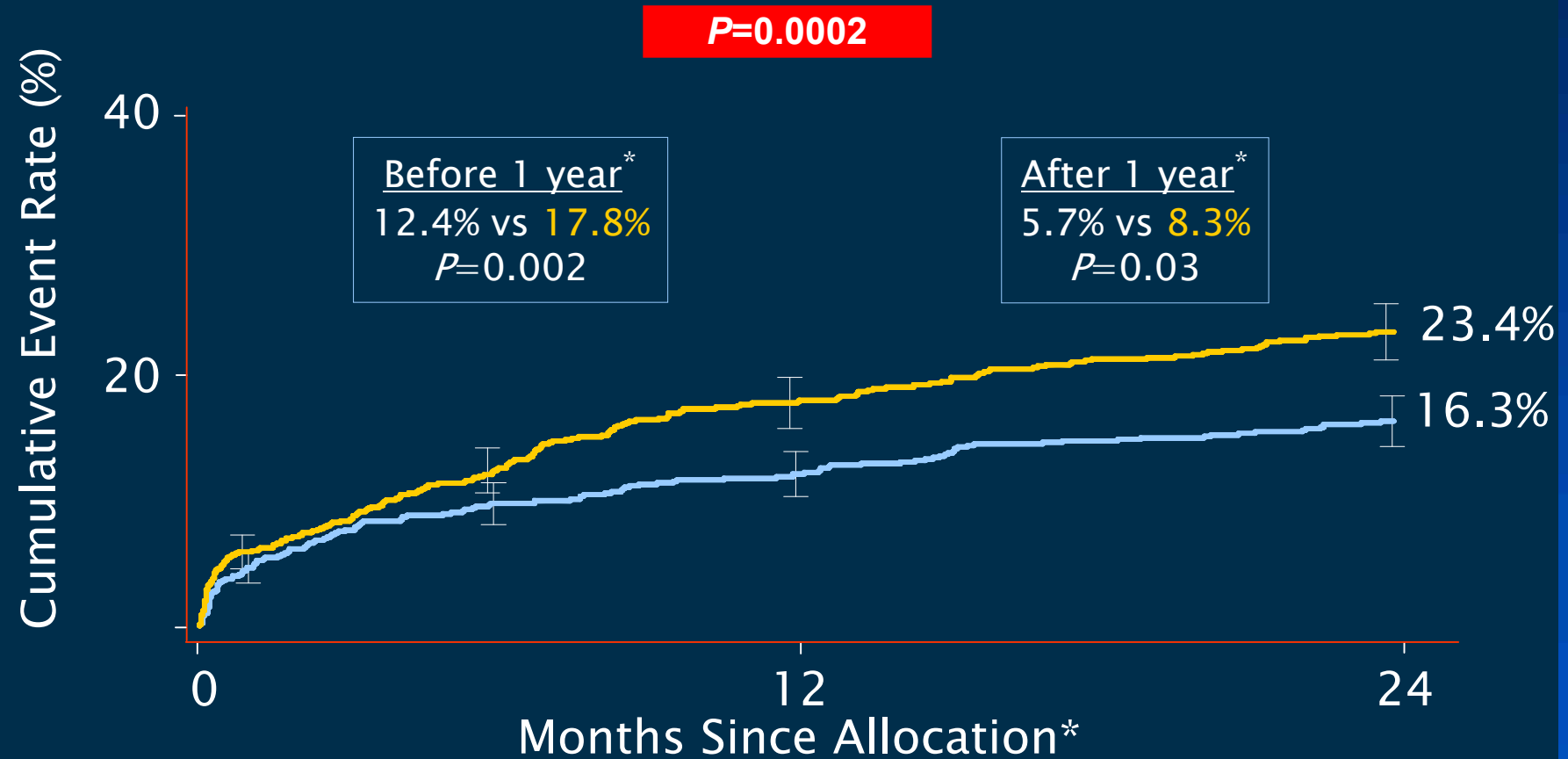
SYNTAX LM

2-Year Outcomes

MACCE to 2 Years

■ CABG (N=897)

■ PCI (N=903)



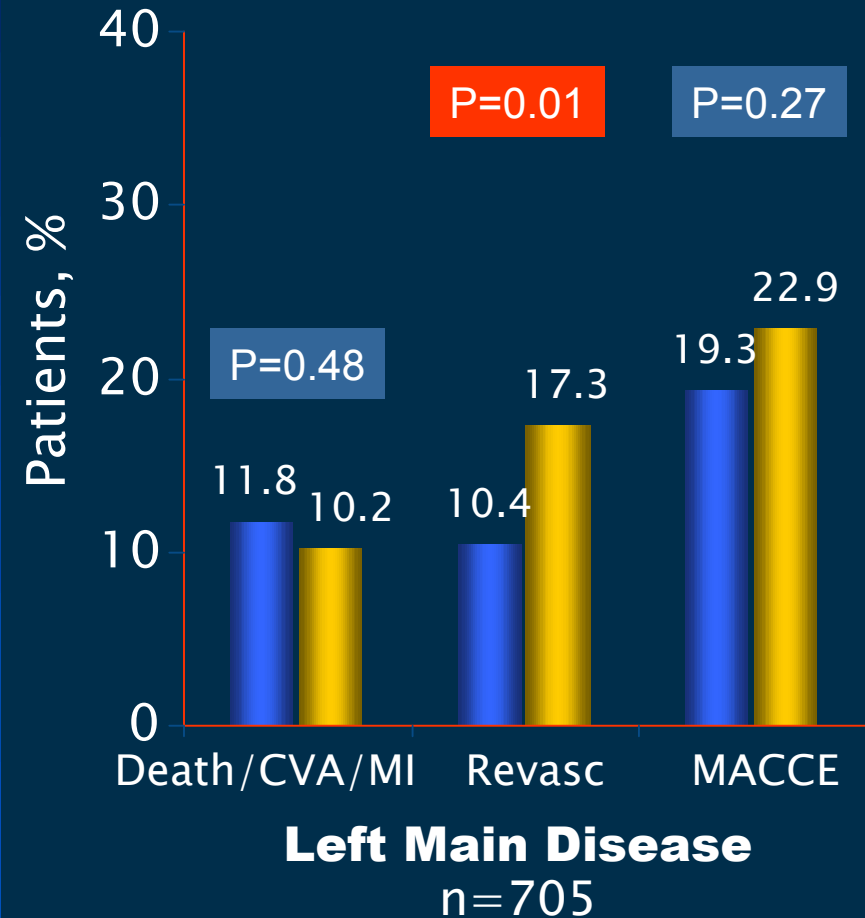
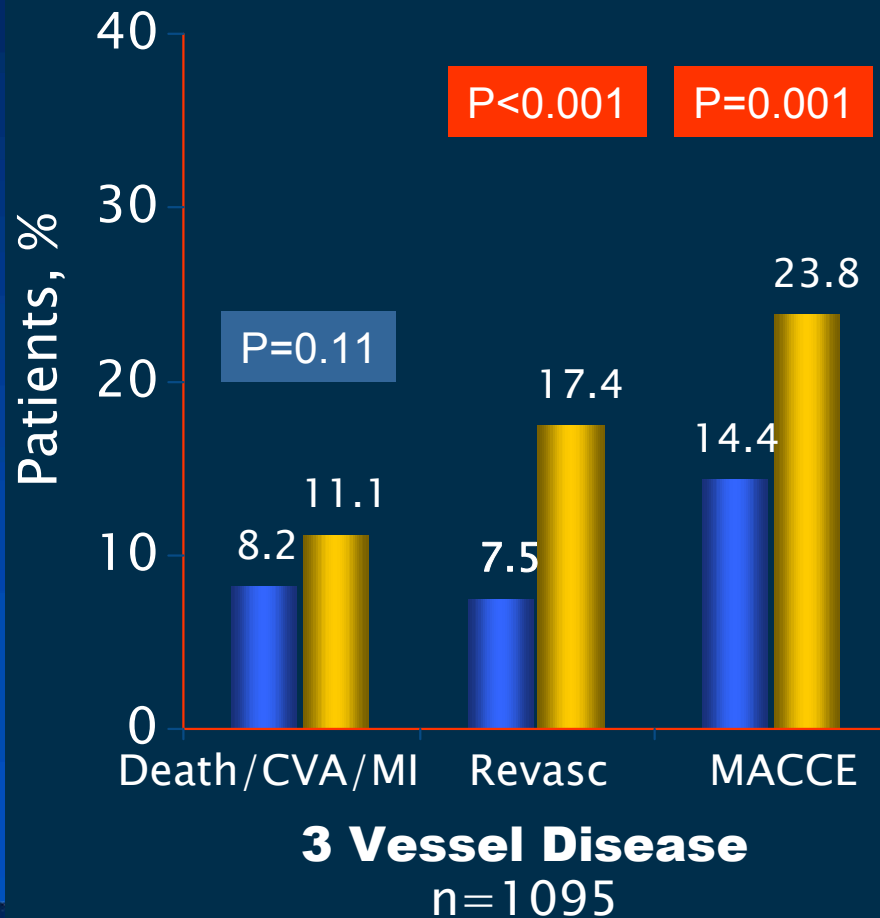
Cumulative KM Event Rate \pm 1.5 SE; log-rank P value; *Binary rates; *Randomization

ITT population

SYNTAX Trial 2 Year Outcomes in 3VD and LM Subgroups

■ CABG (N=315)

■ PCI (N=290)



MACCE to 12 Months by SYNTAX Score Tercile

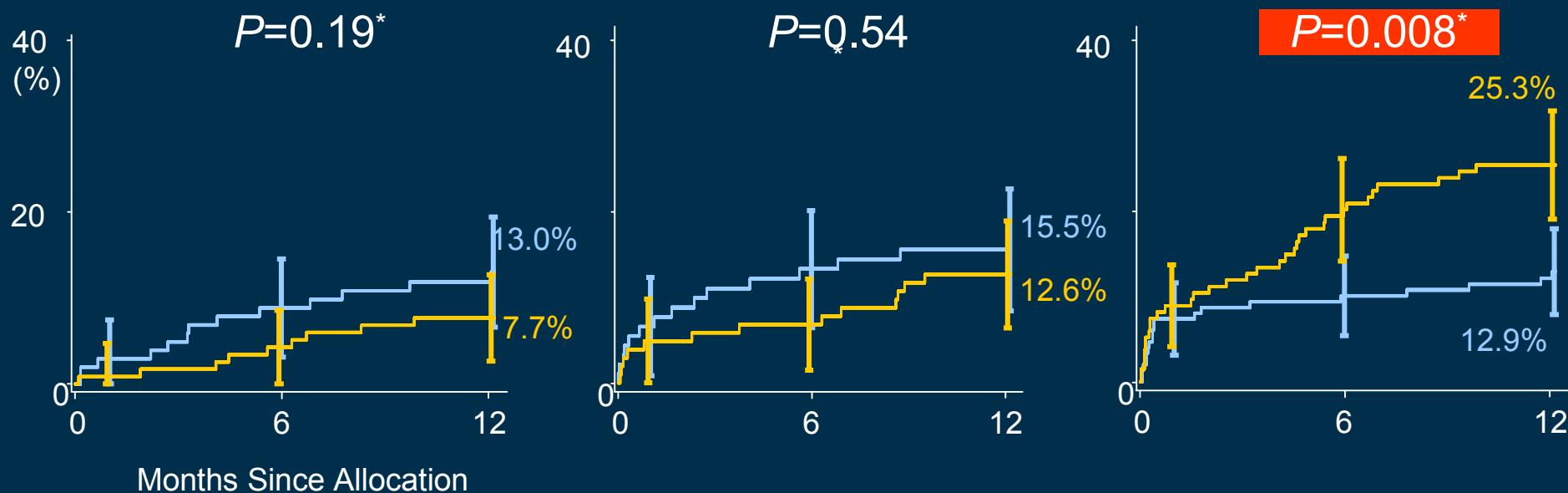
LM Subset

■ CABG (N=103) ■ TAXUS (N=118)

Low
scores (0-22)

Intermediate
scores (23-32)

High
scores (≥ 33)



CABG better

MACCE to 2 Years by SYNTAX Score™ Tercile

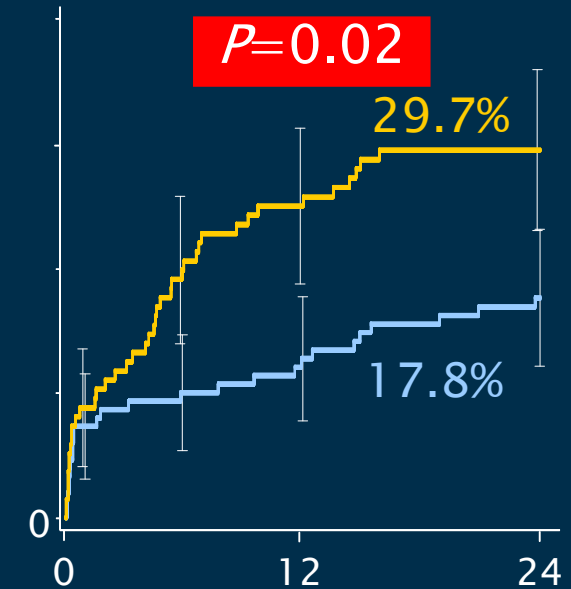
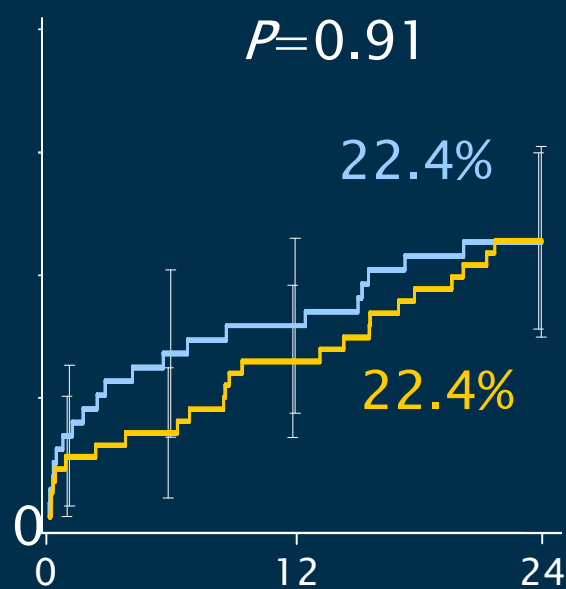
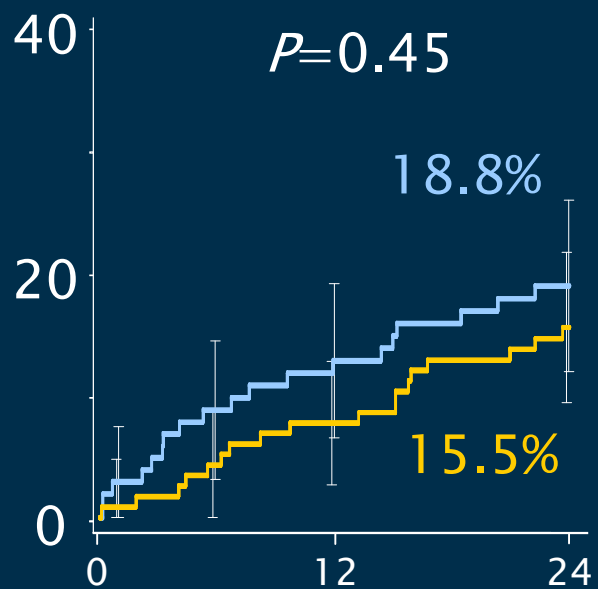
LM subset

■ CABG (N=103) ■ TAXUS (N=118)

Low
scores (0-22)

Intermediate
scores (23-32)

High
scores (≥ 33)



CABG better

Syntax LM subgroup analysis showed,

PCI has comparable clinical outcomes with surgery (no difference in death or MI).
There is higher rate of stroke in surgery and higher rate of TVR in PCI
2-year results confirm the one-year one's.

Message

From MAIN COMPARE registry,
ASAN MAIN registry, SYNTAX LM

STENT vs CABG

for Left Main Disease Treatment

In selected group of LM disease;

- Ostial and shaft LM disease
- Isolated LM disease
- LM with 1 vessel disease
- Syntax Score <33

STENT group may have even better clinical outcomes...

What is NEXT !

PRECOMBAT Study Design

Left Main Disease with or without MVD

Randomize 600 (1:1)

PCI with Cypher
(N=300)

CABG
(N=300)

Registry group
1000

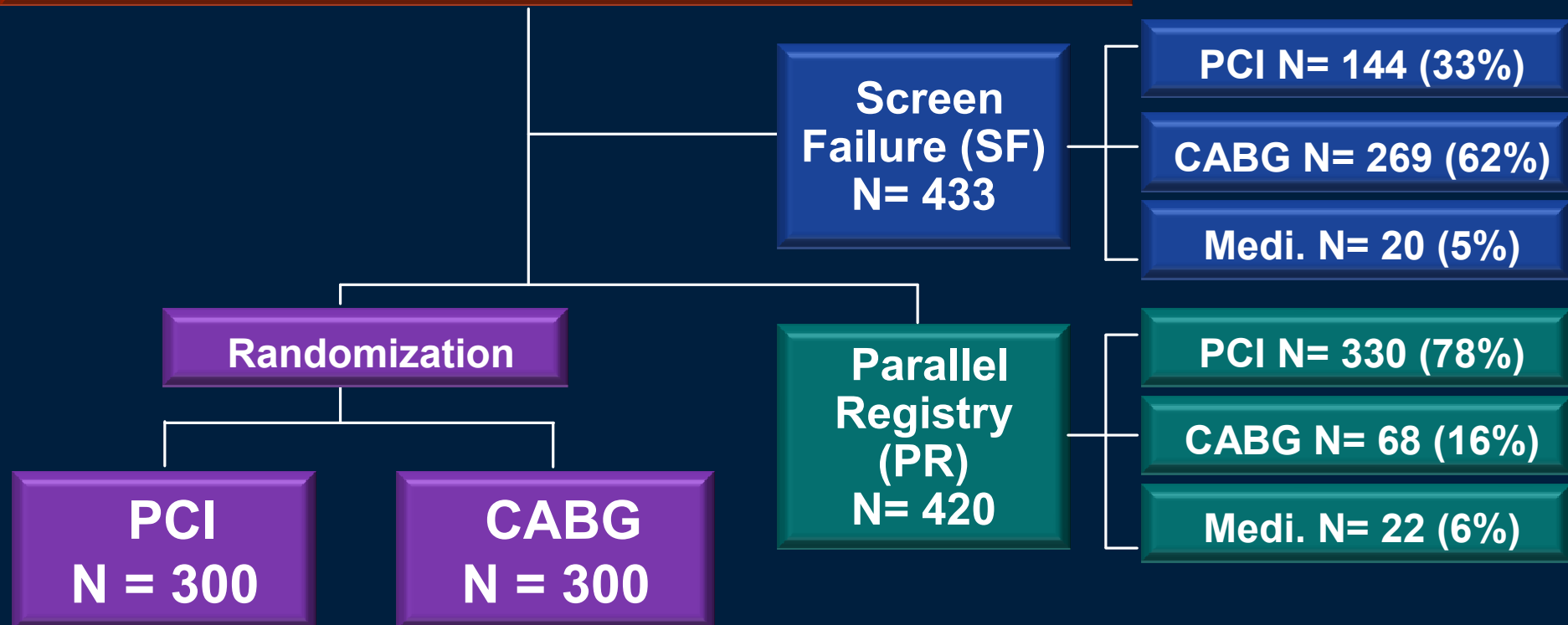
CABG
PCI
Medication

PRIMARY Endpoint: 2-year MACCE (Death/MI/Stroke/TVR)
SECONDARY Endpoints: clinical and angiographic outcomes

PI: Seung-Jung Park
13 centers from Korea

Enrollment (Finished)

**Screening for patients with LMCA stenosis
N = 1453**



Comparison with SYNTAX Patients

	PRECOMBAT (N = 600)	SYNTAX (N = 705)
Age, year	62.1 ± 9.8	65.5 ± 9.9
Male sex, %	73.8	73.8
Diabetes mellitus, %	32.1	22.1
Hypertension, %	53.4	73.5
Hyperlipidemia, %	41.7	75.2
History of smoking, %	46.3	20.9
Total lesion numbers	2.9 ± 1.5	3.2 ± 1.8
Left main + 2 vessel, %	30.0	30.9
Left main + 3 vessel, %	42.0	36.6

PRECOMBAT

- The PRECOMBAT trial is the FIRST randomized clinical trial aimed to compare the safety and effectiveness of DES and CABG for the treatment unprotected LMCA disease with its primary end point of MACCE.
- The final outcome will be available on ACC 2011.

PRECOMBAT-2

PREmier COMparison of Bypass surgery and AngioplasTy-2 Using Everolimus Electing Stent in Patients with Left Main Coronary Disease

Current Trial

PRE-COMBAT

for unprotected left main disease
Up to 13 cardiac centers in Korea

Randomization of 600 (1:1)

PCI with
Cypher
N=300

CABG
N=300

PRE-COMBAT-2

for unprotected left main disease
Up to 13 cardiac centers in Korea

All patients receiving Xience V
For 1 year upto 500

PRECOMBAT-
Eligible Cohort

: Pts Meeting
Randomization
Criteria of
'PRECOMBAT'
N = 300

PRECOMBAT-
Not Eligible
Cohort

N = 200

Primary Endpoint (MACCE): 2-year death, MI, Stroke, and ischemic driven TVR

IRIS - MAIN

(Left **MAIN** Disease – **I**nterventional Cardiology
Research **I**ncorporation **S**ociety)

A Global, Multicenter, and Prospective,
Real World Observational Study

**All Patients with Left Main Disease
(3,000 pts)**

PCI with Any stents
(Approximately 1,500 pts)

CABG
(Approximately 1,500 pts)

Medical Treatment

**Primary Endpoint: 2-year composite of Death, MI, Stroke, and TVR
and annually follow up to 10 years**

PI: Seung-Jung Park, MD

EXCEL Trial

(**E**valuation of **X**ience prime versus **C**oronary artery bypass surgery for **E**ffectiveness of **L**eft main revascularization)

Left Main disease (2,500)
with or without MVD

Randomize
(1:1)

PCI with Xience
(N=1,250)

CABG
(N=1,250)

Primary Endpoint: 2-year composite of death, MI, or stroke

PI: Gregg Stone, Patrick Serruys