Trial of Everolimus-Eluting Stents or Bypass Surgery for Coronary Disease (BEST Trial)

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On behalf of the BEST investigators

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Introduction

- Recent studies have demonstrated that the rates of most adverse clinical outcomes in patients with multivessel coronary-artery disease are lower following CABG than with PCI.

- However, previous studies may have been limited by their use of first-generation drug-eluting stents. Although these stents reduced the rate of restenosis, their use was associated with a relatively high rate of stent-related thrombotic events.

BEST Trial

Design

- DESIGN: a prospective, open-label, randomized trial
- OBJECTIVE: To compare PCI with everolimus-eluting stents and CABG for optimal revascularization of patients with multivessel coronary artery stenosis.
- PRINCIPAL INVESTIGATOR
  Seung-Jung Park, MD, PhD, Asan Medical Center, Seoul, Korea

Participating Centers (N=27)

Country	Site	Investigator
Korea	Asn Medical center	Seung-Jung Park
Korea	Keimyung University Dongsan Medical Center	Seung Ho Hur
Korea	The Catholic University of Korea Seoul St. Mary's Hospital	Ki Bae Seung
Thailand	Siriraj Hospital	Damras Tresukosol
Korea	Gachon University Gil Hospital	Tae hoon Ahn
Korea	Gangnam Severance Hospital	Hyuck Moon Kwon
Korea	Korea University Guro Hospital	Seung Un Na
Korea	Korea University Anam Hospital	Do Sun Lim
Korea	Chonnam National University Hospital	Myung-Ho Jeong
Korea	Kangwon National University Hospital	Bong-Ki Lee
China	Sir Run Run Shaw Hospital	Guo Sheng Fu
Korea	Hanyang University Medical Center	Kyoung Soo Kim
Korea	Konyang University Hospital	Jang Ho Bae
Korea	Inje University Sanggye Paik Hospital	Byung Ok Kim
Malaysia	Sarawak General Hospital	Tiong Kiam Ong
Korea	Wonju Christian Hospital	Junghan Yoon
Korea	Inje University Pusan Paik Hospital	Tae-Hyun Yang
Korea	Severance Hospital	Yang-Soo Jang
Korea	National Health Insurance Corporation Ilsan Hospital	Joo-Young Yang
Korea	Yeungnam University Medical Center	Jong-Seon Park
China	Zhongshan Hospital	JunBo Ge
Korea	Inje University Ilsan Paik Hospital	Sung Yun Lee
Korea	Pusan National University Yangsan Hospital	Jun Hong Kim
Korea	St.carollo Hospital	Jang-Hyun Cho
Korea	The Catholic University of Korea, Yeouido St. Mary's Hospital	Yun Seok Choi
Korea	Ulsan University Hospital	Sang-Gon Lee
Malaysia	National Heart Institute	Robaaya Zambahari

Major Inclusion Criteria

- ≥ 18 years of age.
- Angiographically confirmed mutivessel coronary artery disease (>70%)
- Suitable candidates for either PCI or CABG by their treating physicians and surgeons
- Symptoms of angina and/or objective evidence of myocardial ischemia.

Major Exclusion Criteria

- Any contraindication to dual antiplatelet therapy
- Severe heart failure (NYHA III or IV)
- Planned surgery
- Previous CABG
- Prior PCI with DES implantation within 1 year
- CTO ≥2
- STEMI within 72 hours
- Elevated cardiac enzyme
- Disabled stroke
- Other comorbidity

Study Procedures

- **Everolimus-Eeluting Xience Stent** for all lesions
- Strong recommendation of IVUS-guidance
- Other adjunctive devices at the physician's discretion
- Use of LIMA to LAD anastomosis
- Off- or on-pump surgery at the surgeon's discretion
- DAPT at least for 1 year after PCI
- Standard medical treatment after PCI and CABG

Follow-up

- Clinical follow-up at 30 days and 6, 9, and 12 months , and annually thereafter, via clinic visit or telephone interview.
- Secondary preventive medication was strongly recommended according to clinical guideline
- Routine angiographic follow-up was strongly discouraged for all patients to reduce the occurrence of repeat revascularization driven by angiography alone without signs or symptoms of ischemia.

Primary End Point

- A composite of major adverse cardiac events (MACE) for the 2 years after randomization including
  - Death from any cause
  - Myocardial infarction
  - Target vessel revascularization

Original Power Calculation

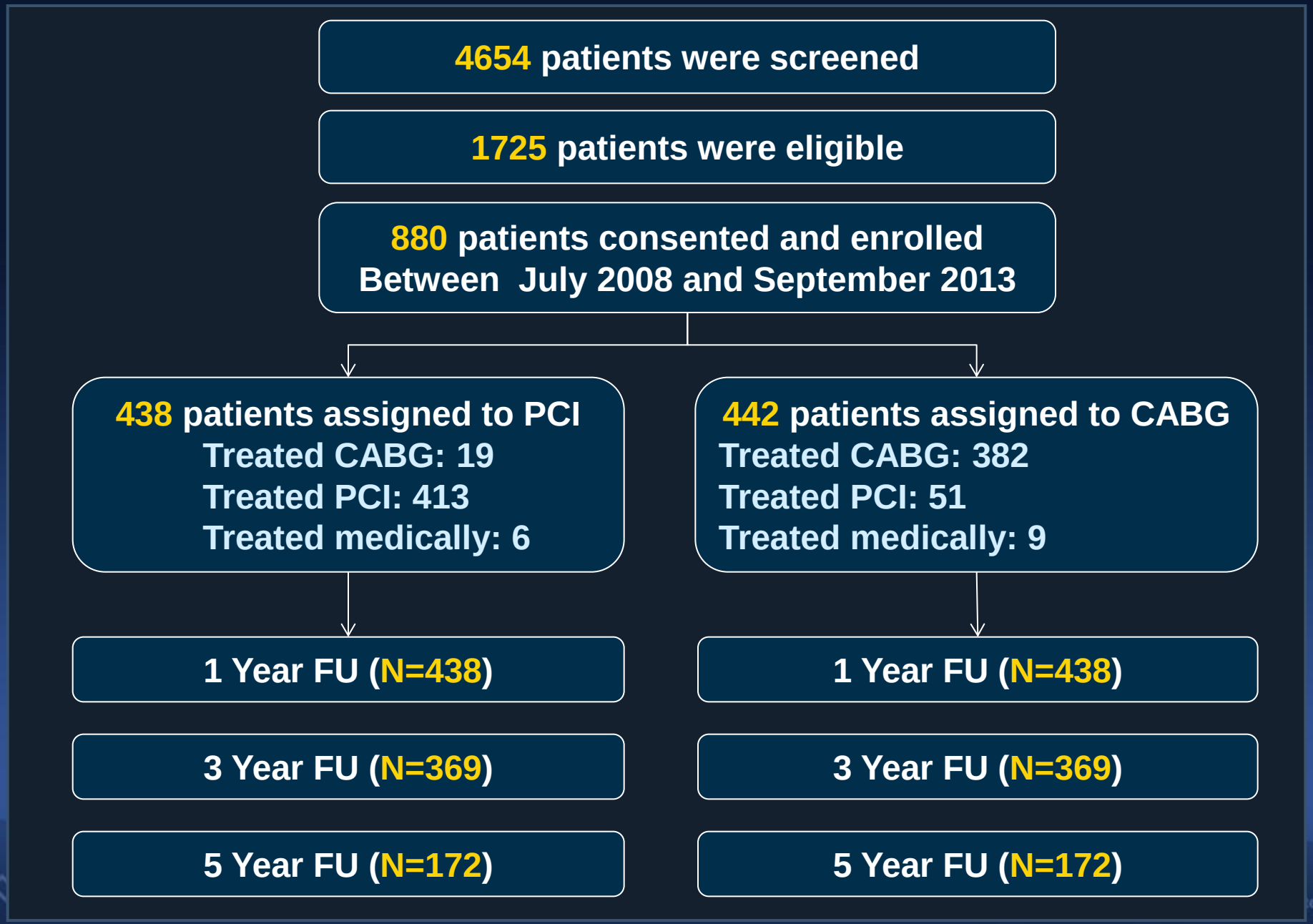
Non-inferiority Design for Primary Endpoint

- Assumed MACE rate: 12% at 2 years
- A noninferiority margin : 4%
- A one-sided type I error rate : 0.05
- Power : 80%
- Dropout rate: 5%
- Assumed sample size: 1776 patients

Premature Termination of Trial

- The enrollment rate was slower than expected, which was thought to be a consequence of the rapid spread of measurement of fractional flow reserve in clinical practice.
- The data and safety monitoring board recommended stopping enrollment in October 2013 when 880 patients had been enrolled.
- We extended the follow-up period with a median of 4.6 years.

Patient Flow



Statistical Analysis

- Kaplan-Meier method to estimate survivals with comparison using log-rank test.
- Noninferiority test using the Z-test with 95% CI of difference in the 2-year MACE rate.
- Survival analyses using longer-term outcomes using all available follow-up data as an exploratory analyses.
- Subgroups analysis using the Cox regression model with tests for interaction.
- Primary analysis in intention-to-treat principle

Baseline Clinical Characteristics

	PCI (N=438)	CABG (N=442)	P value
Age, years	64.0 ± 9.3	64.9 ± 9.4	0.13
Male sex	304 (69.4)	325 (73.5)	0.18
Body mass index	24.7 ± 2.9	2.0 ± 2.9	0.16
Diabetes	177 (40.4)	186 (42.1)	0.62
Hypertension	296 (67.6)	295 (66.7)	0.79
Hyperlipidemia	239 (54.6)	222 (50.2)	0.20
Current smoker	88 (20.1)	89 (20.1)	0.99
Previous PCI	30 (6.8)	38 (8.6)	0.33
Previous myocardial infarction	25 (5.7)	29 (6.6)	0.60
Previous congestive heart failure	16 (3.7)	12 (2.7)	0.43

Baseline Clinical Characteristics

	PCI (N=438)	CABG (N=442)	P value
Chronic renal failure	9 (2.1)	7 (1.6)	0.60
Peripheral vascular disease	15 (3.4)	12 (2.7)	0.54
Chronic pulmonary disease	8 (1.8)	6 (1.4)	0.58
Clinical manifestation			0.68
Stable angina or asymptomatic	210 (47.9)	204 (46.2)	
Unstable angina	185 (42.2)	199 (45.0)	
Recent acute myocardial infarction	43 (9.8)	39 (8.8)	
Ejection fraction, %	59.1 ± 8.5	59.9 ± 8.1	0.12
Three vessel disease	330 (75.3)	349 (79.0)	0.20
EuroSCORE value	2.9 ± 2.0	3.0 ± 2.1	0.55
SYNTAX score value	24.2 ± 7.5	24.6 ± 8.1	0.47

Procedural Characteristics*

PCI	464
Total stents number	3.4 ± 1.4
Total stent length, mm	85.3 ± 38.2
Mean stent diameter, mm	3.1 ± 0.3
IVUS guidance	333 (71.8)
Complete revascularization	236 (50.9)†
CABG	401
Total no. of grafted vessels	3.1 ± 0.9
Total no. of arterial grafts	2.1 ± 1.1
Total no. of vein grafts	1.0 ± 0.8
Left internal mammary artery graft	398 (99.3)
Off-pump surgery	258 (64.3)
Complete revascularization	274/383 (71.5)†

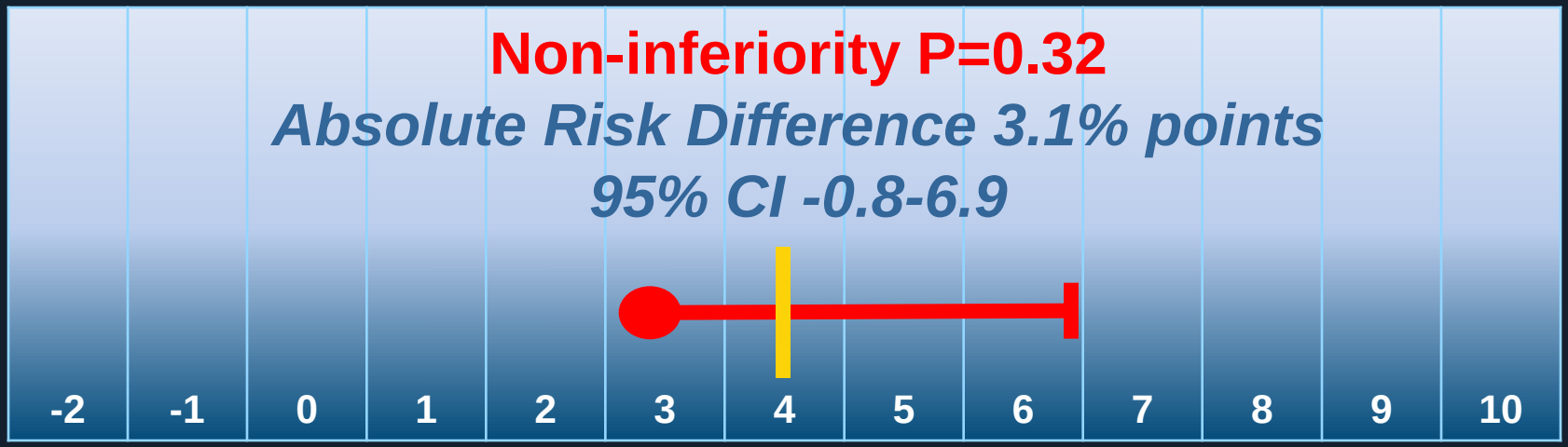
* Data were summarized according to the as-treated analysis

† P<0.05 between PCI and CABG group

Noninferiority Test for
Primary End Point of 2-Year MACE

2-year MACE rate **CABG: 11.0%** **PCI: 7.9%**

Prespecified non-inferiority margin: 4%

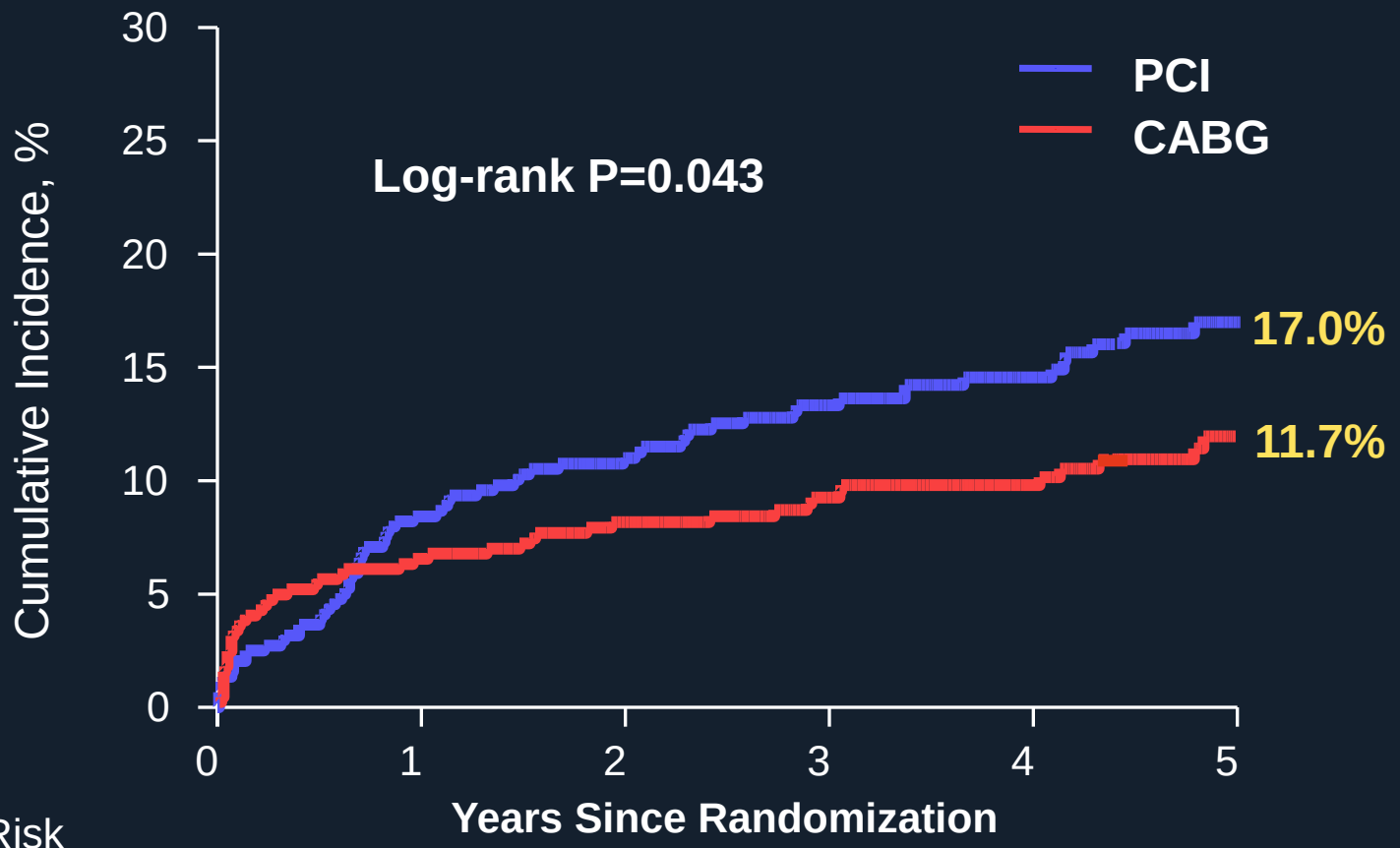


Difference (percentage point) of 2-year MACE rate (PCI – CABG)

Upper 1-sided 95% CI

Long-Term Follow-up

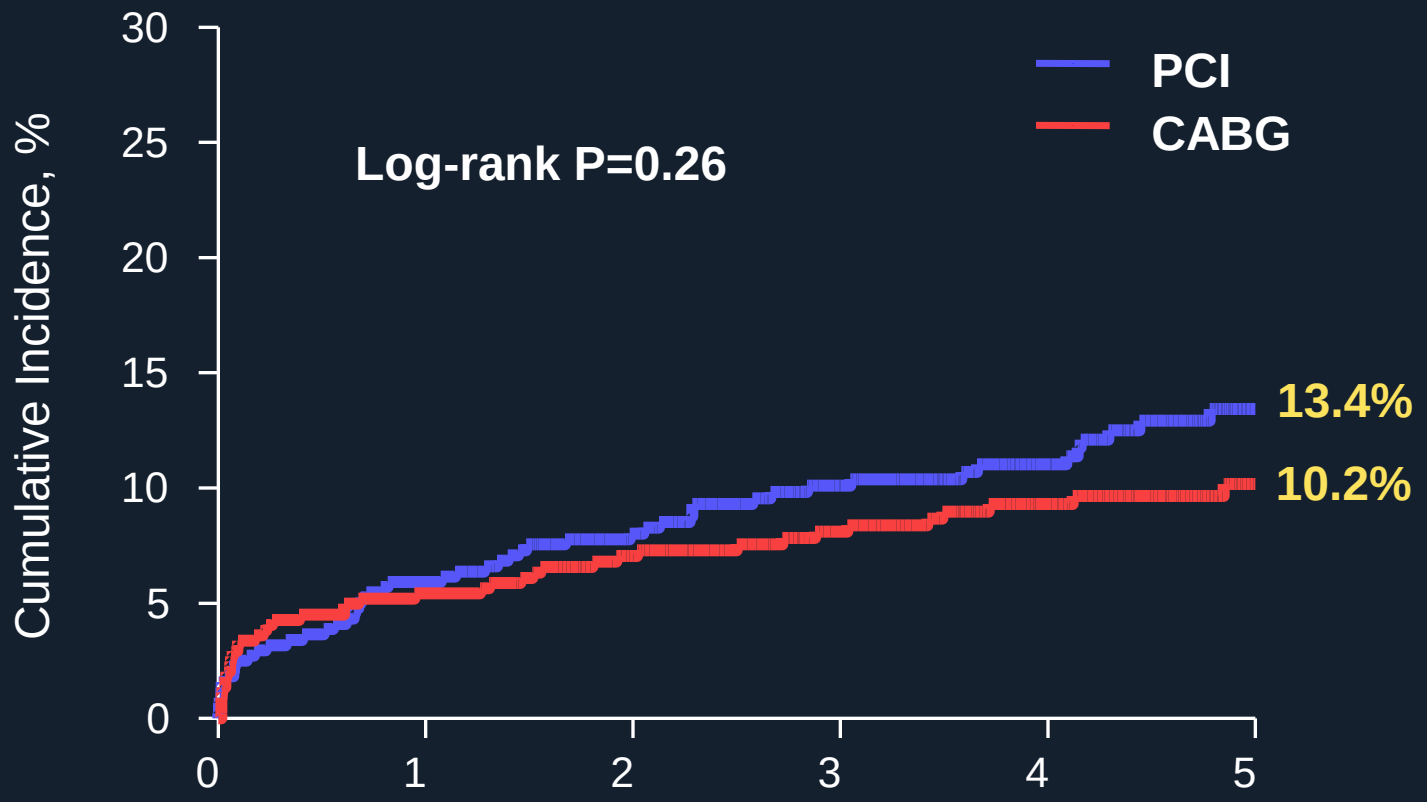
Primary End Point of MACE



No. at Risk						
PCI	438	402	362	305	242	126
CABG	442	415	377	326	262	145

Event rates were derived from Kaplan-Meier estimates

Death, MI or Stroke

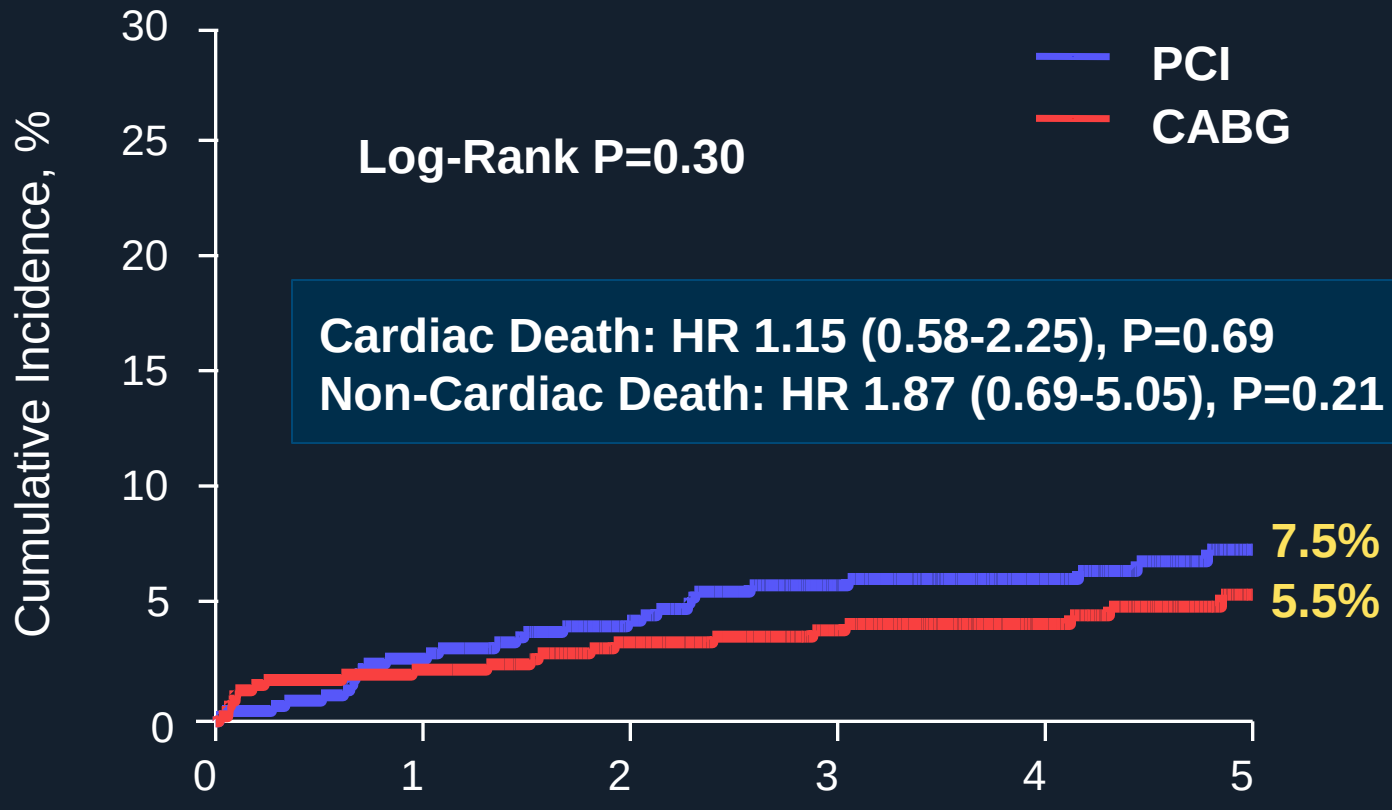


No. at Risk

PCI	438	413	373	318	255	133
CABG	442	419	381	329	263	144

Event rates were derived from Kaplan-Meier estimates

Death

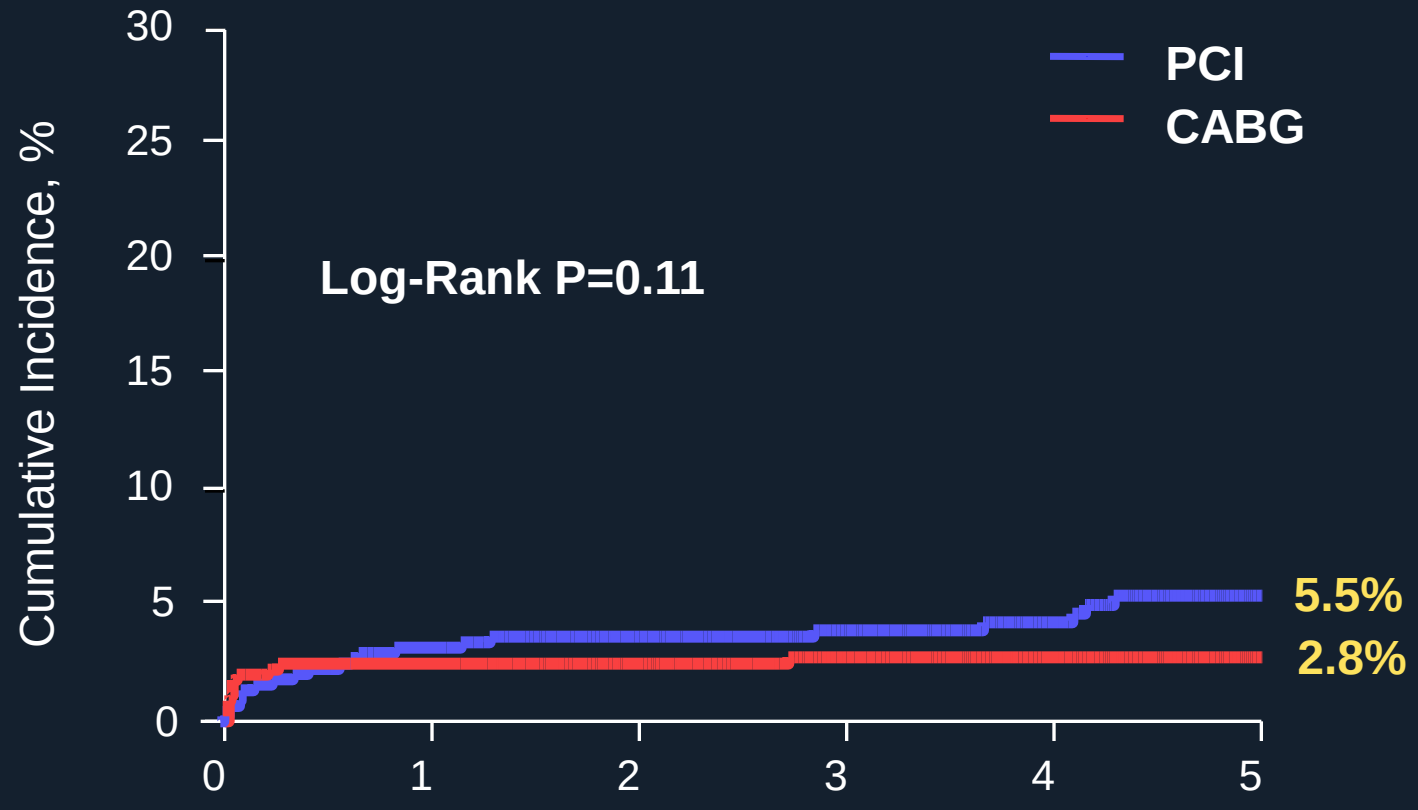


No. at Risk

PCI	438	426	387	333	268	146
CABG	442	433	397	346	278	154

Event rates were derived from Kaplan-Meier estimates

Myocardial Infarction

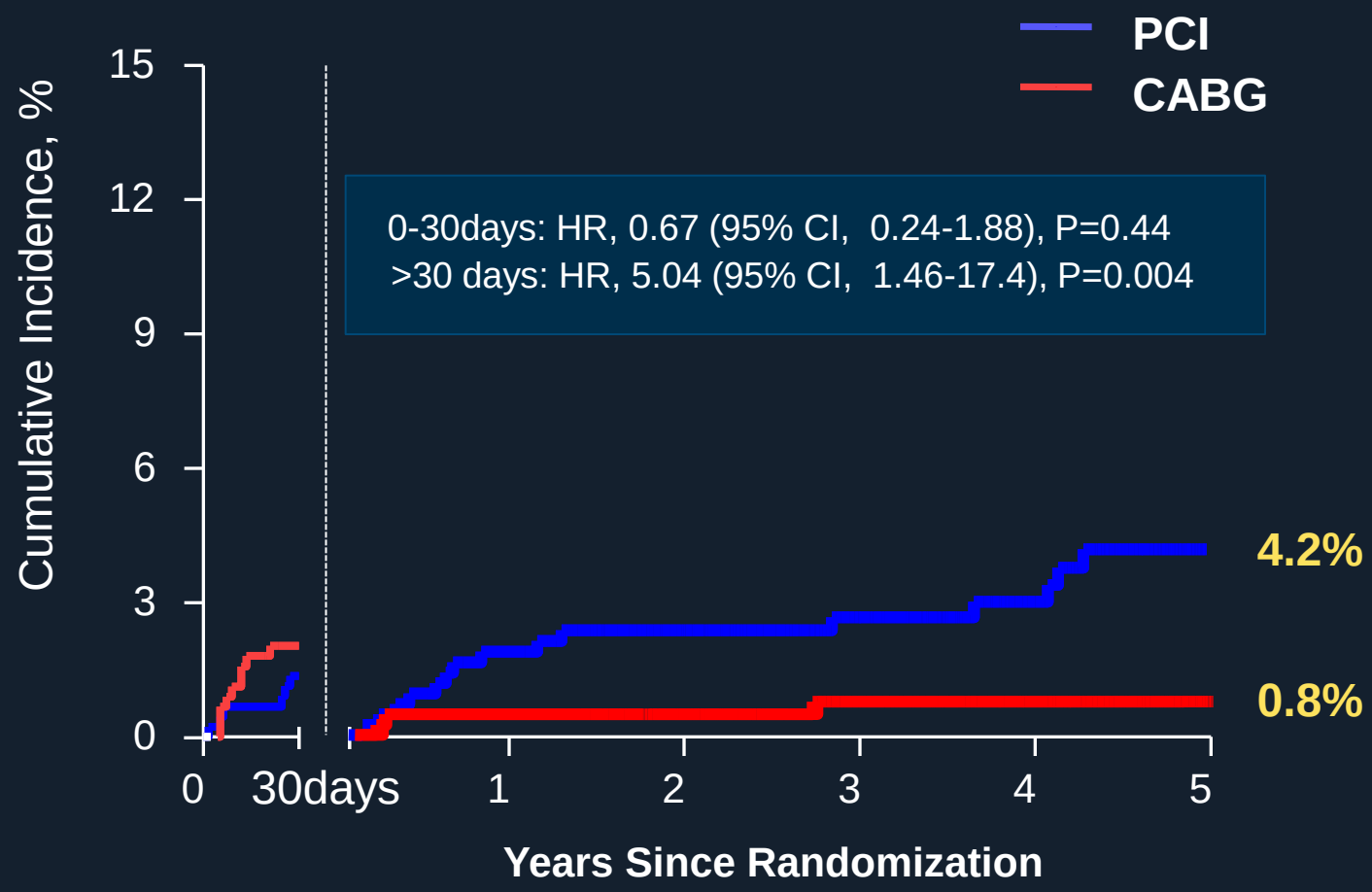


No. at Risk

PCI	438	419	382	325	261	140
CABG	442	422	386	335	271	151

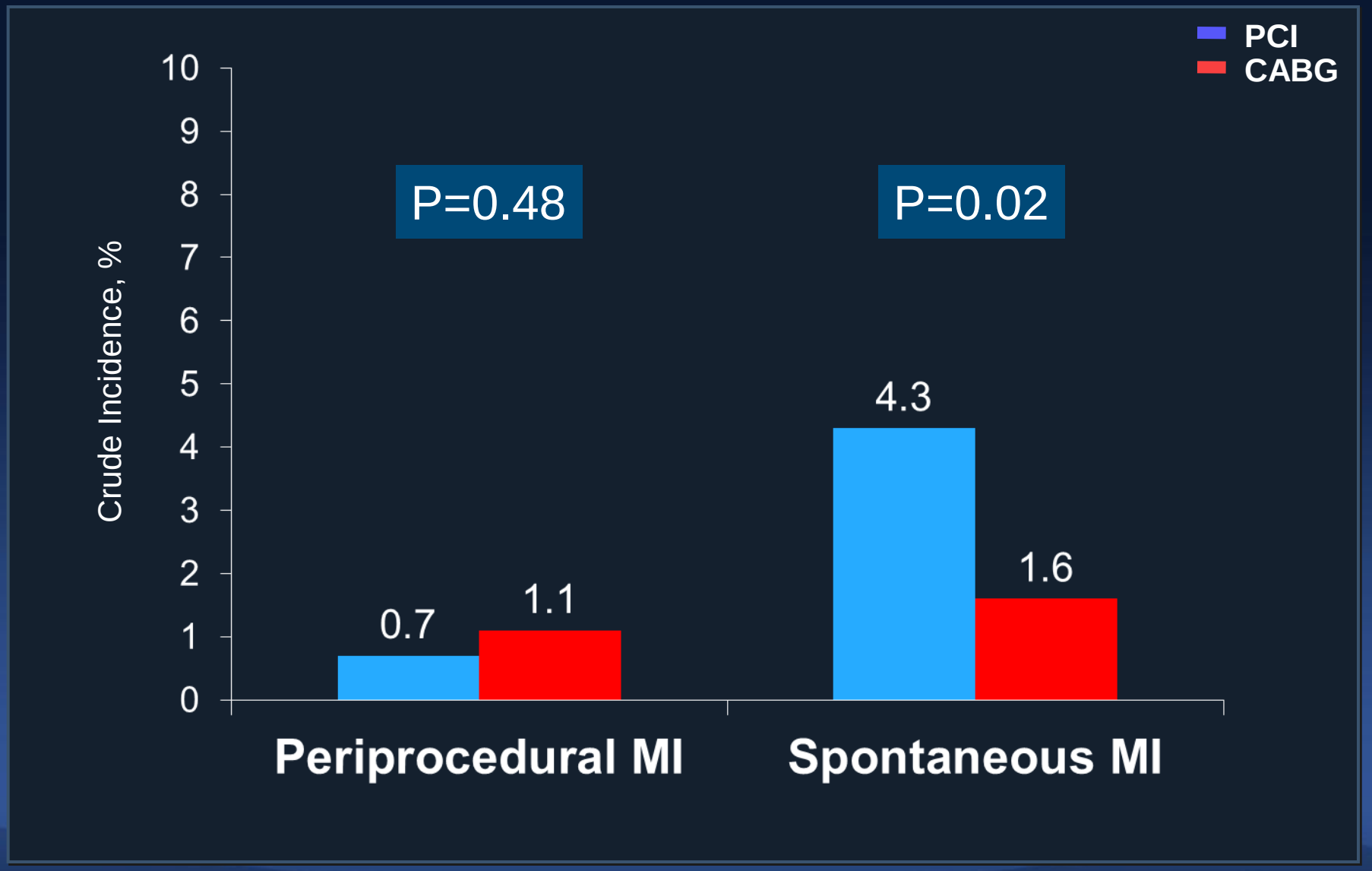
Event rates were derived from Kaplan-Meier estimates

Land Mark Analysis of MI



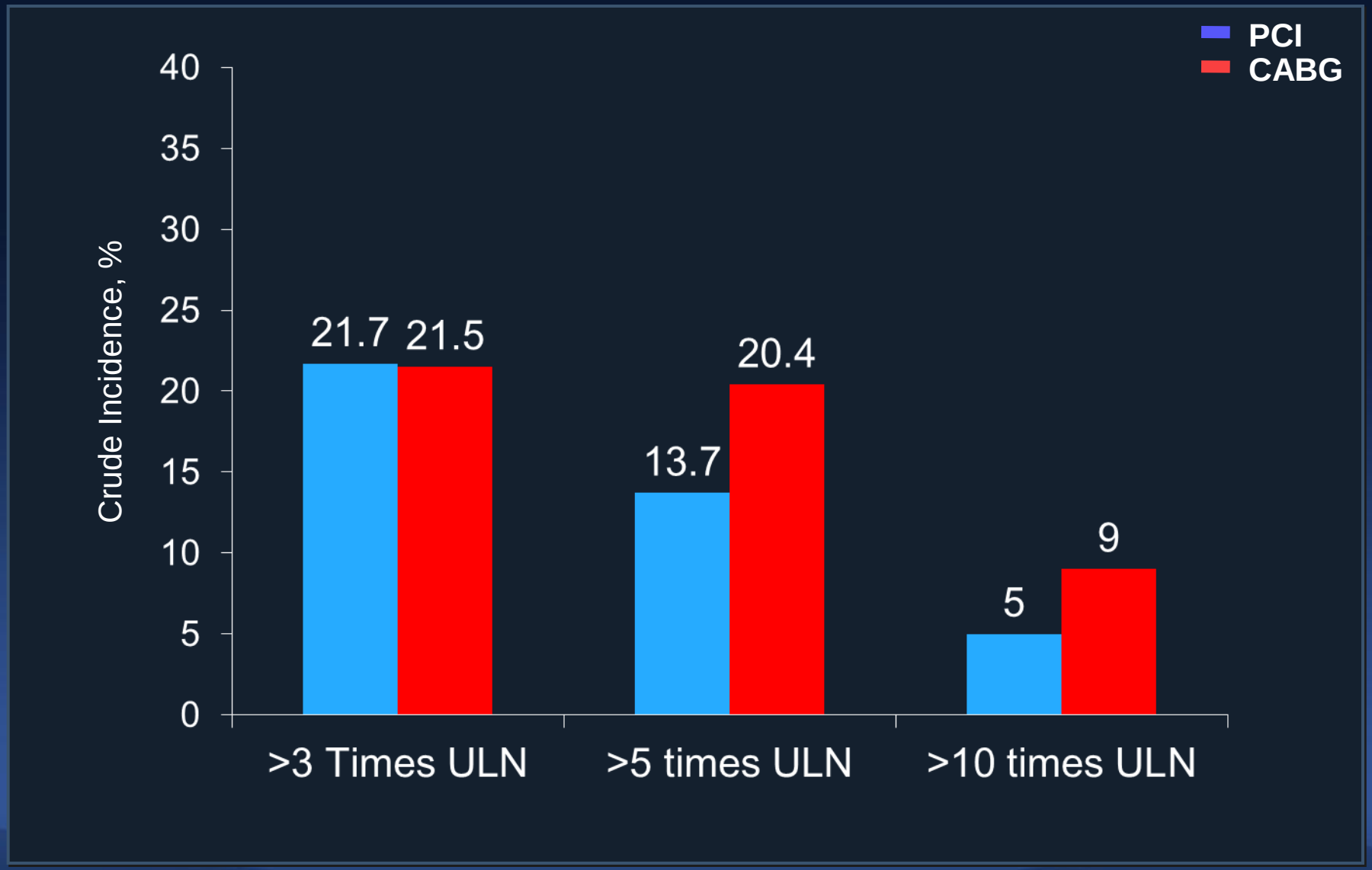
Event rates were derived from Kaplan-Meier estimates

Myocardial Infarction



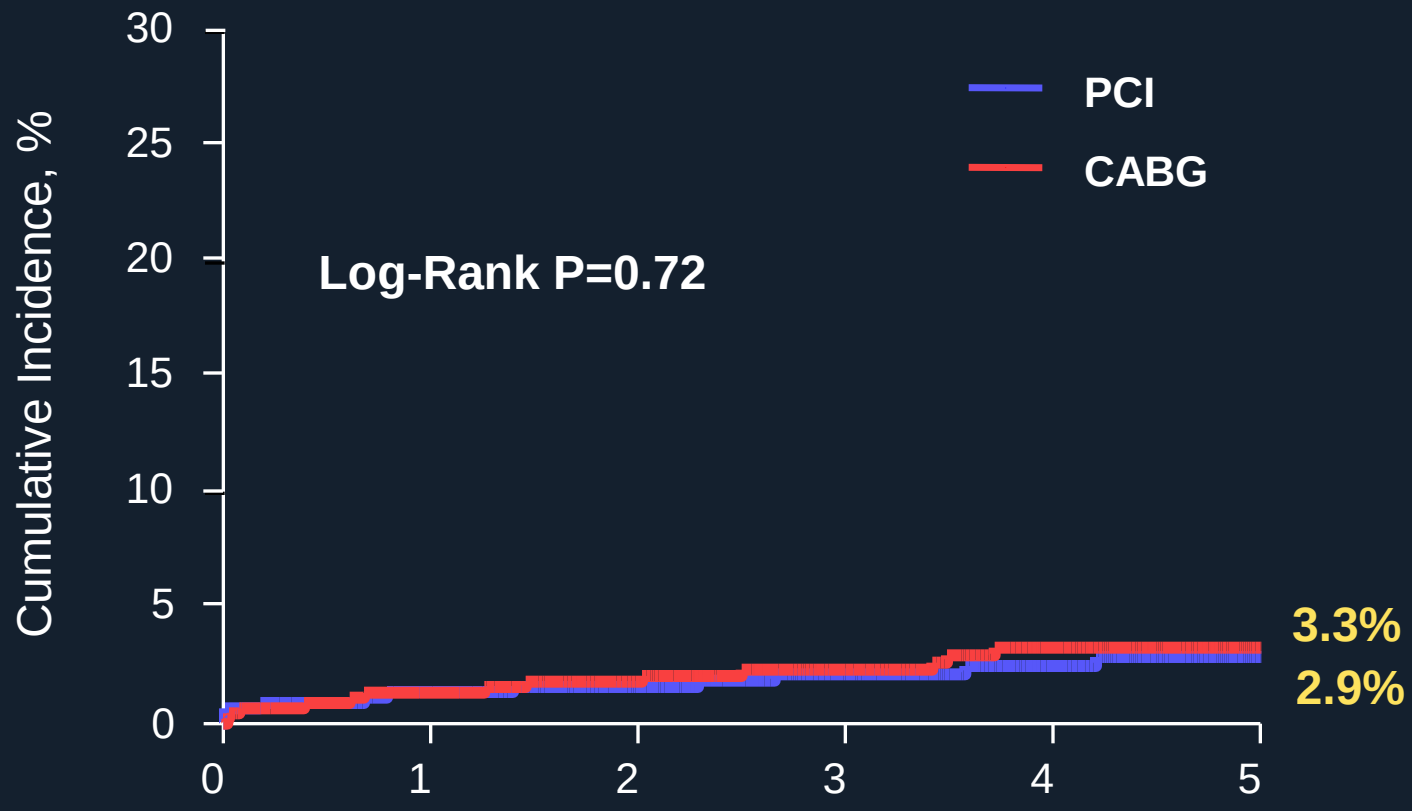
Percentages are crude rates throughout the available follow-up period

CK-MB Elevation Post-Procedure



Percentages are crude rates throughout the available follow-up period

Stroke

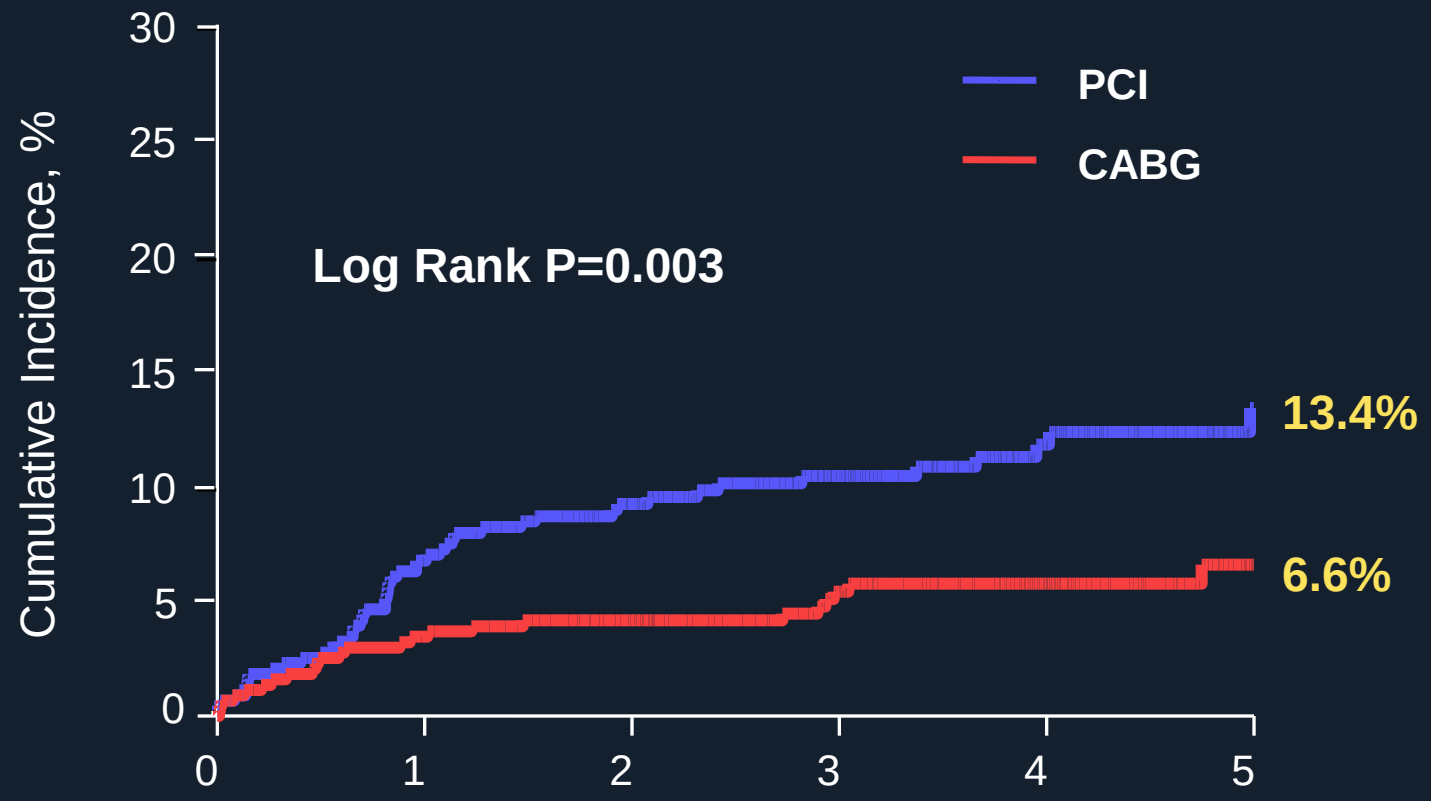


No. at Risk

PCI	438	421	383	326	262	140
CABG	442	427	389	338	271	152

Event rates were derived from Kaplan-Meier estimates

Any Repeat Revascularization

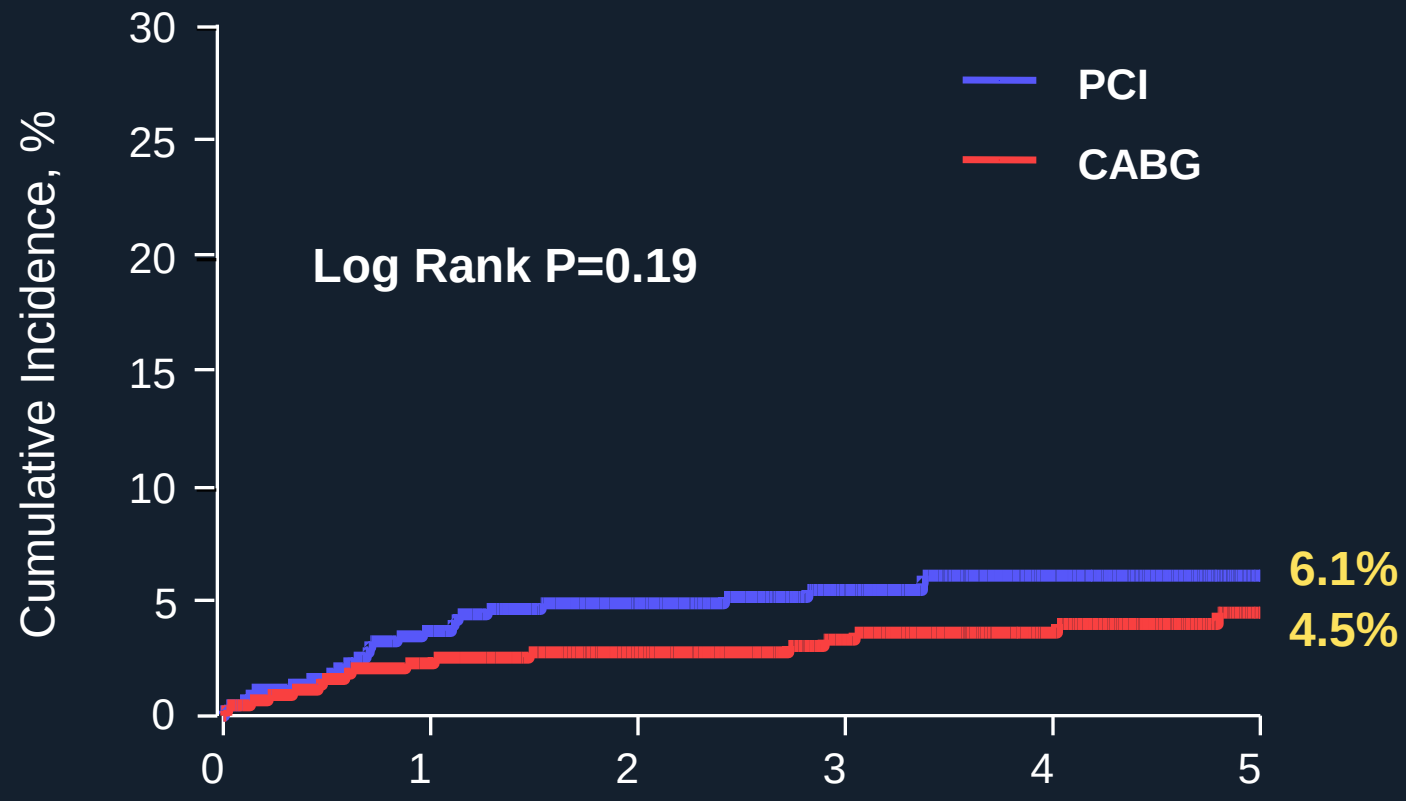


No. at Risk

PCI	438	393	335	257	164	80
CABG	442	414	365	286	189	87

Event rates were derived from Kaplan-Meier estimates

Target Lesion Revascularization

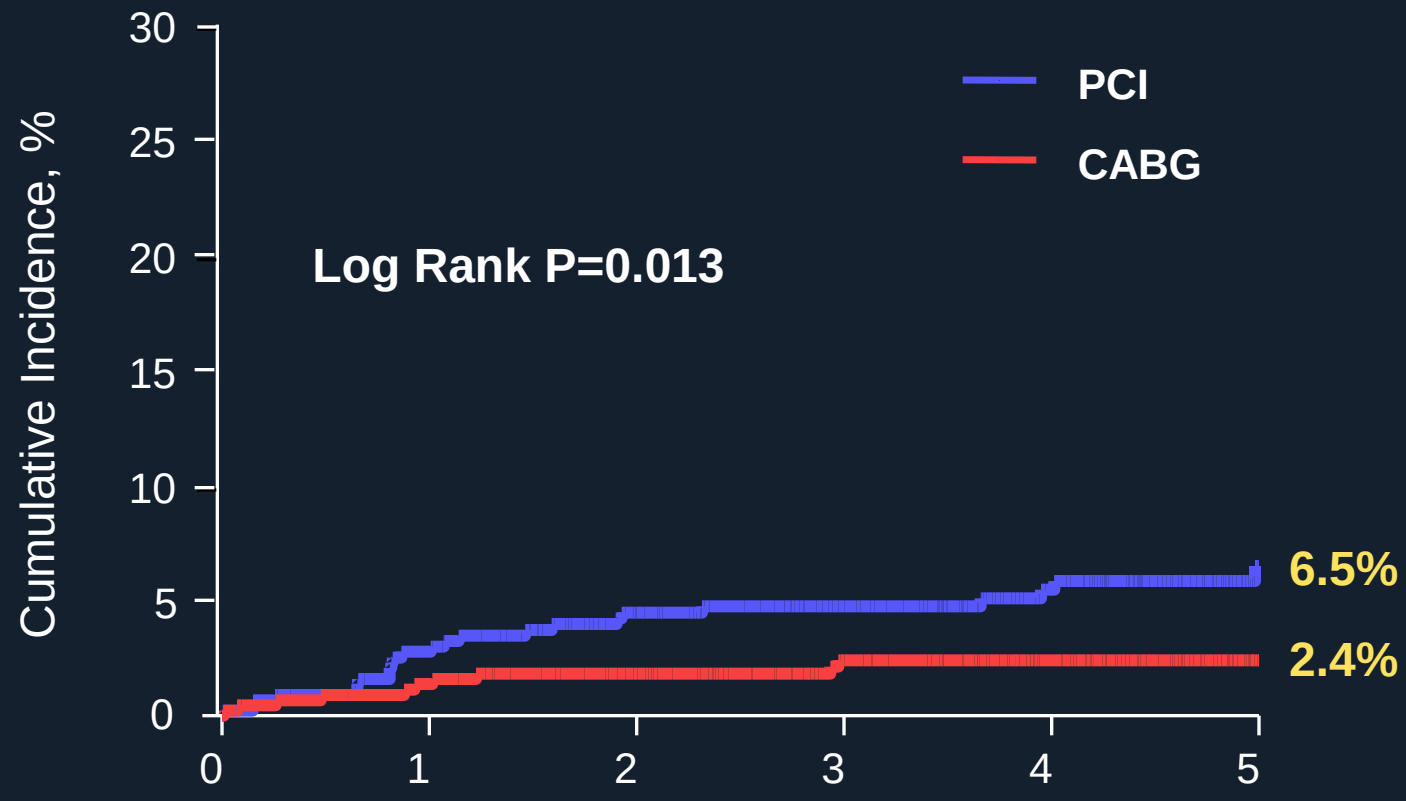


No. at Risk

PCI	438	408	365	310	247	130
CABG	442	424	386	334	267	147

Event rates were derived from Kaplan-Meier estimates

New Lesion Revascularization

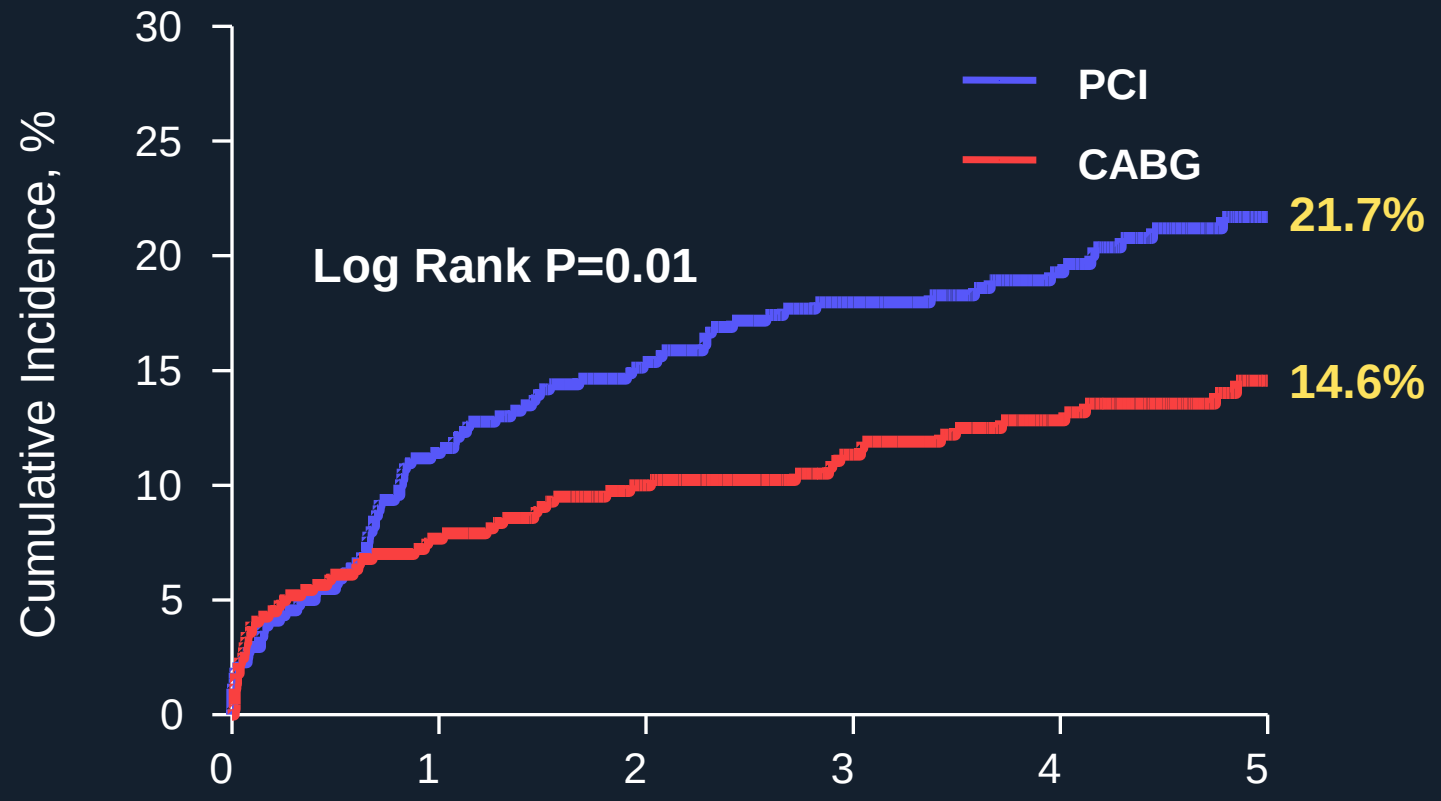


No. at Risk

PCI	438	416	370	317	254	138
CABG	442	427	389	337	270	149

Event rates were derived from Kaplan-Meier estimates

Death, MI, Stroke or RR

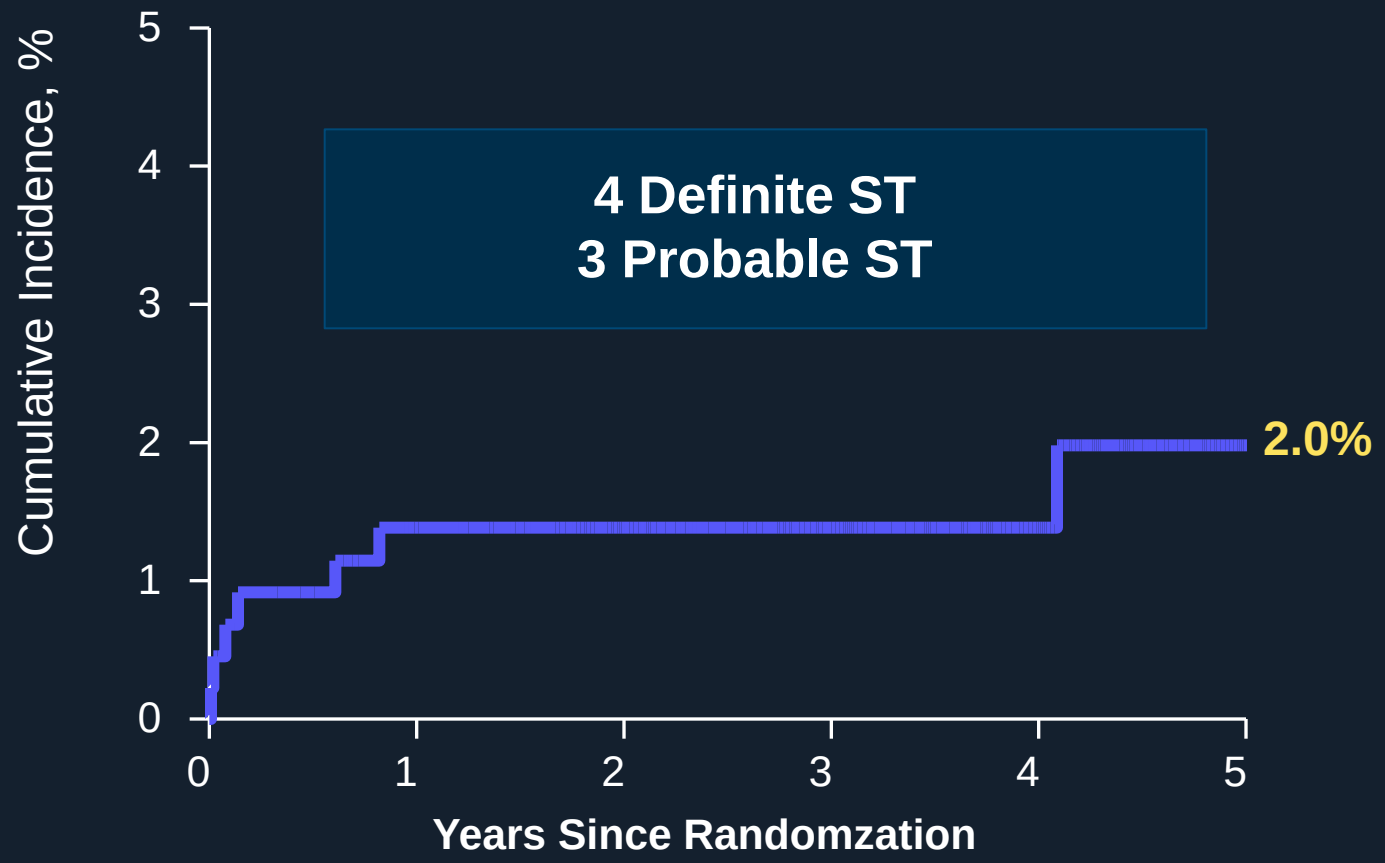


No. at Risk

PCI	438	389	341	288	229	117
CABG	442	409	368	317	250	137

Event rates were derived from Kaplan-Meier estimates

Definite or Probable Stent Thrombosis



Event rates were derived from Kaplan-Meier estimates

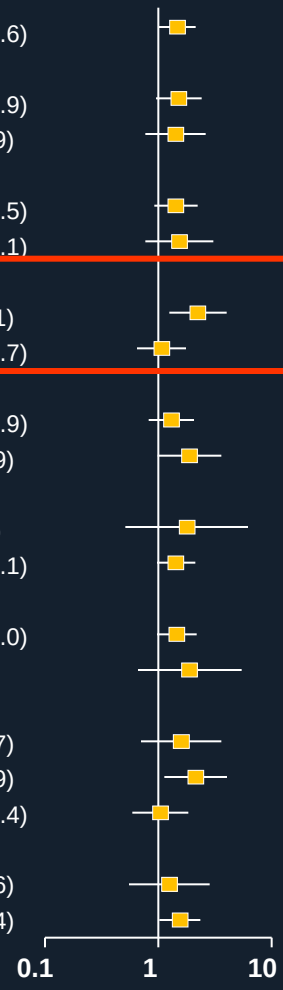
Long-Term Outcomes

End points	PCI (N=464)	CABG (N=401)	Hazard ratio (95% CI)	P-value
Primary End Points: MACE	67 (15.3)	47 (10.6)	1.47 (1.01-2.13)	**0.043**
Secondary End Points				
Death	29 (6.6)	22 (5.0)	1.34 (0.77-2.34)	0.30
Myocardial Infarction	21 (4.8)	12 (2.7)	1.76 (0.87-3.58)	0.11
Spontaneous MI	19 (4.3)	7 (1.6)	2.75 (1.16-6.54)	**0.017**
Stroke	11 (2.5)	13 (2.9)	0.86 (0.39-1.93)	0.72
Death, Myocardial Infarction, or stroke	52 (11.9)	42 (9.5)	1.26 (0.84-1.89)	0.26
Any Repeat Revascularization	48 (11.0)	24 (5.4)	2.09 (1.28-3.41)	**0.003**
Target Lesion Revascularization	25 (5.7)	17 (3.8)	1.51 (0.82-2.80)	0.19
New Lesion Revascularization	24 (5.5)	10 (2.3)	2.47 (1.18-5.17)	**0.013**
Death, MI, Stroke, or Any RR	87 (19.9)	59 (13.3)	1.54 (1.11-2.14)	**0.01**
Bleeding				
TIMI Major Bleeding‡	30 (6.8)	132 (29.9)	0.20 (0.14-0.30)	**<0.001**
Fatal Bleeding	3 (0.7)	7 (1.6)	0.44 (0.11-1.68)	0.21

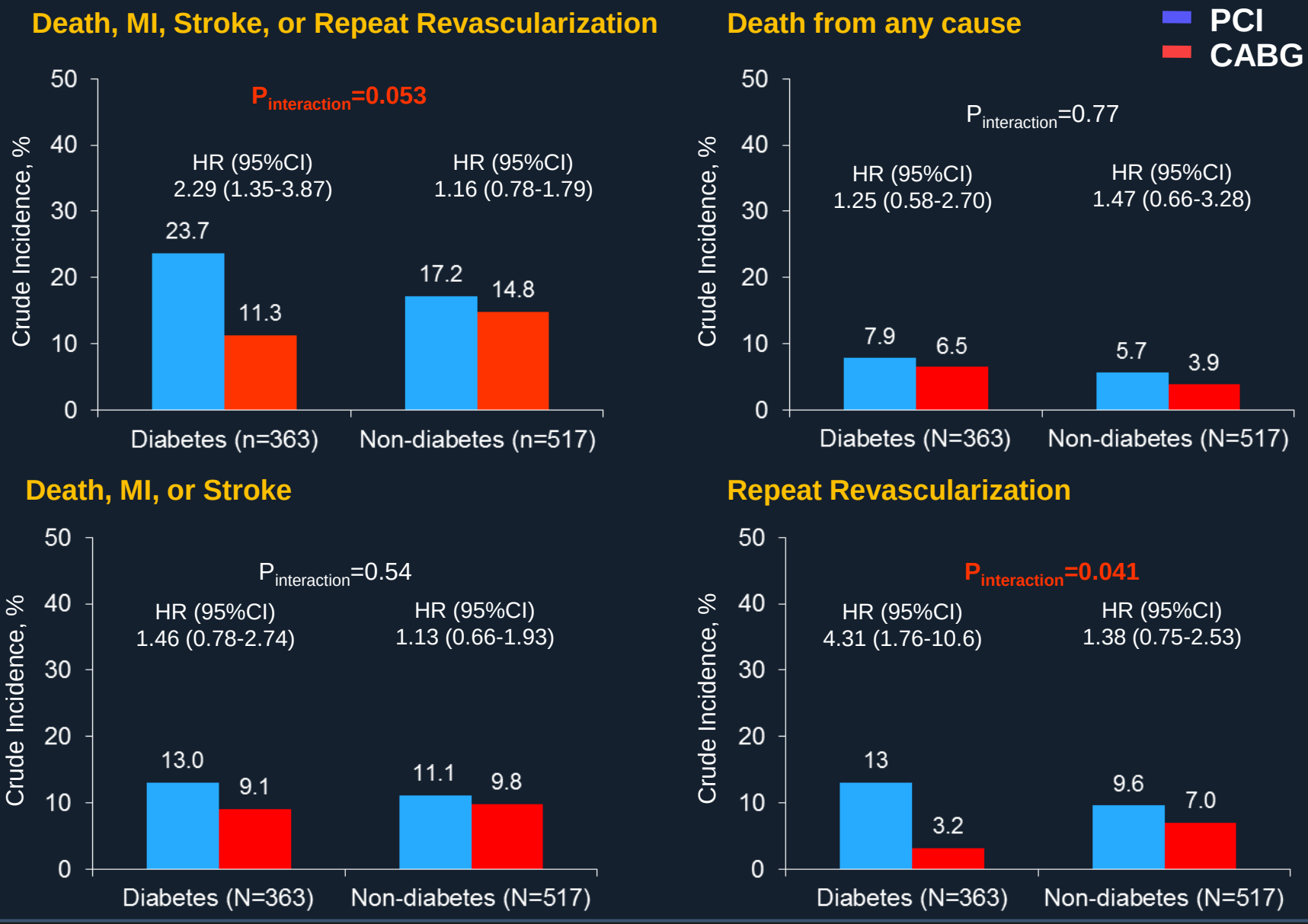
Percentages are crude rates throughout the available follow-up period

Subgroup Analysis for MACE

Subgroup	Primary Outcome		Hazard Ratio (95% CI)	P value for Interaction
	PCI	CABG		
	n / total n. (%)			
Overall	67/438 (15.3)	47/442 (10.6)	1.47 (1.01-2.13)	-
Age				0.90
≥65 yr	41/229 (17.9)	30/252 (11.9)	1.51 (0.95-2.42)	
<65 yr	26/209 (12.4)	17/190 (8.9)	1.43 (0.77-2.63)	
Sex				0.88
Male	45/304 (14.8)	34/325 (10.5)	1.43 (0.92-2.24)	
Female	22/134 (16.4)	13/117 (11.1)	1.53 (0.77-3.05)	
Diabetes				0.06
Yes	34/177 (19.2)	17/186 (9.1)	2.24 (1.25-4.00)	
No	33/261 (12.6)	30/256 (11.7)	1.07 (0.65-1.76)	
ACS				0.35
Yes	40/228 (17.5)	33/238 (13.9)	1.30 (0.82-2.06)	
No	27/210 (12.9)	14/204 (6.9)	1.89 (0.99-3.60)	
Ejection fraction				0.65
≤40%	7/17 (41.2)	4/17 (23.5)	1.79 (0.51-6.21)	
>40%	60/421 (14.3)	43/425 (10.1)	1.43 (0.97-2.12)	
Vascular extent				0.65
3VD	56/330 (17.0)	42/349 (12.0)	1.45 (0.97-2.17)	
2VD	11/108 (10.2)	5/93 (5.4)	1.89 (0.66-5.43)	
SYNTAX score				0.25
Score ≥33	13/66 (19.7)	10/79 (12.7)	1.59 (0.70-3.62)	
Score 23 - 32	30/187 (16.0)	14/177 (7.9)	2.14 (1.13-4.03)	
Score ≤22	24/185 (13.0)	23/186 (12.4)	1.04 (0.59-1.84)	
EuroSCORE				0.65
≥6	12/51 (23.5)	11/59 (18.6)	1.25 (0.55-2.84)	
<6	55/387 (14.2)	36/383 (9.4)	1.55 (1.02-2.35)	

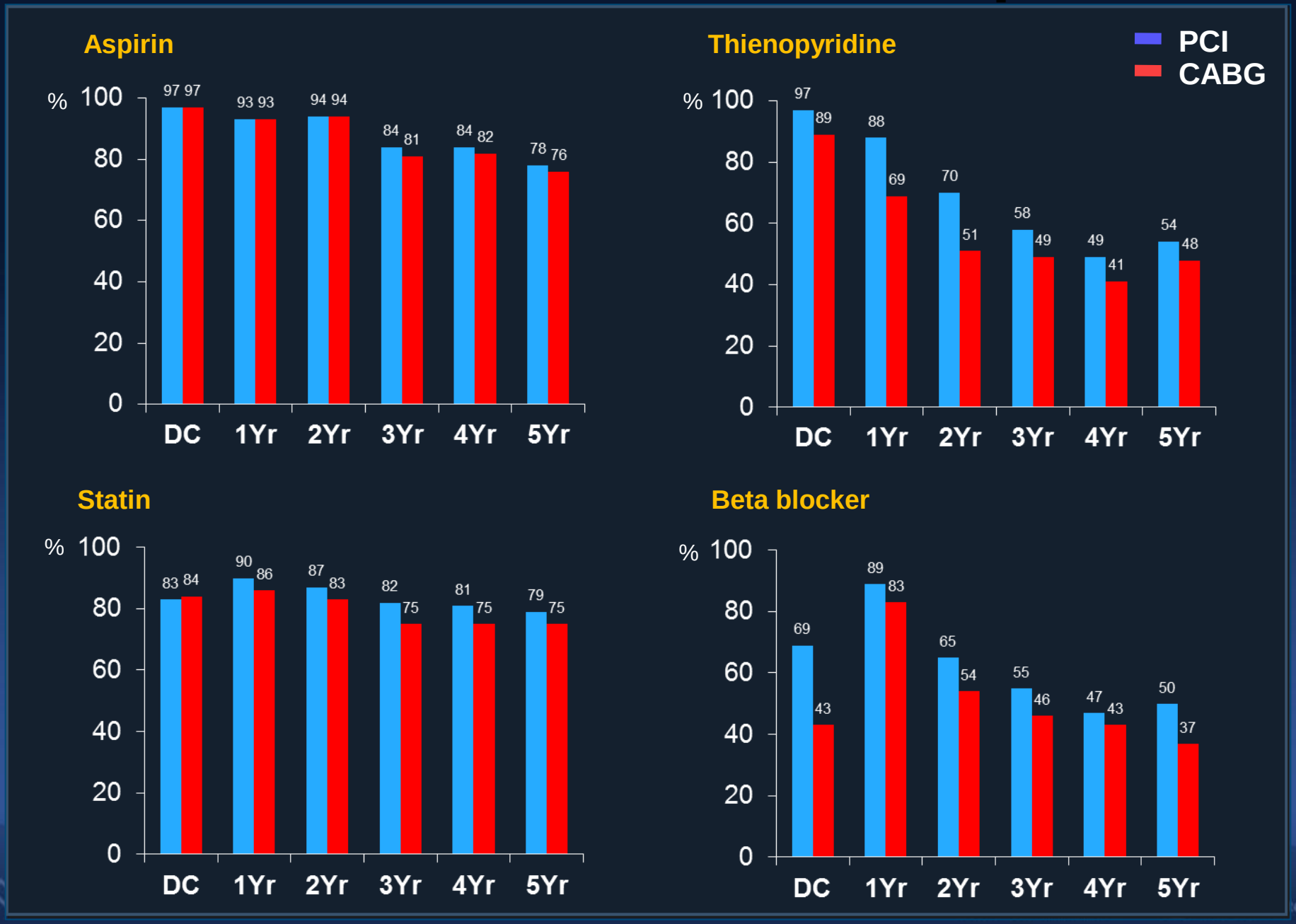


Diabetic Subgroup



Percentages are crude rates throughout the available follow-up period

Medication at Follow-Up

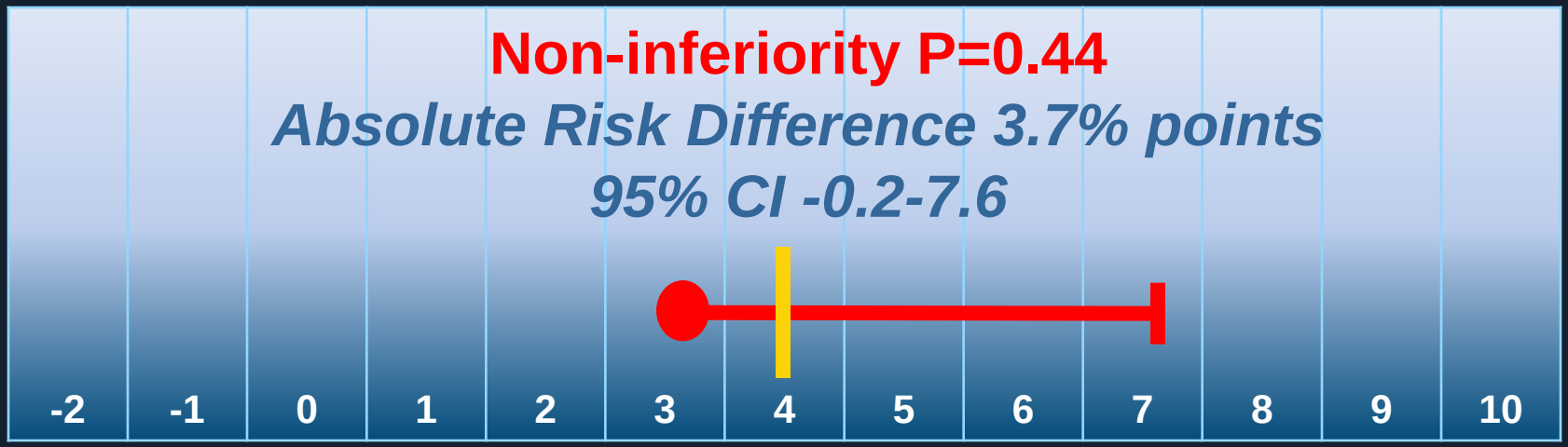


As Treated Analysis

Noninferiority Test for
Primary End Point of 2-Year MACE

2-year MACE rate **CABG: 11.2%** **PCI: 7.5%**

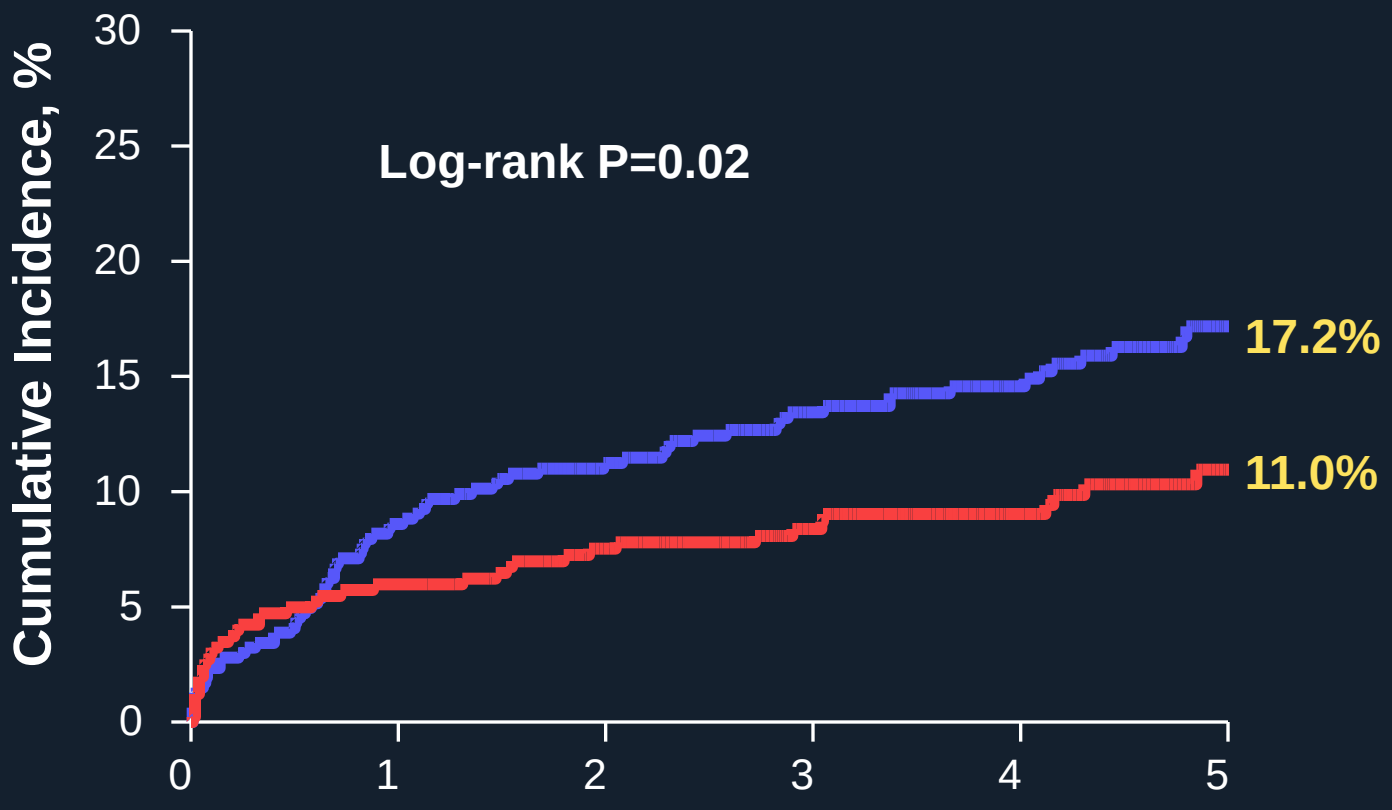
Prespecified non-inferiority margin: 4%



Difference (percentage point) of 2-year MACE rate (PCI – CABG)

Upper 1-sided 95% CI

Primary End Point of MACE



No. at Risk						
PCI	464	425	385	328	267	148
CABG	401	378	343	295	230	125

Event rates were derived from Kaplan-Meier estimates

Long-Term Outcomes In As-Treated Analysis

End points	PCI (N=464)	CABG (N=401)	Hazard ratio (95% CI)	P-value
Primary End Points: MACE	72 (15.5)	40 (10.0)	1.57 (1.07-2.31)	**0.02**
Secondary End Points				
Death	28 (6.0	22 (5.5)	1.08 (0.62-1.89)	0.78
Myocardial Infarction	22 (4.7)	10 (2.5)	1.88 (0.89-3.97)	0.09
Spontaneous MI	20 (4.3)	5 (1.2)	3.43 (1.29-9.13)	**0.009**
Stroke	12 (2.6)	10 (2.5)	1.03 (0.45-2.39)	0.94
Death, Myocardial Infarction, or stroke	53 (11.4)	39 (9.7)	1.17 (0.77-1.77)	0.46
Any Repeat Revascularization	54 (11.6)	17 (4.2)	2.82 (1.64-4.87)	**<0.001**
Target Lesion Revascularization	30 (6.5)	12 (3.0)	2.18 (1.12-4.26)	0.19
New Lesion Revascularization	27 (5.8)	6 (1.5)	3.93 (1.62-9.52)	**0.001**
Death, MI, Stroke, or Any RR	92 (19.8)	52 (13.0)	1.57 (1.12-2.20)	**0.009**
Bleeding				
TIMI Major Bleeding‡	23 (5.0)	139 (34.7)	0.12 (0.08-0.19)	**<0.001**
Fatal Bleeding	5 (1.1)	5 (1.2)	0.85 (0.25-2.94)	0.80

Percentages are crude rates throughout the available follow-up period

Conclusion

- The BEST trial failed to show that PCI with everolimus-eluting stents was noninferior to CABG with respective to the primary end point of death, myocardial infarction, or target vessel revascularization at 2 years.

- At longer-term follow-up (median 4.6 years), PCI was associated with a significant increase in the incidence of the primary end point compared with CABG.

Full Report Available on-line at www.nejm.org

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Everolimus-Eluting Stents or Bypass Surgery for Coronary Disease

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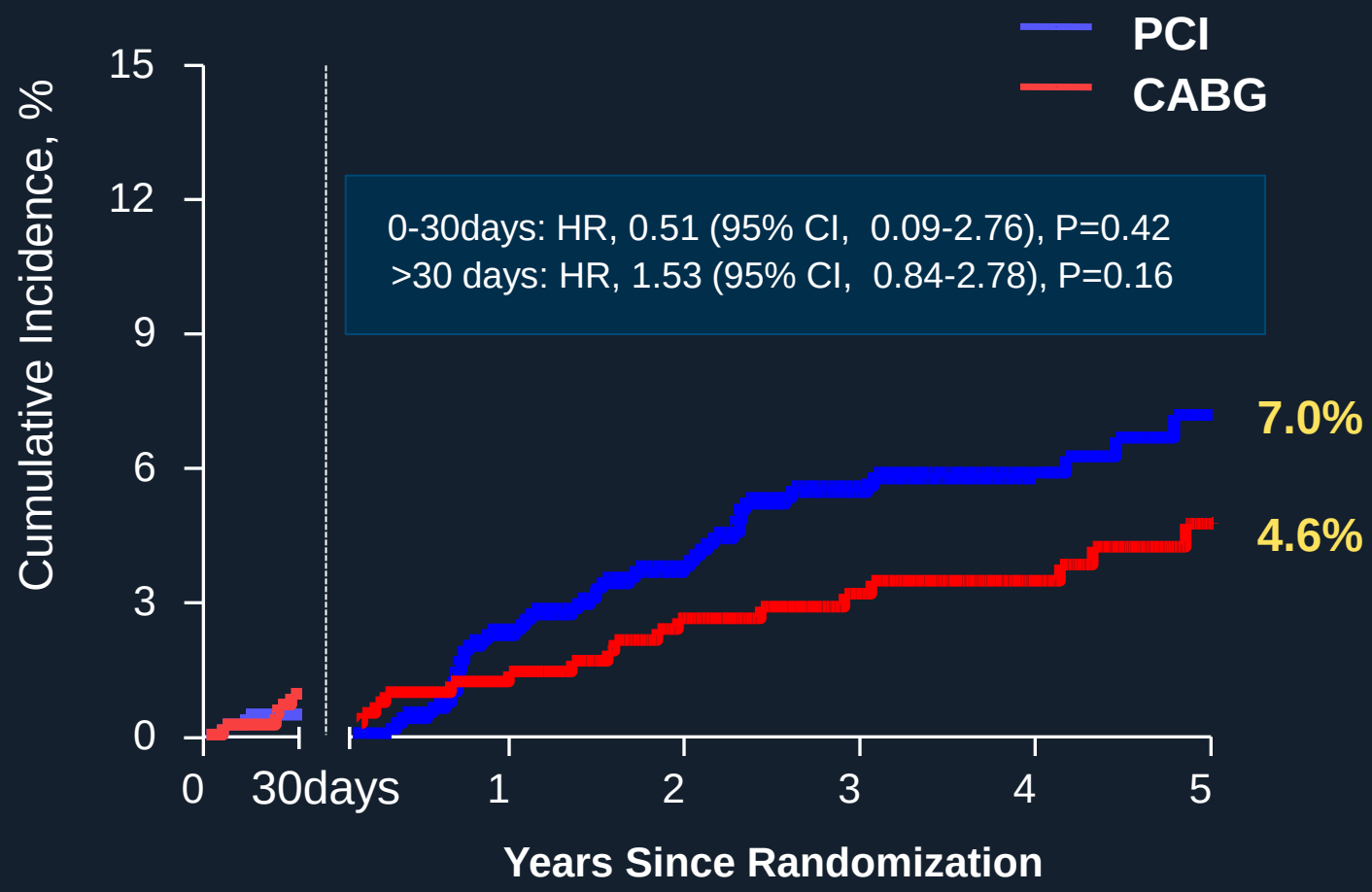
Reasons for Screening Failure for Enrollment

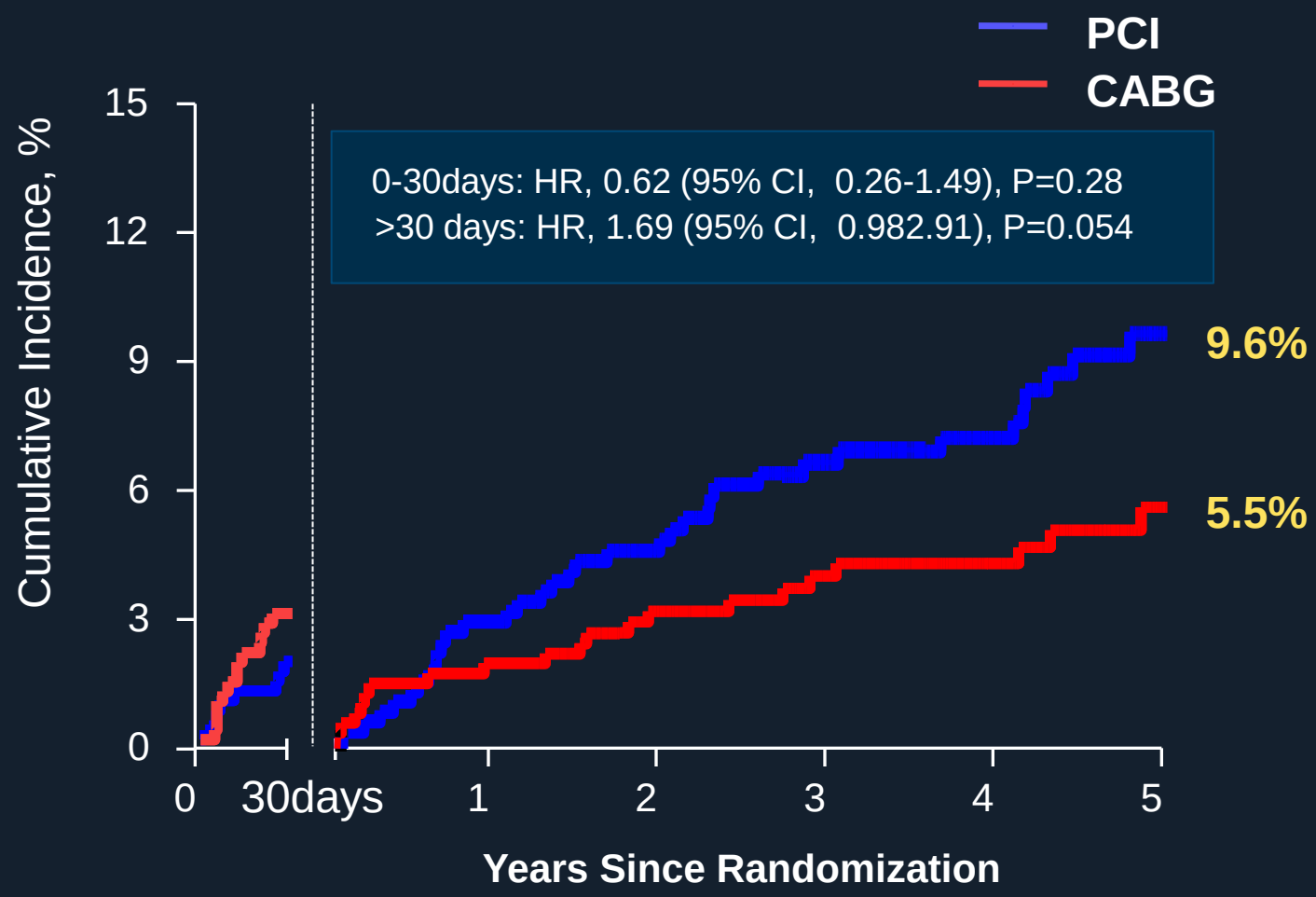
Reasons	Number
Left main stenosis	766
Concurrent enrollment in another clinical trial	639
CTO $\geq$ 2 in major epicardial coronary artery	248
Planned surgical procedure other than CABG	235
Prior CABG surgery	209
Acute ST-elevation MI (Q-wave) within 72 hours	253
Prior PCI with DES implantation within 1 year	192
Elevated cardiac enzymes at time of randomization	145
Serious extra-cardiac illness	100
Heart failure (NYHA class III or IV)	83
Previous stroke within 6 months	30
Prior history of significant bleeding (< 6 months)	10
Not possible to access the research center	7
Hypersensitivity or contraindication to medication	6
Intolerance to antiplatelet agent	6

Land Mark Analysis of Death



Event rates were derived from Kaplan-Meier estimates

Land Mark Analysis of Death and MI



Event rates were derived from Kaplan-Meier estimates

Repeat Revascularization

Target Vessel (N=48)	Non-Target Vessel (N=24)
Target Lesion (N=36)	
Target Lesion plus New Lesion (N=6)	
New Lesion (N=4)	
Unknown (N=2)	

Baseline Clinical Characteristics

	PCI (N=438)	CABG (N=442)	P value
Age, years	64.0 ± 9.3	64.9 ± 9.4	0.13
Male sex	304 (69.4)	325 (73.5)	0.18
Body mass index	24.7 ± 2.9	2.0 ± 2.9	0.16
Diabetes	177 (40.4)	186 (42.1)	0.62
Hypertension	296 (67.6)	295 (66.7)	0.79
Hyperlipidemia	239 (54.6)	222 (50.2)	0.20
Current smoker	88 (20.1)	89 (20.1)	0.99
Previous PCI	30 (6.8)	38 (8.6)	0.33
Previous myocardial infarction	25 (5.7)	29 (6.6)	0.60
Previous congestive heart failure	16 (3.7)	12 (2.7)	0.43

Baseline Clinical Characteristics

	PCI (N=438)	CABG (N=442)	P value
Chronic renal failure	9 (2.1)	7 (1.6)	0.60
Peripheral vascular disease	15 (3.4)	12 (2.7)	0.54
Chronic pulmonary disease	8 (1.8)	6 (1.4)	0.58
Clinical manifestation			0.68
Stable angina or asymptomatic	210 (47.9)	204 (46.2)	
Unstable angina	185 (42.2)	199 (45.0)	
Recent acute myocardial infarction	43 (9.8)	39 (8.8)	
Ejection fraction, %	59.1 ± 8.5	59.9 ± 8.1	0.12
Three vessel disease	330 (75.3)	349 (79.0)	0.20
EuroSCORE value	2.9 ± 2.0	3.0 ± 2.1	0.55
SYNTAX score value	24.2 ± 7.5	24.6 ± 8.1	0.47