EXCEL

Five-year Outcomes from a Randomized Trial of PCI vs. CABG in Patients with Left Main Coronary Artery Disease

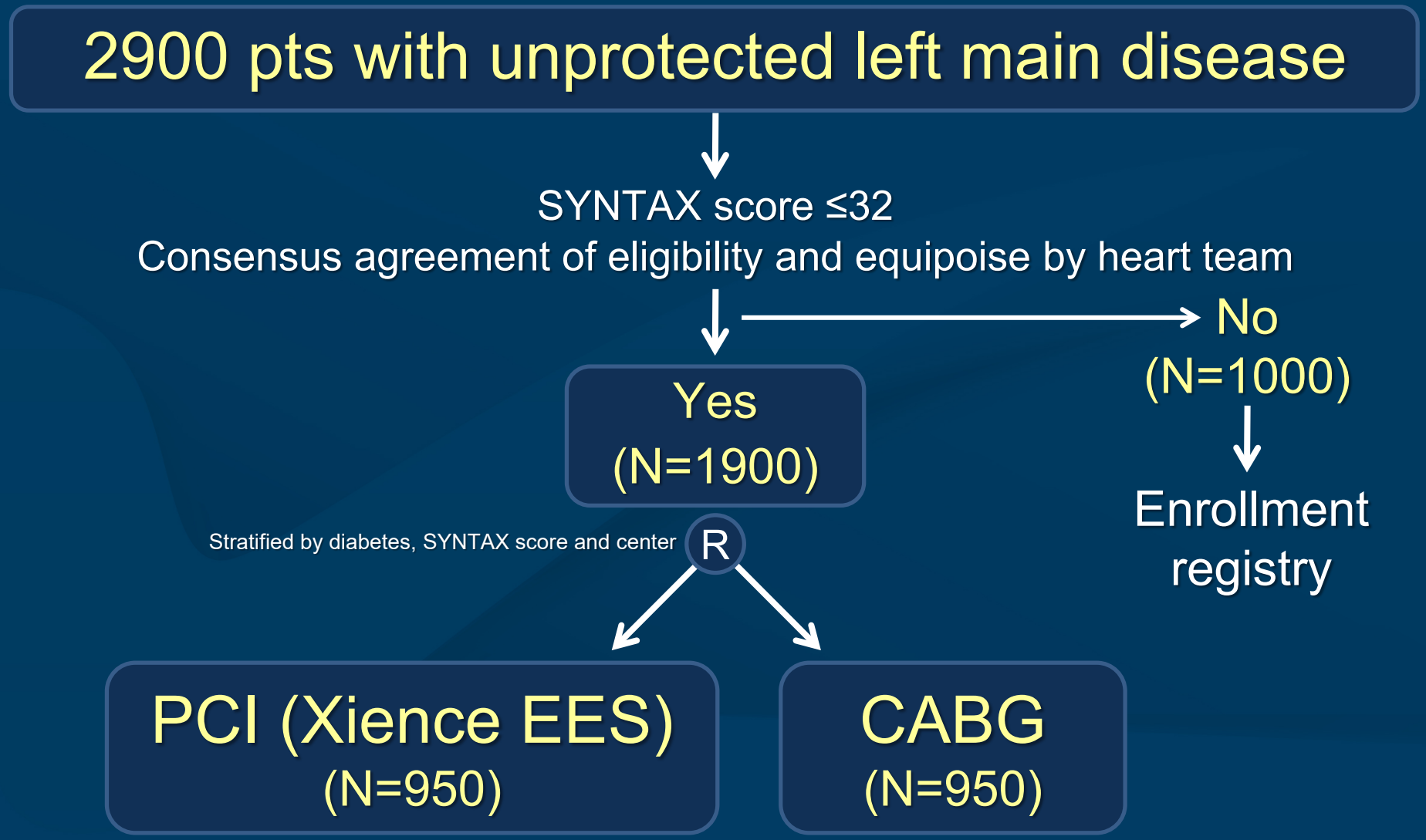
Gregg W. Stone MD

for A. Pieter Kappetein, Joseph F. Sabik,
Patrick W. Serruys and the EXCEL investigators

EXCEL Background

- Patients with left main coronary artery disease (LMCAD) have high morbidity and mortality due to the large amount of myocardium at risk
- Subset analysis from the SYNTAX trial suggested that DES may be an acceptable option for pts with LMCAD and low or moderate CAD complexity
- Since SYNTAX, PCI and surgical outcomes have both improved, necessitating a contemporary trial examining revascularization alternatives in LMCAD

Study Design



Follow-up: 1 month, 6 months, 1 year, annually through 5 years

Primary endpoint: Measured at a median 3-yr FU, minimum 2-yr FU

Design Imperatives

- Academically-driven trial organized and led equally by interventional cardiologists and cardiac surgeons
- PCI and CABG arms utilize the best available devices and techniques
- Large enough for a meaningful primary endpoint:
  - Death, stroke or MI (without revascularization) at a median follow-up duration of 3 years
  - MI definition is prognostically important, identical for PCI and CABG, and chosen to minimize ascertainment bias
- Screening registry incorporated to evaluate the generalizability of the trial results

EXCEL

Major Inclusion Criteria

- Unprotected LMCAD with ≥70% DS, *or* ≥50% - <70% with either i) non-invasive evidence of LM ischemia, ii) IVUS MLA ≤6.0 mm^2, or iii) FFR ≤0.80
- Syntax score ≤32
- Clinical and anatomic eligibility for both PCI and CABG as agreed to by the local Heart Team

Major Exclusion Criteria

- Prior CABG or LM PCI anytime
- Prior non-LM PCI within 1 year
- Need for cardiac surgery other than CABG
- Inability to tolerate DAPT for 1 year
- CK-MB >ULN

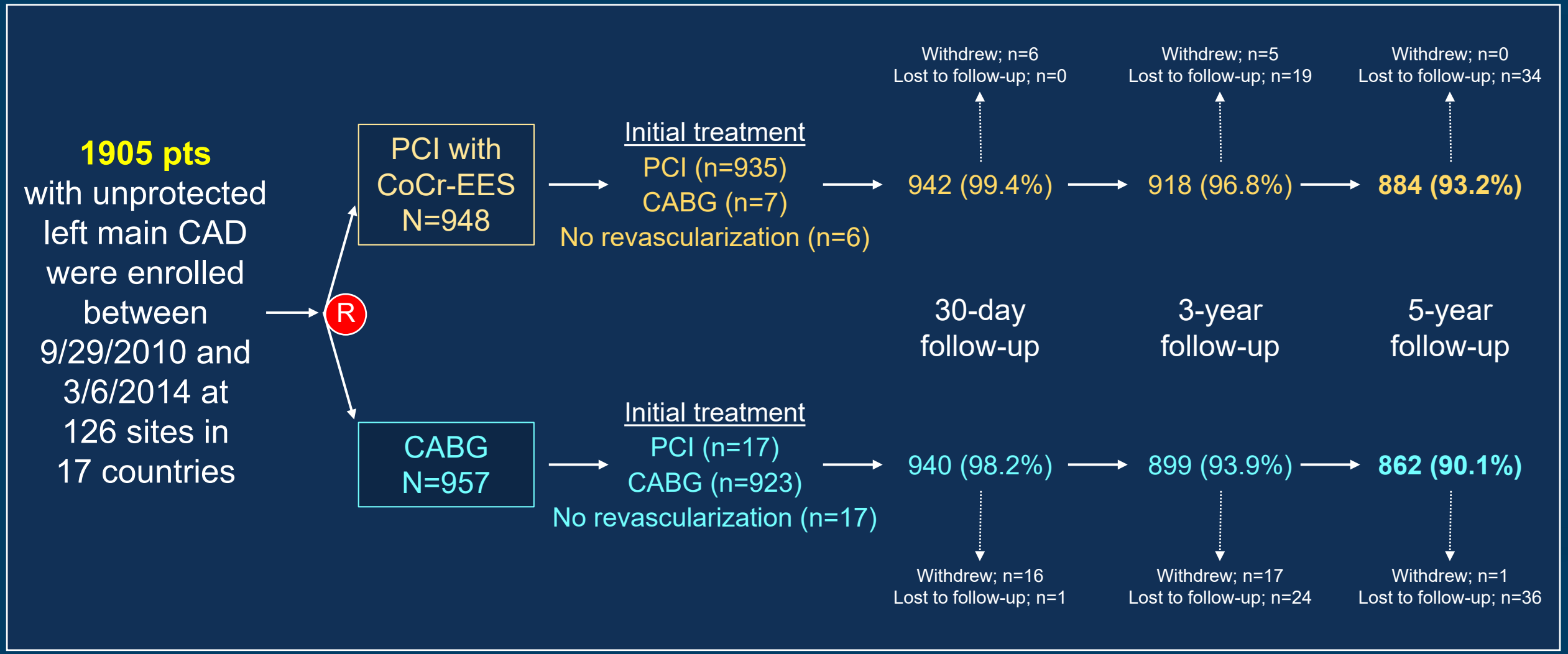
Statistical Methodology for the 5-Year Analysis (i)

- Only the 5-year composite primary outcome measure of death, stroke or MI was powered for superiority testing
- All other individual endpoints were non-powered and not adjusted for multiplicity, and thus are hypothesis generating
  - The only P-value provided is for the original 3-year primary endpoint at 5 years
- More pts were lost to FU after CABG than after PCI
  - Multiple imputation was performed as a sensitivity analysis to account for missing follow-up data

Statistical Methodology for the 5-Year Analysis (ii)

- **The proportional hazards assumption for most endpoints was not met**
  - Principal comparisons of KM event rates were thus performed by logistic regression with FU time included as a log-transformed offset variable
  - We also evaluated piecewise hazards models separately within 0 to 30 days (the peri-procedural period), 30 days to 1 year (the major risk period for stent restenosis), and 1 year though 5 years (long-term follow-up), intervals during which proportional hazards were preserved
  - Net treatment effects were also examined using restricted mean survival time (RMST) analysis, the mean time free from an outcome event adjusted for loss to FU, reflecting the area under the survival curve

Randomization and Follow-up



EXCEL

Selected Baseline Data

	PCI (N=942)	CABG (N=936)
Age (years)	66.0 ± 9.6	65.9 ± 9.5
Male	76.2%	77.5%
Diabetes	30.2%	28.0%
Clinical presentation		
- Recent MI (within 7 days)	14.9%	14.8%
- Unstable angina, biomarker negative	24.2%	24.8%
- Stable angina	53.1%	53.1%
- Silent ischemia or other	7.7%	7.4%
Distal LM bifurcation or trifurcation ds.*	81.8%	79.2%
# Diseased non-LM coronary arteries*		
- 0	17.3%	17.8%
- 1	31.0%	31.2%
- 2	34.5%	31.5%
- 3	17.2%	19.4%

*DS ≥50% by QCA (core lab analysis)

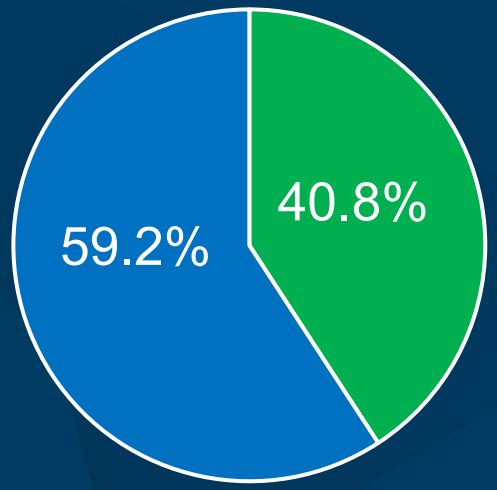
SYNTAX Score

Site Reported

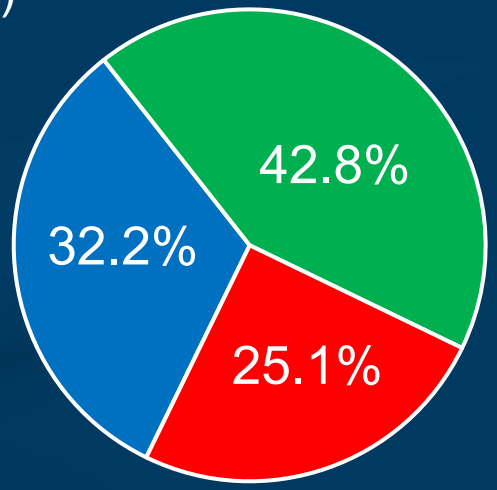
Core Lab

Low (≤22)
Intermediate (23-32)
High (≥33)

PCI

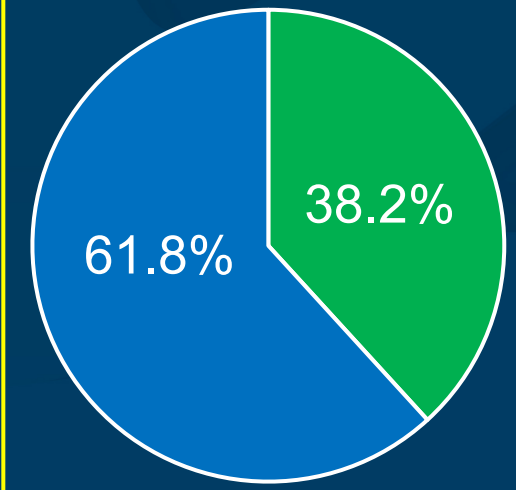


Mean 20.6 ± 6.2

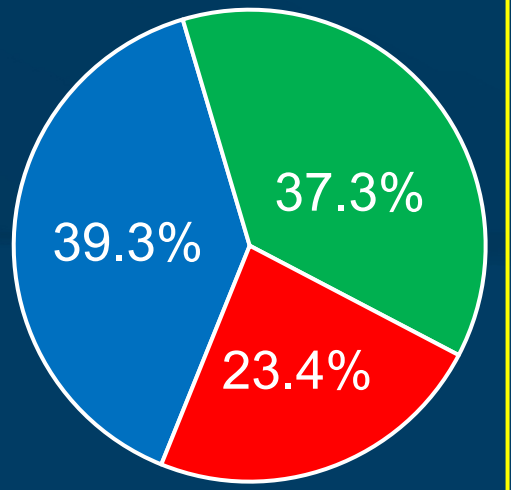


Mean 26.9 ± 8.8

CABG



Mean 20.5 ± 6.1



Mean 26.0 ± 9.8

P=0.52

P=0.005

PCI Procedure

935 patients, 1021 planned procedures, 2287 stents

Planned staged procedures	9.1%
Arterial access site*	
- Femoral	72.9%
- Radial	26.9%
- Brachial	0.2%
IVUS guidance	77.2%
FFR assessment	9.0%
Hemodynamic support device*	5.2%
Contrast use* (cc)	256 ± 127
Fluoroscopy time* (min)	24 ± 16

# Vessels treated per pt*†	1.7 ± 0.8
- LM	100.0%**
- LAD	28.4%
- LCX	16.6%
- RCA	26.7%
# Lesions treated per pt*	1.9 ± 1.1
# Stents implanted per pt*	2.4 ± 1.5
- Total stent length (mm)*	49.2 ± 35.7
Type of stents implanted*	
- DES	99.8%
- EES	99.2%
- XIENCE	98.4%

*All procedures (index + planned staged); **Excludes pts with LM equivalent ds;
†Max 4 vessels, including LM as a separate vessel

CABG Procedure

923 patients and procedures

Off-pump CABG	29.4%
On-pump bypass duration (min)	83 ± 45
- Cross clamp duration (min)	55 ± 27
Epi-aortic ultrasound	13.1%
Transesophageal ultrasound	42.3%
Hemodynamic support device	3.5%

# Conduits per pt	2.6 ± 0.8
- Arterial conduits	1.4 ± 0.6
- Venous conduits	1.2 ± 0.9
Any IMA used	98.8%
Bilateral IMA used	24.0%
Any radial artery used	6.0%
Only arterial conduits used	24.8%
Vessels bypassed per pt	
- LAD	98.8%
- LCX	88.2%
- RCA	37.8%

Medication Use

	At discharge			At 5 years		
	PCI (N=931)[1]		CABG (N=911)[1]	PCI (N=829)[2]		CABG (N=868)[2]
Aspirin	99.4%		98.9%	93.0%		93.6%
P2Y12 receptor inhibitor	98.2%	*	33.4%	61.6%	*	21.0%
- Clopidogrel or ticlopidine	72.9%		32.7%	50.0%		20.3%
- Clopidogrel	72.9%		32.6%	50.0%		20.2%
- Ticlopidine	0%		0.1%	0.0%		0.1%
- Prasugrel or ticagrelor	25.2%		0.7%	11.6%		0.8%
- Prasugrel	18.5%		0.4%	8.5%		0.4%
- Ticagrelor	7.0%		0.2%	3.1%		0.4%
Chronic oral anticoagulant	1.3%	*	4.3%	5.2%	*	10.8%
Beta-blockers	83.2%	*	92.5%	86.6%	*	94.3%
ACE inhibitors or ARB	56.7%	*	42.2%	66.7%	*	59.4%
Calcium channel blockers	5.9%		7.1%	18.3%		19.1%
Aldosterone antagonist	0.1%		0.8%	1.6%		1.7%
Diuretic	3.5%	*	24.4%	17.1%	*	38.8%
Anti-arrhythmic agent	0.5%	*	11.6%	3.1%	*	17.4%
Statins	96.5%		92.4%	97.5%		96.2%

*Significant difference. [1]Patients with assigned revascularization procedure performed; [2]Denominator includes all intention-to-treat patients alive at 5 years

Adjudicated Outcomes at 30 Days

	PCI (n=948)	CABG (n=957)	HR [95%CI]	P-value
Death, stroke or MI (2˚ endpoint)	4.9%	7.9%	0.61 [0.42, 0.88]	0.008
- Death	1.0%	1.1%	0.90 [0.37, 2.22]	0.82
- Stroke	0.6%	1.3%	0.50 [0.19, 1.33]	0.15
- MI	3.9%	6.2%	0.63 [0.42, 0.95]	0.02
- Peri-procedural	3.6%	5.9%	0.61 [0.40, 0.93]	0.02
- Non-peri-procedural	0.3%	0.3%	1.00 [0.20, 4.95]	1.00
- STEMI	0.7%	2.3%	0.32 [0.14, 0.74]	0.005
- Non-STEMI	3.2%	3.9%	0.82 [0.50, 1.32]	0.41
Death, stroke, MI or IDR	4.9%	8.4%	0.57 [0.40, 0.82]	0.002
- Ischemia-driven revasc (IDR)	0.6%	1.4%	0.46 [0.18, 1.21]	0.11
Stent thrombosis, def/prob	0.6%	0.0%	-	0.01
Graft occlusion, symptomatic	0.0%	1.2%	-	<0.001
Definite stent thrombosis or symptomatic graft occlusion	0.3%	1.2%	0.27 [0.08, 0.97]	0.03

Stone GW et al. N Engl J Med 2016;375:2223-35

Major Adverse Events Within 30 Days

	PCI (n=948)	CABG (n=957)	RR [95%CI]	P-value
Peri-procedural MAE, any	12.4%	44.0%	0.28 [0.24, 0.34]	<0.001
- Death*	0.9%	1.0%	0.91 [0.39, 2.23]	0.83
- Stroke*	0.6%	1.3%	0.50 [0.19, 1.34]	0.16
- Myocardial infarction*	3.9%	6.2%	0.63 [0.42, 0.95]	0.02
- Ischemia-driven revascularization*	0.6%	1.4%	0.47 [0.18, 1.22]	0.11
- TIMI major/minor bleeding	3.7%	8.9%	0.42 [0.28, 0.61]	<0.001
- Transfusion ≥2 units	4.0%	17.0%	0.24 [0.17, 0.33]	<0.001
- Major arrhythmia**	2.1%	16.1%	0.13 [0.08, 0.21]	<0.001
- Surgery/radiologic procedure	1.3%	4.1%	0.31 [0.16, 0.59]	<0.001
- Renal failure†	0.6%	2.5%	0.25 [0.10, 0.61]	<0.001
- Sternal wound dehiscence	0.0%	2.0%	0.03 [0.00, 0.43]	<0.001
- Infection requiring antibiotics	2.5%	13.6%	0.18 [0.12, 0.28]	<0.001
- Prolonged intubation (>48 hours)	0.4%	2.9%	0.14 [0.05, 0.41]	<0.001
- Post-pericardiotomy syndrome	0.0%	0.4%	0.11 [0.01, 2.08]	0.12

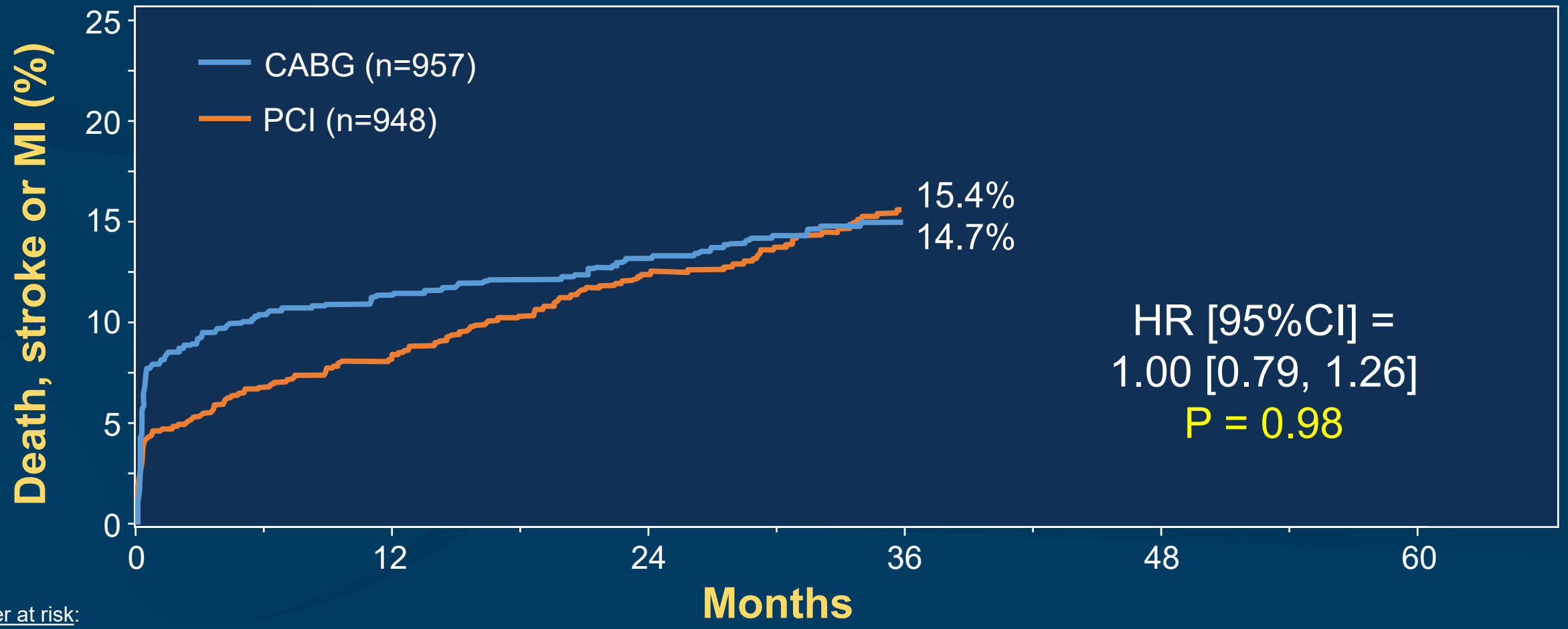
*Adjudicated events; others are site-reported. **SVT requiring cardioversion, VT or VF requiring treatment, or bradyarrhythmia requiring temp or perm pacemaker.
†SCr increased by ≥0.5 mg/dL from baseline or need for dialysis.

Stone GW et al. N Engl J Med 2016;375:2223-35

EXCEL

Primary Endpoint

All-cause Death, Stroke or MI at Median 3 Years



Number at risk:

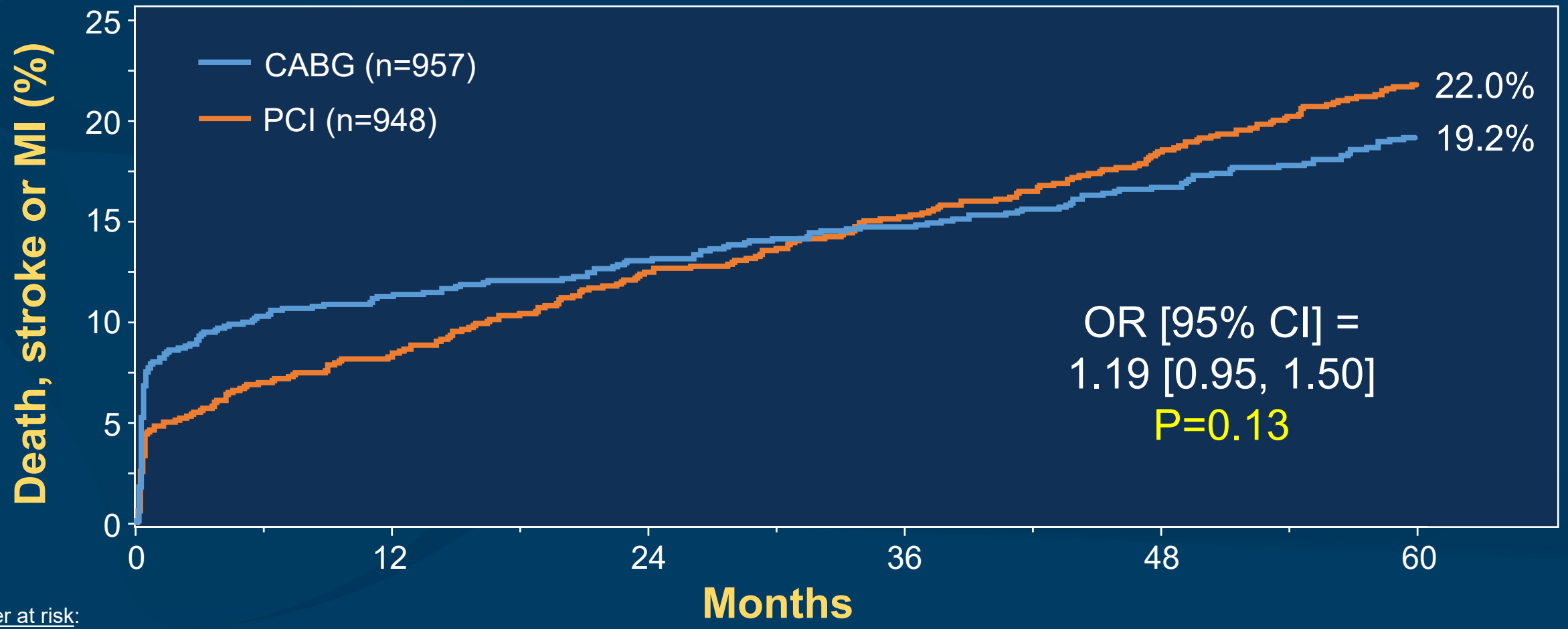
PCI	948	850	784	445
CABG	957	817	763	458

Stone GW et al. N Engl J Med 2016;375:2223-35

EXCEL

Primary Endpoint

All-cause Death, Stroke or MI at 5 Years



Number at risk:

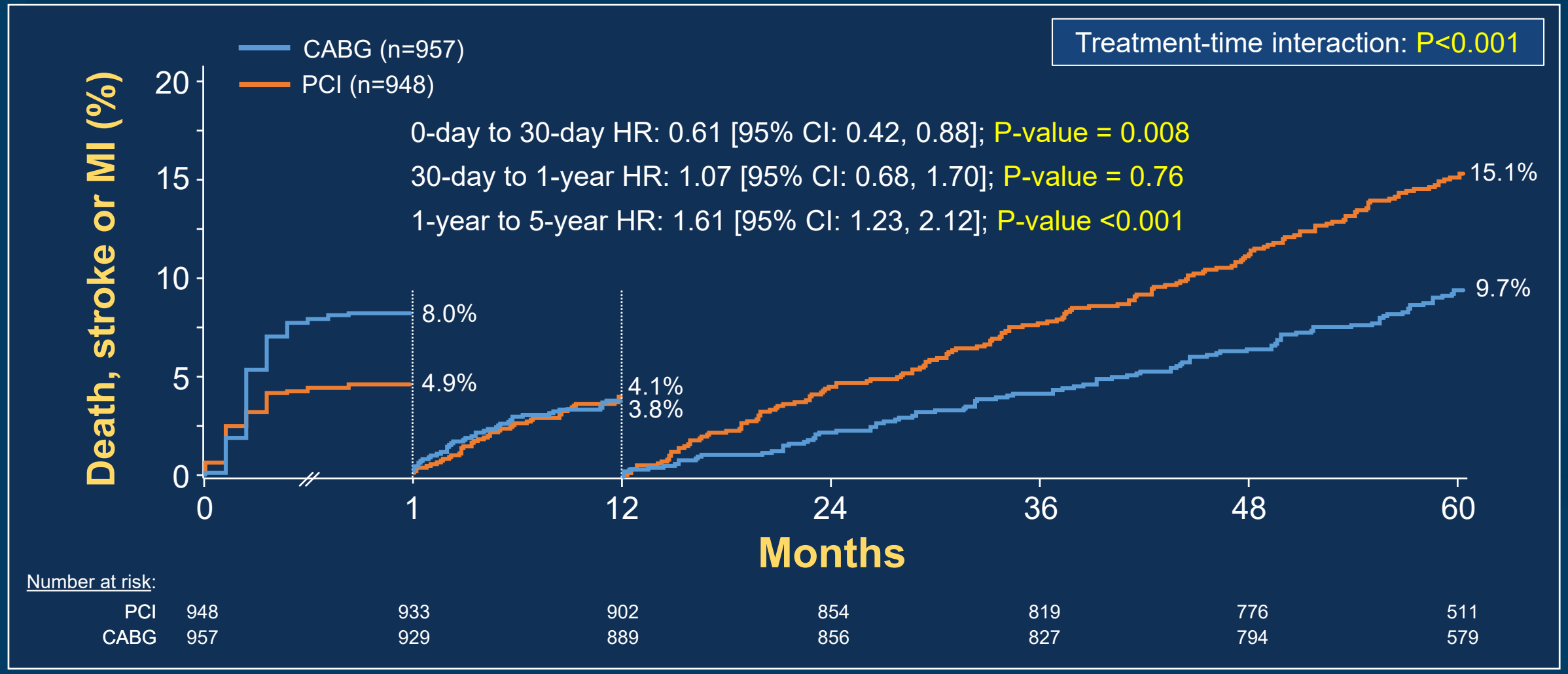
PCI	948	854	809	778	738	486
CABG	957	818	789	763	734	532

EXCEL

Piecewise Hazards

All-cause Death, Stroke or MI

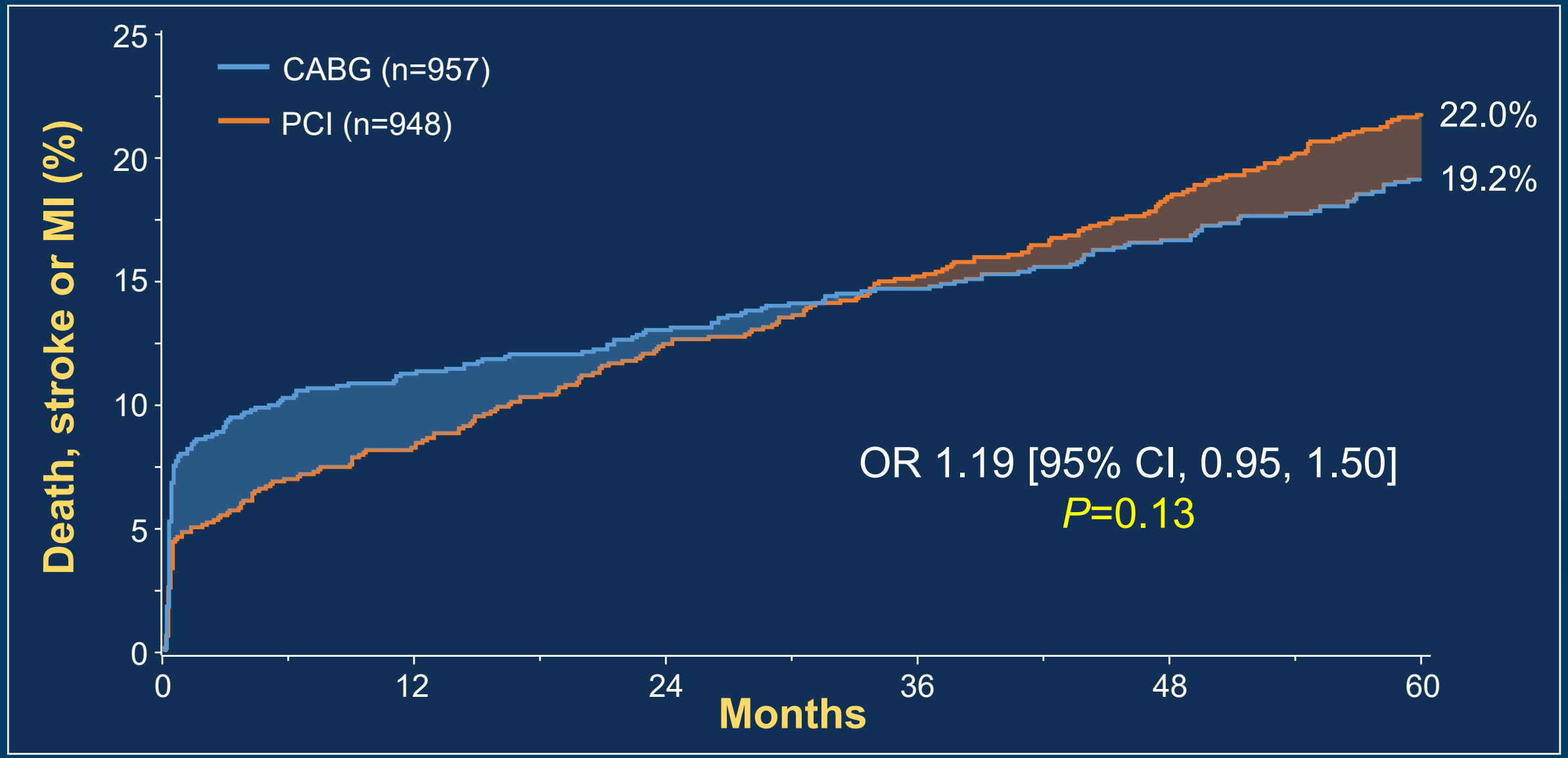
Three distinct periods of varying relative risk



EXCEL

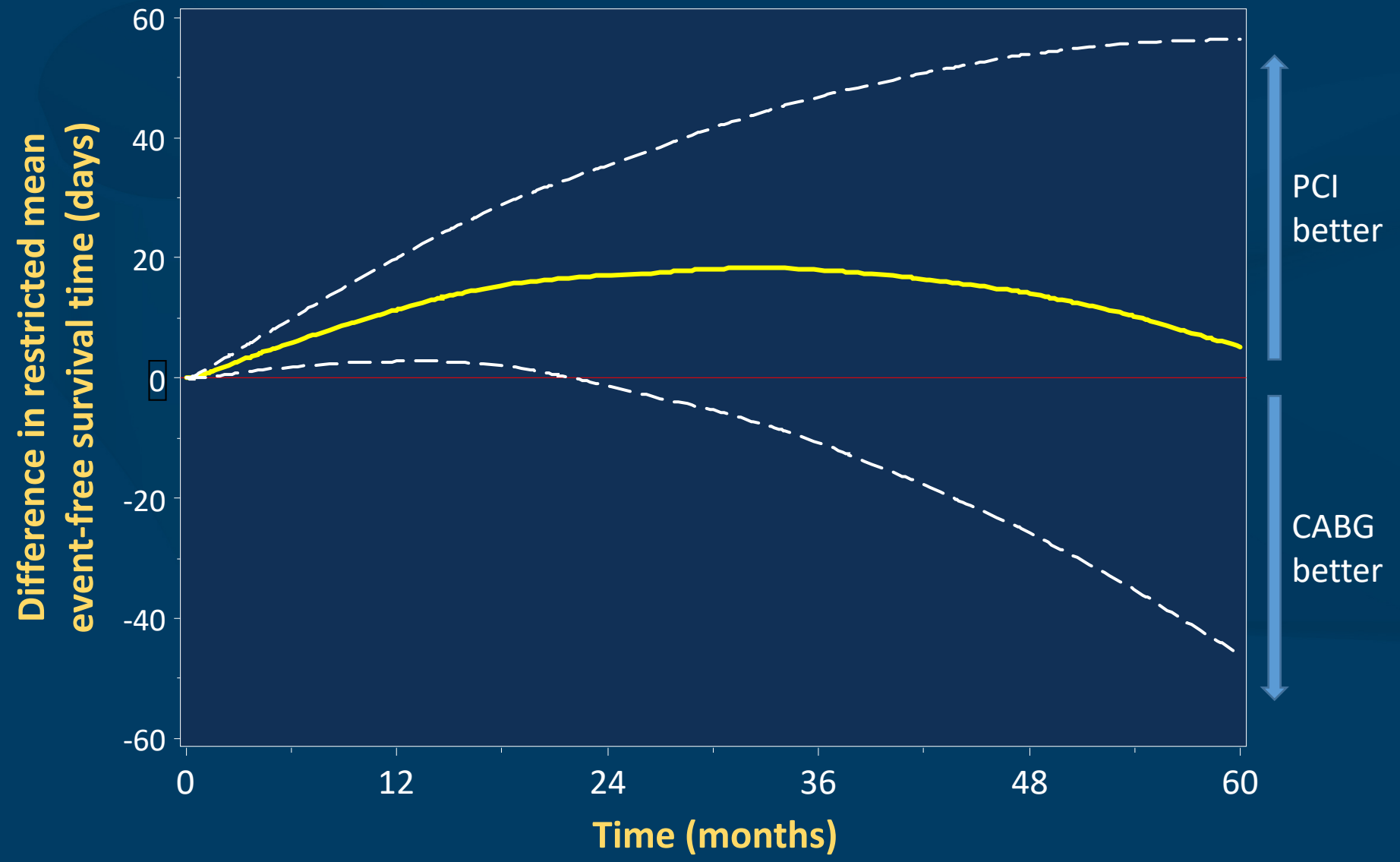
Restricted Mean Survival Time Analysis

All-cause Death, Stroke or MI



Restricted Mean Survival Time Analysis

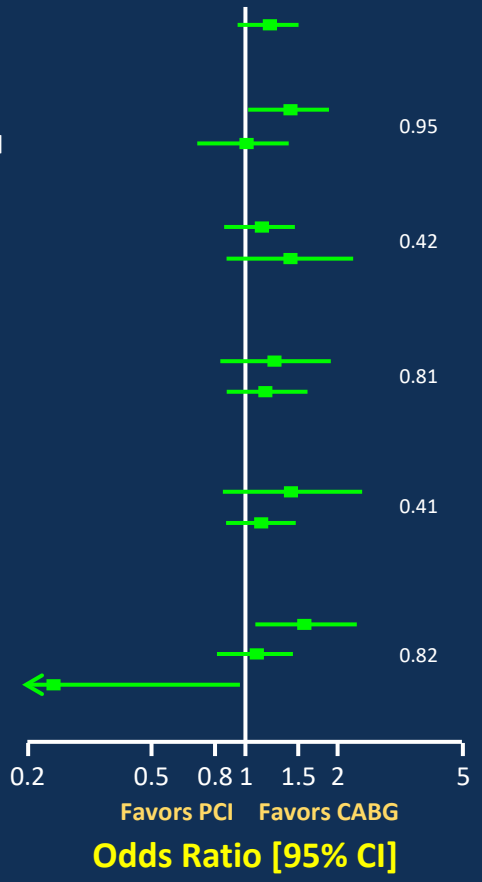
All-cause Death, Stroke or MI



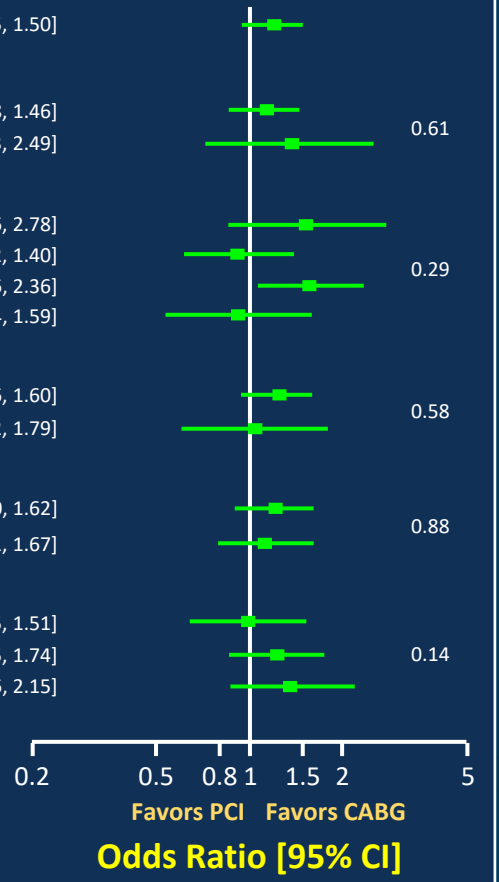
At the end of the 5-year follow-up period, event-free survival time was 5.2 days (95% CI -46.1 to 56.5 days) longer after PCI compared with CABG

Analysis of 10 pre-specified subgroups
All-cause Death, Stroke or MI at 5 Years

Subgroup	PCI N=948	CABG N=957	OR [95% CI]	P_{int}
All patients	22.0% (203/948)	19.2% (176/957)	1.19 [0.95, 1.50]	
Age (median cutoff)				
- ≥67 years	27.2% (123/466)	21.8% (98/472)	1.39 [1.02, 1.89]	0.95
- <67 years	16.9% (80/482)	16.6% (78/485)	1.00 [0. 71, 1.40]	
Sex				
- Male	20.6% (145/722)	18.7% (134/742)	1.12 [0.86, 1.46]	0.42
- Female	26.3% (58/226)	21.1% (42/215)	1.39 [0.88, 2.20]	
Diabetes mellitus, medically treated				
- Yes	29.0% (72/256)	25.5% (62/249)	1.24 [0.83, 1.86]	0.81
- No	19.4% (131/692)	16.9% (114/707)	1.17 [0.89, 1.55]	
Chronic kidney disease				
- eGFR ≤60 ml/min	34.0% (54/164)	27.6% (37/144)	1.44 [0.86, 2.39]	0.41
- eGFR >60 ml/min	19.5% (147/770)	17.6% (135/791)	1.13 [0.87, 1.47]	
Geographic location				
- North America	24.2% (89/381)	17.3% (61/371)	1.57 [1.09, 2.26]	0.82
- Europe	21.1% (111/534)	19.6% (102/541)	1.09 [0.81, 1.48]	
- Other	9.6% (3/33)	29.6% (13/45)	0.24 [0.06, 0.96]	



Subgroup	PCI N=948	CABG N=957	OR [95% CI]	P_{int}
All patients	22.0% (203/948)	19.2% (176/957)	1.19 [0.95, 1.50]	
Left ventricular ejection fraction				
- ≥50%	20.6% (158/782)	18.7% (144/796)	1.14 [0.88, 1.46]	0.61
- <50%	31.5% (33/111)	24.2% (26/115)	1.35 [0.73, 2.49]	
Non-left main diseased coronary arteries (core lab assessment)				
- 0	20.7% (33/163)	14.3% (23/167)	1.55 [0.86, 2.78]	0.29
- 1	21.2% (60/292)	21.9% (61/292)	0.94 [0.62, 1.40]	
- 2	25.0% (79/325)	17.8% (50/295)	1.58 [1.06, 2.36]	
- 3	19.2% (31/162)	20.7% (37/182)	0.93 [0.54, 1.59]	
Left main bifurcation or trifurcation stenosis ≥50% (core lab assessment)				
- Yes	22.7% (171/771)	19.0% (136/741)	1.24 [0.96, 1.60]	0.58
- No	19.2% (32/171)	18.9% (35/195)	1.05 [0.62, 1.79]	
Syntax score (site reported)				
- ≤22	21.9% (119/560)	18.7% (106/588)	1.21 [0.90, 1.62]	0.88
- 23 - 32	22.2% (84/386)	20.0% (70/366)	1.16 [0.81, 1.67]	
Syntax score (core lab assessment)				
- ≤22	17.2% (49/294)	16.7% (58/364)	0.99 [0.65, 1.51]	0.14
- 23 - 32	23.7% (91/392)	20.7% (69/346)	1.22 [0.85, 1.74]	
- ≥33	25.0% (56/228)	20.2% (42/216)	1.36 [0.86, 2.15]	



No significant interactions

Primary Endpoint at 5 Years

	PCI (N=948)	CABG (N=957)	Difference [95% CI]	Odds ratio [95% CI]
Death, stroke or MI	22.0% (203)	19.2% (176)	2.8% [-0.9%, 6.5%]	1.19 [0.95, 1.50]
Death, all-cause	13.0% (119)	9.9% (89)	3.1% [0.2%, 6.1%]	1.38 [1.03, 1.85]
- Cardiovascular	6.8% (61)	5.5% (49)	1.3% [-0.9%, 3.6%]	1.26 [0.85, 1.85]
- Definite cardiovascular	5.0% (45)	4.5% (40)	0.5% [-1.4%, 2.5%]	1.13 [0.73, 1.74]
- Undetermined cause	1.9% (16)	1.1% (9)	0.9% [-0.3%, 2.0%]	1.78 [0.78, 4.06]
- Non-cardiovascular	6.6% (58)	4.6% (40)	2.0% [-0.2%, 4.2%]	1.47 [0.97, 2.23]
Cerebrovascular events	3.3% (29)	5.2% (46)	-1.9% [-3.8%, 0.0%]	0.61 [0.38, 0.99]
- Stroke	2.9% (26)	3.7% (33)	-0.8% [-2.4%, 0.9%]	0.78 [0.46, 1.31]
- Transient ischemic attack	0.3% (3)	1.6% (14)	-1.3% [-2.2%, -0.4%]	0.21 [0.06, 0.74]
Myocardial infarction	10.6% (95)	9.1% (84)	11.4% [-1.3%, 4.2%]	1.14 [0.84, 1.55]
- Peri-procedural	3.9% (37)	6.1% (57)	-2.1% [-4.1%, -0.1%]	0.63 [0.41, 0.96]
- Non-peri-procedural	6.8% (59)	3.5% (31)	3.2% [1.2%, 5.3%]	1.96 [1.25, 3.06]

Adjudicated Causes of Death

	PCI (N=948)	CABG (N=957)	Difference [95% CI]
All-cause death	13.0% (119)	9.9% (89)	3.1% [0.2%, 6.1%]
- Definite cardiovascular	5.0% (45)	4.5% (40)	0.5% [-1.4%, 2.5%]
Sudden cardiac death	1.7% (15)	1.2% (10)	0.5% [-0.6%, 1.6%]
Myocardial infarction	1.0% (9)	0.6% (5)	0.4% [-0.4%, 1.2%]
Heart failure or cardiogenic shock	0.6% (5)	1.1% (9)	-0.5% [-1.3%, 0.4%]
Stroke	1.0% (9)	0.9% (8)	0.1% [-0.8%, 1.0%]
Bleeding	0.0% (0)	0.3% (3)	-0.3% [-, -]
Other cardiovascular cause	1.0% (8)	0.6% (5)	0.4% [-0.4%, 1.2%]
- Definite non-cardiovascular	6.6% (58)	4.6% (40)	2.0% [-0.2%, 4.2%]
Pulmonary	1.0% (8)	0.6% (5)	0.4% [-0.5%, 1.2%]
Infection (includes sepsis)	1.6% (14)	0.8% (7)	0.8% [-0.2%, 1.8%]
Gastrointestinal	0.1% (1)	0.2% (2)	-0.1% [-0.5%, 0.3%]
Malignancy	3.4% (29)	2.7% (23)	0.7% [-1.0%, 2.3%]
Accident/trauma	0.3% (3)	0.2% (2)	0.1% [-0.4%, 0.6%]
Non-cardiovascular organ failure	0.2% (2)	0.0% (0)	0.2% [-, -]
Other non-cardiovascular cause	0.0% (0)	0.2% (2)	-0.2% [-, -]
- Undetermined cause	1.9% (16)	1.1% (9)	0.9% [-0.3%, 2.0%]

Additional Outcomes at 5 Years

	PCI (N=948)	CABG (N=957)	Difference [95% CI]	Odds ratio [95% CI]
Death, stroke, MI or IDR	31.3% (290)	24.9% (228)	6.5% [2.4%, 10.6%]	1.39 [1.13, 1.71]
- ID-revascularization	16.9% (150)	10.0% (88)	6.9% [3.7%, 10.0%]	1.84 [1.39, 2.44]
- PCI	14.1% (125)	9.1% (80)	4.9% [1.9%, 7.9%]	1.65 [1.22, 2.22]
- CABG	4.3% (38)	0.9% (8)	3.4% [1.9%, 4.9%]	4.90 [2.27, 10.56]
All revascularization	17.2% (153)	10.5% (92)	6.7% [3.5%, 9.9%]	1.79 [1.36, 2.36]
Stent thrombosis	1.8% (16)	0% (0)	-	-
- Definite	1.1% (10)	0% (0)	-	-
- Probable	0.7% (6)	0% (0)	-	-
Symptomatic graft occlusion	0% (0)	6.5% (58)	-	-
Therapy failure*	1.1% (10)	6.5% (58)	-5.4% [-7.2%, -3.6%]	0.16 [0.08, 0.32]

*Definite stent thrombosis or symptomatic graft occlusion. ID = ischemia-driven.

EXCEL

Primary Endpoint at 5 Years

All-cause Death, Stroke or MI after Multiple Imputation to Account for Missing Follow-up Data

Population	Kaplan-Meier rate (n events)		
	PCI	CABG	Odds ratio [95% CI]
All-cause death, stroke or MI	21.8%	19.5%	1.15 [0.92, 1.45]
- All-cause death	13.0%	10.1%	1.32 [0.99, 1.77]
- Stroke	3.1%	3.7%	0.83 [0.48, 1.44]
- Myocardial infarction	10.2%	9.6%	1.08 [0.79, 1.46]

Event rates are binary proportions. Odds ratios and 95% confidence intervals were estimated from time offset logistic regression.

Limitations

- Blinding of PCI vs. CABG was not possible; some degree of event ascertainment bias cannot be excluded
- Analyses of secondary endpoints were not adjusted for multiplicity – all hypothesis generating – but all observed differences were relatively modest in magnitude given the 5-year time frame of the present study
- Under-powered for subgroups; e.g. primary endpoint results were consistent in high SYNTAX score subgroup (25% of pts) - however, further studies are required to determine whether PCI is an acceptable alternative to CABG in LMCAD pts with high anatomic complexity
- Ten-year follow-up (or longer) is required to characterize the very late safety profile of PCI and CABG as both stents and bypass grafts progressively fail over time

Conclusions

- In the EXCEL trial, treatment of patients with LMCAD and visually-assessed low or intermediate SYNTAX scores with CoCr-EES resulted in similar rates of the clinically meaningful composite outcome of death, stroke or MI at 5 years
- The early benefits of PCI due to reduced peri-procedural risk were attenuated by the greater number of events occurring during follow-up with CABG, such that at 5 years the cumulative mean time free from adverse events was similar with both treatments

Conclusions

- PCI may thus be considered an acceptable revascularization modality for selected patients with LMCAD, a decision which should be made after heart team discussion, taking into account each patient's individual risk factors and preferences