Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease

PRECOMBAT Trial

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On behalf of the PRECOMBAT Investigators

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Introduction

- Recent registry and substudy results have shown that percutaneous coronary intervention (PCI) is safe and effective in patients with unprotected left main coronary artery (ULMCA) stenosis.

- However, due to the lack of randomized clinical trials, the comparability of PCI with coronary artery bypass graft (CABG) remains uncertain.

PRECOMBAT Trial

Design

- DESIGN: a prospective, open-label, randomized trial
- OBJECTIVE: To compare PCI with sirolimus-eluting stents and CABG surgery for optimal revascularization of patients with ULMCA stenosis.
- PRINCIPAL INVESTIGATOR
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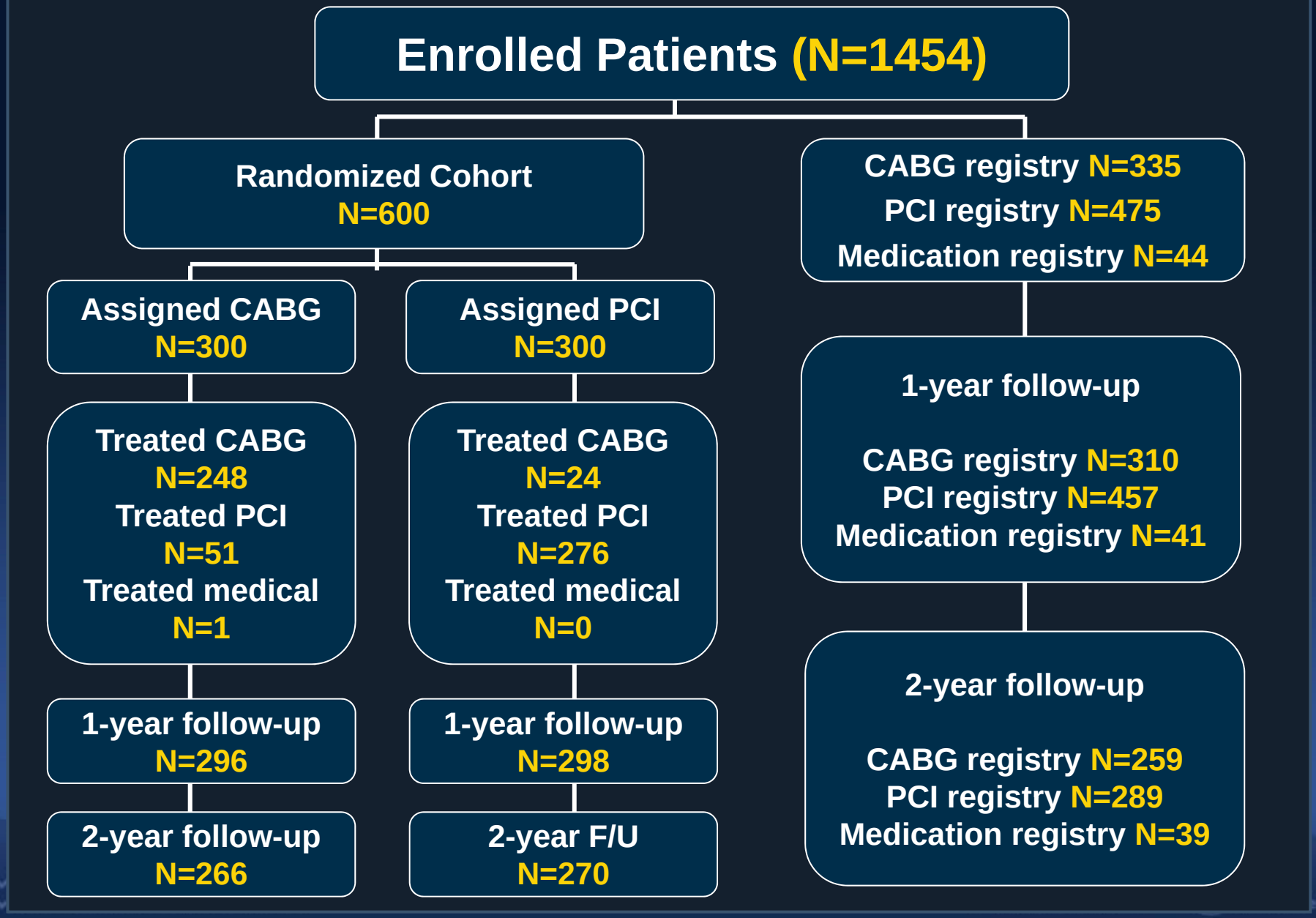
Patient Flow



Reasons Enrolled to the Registry

CABG		PCI	
Declined to be participated in randomization	220 (65.6)	Declined to be participated in randomization	254 (53.5)
Exclusion criteria		Exclusion criteria	
PCI within 1 year	36 (10.7)	Co-morbid condition	69 (14.5)
Acute MI within 1 week	24 (7.2)	Poor distal run-off	54 (11.4)
Non-cardiac surgery	22 (6.6)	PCI within 1 year	40 (8.4)
Patients with EF<30%.	12 (3.6)	Acute MI within 1 week	16 (3.4)
Inability for follow-up	12 (3.6)	Previous bypass surgery	13 (2.7)
Co-morbid condition	3 (0.9)	Gastrointestinal bleeding	4 (0.8)
Previous stroke	3 (0.9)	Non-cardiac surgery	4 (0.8)
Previous CABG	1 (0.3)	Previous stroke	4 (0.8)
Bleeding tendency	1 (0.3)	Renal failure	4 (0.8)
Hypersensitivity to aspirin	1 (0.3)	CTO $\geq$ 2	4 (0.8)
		In other clinical trial	3 (0.6)
		Inability for follow-up	2 (0.4)
		Hypersensitivity	2 (0.4)
		Patients with EF<30%.	1 (0.2)
		Child bearing potential	1 (0.2)

Major Inclusion Criteria

- ≥ 18 years of age.
- Significant de novo ULMCA stenosis (>50%)
- Left main lesion and lesions outside ULMCA (if present) potentially comparably treatable with PCI and CABG, determined by physician and operators
- Objective evidence of ischemia or ischemic symptom with angina or NSTEMI

Major Exclusion Criteria

- Any contraindication to dual antiplatelet therapy
- Any previous PCI within 1 year
- Previous CABG
- Chronic total occlusion > 1
- AMI within 1 week
- Shock or LV EF < 30%
- Planed surgery
- Disabled stroke
- Other comorbidity, such as CRF, liver disease, etc

Study Procedures

- Sirolimus-eluting Cypher stent for all lesions
- Strong recommendation of IVUS-guidance
- Other adjunctive devices at the operator's discretion
- Use of LIMA to LAD anastomosis
- Off- or on-pump surgery at the operator's discretion
- Dual antiplatelet therapy at least for 6 months after PCI
- Standard medical treatment after PCI and CABG

Follow-up

- Clinical follow-up at 30 days and 6, 9, and 12 months via clinic visit or telephone interview.
- Routine angiographic follow-up at 8-10 months after PCI.
- Ischemia-guided angiographic follow-up after CABG.
- Retrospective SYNTAX score measurement in the Core Lab, CVRF, Seoul, Korea

Primary End Point

- A composite of major adverse cardiac or cerebrovascular events (MACCE) for the 12-month period after randomization including
  - Death from any cause
  - Myocardial infarction (MI)
  - Stroke
  - Ischemia-driven target vessel revascularization (TVR)

Definition

- MI
  - Within 48 hours: new Q waves AND CK-MB ≥ 5 times
  - After 48 hours: new Q waves OR CK-MB > 1 time plus ischemic symptoms or signs
- Stroke: confirmed by imaging studies and neurologist
- TVR
  - Ischemia-driven: ischemic symptom, sign OR angiographic stenosis > 70%
  - Clinical-driven: ischemia symptom or sign

Power Calculation

- Assumed primary end point of 1-year MACCE in the CABG group : 13%.
- A noninferiority margin : 7%
- A one-sided type I error rate : 0.05
- Power : 80%
- Assumption : a total of 572 patients (286 per group)
- A final sample size : 600 patients (300 per group) assuming 5% of loss

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 1-year MACCE rate.
- Survival analyses to 2 years because the MACCE rate at 1 year did not reach the anticipated level.
- Subgroups analysis using the Cox regression model with tests for interaction.
- Primary analysis in intention-to-treat peinciple

Baseline Clincal Characteristics

	PCI (N=300)	CABG (N=300)	P value
Age, years	61.8±10.0	62.7±9.5	0.24
Male sex	228 (76.0)	231 (77.0)	0.77
Body mass index	24.6±2.7	24.5±3.0	0.74
Medically treated diabetes			
Any	102 (34.0)	90 (30.0)	0.29
Requiring insulin	10 (3.3)	9 (3.0)	0.82
Hypertension	163 (54.3)	154 (51.3)	0.46
Hyperlipidemia	127 (42.3)	120 (40.0)	0.56
Current smoker	89 (29.7)	83 (27.7)	0.59
Previous PCI	38 (12.7)	38 (12.7)	1.0
Previous myocardial infarction	13 (4.3)	20 (6.7)	0.21
Previous congestive heart failure	0 (0)	2 (0.7)	0.16

Baseline Clinical Characteristics

	PCI (N=300)	CABG (N=300)	P value
Chronic renal failure	4 (1.3)	1(0.3)	0.37
Peripheral vascular disease	15 (5.0)	7 (2.3)	0.08
Chronic pulmonary disease	6 (2.0)	10 (3.3)	0.31
Clinical manifestation			0.12
Stable angina or asymptomatic	160 (53.3)	137 (45.7)	
Unstable angina	128 (42.7)	144 (48.0)	
Recent acute myocardial infarction	12 (4.0)	19 (6.3)	
Ejection fraction, %	61.7±8.3	60.6±8.5	0.12
EuroSCORE value	2.6±1.8	2.8±1.9	0.16
Electrocardiographic findings			0.77
Sinus rhythm	286 (96.6)	289 (97.3)	
Atrial fibrillation	5 (1.7)	5 (1.7)	
Others	5 (1.7)	3 (1.0)	

Baseline Angiographic Characteristics

	PCI (N=300)	CABG (N=300)	P value
Extent of disease vessel			0.68
LM only	27 (9.0)	34 (11.3)	
LM plus 1-vessel	50 (16.7)	53 (17.7)	
LM plus 2-vessel	101 (33.7)	90 (30.0)	
LM plus 3-vessel	122 (40.7)	123 (41.0)	
Bifurcation left main involvement	200 (66.9)	183 (62.2)	0.24
Diameter stenosis of left main, %			0.12
$>$ 50 and $\leq$ 70	160 (53.3)	141 (47.0)	
$>$ 70	140 (46.7)	159 (53.0)	
Right coronary artery disease	149 (49.7)	159 (53.0)	0.41
Restenotic lesion	1 (0.3)	2 (0.7)	0.56
Chronic total occlusion	2 (0.7)	2 (0.7)	1.0
SYNTAX score	24.4±9.4	25.8±10.5	0.09

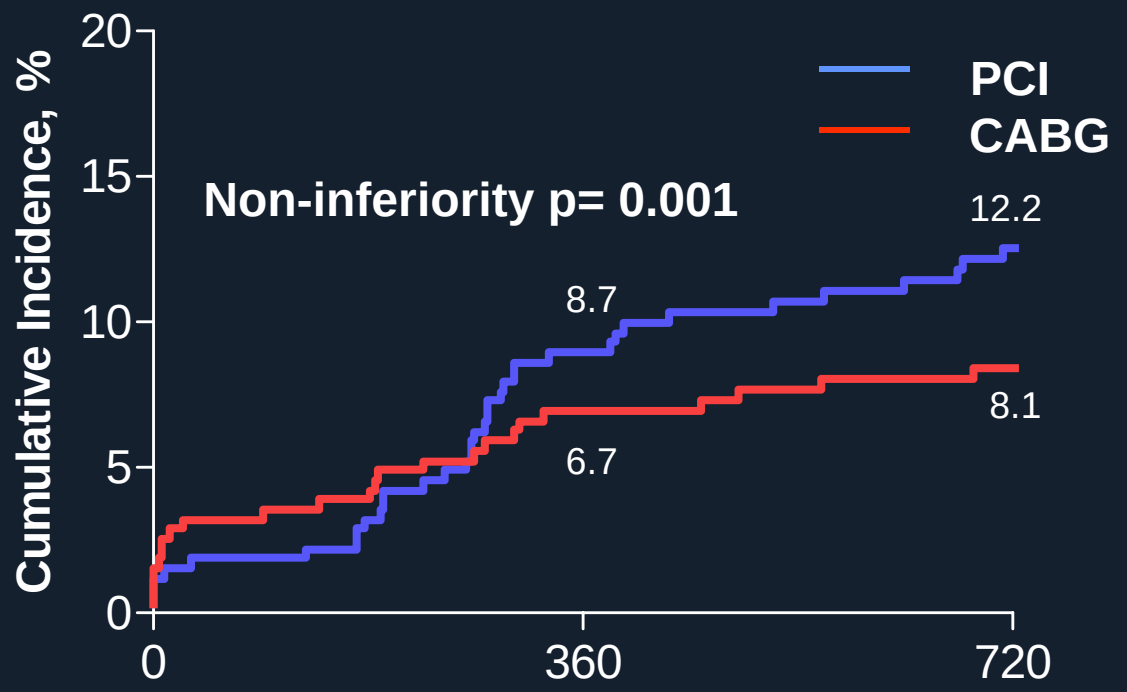
Procedural Characteristics

PCI (N=300)	
Stents number in LM	1.6±0.8
Stent length in LM, mm	44.0±31.9
Stents per pt	2.7±1.4
Stent length per pt, mm	60.0±42.1
IVUS guidance	250 (91.2)
Bifurcation treatment	
1-stent technique	87 (46.3)
2-stent technique	
Crush	33 (17.9)
Kissing	33 (17.9)
T stent	25 (13.6)
V stent	4 (2.2)
Others	2 (1.1)
Final kissing balloon	129 (70.1)

CABG (N=300)	
Grafts per patient	2.7±0.9
Arterial grafts	2.1±0.9
Vein graft	0.7±0.8
Use of LIMA	233 (93.6)
Off-pump surgery	155 (63.8)

	PCI	CABG	P
Complete revascularization	205 (68.3)	211 (70.3)	0.60

Primary End Point of MACCE

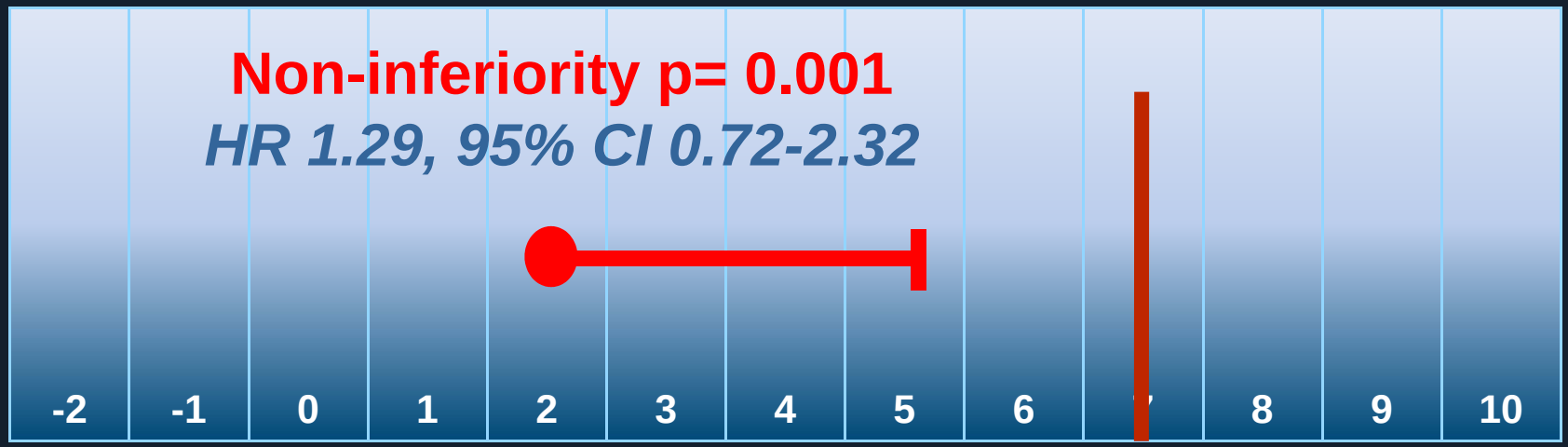


No. at Risk			
PCI	300	272	236
CABG	300	276	239

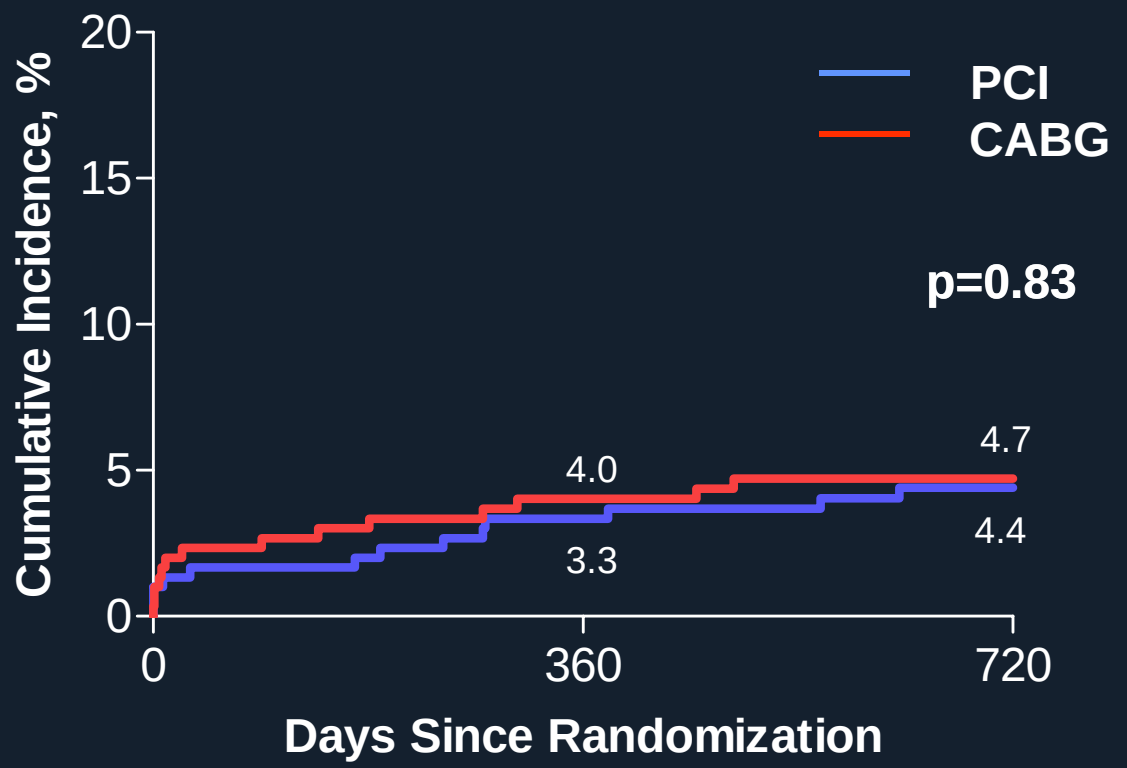
Noninferiority Test for
Primary End Point of 1-Year MACCE

1-year MACCE rate **CABG: 6.7%** **PCI: 8.7%**

Prespecified non-inferiority margin: 7%

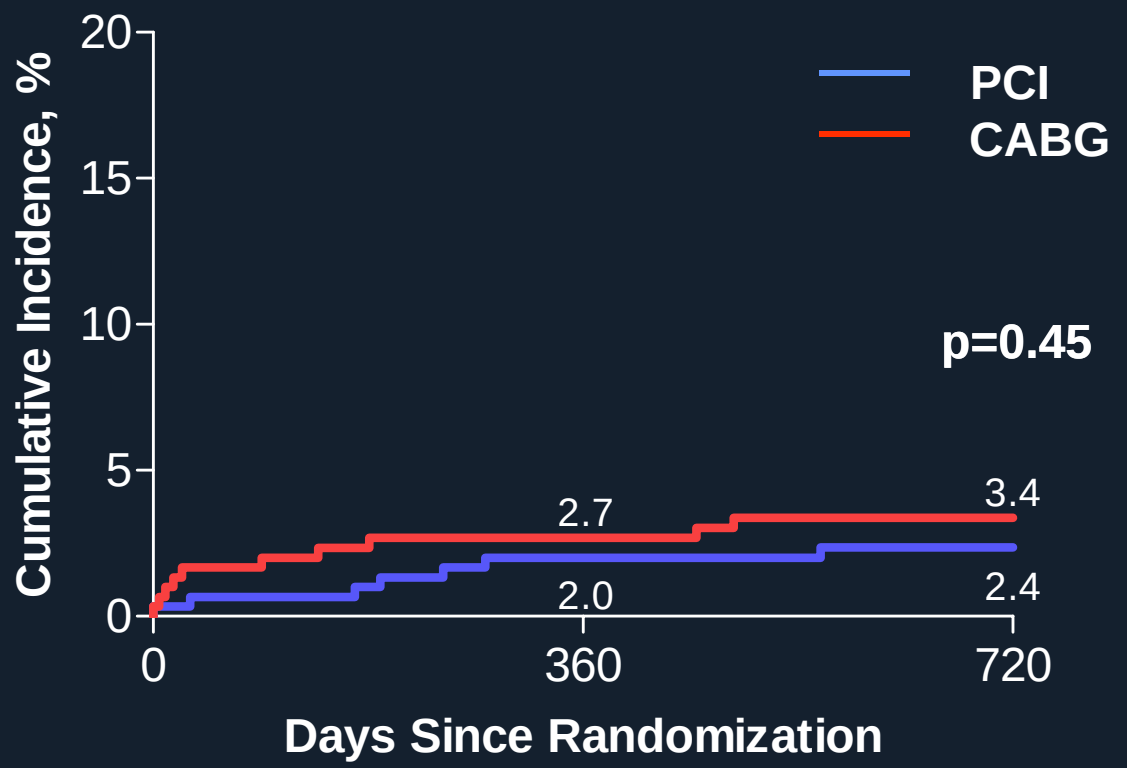


Death, MI or Stroke



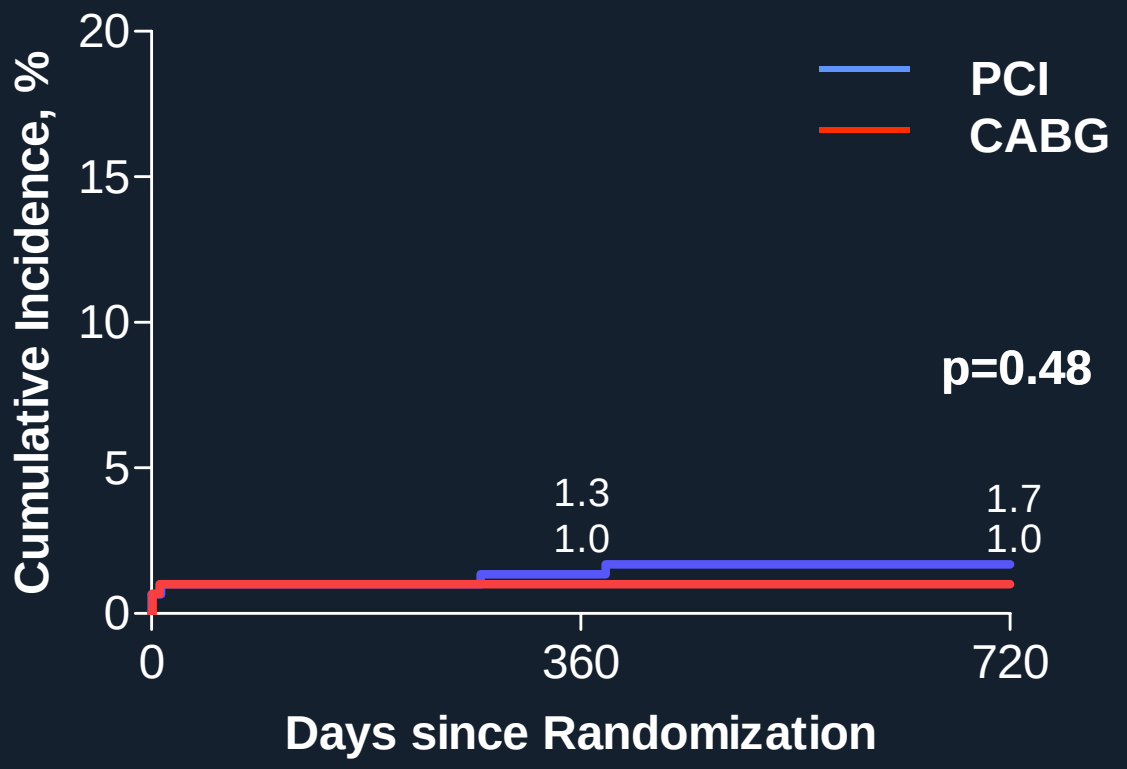
No. at Risk			
PCI	300	288	256
CABG	300	284	248

Death



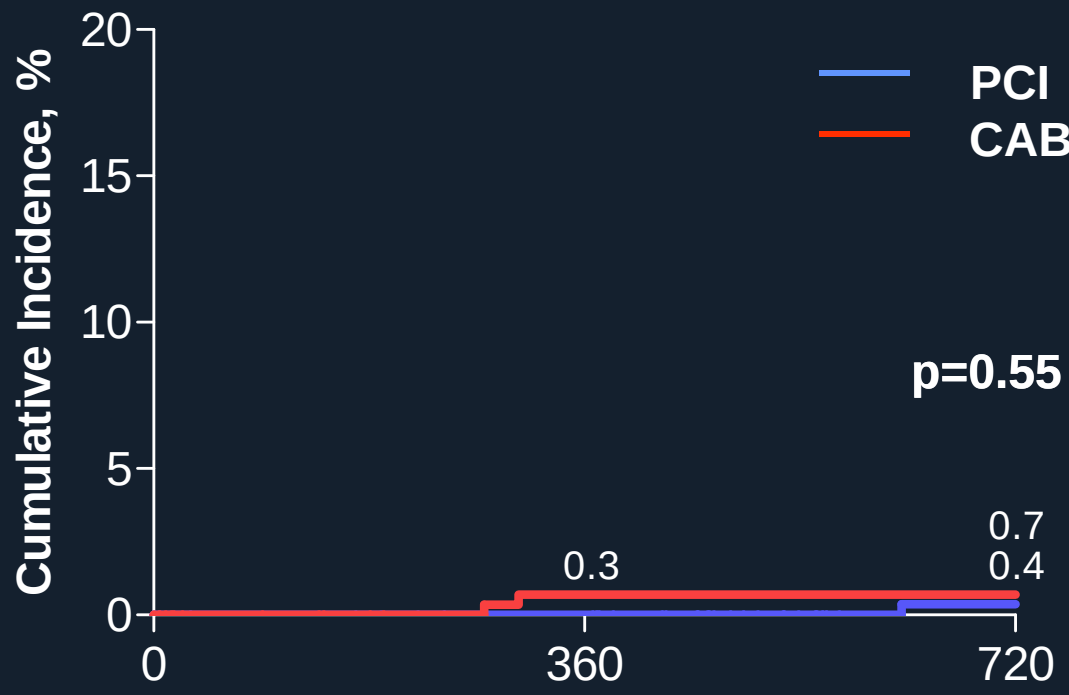
No. at Risk			
PCI	300	292	261
CABG	300	287	251

Myocardial Infarction



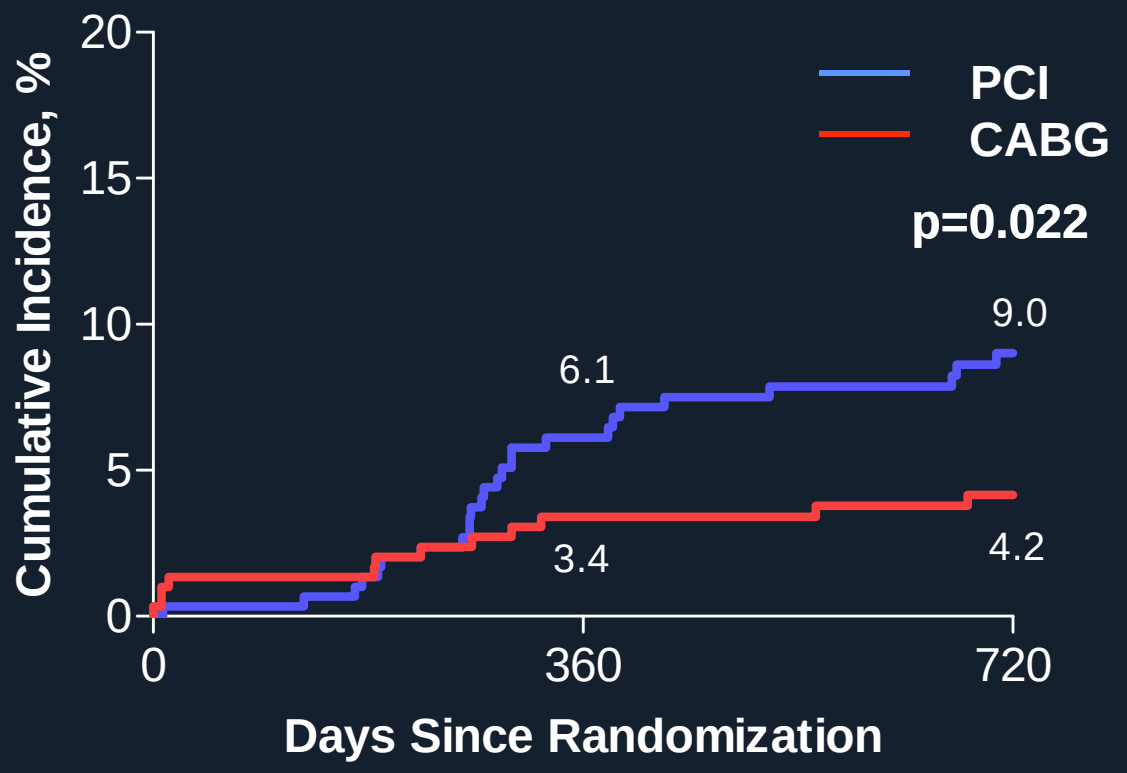
No. at Risk			
PCI	300	287	254
CABG	300	285	249

Stroke



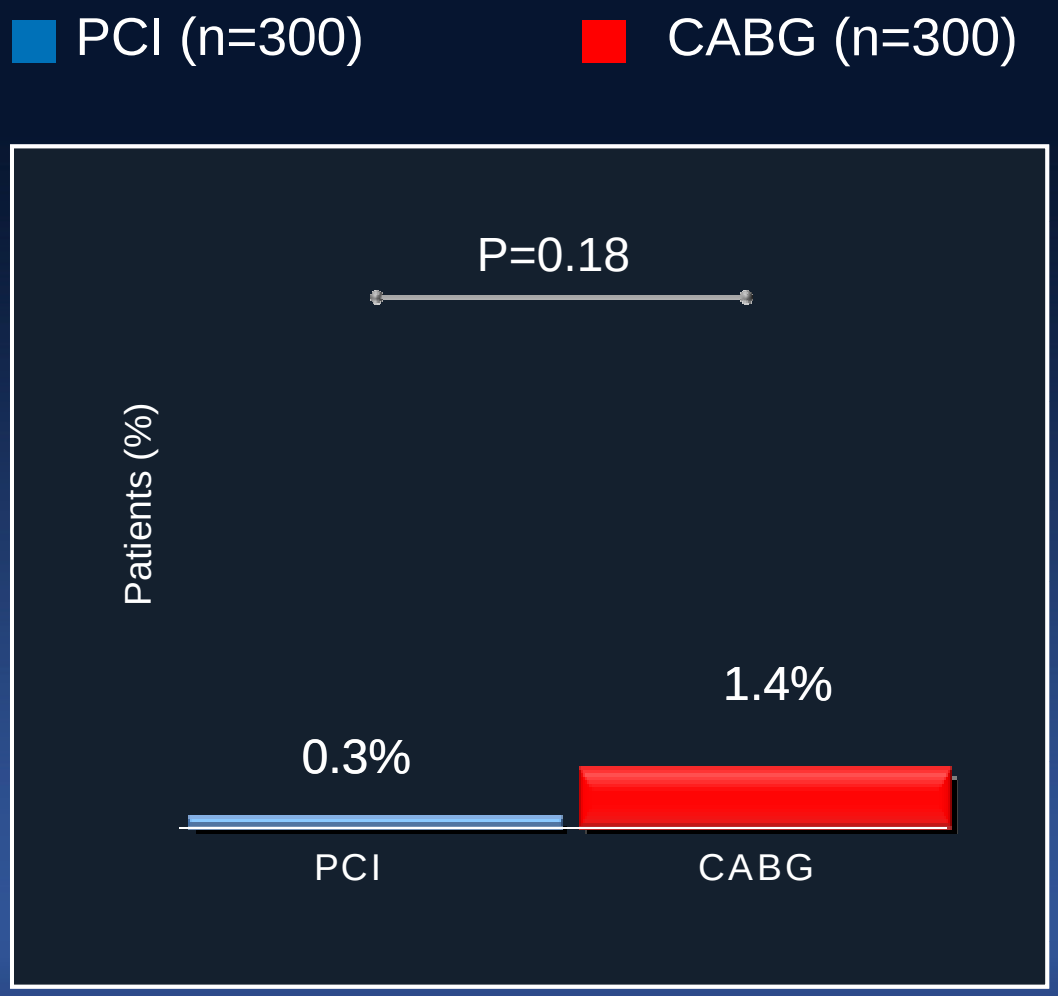
No. at Risk			
PCI	300	292	260
CABG	300	286	250

Ischemia-Driven TVR



No. at Risk			
PCI	300	274	237
CABG	300	279	242

Symptomatic Graft Occlusion & Stent Thrombosis to 2 Years



Post-procedure; ITT population

Conclusion

The PRECOMBAT randomized trial suggests that PCI with sirolimus-eluting stent appears a potential alternative to CABG with a noninferior incidence of 2-year MACCE for patients with ULMCA stenosis.