Women In Innovations @ TCT AP 2011

Update of Left Main/Multi-vessel PCI: Lessons from Syntax, A View to EXCEL

Roxana Mehran, MD

Professor of Medicine (Cardiology)

Director, Interventional Cardiovascular Research and Clinical Trials

Mount Sinai School of Medicine

Chief Scientific Officer

Cardiovascular Research Foundation

MOUNT SINAI SCHOOL OF MEDICINE

CARDIOVASCULAR RESEARCH FOUNDATION
A Passion for Innovation

Mount Sinai™ HEART

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• **Grant/Research Support**	• Sanofi/BMS- Significant
• **Consultant**	• Astra Zeneca,Abbott Vascular, Orho McNeal, Regado Biosciences

CARDIOVASCULAR RESEARCH FOUNDATION
A Passion for Innovation

Mount Sinai HEART

Outline of this Lecture:

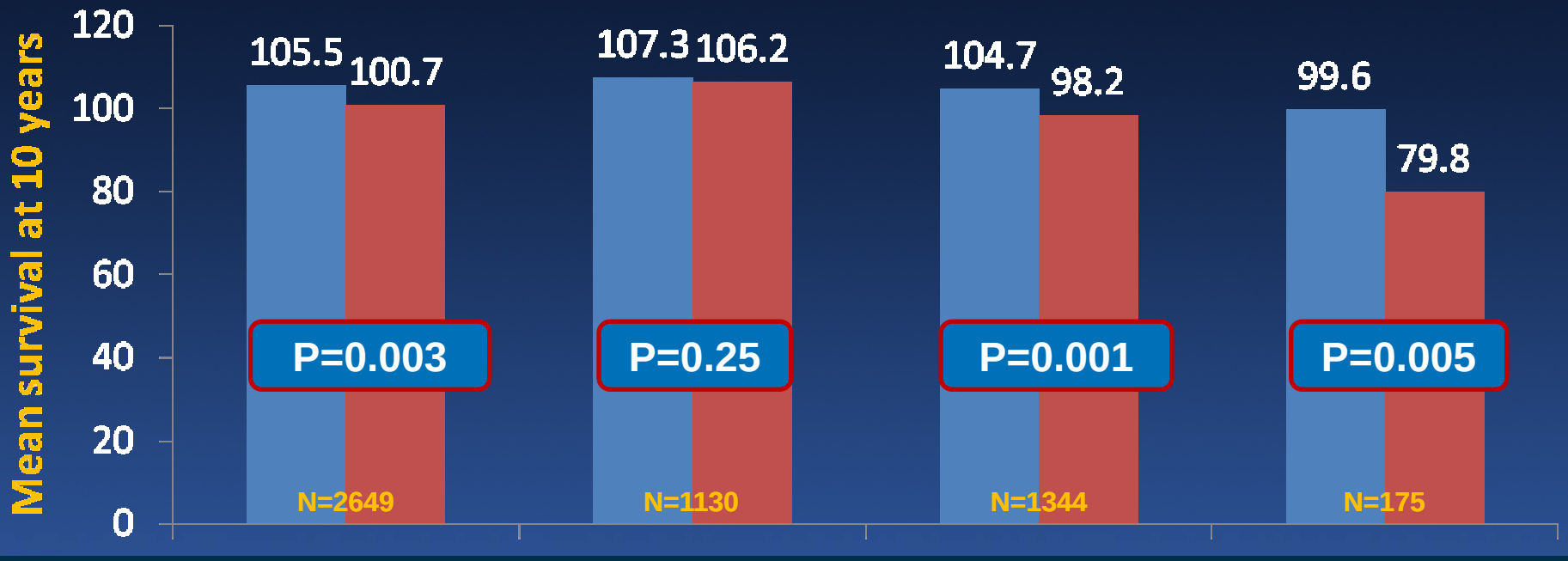
- Current Guidelines for LM Revascularization
- Data from Randomized Trials: Syntax and more
- The EXCEL Study

CABG vs. Medical Therapy in LM Disease

175 pts with left main disease were randomized to CABG vs. medical therapy in 2 studies (VA and EU)

Note: 42% and 65% of med pts crossed over to CABG by 5 and 10 yrs

Mortality at 5 years: Med Rx 36.5% vs. CABG 16.0%
(OR 0.32 [0.15, 0.70], P=0.004)



From 7 RCTs

Yusuf S et al. Lancet 1994;344:563-70

ACC/AHA Guidelines

IIa

LMCA PCI is reasonable in pts with class III angina and >50% LM stenosis who are not eligible for CABG

IIb

Stenting of the LMCA as an alternative to CABG may be considered in pts with anatomic conditions that are associated with a low risk of PCI procedural complications and clinical conditions that predict an increased risk of adverse surgical outcomes

ACC/AHA 2009 Focused Updates for STEMI and PCI. Circulation 2009;120:2271–2306

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 5, 2009 VOL. 360 NO. 10

Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease

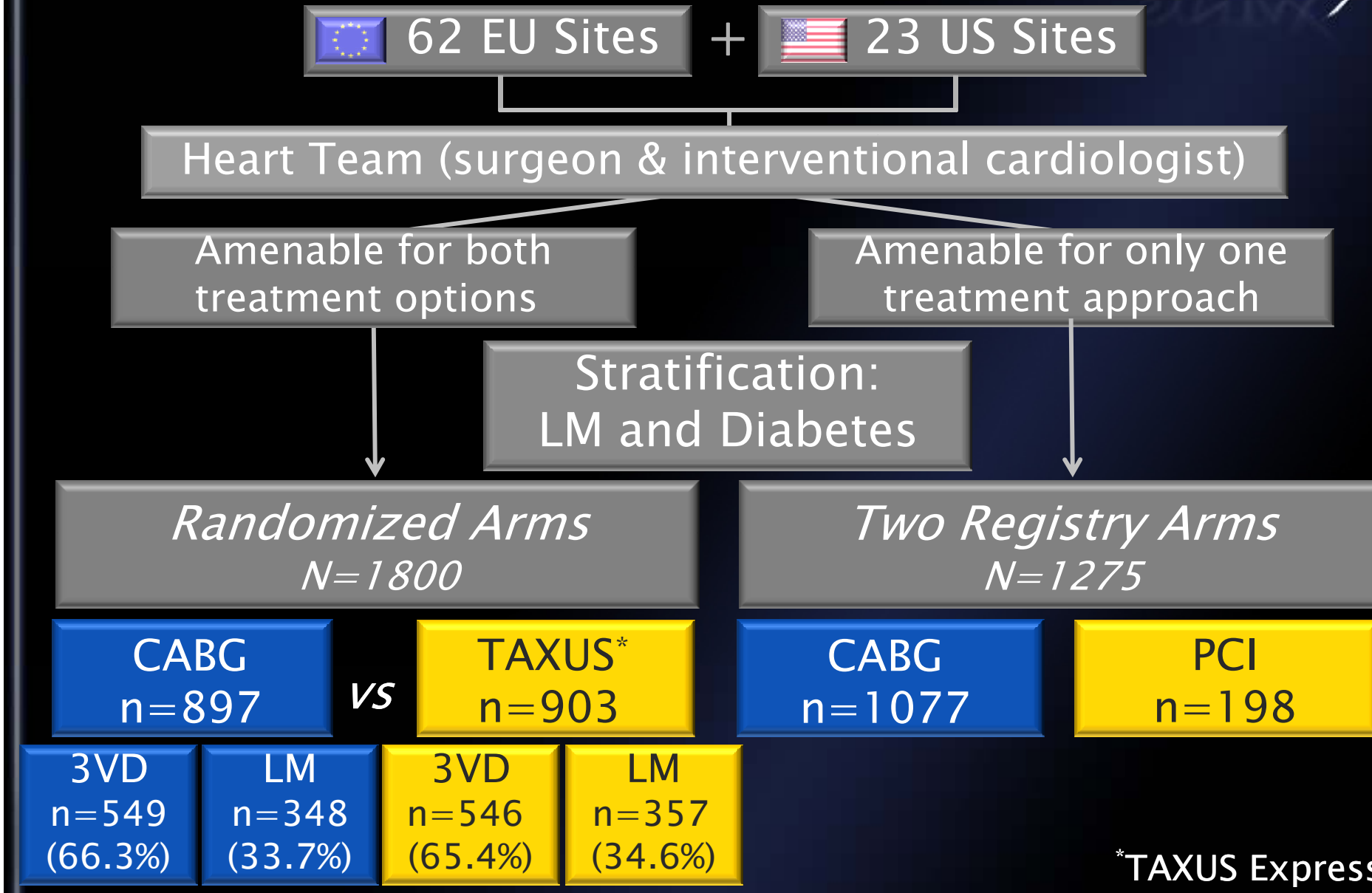
Patrick W. Serruys, M.D., Ph.D., Marie-Claude Morice, M.D., A. Pieter Kappetein, M.D., Ph.D., Antonio Colombo, M.D., David R. Holmes, M.D., Michael J. Mack, M.D., Elisabeth Ståhle, M.D., Ted E. Feldman, M.D., Marcel van den Brand, M.D., Eric J. Bass, B.A., Nic Van Dyck, R.N., Katrin Leadley, M.D., Keith D. Dawkins, M.D., and Friedrich W. Mohr, M.D., Ph.D., for the SYNTAX Investigators*

ABSTRACT

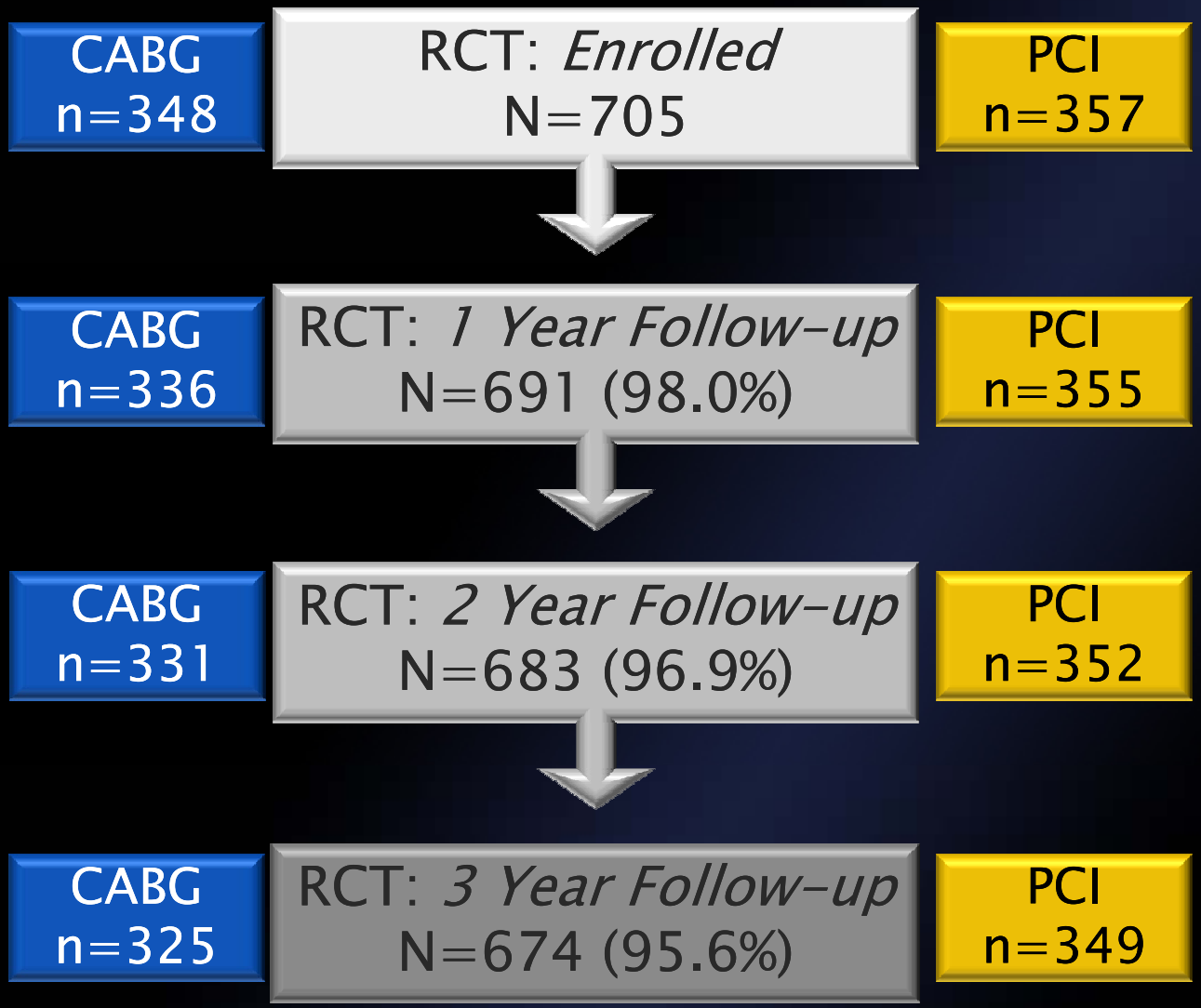
CONCLUSIONS

CABG remains the standard of care for patients with three-vessel or left main coronary artery disease, since the use of CABG, as compared with PCI, resulted in lower rates of the combined end point of major adverse cardiac or cerebrovascular events at 1 year. (ClinicalTrials.gov number, NCT00114972.)

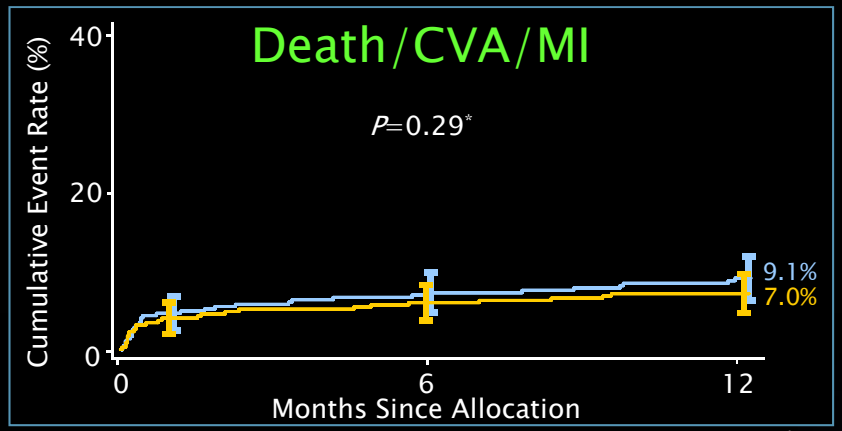
SYNTAX Trial Design



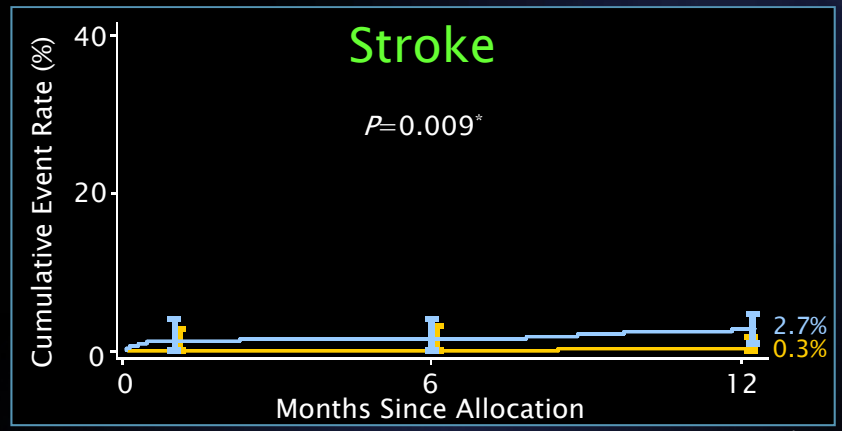
Patients in SYNTAX
Left Main (LM) Subset



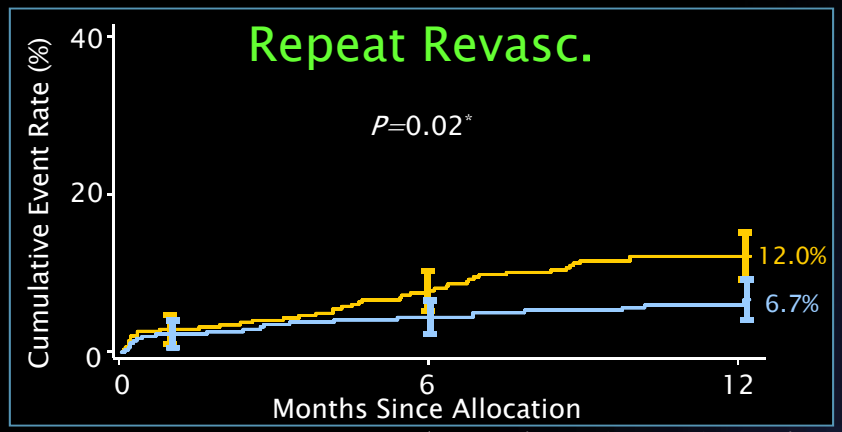
Summary of 1-Year Results
LM Subset



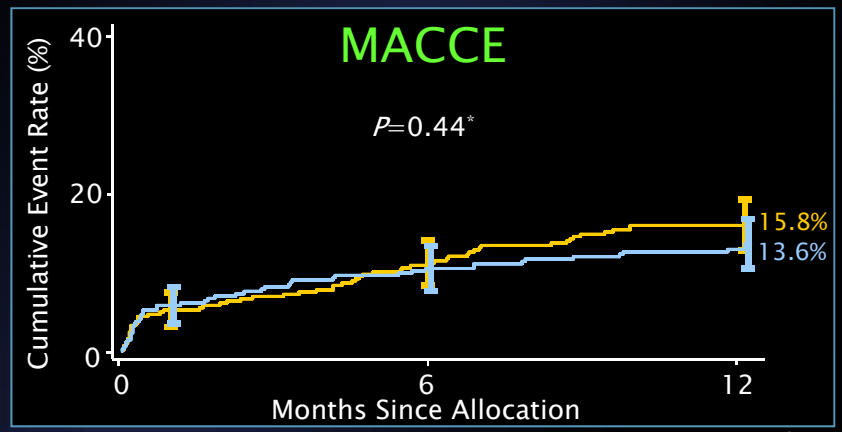
Event rate ± 1.5 SE, *Fisher exact test ITT population



Event rate ± 1.5 SE, *Fisher exact test ITT population



Event rate ± 1.5 SE, *Fisher exact test *Any revascularization (PCI or CABG); ITT population

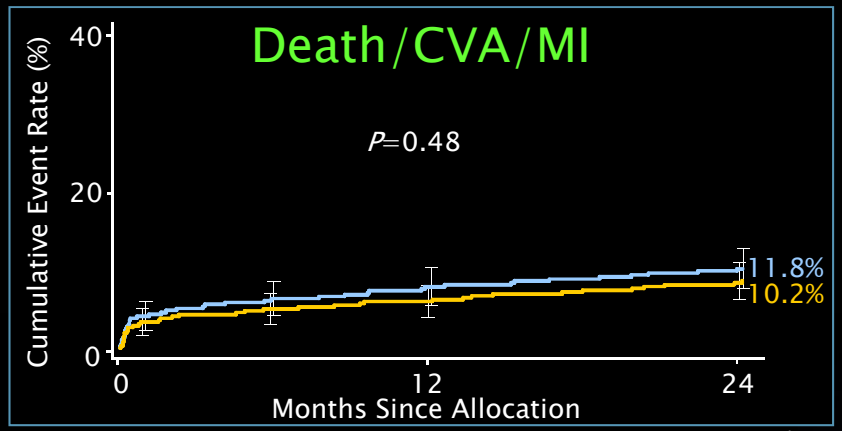


Event rate ± 1.5 SE, *Fisher exact test ITT population

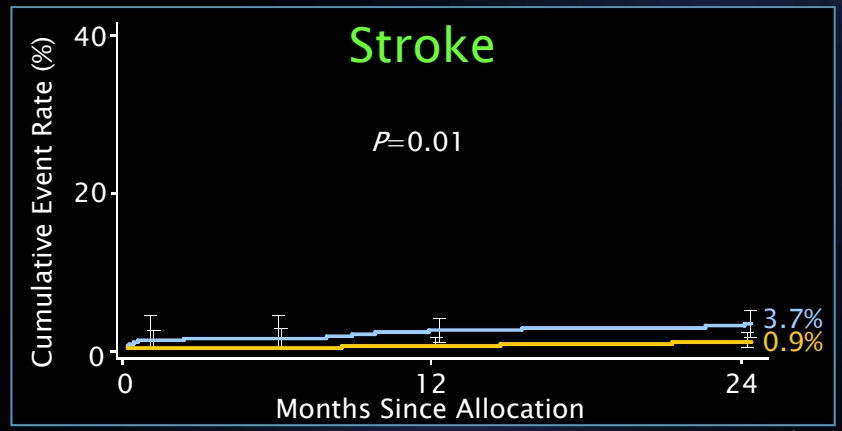
- Death/Stroke/MI and MACCE rates were similar between groups
- Stroke was significantly increased in CABG and revacularization in PCI

CABG (N=897) PCI (N=903)

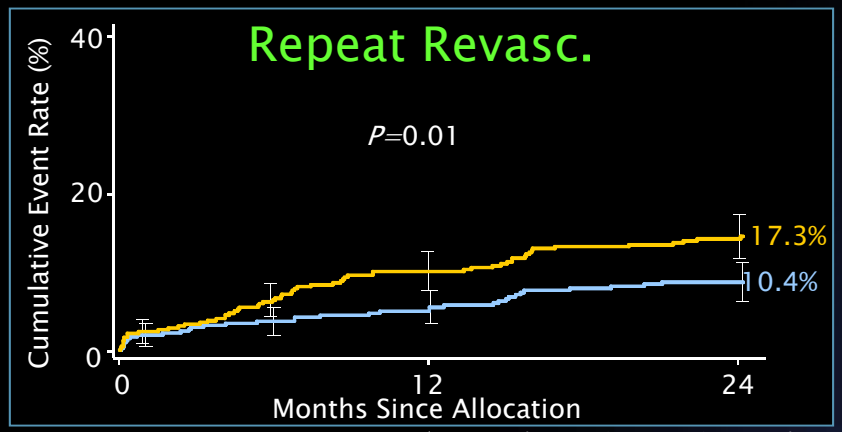
Summary of 2-Year Results
LM Subset



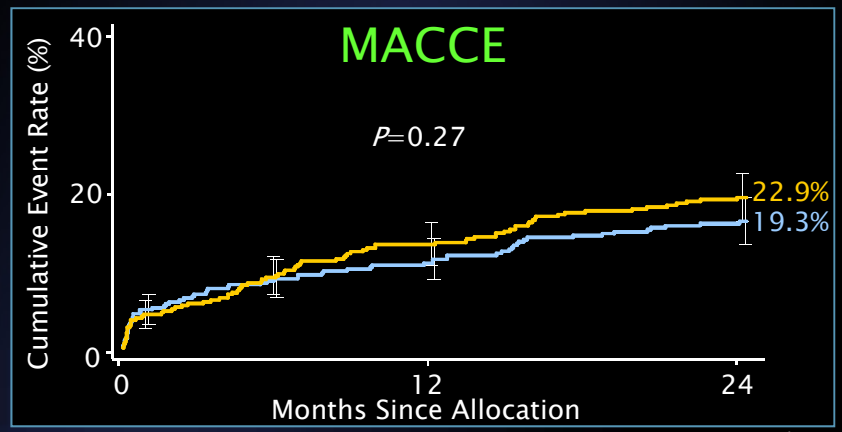
Event rate ± 1.5 SE, *Fisher exact test ITT population



Event rate ± 1.5 SE, *Fisher exact test ITT population



Event rate ± 1.5 SE, *Fisher exact test *Any revascularization (PCI or CABG); ITT population



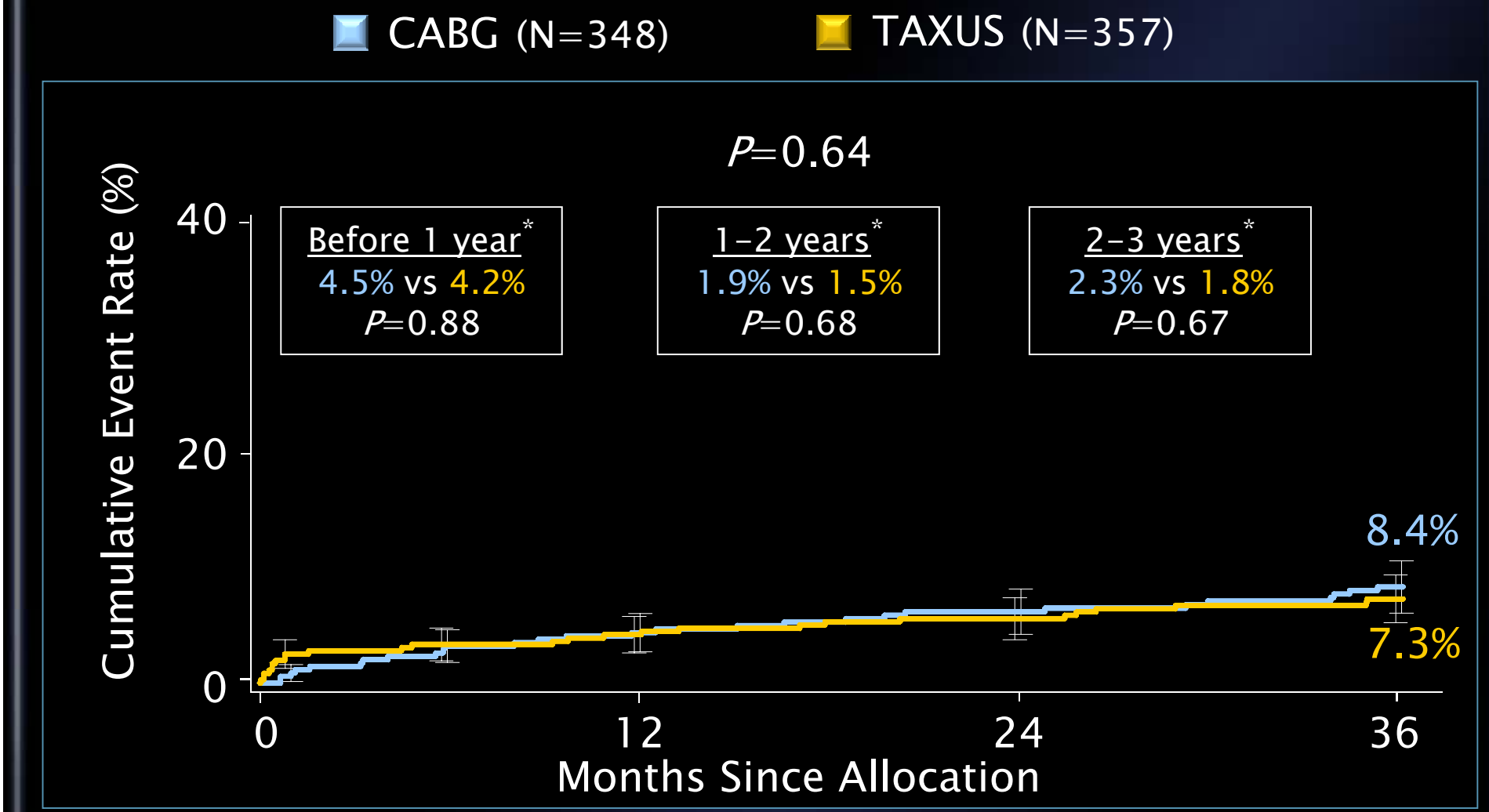
Event rate ± 1.5 SE, *Fisher exact test ITT population

- Death/Stroke/MI and MACCE rates were similar between groups
- Stroke was significantly increased in CABG and revacularization in PCI

CABG (N=897) PCI (N=903)

All-Cause Death to 3 Years

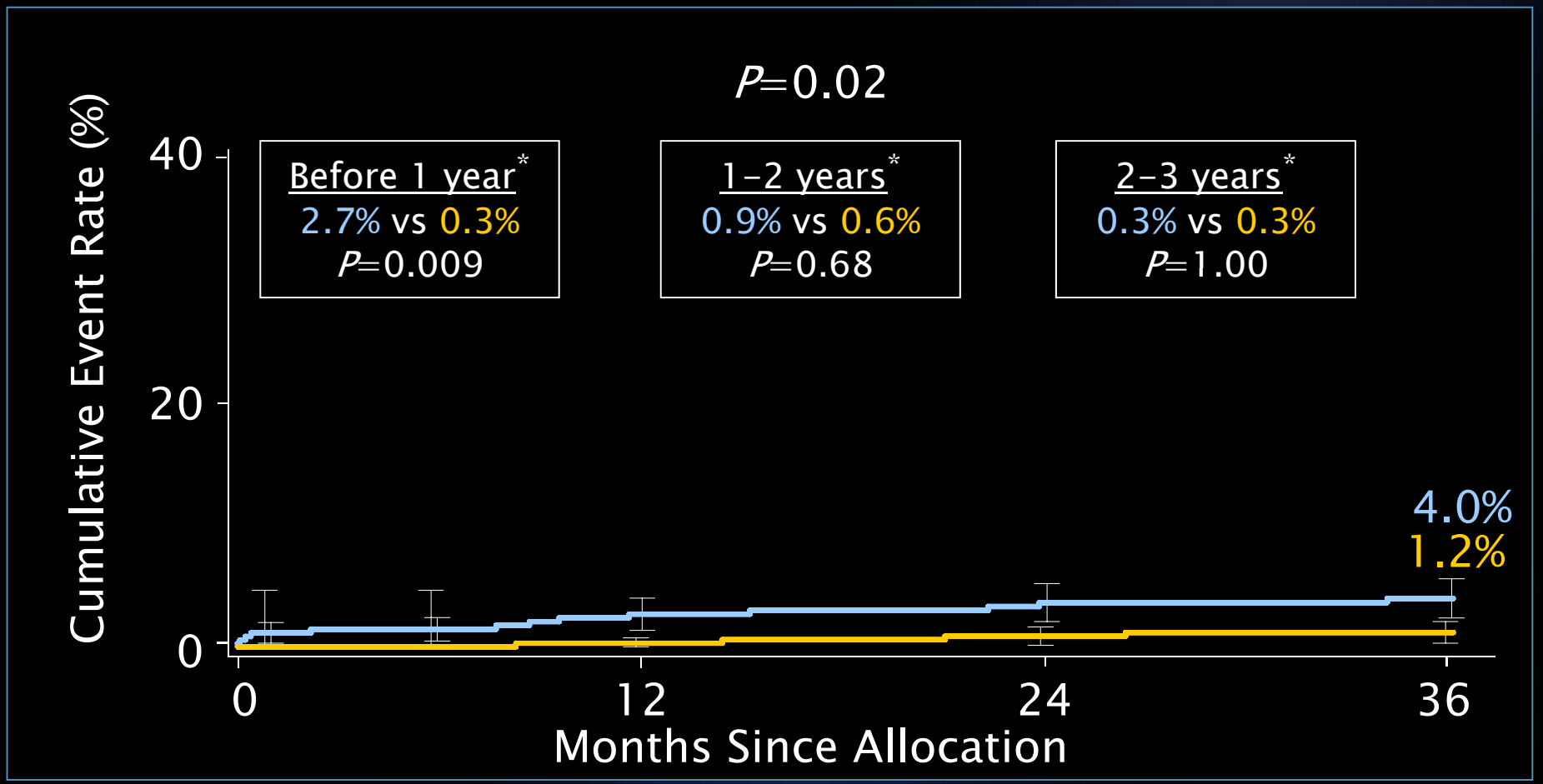
LM Subset



Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value; *Binary rates

ITT population

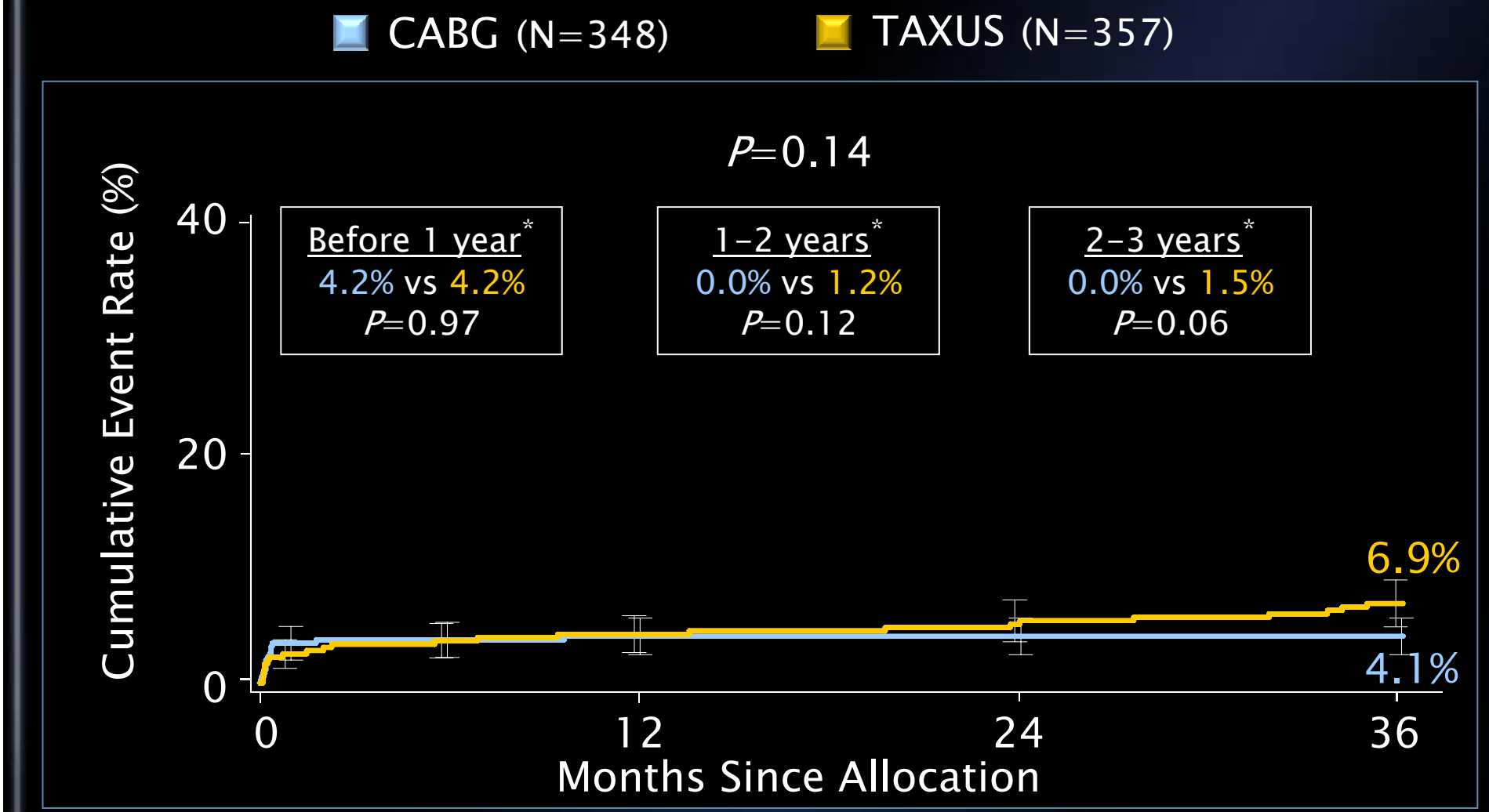
CVA to 3 Years
LM Subset



Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value; *Binary rates

ITT population

Myocardial Infarction to 3 Years
LM Subset

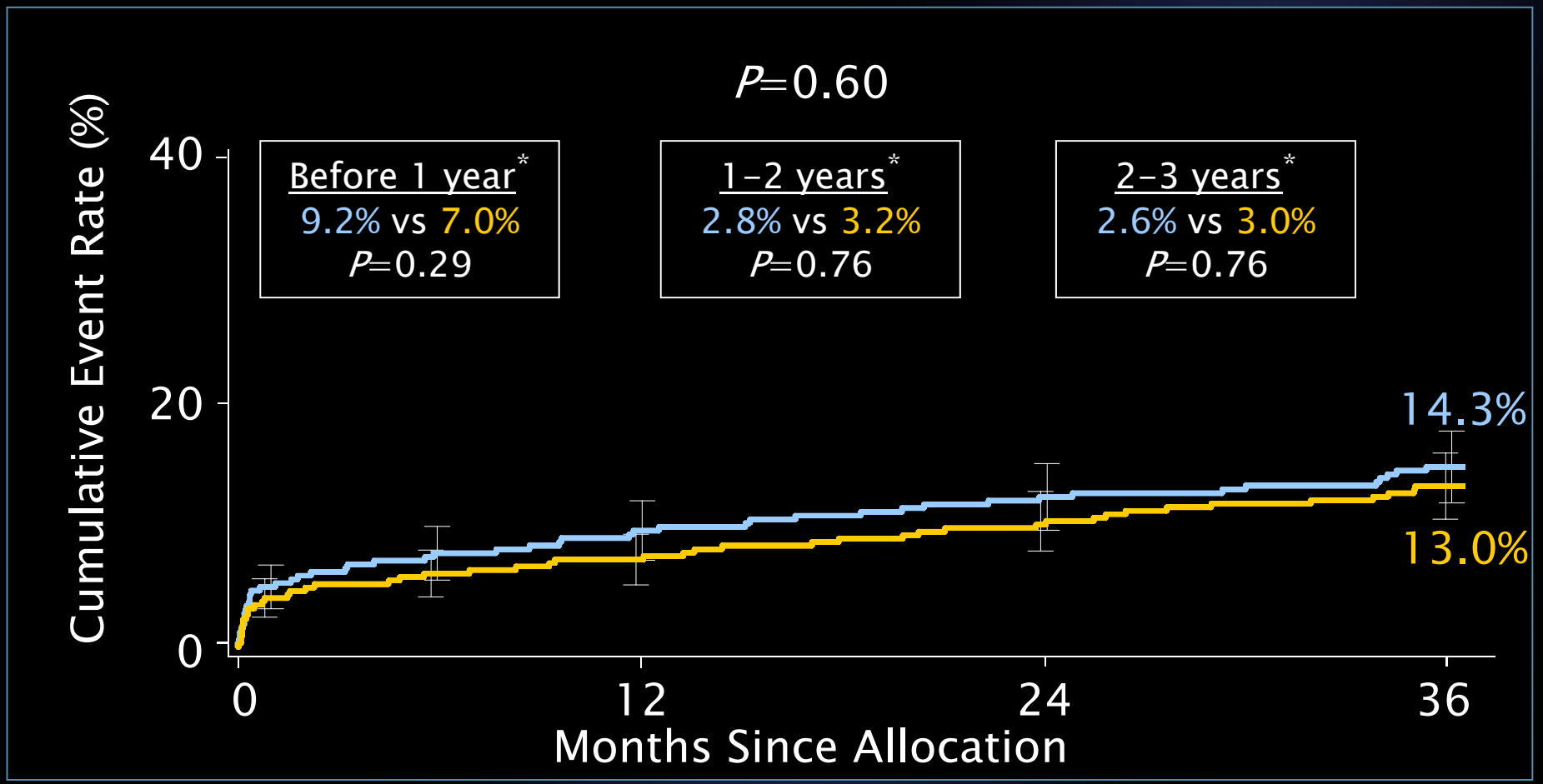


Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value; *Binary rates

ITT population

All-Cause Death/CVA/MI to 3 Years

LM Subset

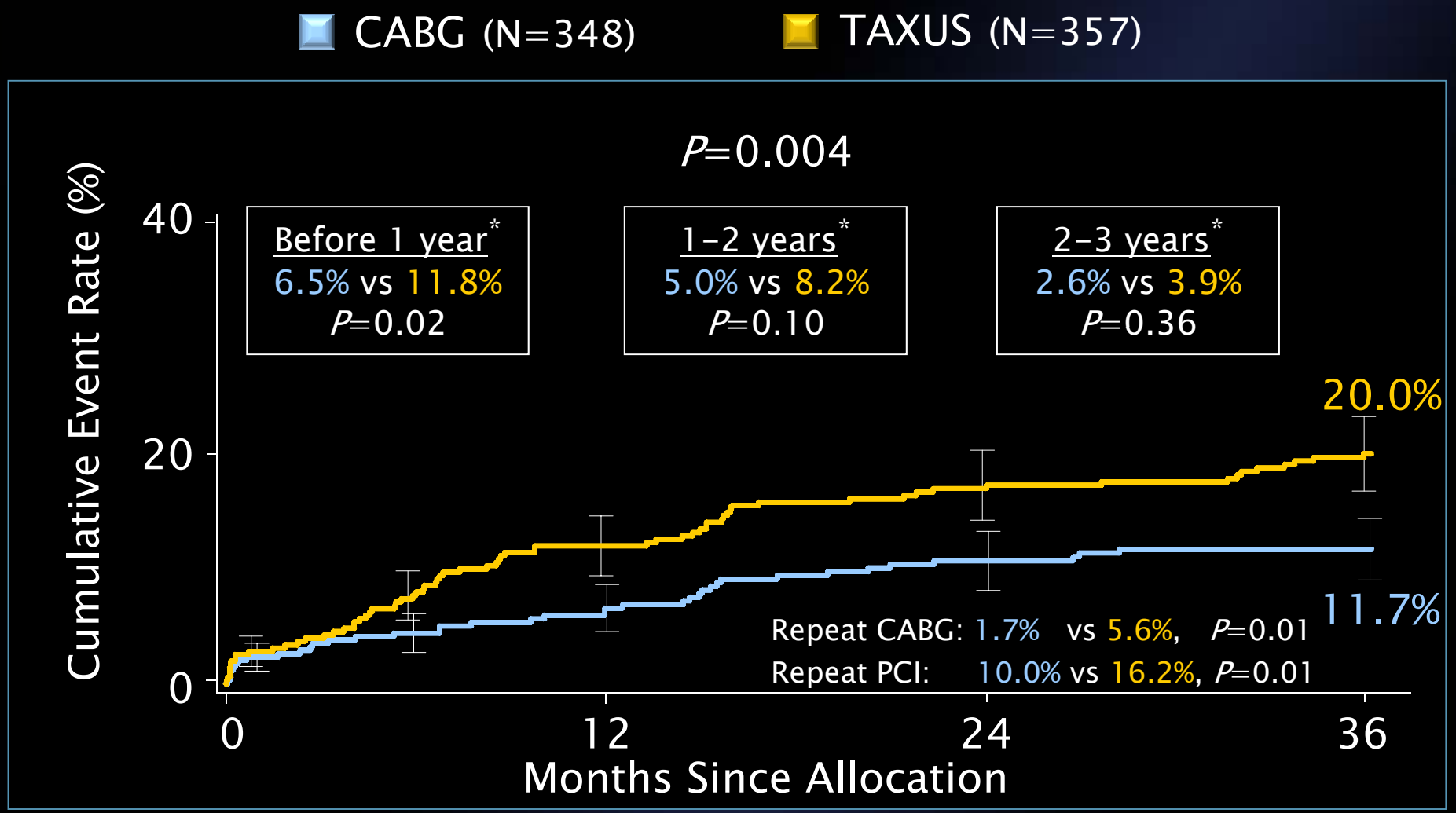


Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value; *Binary rates

ITT population

Repeat Revascularization to 3 Years

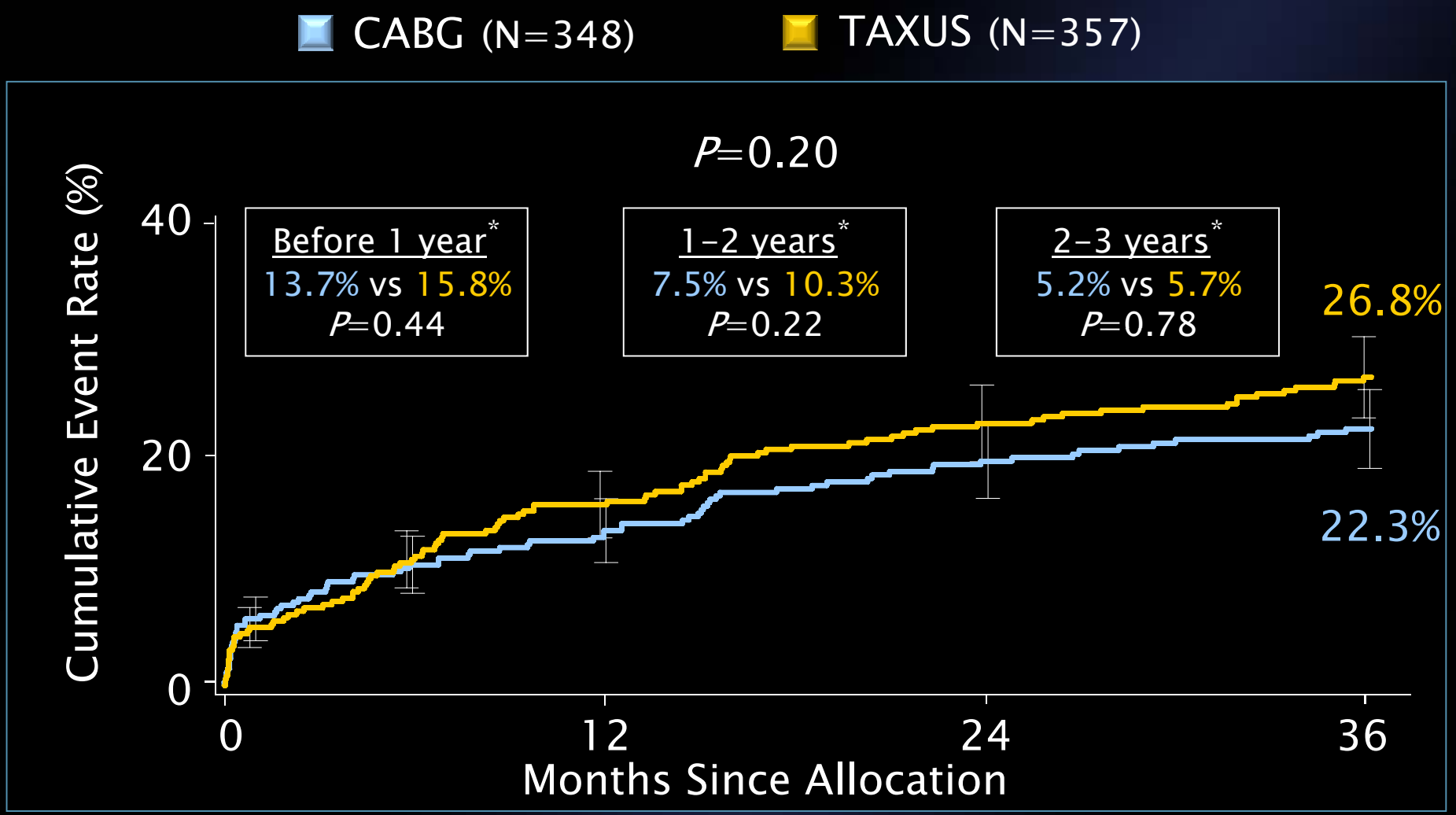
LM Subset



Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value; *Binary rates

ITT population

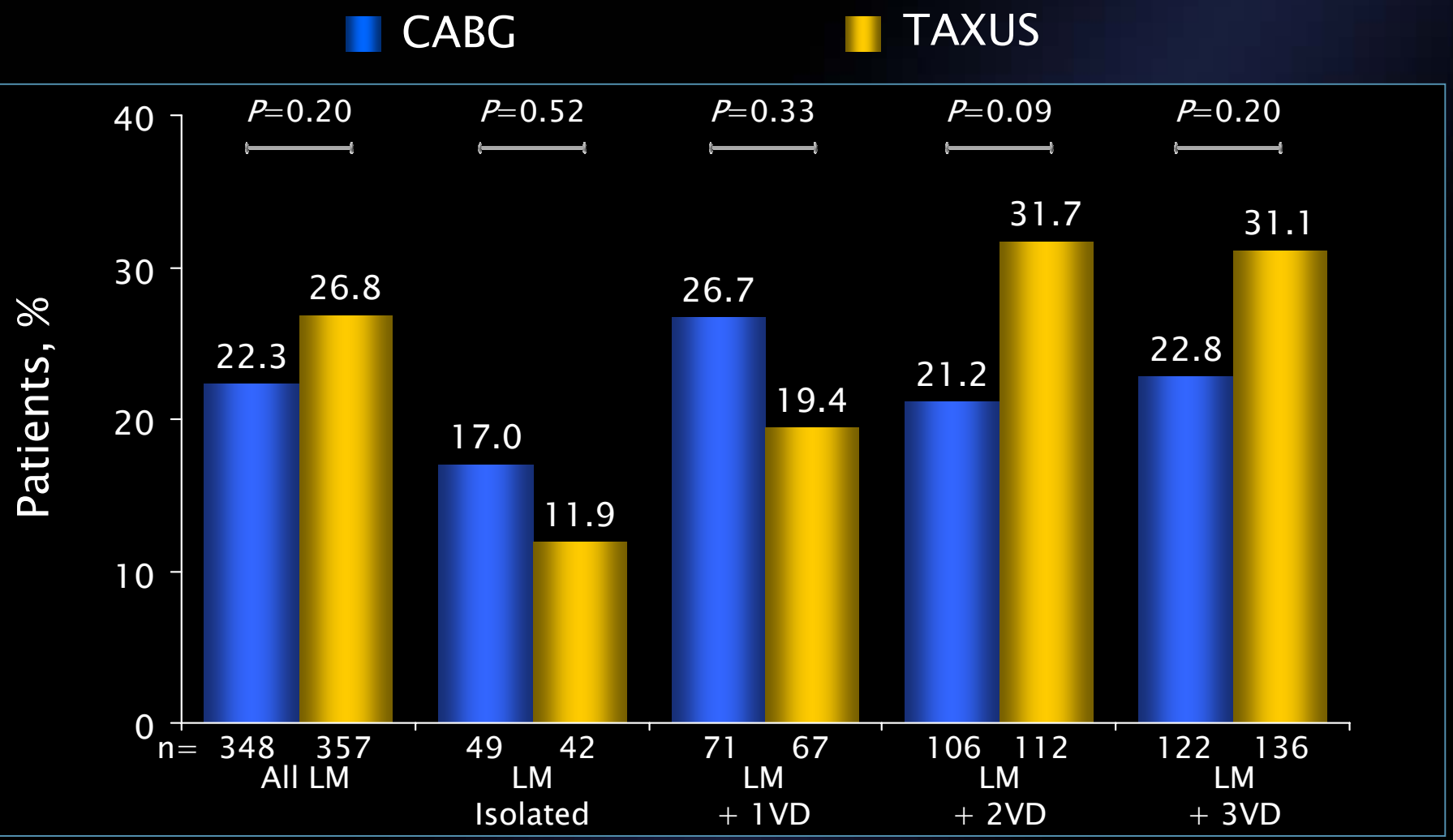
MACCE to 3 Years
LM Subset



Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value; *Binary rates

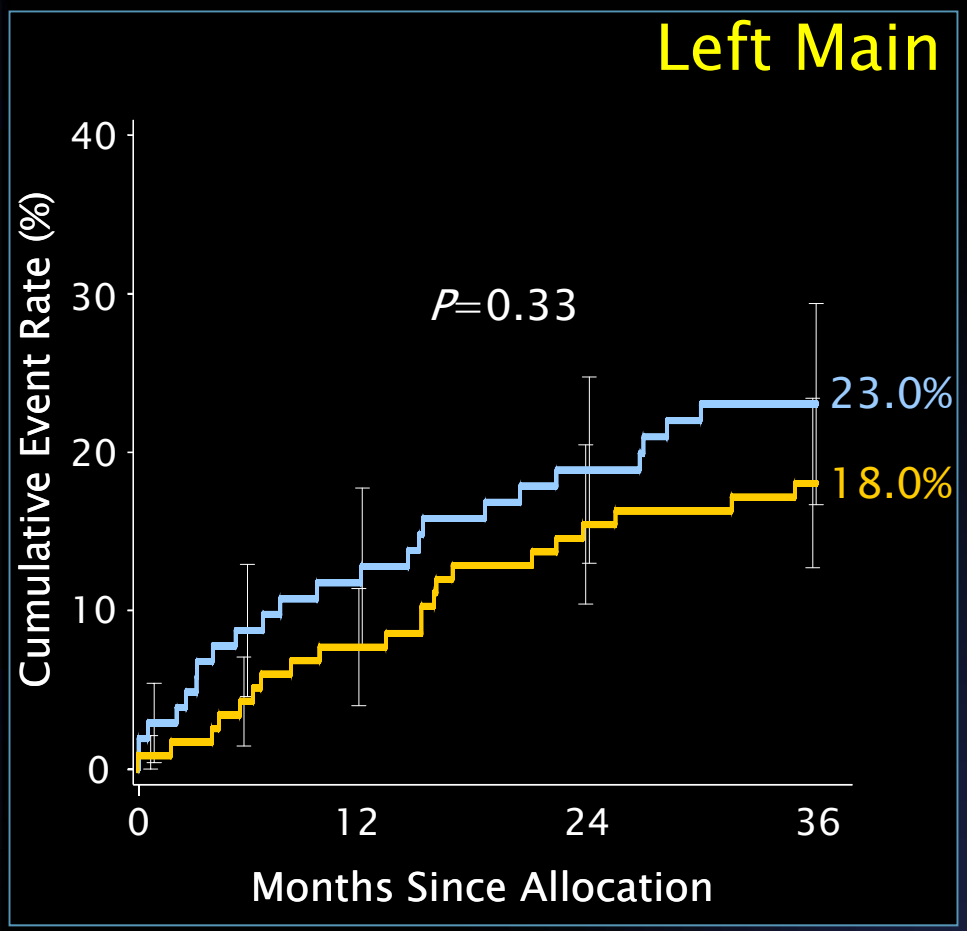
ITT population

MACCE to 3 Years in LM Subgroups



Cumulative KM Event Rate; log-rank *P* value; *Binary rates

MACCE to 3 Years by SYNTAX Score Tercile *Low Scores (0–22)*

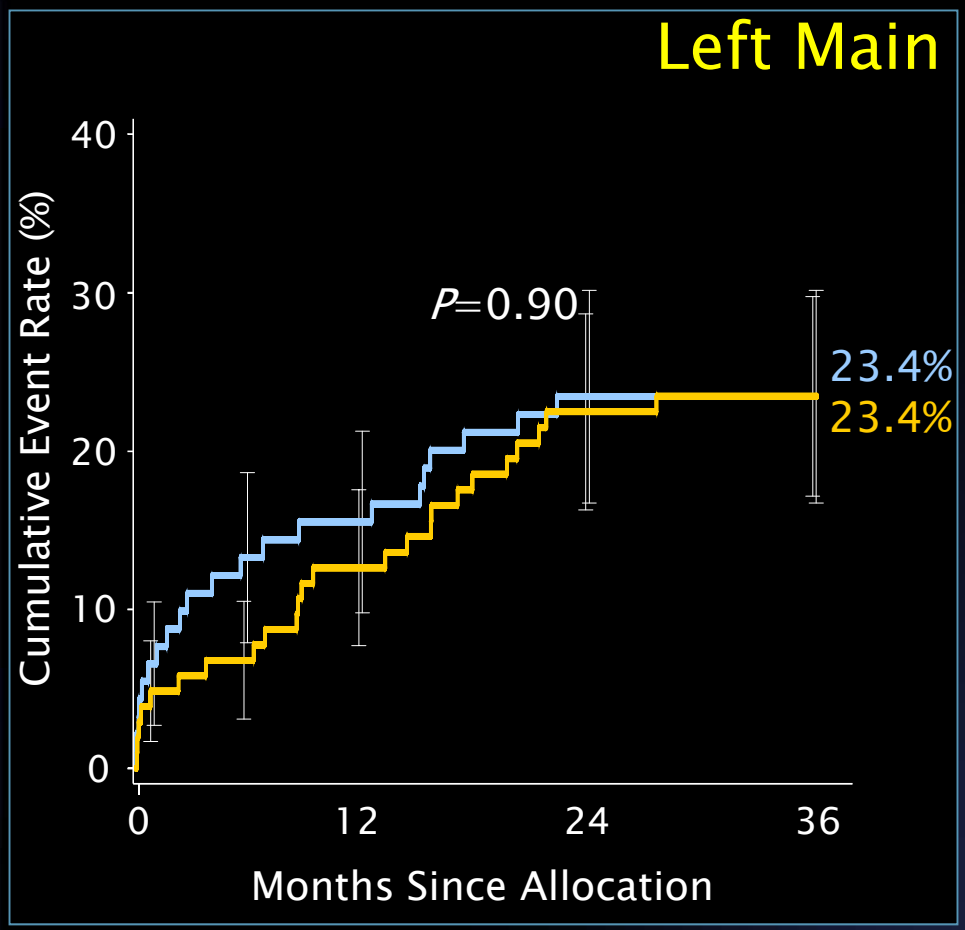


	CABG	PCI	*P* value
Death	6.0%	2.6%	0.21
CVA	4.1%	0.9%	0.12
MI	2.0%	4.3%	0.36
Death, CVA or MI	11.0%	6.9%	0.26
Revasc.	13.4%	15.4%	0.69

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Site-reported Data; ITT population

MACCE to 3 Years by SYNTAX Score Tercile *Intermediate Scores (23–32)*

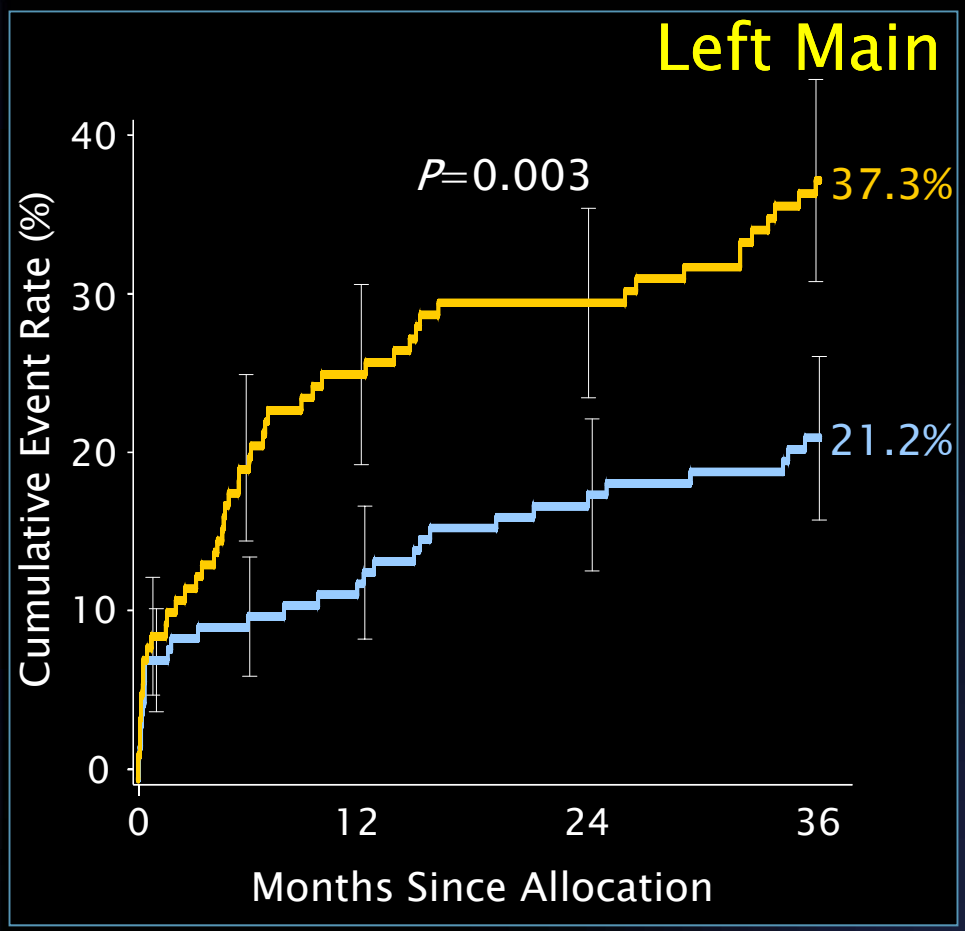


	CABG	PCI	*P* value
Death	12.4%	4.9%	0.06
CVA	2.3%	1.0%	0.46
MI	3.3%	5.0%	0.63
Death, CVA or MI	15.6%	10.8%	0.29
Revasc.	14.0%	15.9%	0.75

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Site-reported Data; ITT population

MACCE to 3 Years by SYNTAX Score Tercile *Left Main SYNTAX Score ≥33*



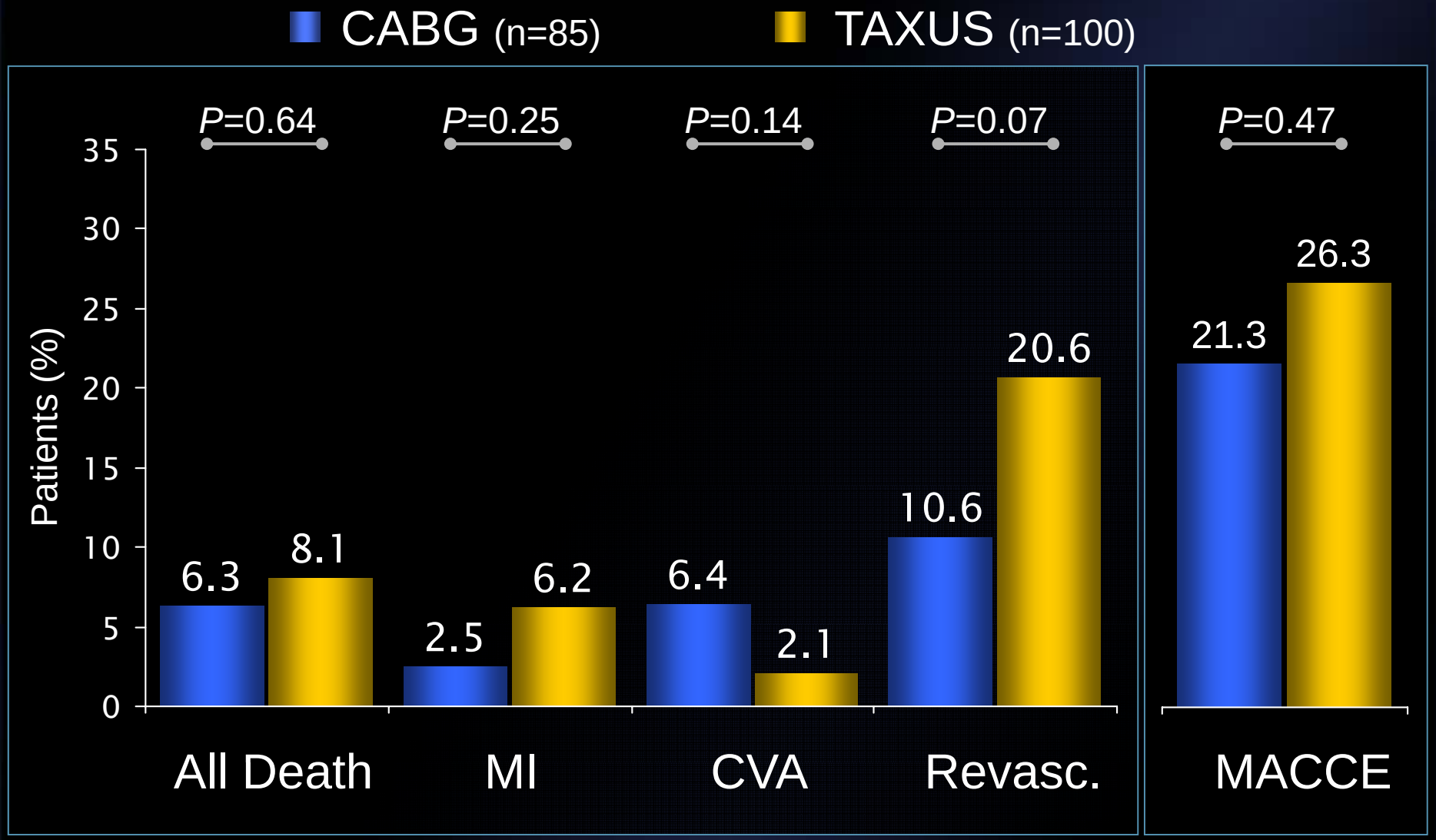
	CABG	PCI	*P* value
Death	7.6%	13.4%	0.10
CVA	4.9%	1.6%	0.13
MI	6.1%	10.9%	0.18
Death, CVA or MI	15.7%	20.1%	0.34
Revasc.	9.2%	27.7%	<0.001

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Site-reported Data; ITT population

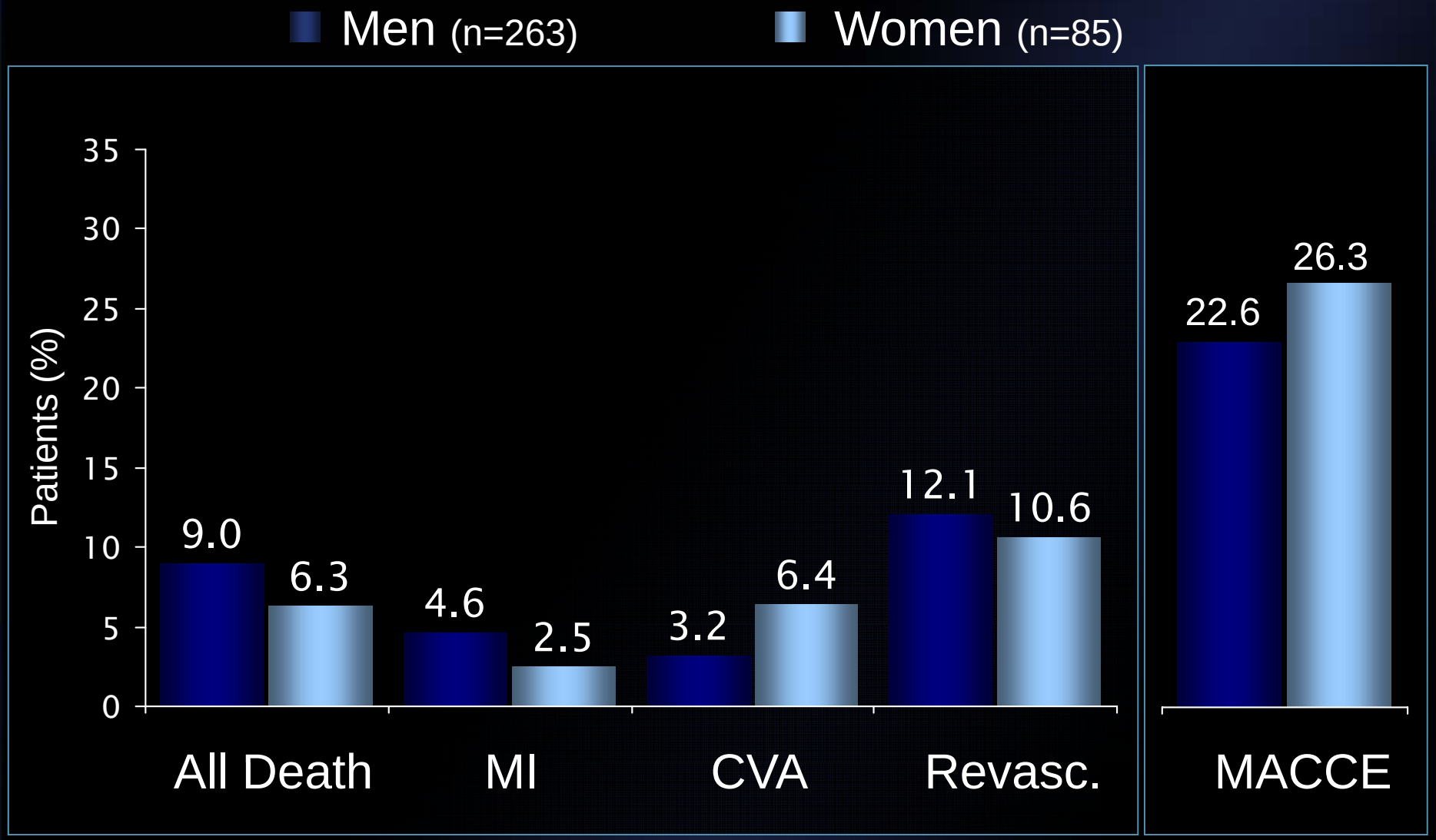
MACCE and Components to 3 Years

In Women (LM lesions)



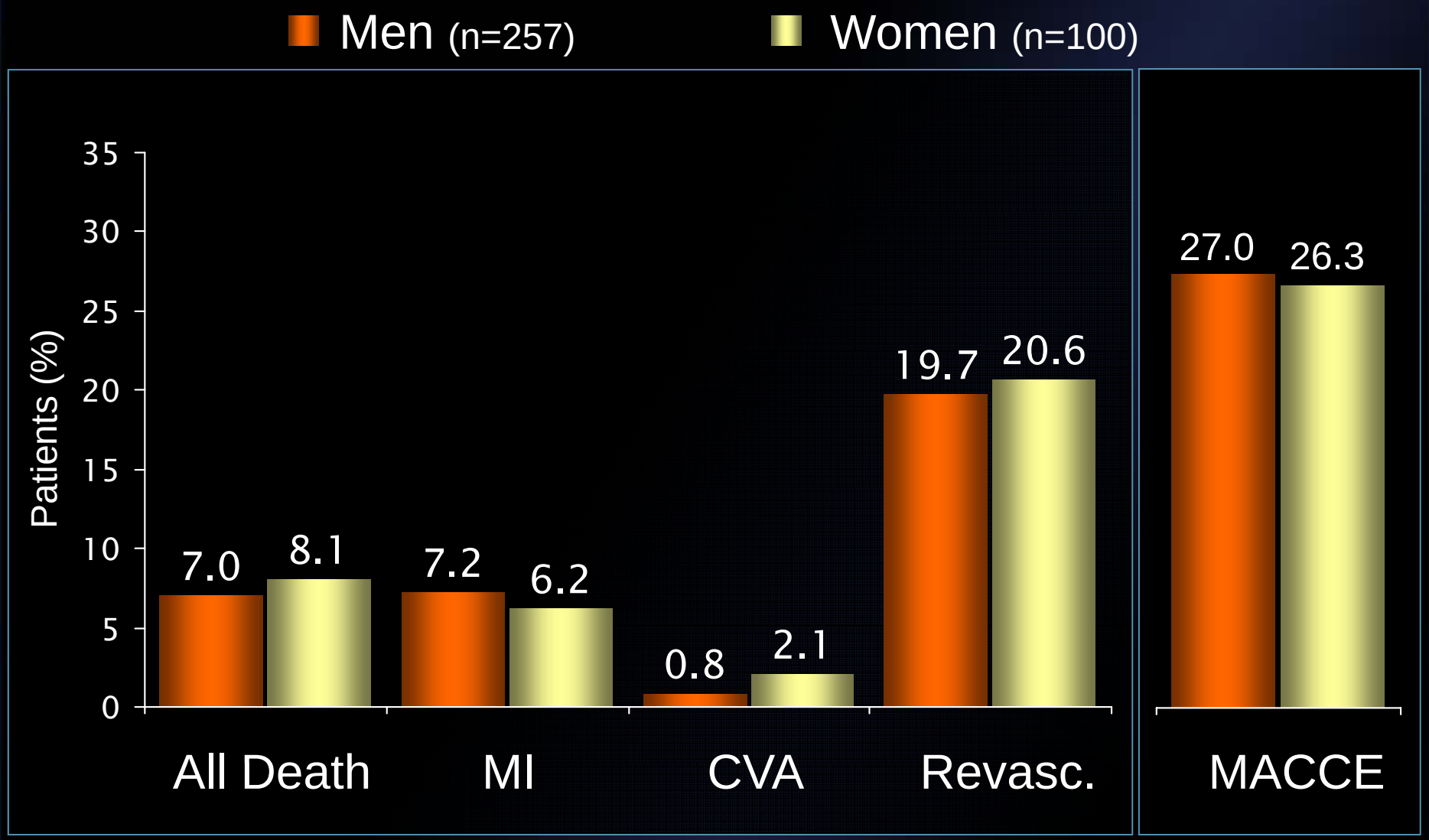
MACCE and Components to 3 Years

CABG arm: Men vs Women (LM lesions)



MACCE and Components to 3 Years

PCI Arm: Men vs Women (LM lesions)



Contemporary Trials of LM PCI vs CABG

Trial*	N	Death	MI	Stroke	Revasc
Sanmartin 2007	341	ND	ND	n/a	CABG better
MAIN-COMPARE 2008	1102				
LEMANS 2008	105				
Palmerini 2006	311				
Chieffo 2006	249		PCI better	PCI better	
Lee 2006	173	ND	ND	ND	ND
Makikallio 2008	287				
Brener 2008	287		n/a	n/a	n/a
White 2008	343				
SYNTAX 2008	705		ND	PCI better	CABG better

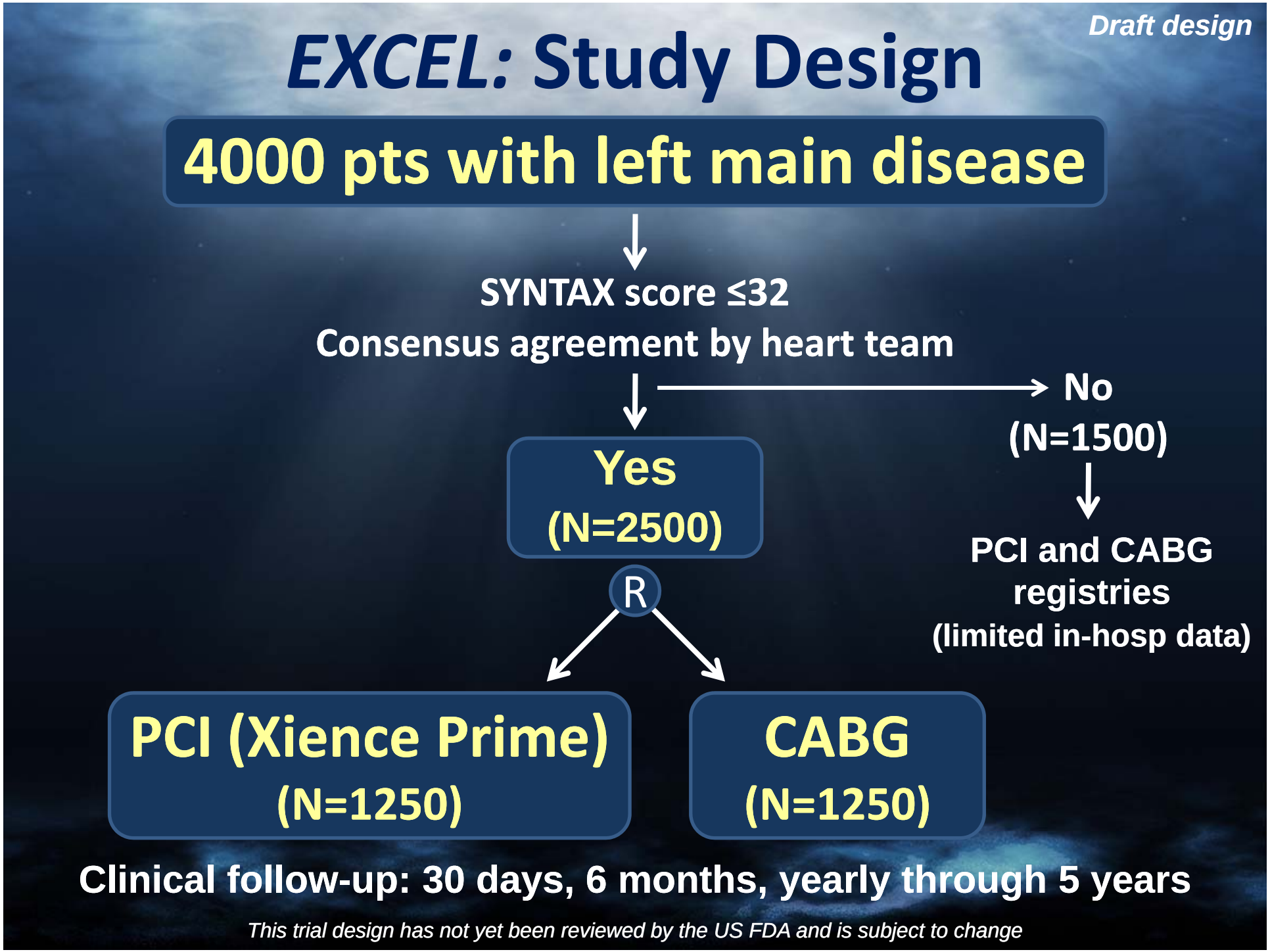
* Studies with >100 patients per arm reported 2000-2008
ND=no difference; n/a=not available/not reported

EXCEL

Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization

What Would an Informative Trial of Left Main DES vs. CABG Look Like?

- It wouldn't be an all-comers trial!
  - Exclude pts who clearly should go to CABG, e.g. high SYNTAX scores
- Optimize PCI technique
  - Pre-specify when/how to use IVUS, staged procedures, RX of distal bifurcation, no routine angio FU, etc.
  - Use the best stent and adjunctive pharmacology
- Optimize CABG technique
  - Minimize waiting time to CABG, maximize pan-arterial revascularization, adjunctive pharmacology, etc.
- Use a meaningful 1º endpoint: Death, CVA or MI
- ~2500 randomized pts


Draft design
EXCEL: Study Design
4000 pts with left main disease
SYNTAX score ≤32
Consensus agreement by heart team
No
(N=1500)
PCI and CABG registries
(limited in-hosp data)
Yes
(N=2500)
R
PCI (Xience Prime)
(N=1250)
CABG
(N=1250)
Clinical follow-up: 30 days, 6 months, yearly through 5 years
This trial design has not yet been reviewed by the US FDA and is subject to change

Draft design

EXCEL: Inclusion Criteria

- Significant LM ds. by heart team consensus
  - Angiographic DS ≥70%, or
  - Angiographic DS ≥50% to <70% with
    - a markedly positive noninvasive study, and/or
    - IVUS MLA <6.0 mm^2, and/or
    - FFR <0.80
- Clinical and anatomic eligibility for both PCI and CABG by heart team consensus
- Silent ischemia, stable angina, unstable angina or recent MI

This trial design has not yet been reviewed by the US FDA and is subject to change

Draft design

EXCEL: Endpoints

- Primary endpoint: Death, MI, or stroke at median follow-up of 3 years
- Major secondary endpoint: Death, MI, stroke or unplanned revascularization at median follow-up of 3 years
  - ❖ Power analysis: Both endpoints are powered for sequential noninferiority and superiority testing
- Quality of life and cost-effectiveness assessments: At regular intervals

This trial design has not yet been reviewed by the US FDA and is subject to change

EXCEL: Organization (i)

- Principal Investigators:
  - Interventional: Patrick W. Serruys, Gregg W. Stone
  - Surgical: A. Pieter Kappetein, Joseph F. Sabik
- Executive Operations Committee:
  - 4 principal investigators, Peter-Paul Kint, Martin B. Leon, Alexandra Lansky, Roxana Mehran, Marie-Angèle Morel, Chuck Simonton, David Taggart, Lynn Vandertie, Gerrit-Anne van Es, Jessie Coe, Poornima Sood, Ali Akavand, Krishnankutty Sudhir, Thomas Engels
- Optimal Therapy Committee Chairs
  - PCI: Martin B. Leon
  - Surgery: David Taggart
  - Medical: Bernard Gersh

EXCEL: Organization (ii)

- Countries and Country Leaders (PCI and CABG)
  - United States: David Kandzari and John Puskas
  - Europe (10): Marie-Claude Morice and David Taggart
  - Brazil: Alex Abizaid and Luis Carlos Bento Sousa
  - Argentina: Jorge Belardi and Daniel Navia
  - Canada: Erick Schampaert and Marc Ruel
  - S. Korea: Seung-Jung Park and Jay-Won Lee
- Statistical Committee
  - Stuart Pocock, Chair
- Data Safety and Monitoring Board
  - Lars Wallentin, Chair
- Academic Research Organizations
  - Cardiovascular Research Foundation and Cardialysis
- Sponsor: Abbott Vascular

EXCEL: Status

- The protocol is finalized
- The site selection process is complete
- FDA meetings and global regulatory submissions are being prepared
- First patient enrolled: 3rd Quarter 2010

Summary

- Coronary artery bypass graft surgery (CABG) remains the clinical standard of care for patients with unprotected left main coronary artery disease
- Society based guidelines do not endorse (Class I recommendation) percutaneous coronary intervention (PCI) of left main disease except for those patients considered ineligible for CABG
- Recently, however, several clinical trials comparing contemporary revascularization of unprotected left main coronary artery disease with drug-eluting stents (DES) versus CABG have challenged this standard .
- Specifically, these studies have demonstrated clinical equipoise between the two revascularization strategies, consistently reporting similar rates of combined safety outcomes including death, myocardial infarction and stroke.

Unresolved Issues:

- Not all L Mains are created equally
- Technique for LM stenting is not standardized
- Use of IVUS imaging to guide stenting not uniform
- No single left main trial has been adequately powered to demonstrate the safety and efficacy of unprotected left main stenting with DES compared to CABG
- Endpoints of interest in pts with LM disease comparing CABG v. PCI is not well delineated
- Duration of follow-up unclear
- Await Results of EXCEL for LM revascularization strategy in the less complex lesion subsets (Syntax score <32)