# Global Evaluation of Left Main PCI
## *The Time Has Come!*

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Angioplasty Summit
TCTAP 2010

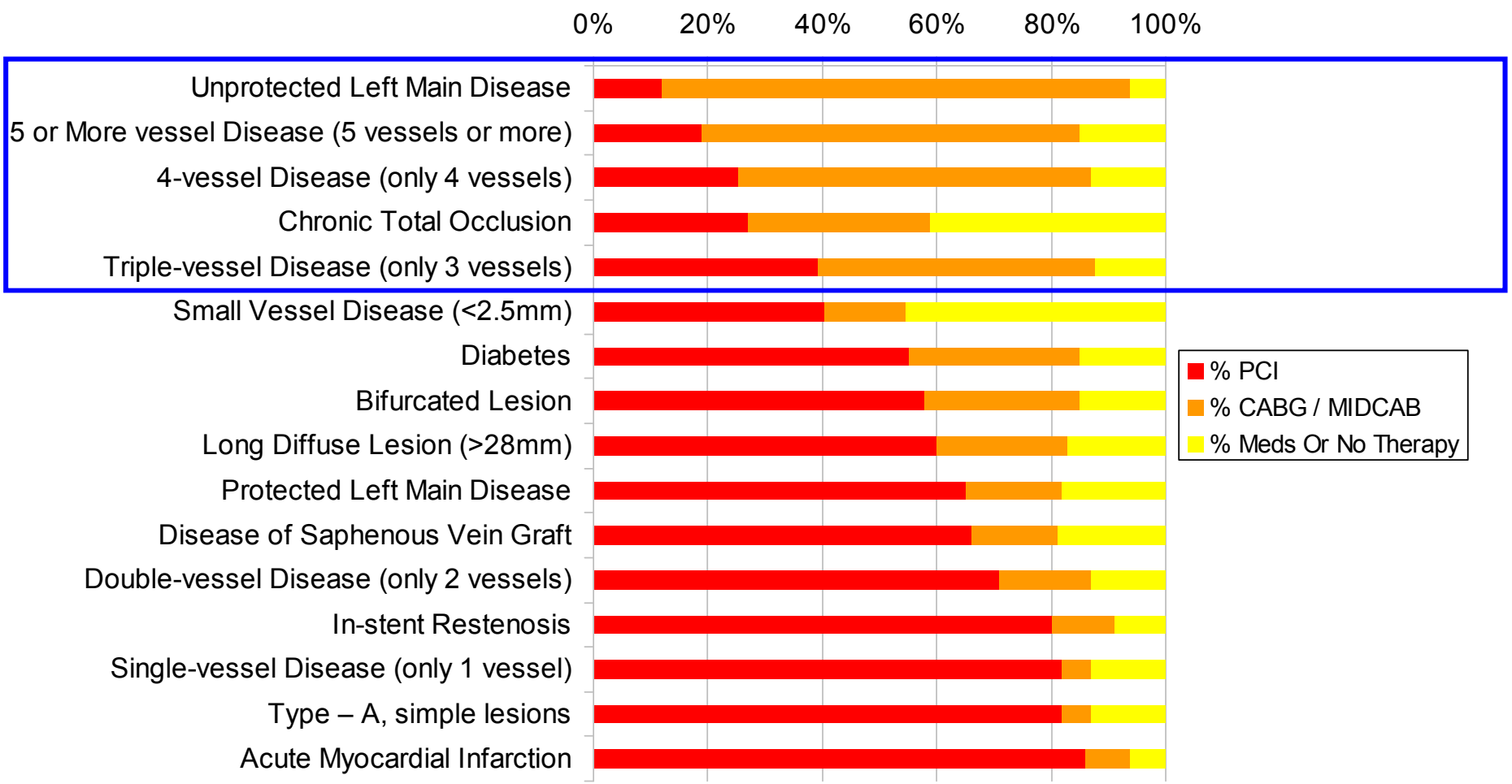
# Disclosures

- Chief Medical Officer
  Divisional Vice President
  Medical Science
  Abbott Vascular
  Santa Clara, California, USA

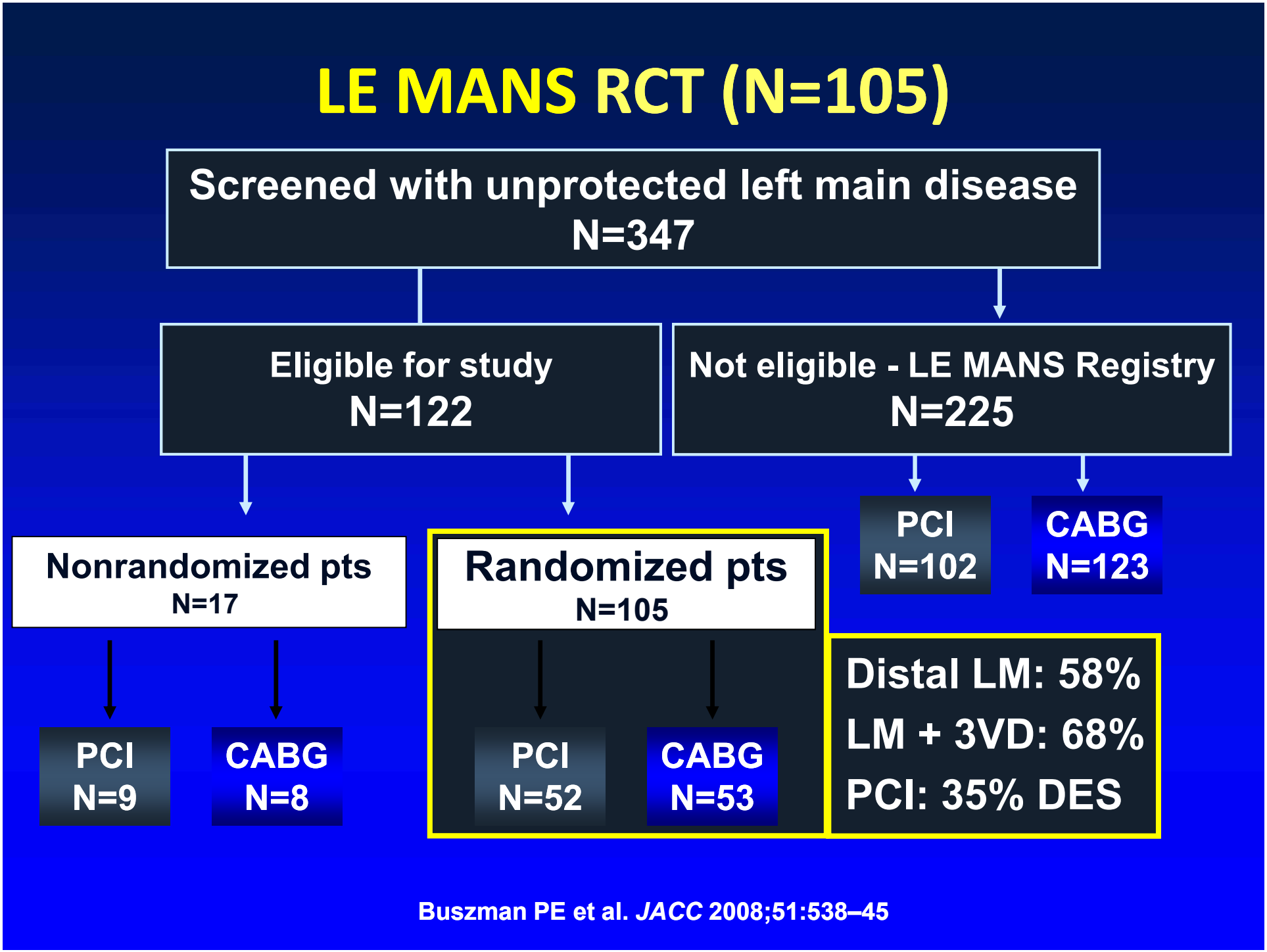
# Overview

- **Left Main Disease is one of the smallest market segments**
  - Left Main Disease accounts for 14% of all patients *diagnosed* with CAD and 4.6% of all patients receiving a DES*
- **PCI is more common for Protected Left Main Disease**
  - Patient with Protected Left Main disease receives PCI 65% of the time and CABG 17% of the time**
  - Patient with Unprotected Left Main disease receives PCI 12% of the time and CABG 82% of the time**
- **DES is more common for Left Main Disease**
  - Patients with Left Main disease receive DES 78% of the time and BMS 14% - 17% of the time***

# Treatment Modality Preference

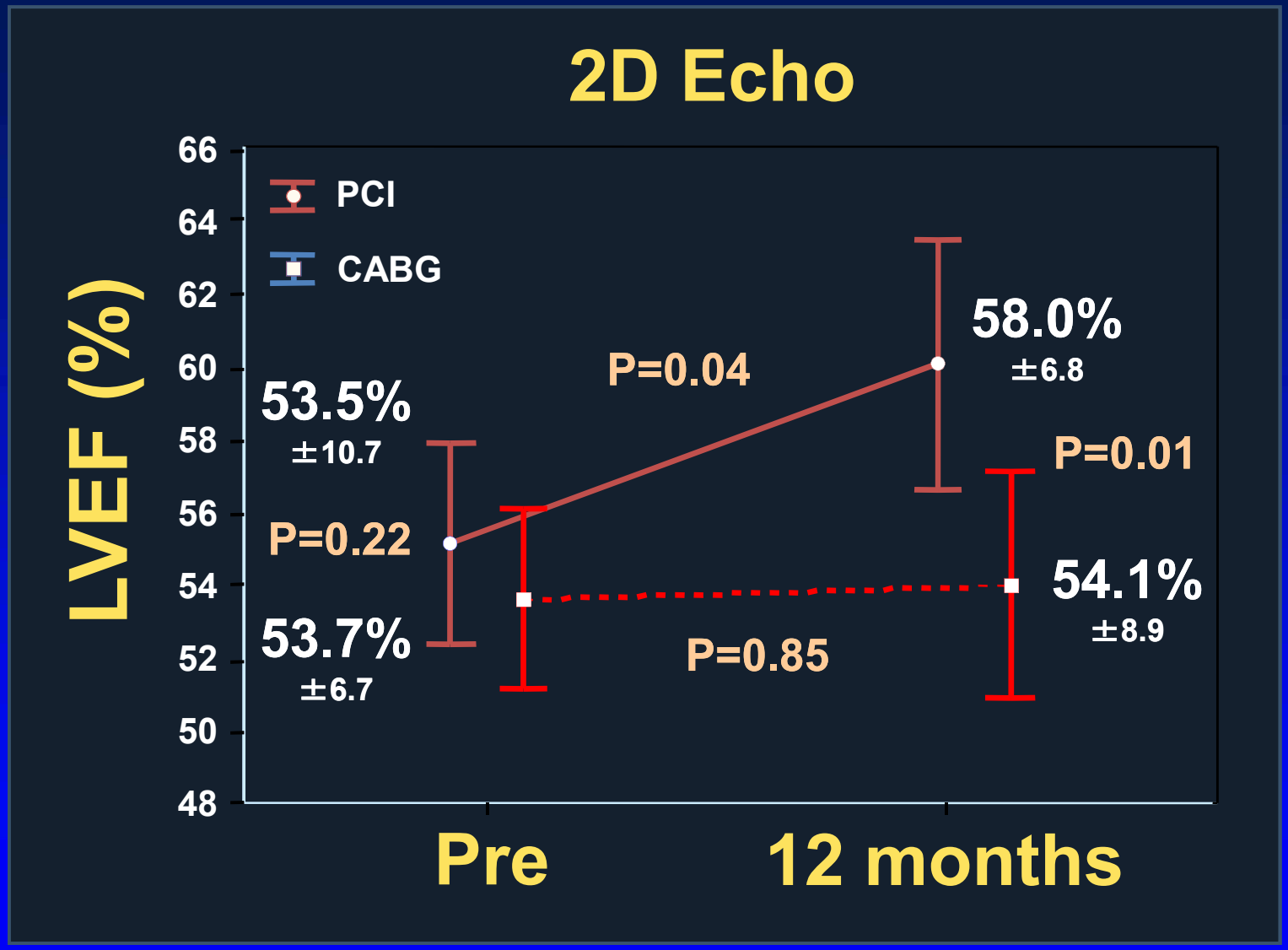


# LE MANS RCT (N=105)




Buszman PE et al. *JACC* 2008;51:538–45

# LE MANS Primary Endpoint: LVEF



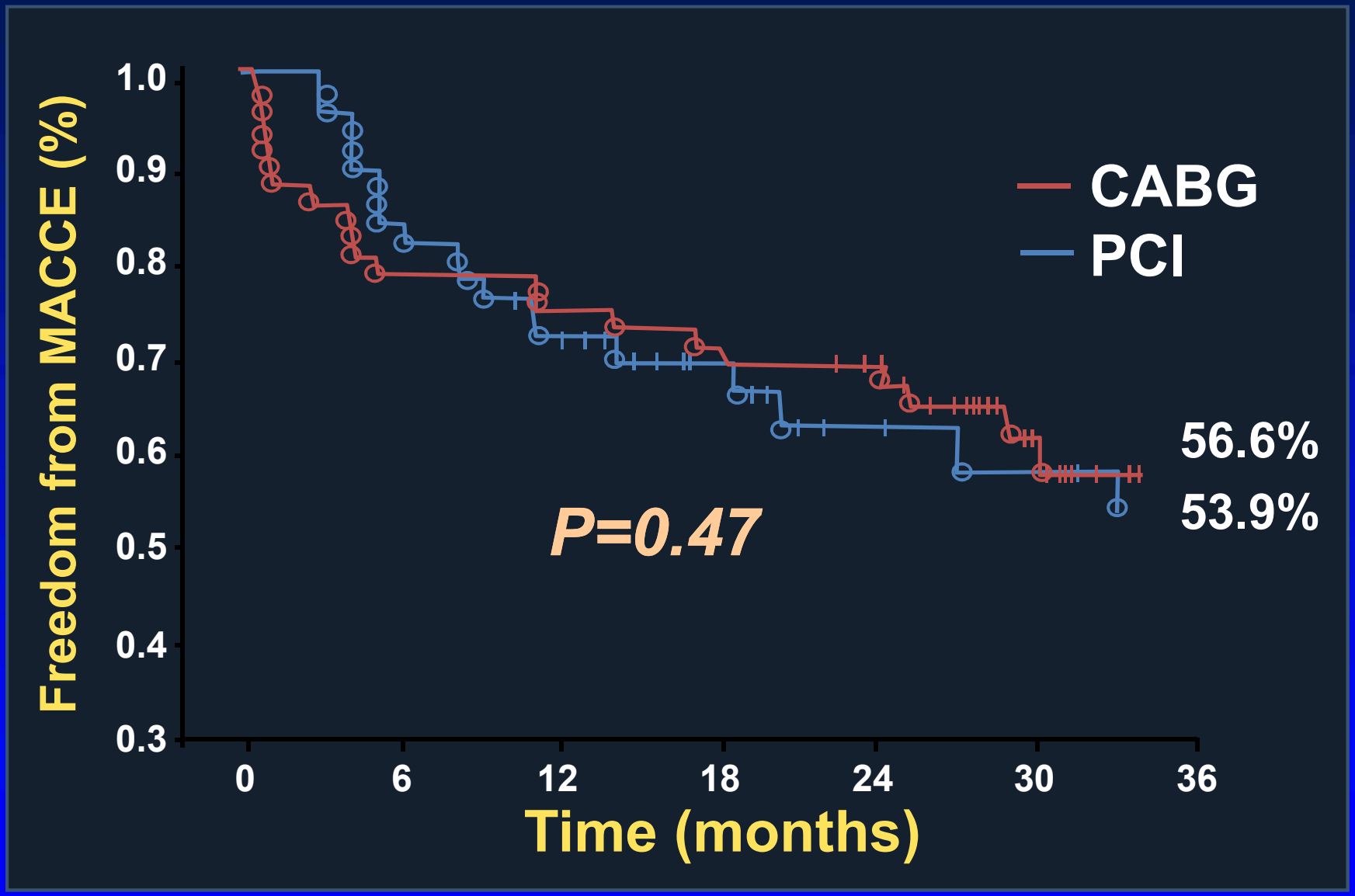

Buszman PE et al. *JACC* 2008;51:538–45

# LE MANS: Adverse Events

| | CABG (n=53) | | PCI (n=52) | |
|---|---|---|---|---|
| | 0 to 30 Days | 0 to 12 Months | 0 to 30 Days | 0 to 12 Months |
| Death | 2 | 4 | 0 | 1 |
| Nonfatal myocardial infarction | 2 | 3 | 1 | 1 |
| Unstable angina | 0 | 3 | 1 | 8 |
| Major bleeding | 3 | 3 | 0 | 0 |
| Stroke | 2 | 2 | 0 | 0 |
| Acute heart failure | 3 | 4 | 2 | 3 |
| Repeat revascularizatin | 0 | 5* | 1 | 15* |
| PCI LM | 0 | 2 | 0 | 5 |
| Other vessel PCI | 0 | 3 | 1 | 9 |
| CABG | 0 | 0 | 0 | 1 |
| Renal insufficiency | 1 | 1 | 0 | 0 |
| Other (infection, post-cardiotomy syndrome, stemal refixation) | 7 | 8 | 0 | 0 |
| Severe arrhythmia (VF, VT, AF) | 3 | 5 | 1 | 3 |
| **Any MACCE** | **7**** | **13** | **1**** | **16** |
| **Any MAE** | **15***** | **24** | **4***** | **20** |

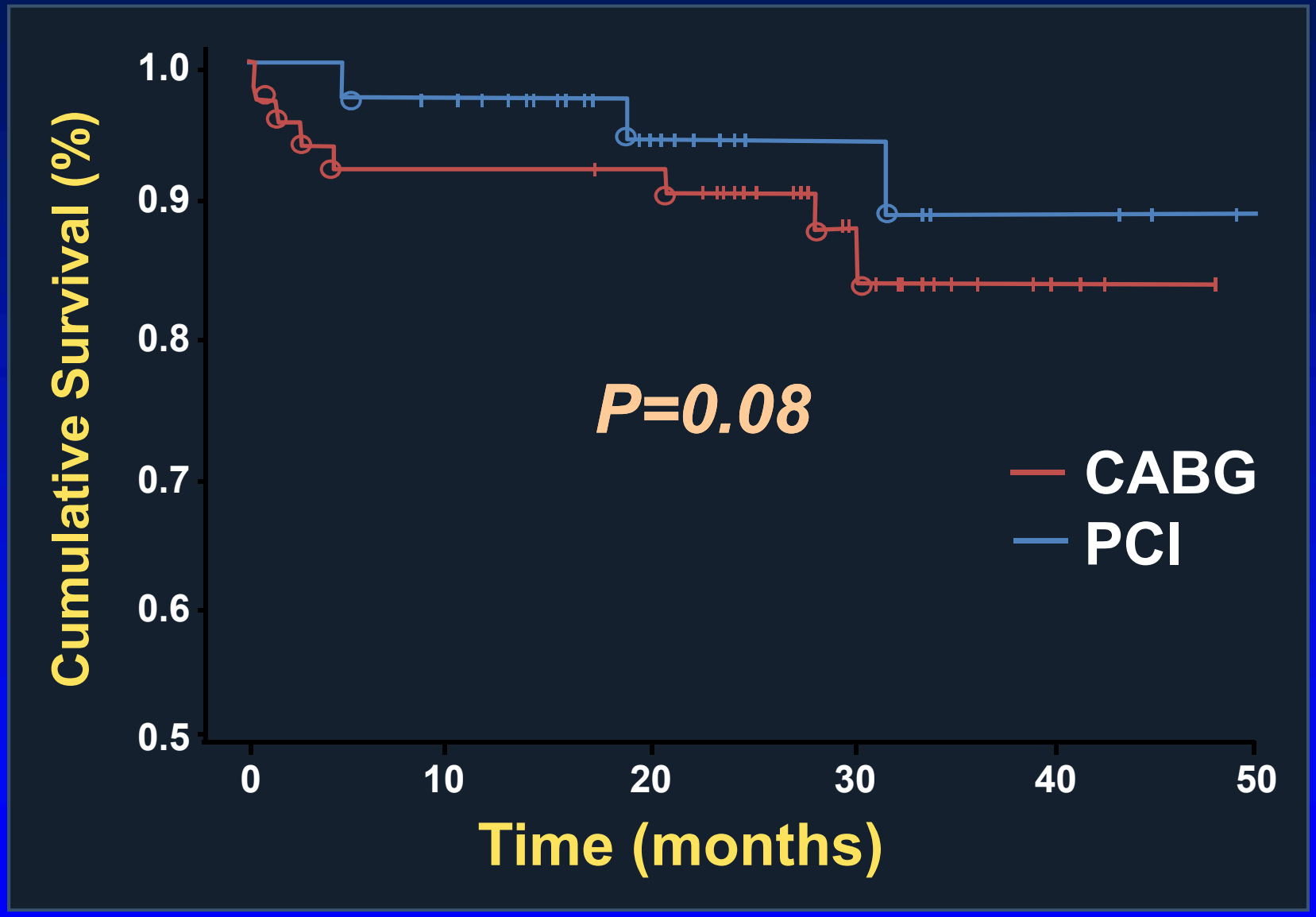
*** p=0.01 **p=0.03 ***p=0.006**

# LE MANS: MACCE (3 years)




Buszman PE et al. *JACC* 2008;51:538–45

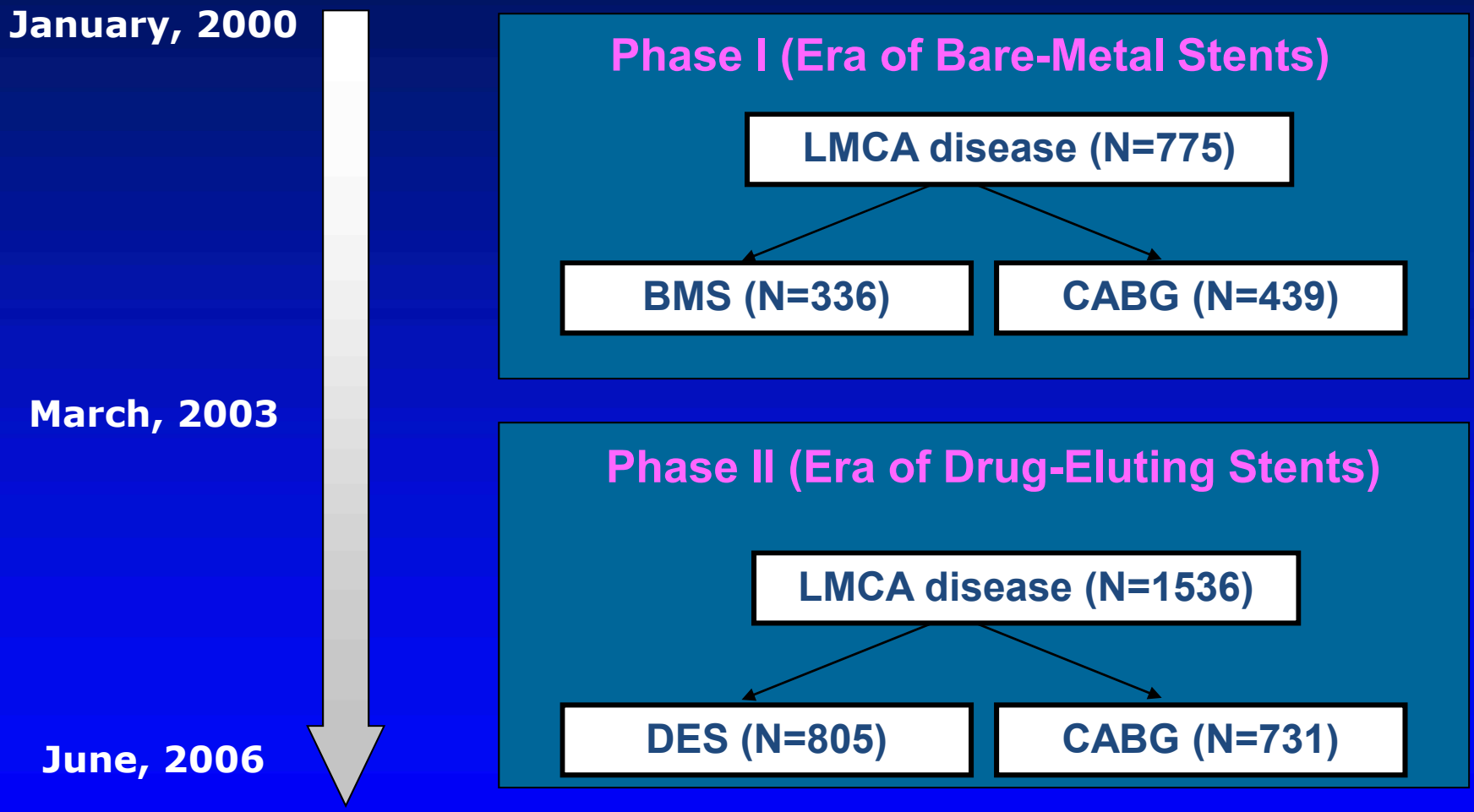
# LE MANS: Mortality (4 years)




Buszman PE et al. *JACC* 2008;51:538–45

# MAIN-COMPARE Registry

## Stenting (BMS vs. DES) vs. CABG




**Total (N=2311)** | **PCI (N=1141)** | **CABG(N=1170)**

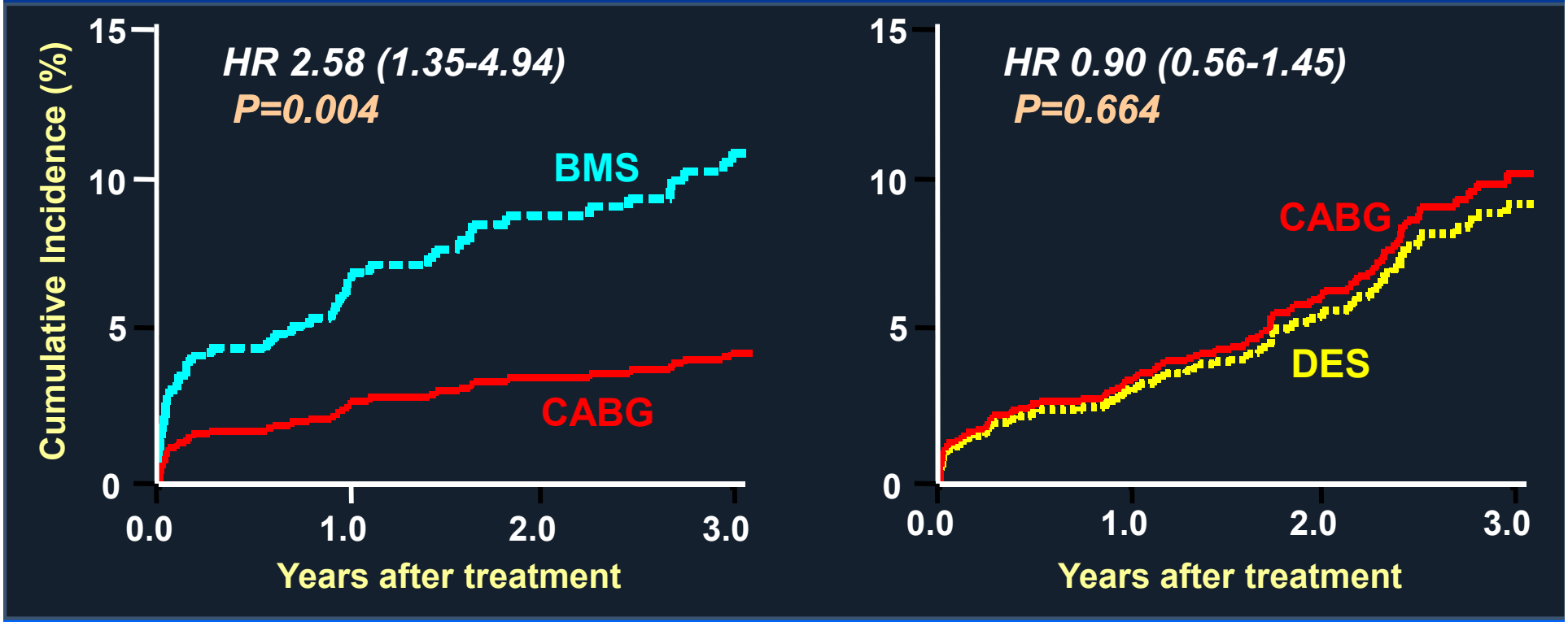
Seung NEJM 2008;358:1781

# Korean Main COMPARE LM Registry

## *Death or Q-wave MI*

Phase I

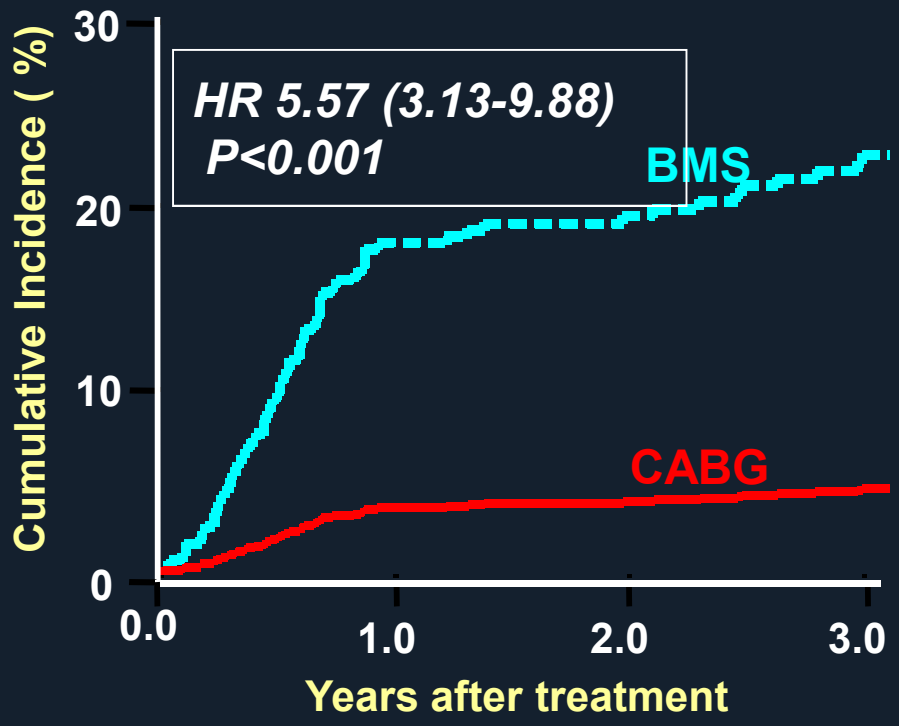
Phase II



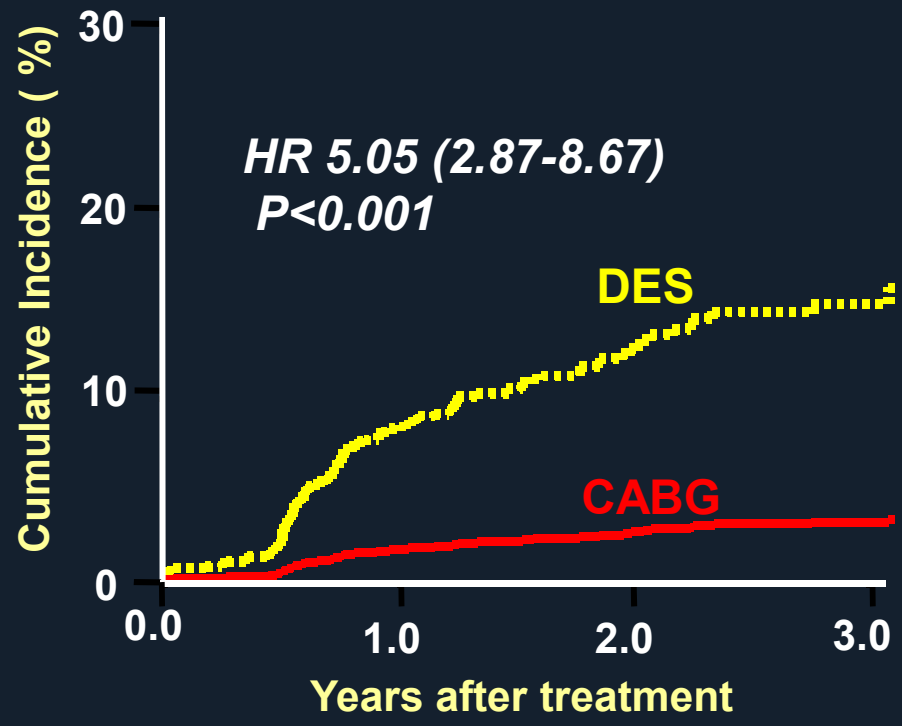

Seung NEJM 2008;358:1781

# Main COMPARE: New Revascularization

## Phase I



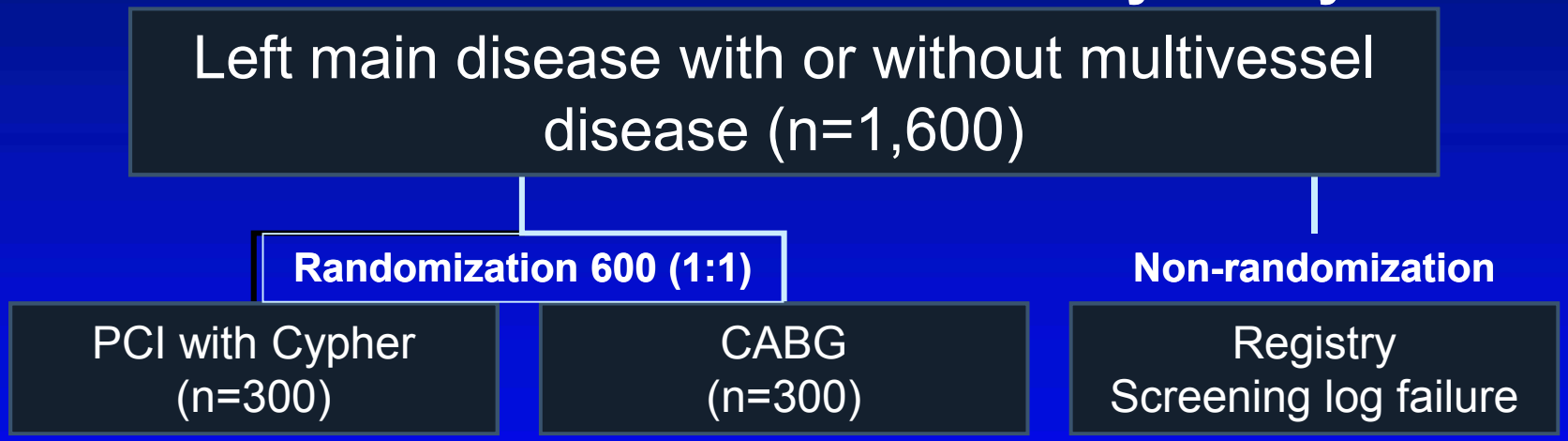

## Phase II




Seung NEJM 2008;358:1781

# PRE-COMBAT

**PREmiere of Randomized COMparison of Bypass Surgery versus AngioplasTy Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease**




**Primary Endpoint: 1-year major cardiac and cerebrovascular event (MACCE) – death, MI, stroke and TVR**

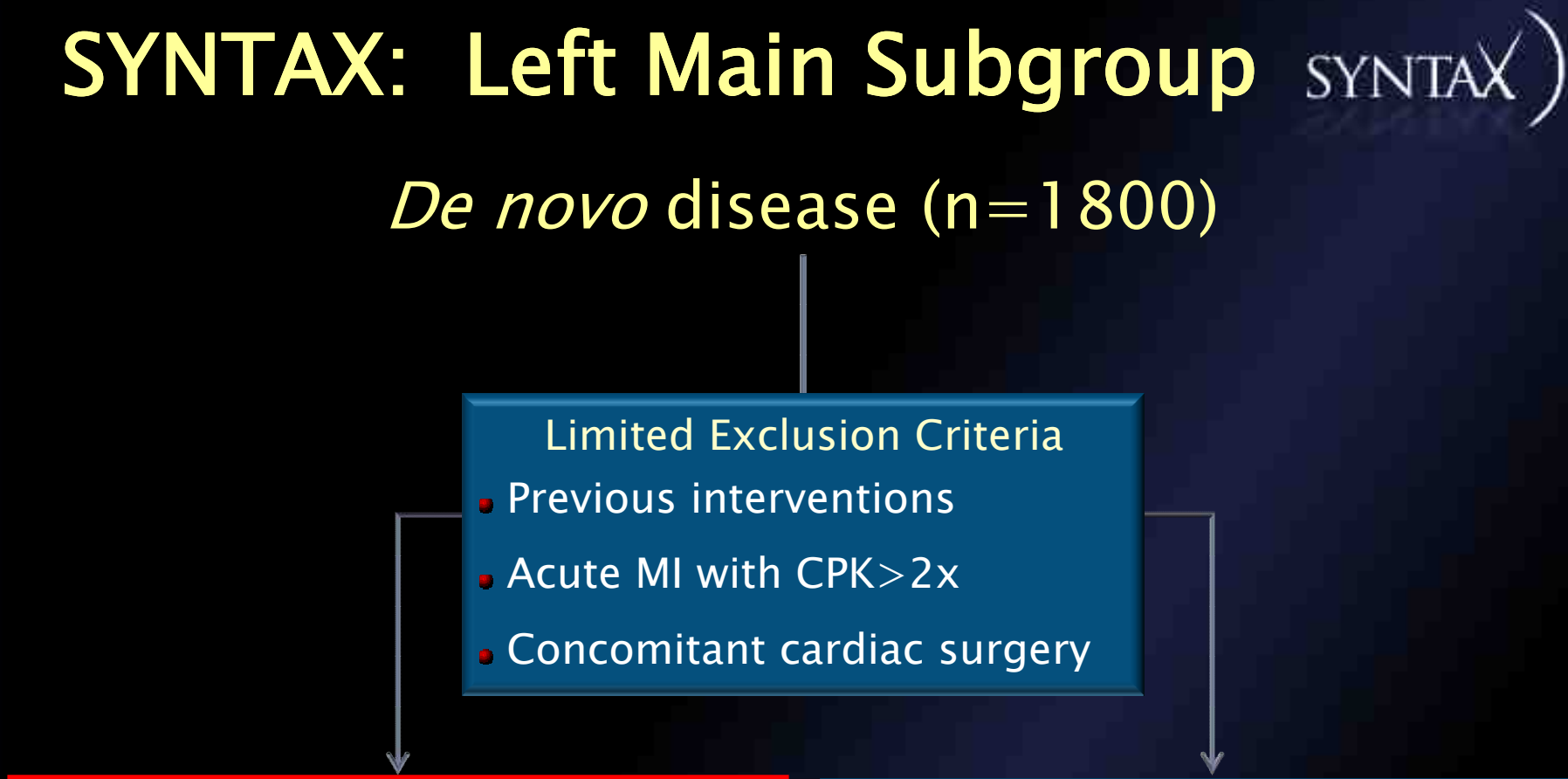
**PI: Seung-Jung Park**
**8 major centers in Korea**

# Pre-COMBAT: Random Group (ITT)

## 1-Year Outcomes (Preliminary Analysis)

| | PCI (n=196) | CABG (n=184) | p |
|---|---|---|---|
| Death | 2 (1.0%) | 5 (2.7%) | 0.347 |
| Cardiac death | 1 (0.5%) | 3 (1.6%) | 0.456 |
| Non-cardiac death | 1 (0.5%) | 2 (1.1%) | 0.612 |
| Myocardial infarction | 9 (4.6%) | 15 (8.2%) | 0.154 |
| Non-Q MI | 9 (4.6%) | 9 (4.9%) | 0.891 |
| Q MI | 0 | 6 (3.3%) | 0.012 |
| Repeat revascularization | 10 (5.1%) | 6 (3.3%) | 0.372 |
| PCI | 9 (4.6%) | 6 (3.3%) | 0.864 |
| CABG | 1 (0.5%) | 0 | 1.000 |
| Stroke | 1 (0.5%) | 0 | 1.000 |
| Total MACCE | 19 (9.7%) | 23 (12.5%) | 0.416 |

# SYNTAX: Left Main Subgroup

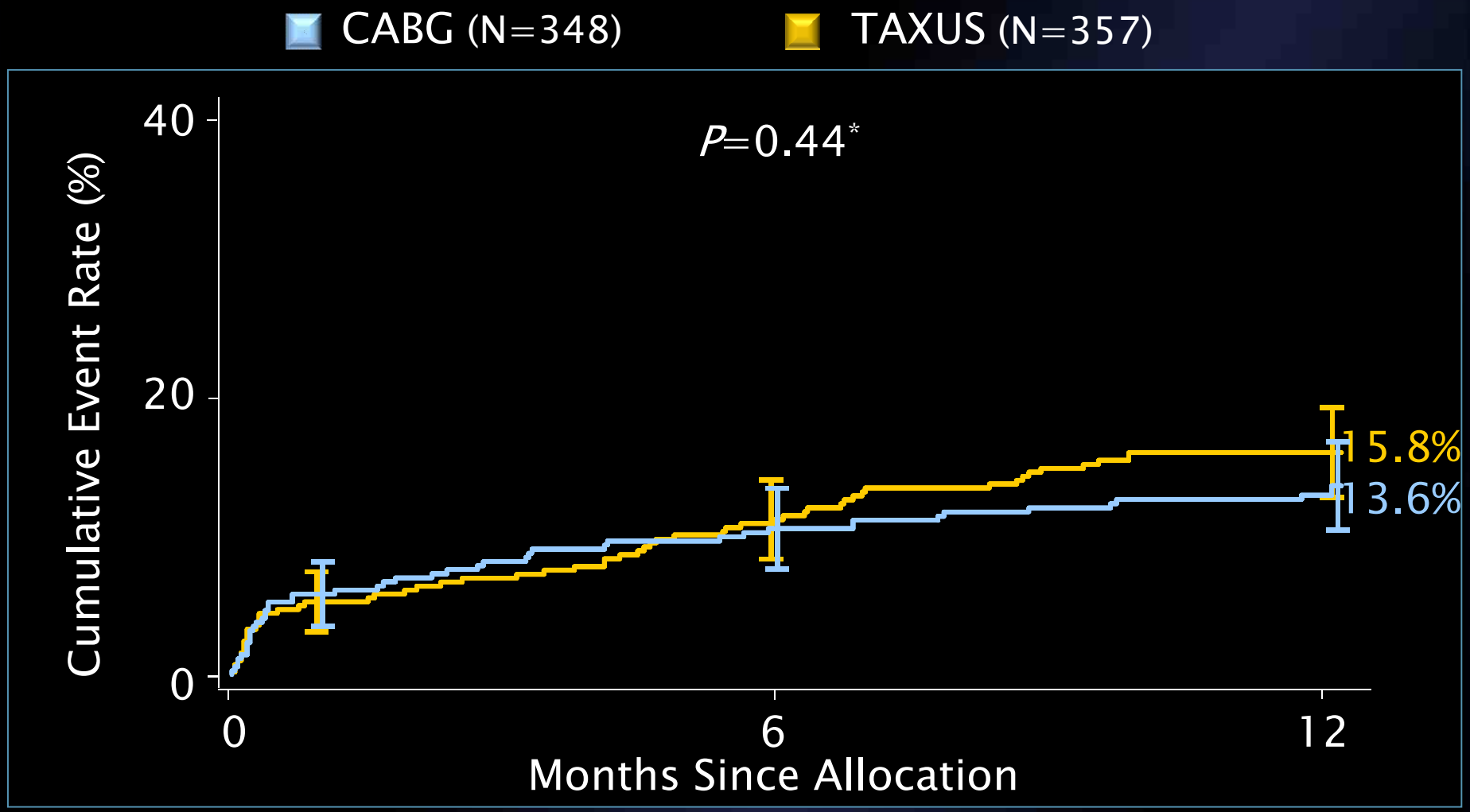



Serruys PW et al. NEJM 2009;360:961-72

# MACCE to 12 Months

## *Left Main Subset*

SYNTAX



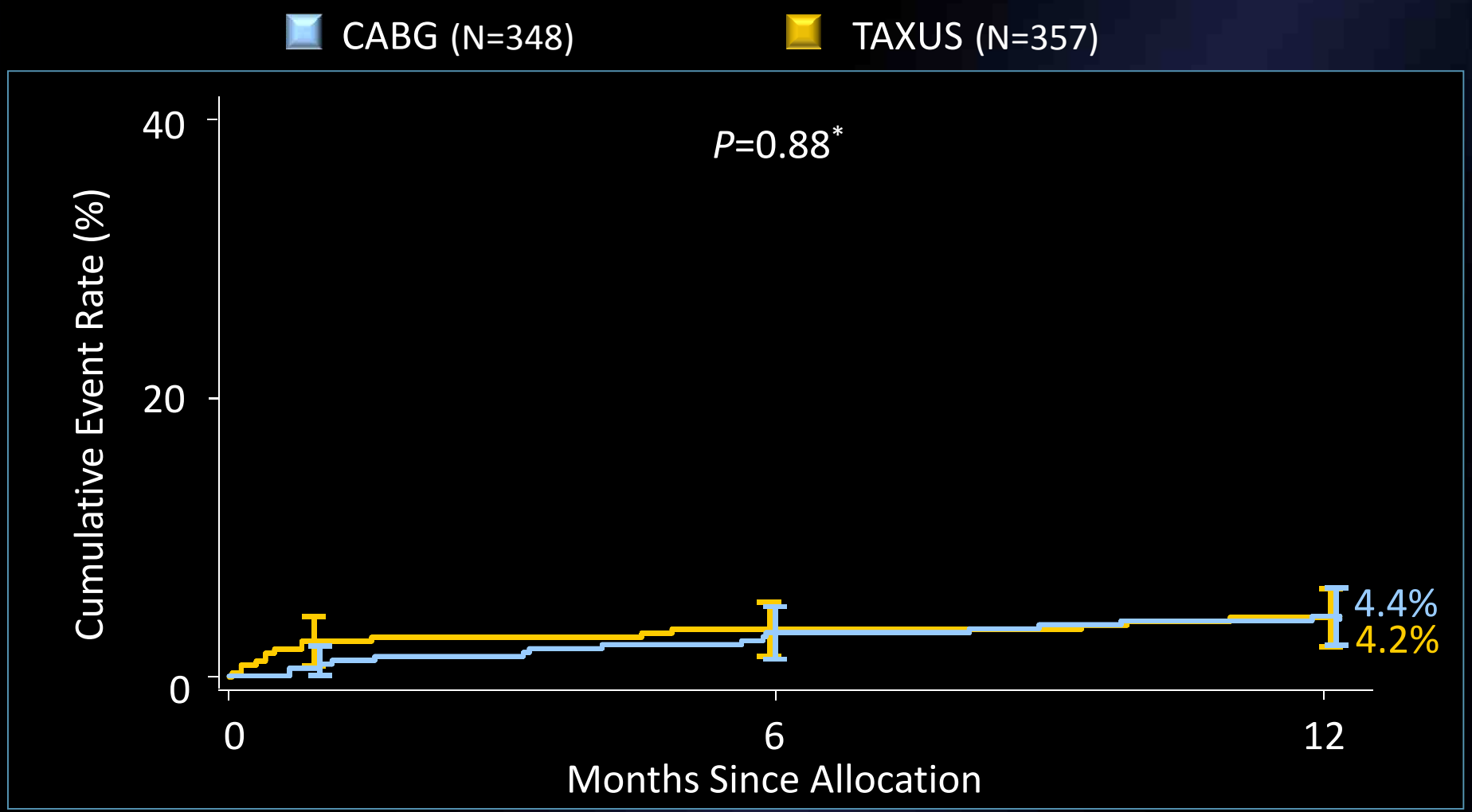

Event rate ± 1.5 SE, *Fisher exact test

ITT population

Serruys PW. TCT 2008

# Death (All-cause) to 12 Months

## *Left Main Subset*



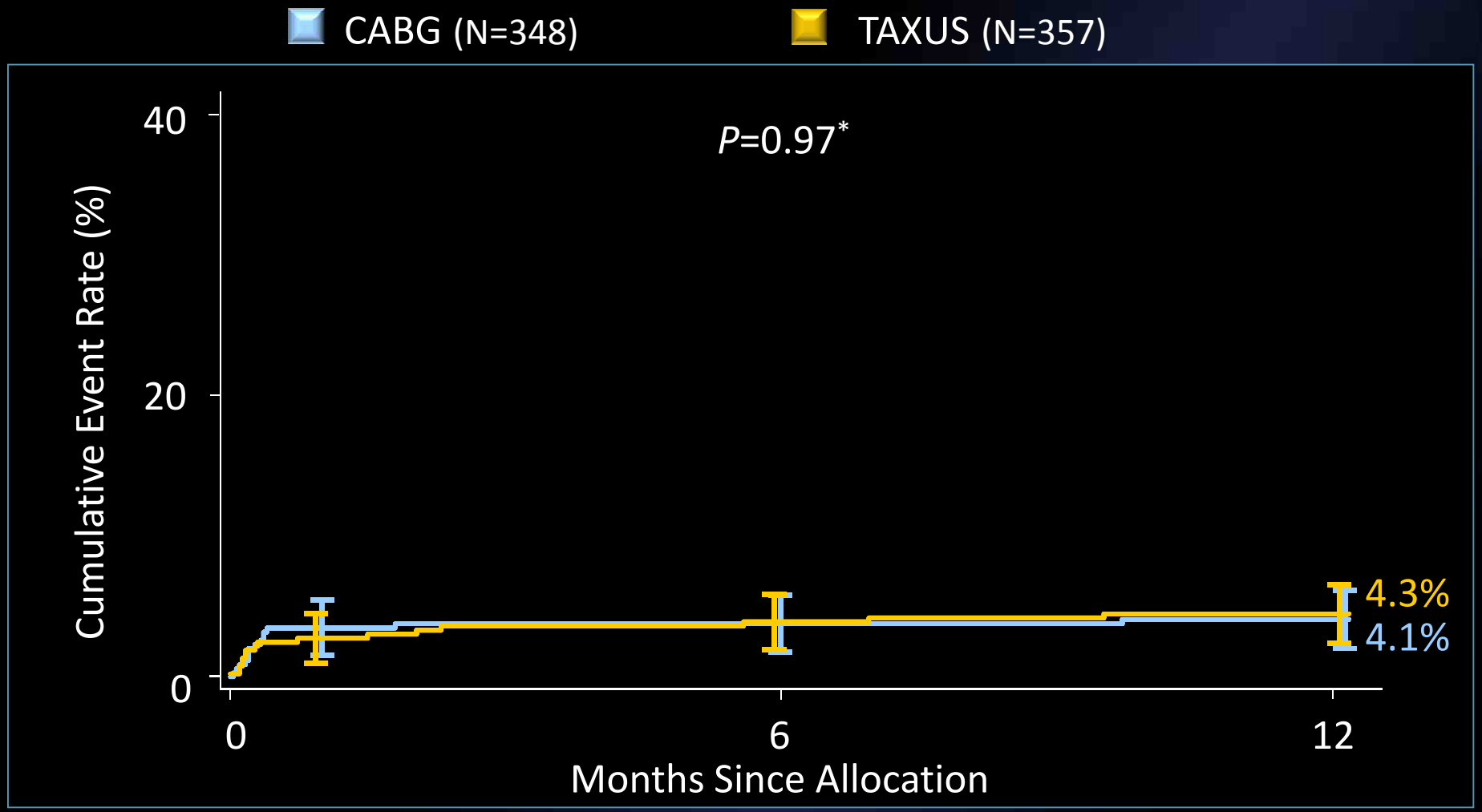

Event rate ± 1.5 SE, *Fisher exact test

ITT population

Serruys PW. TCT 2008

# Myocardial Infarction to 12 Months

## *Left Main Subset*



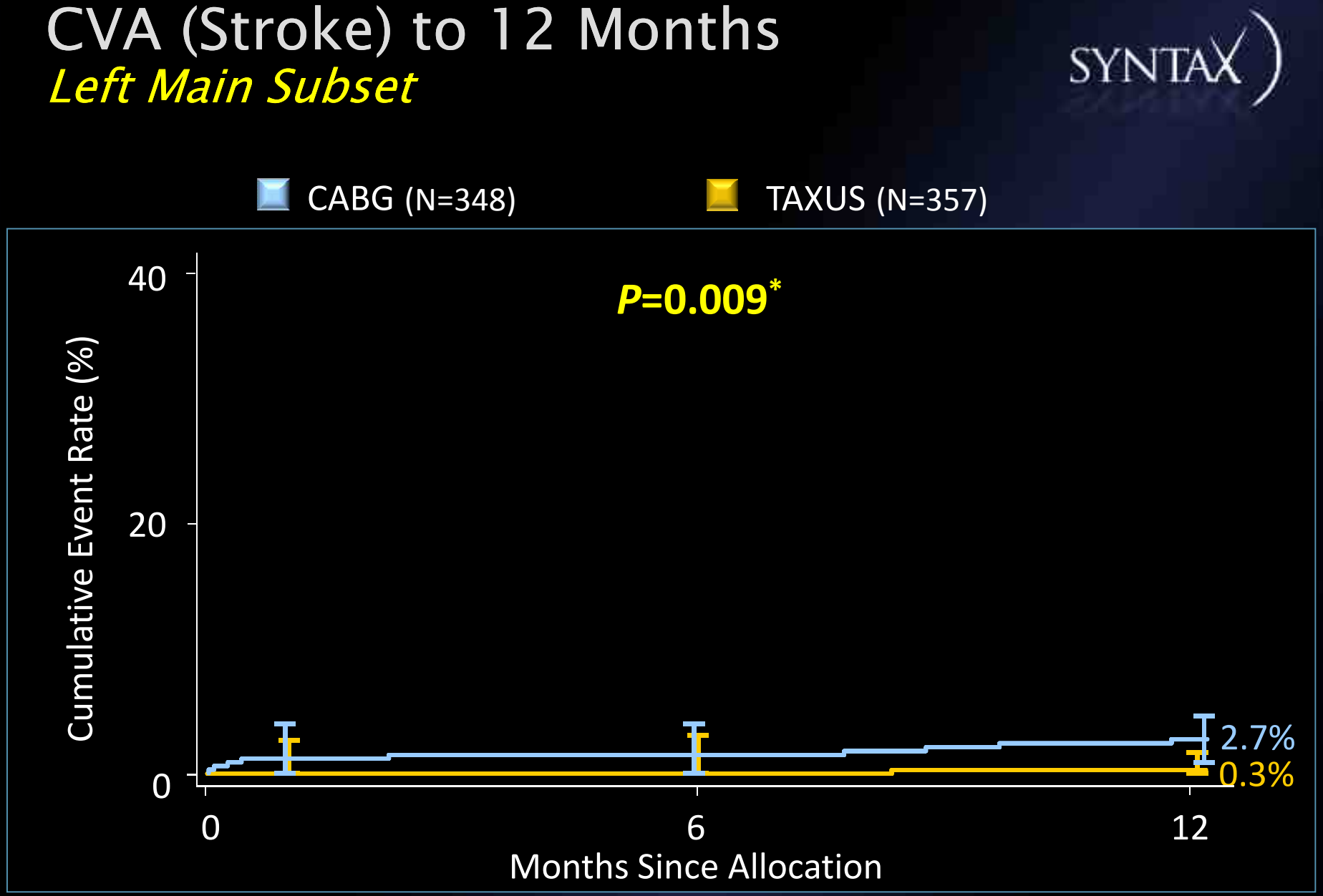

Event rate ± 1.5 SE, *Fisher exact test

ITT population

Serruys PW. TCT 2008

# CVA (Stroke) to 12 Months

## *Left Main Subset*



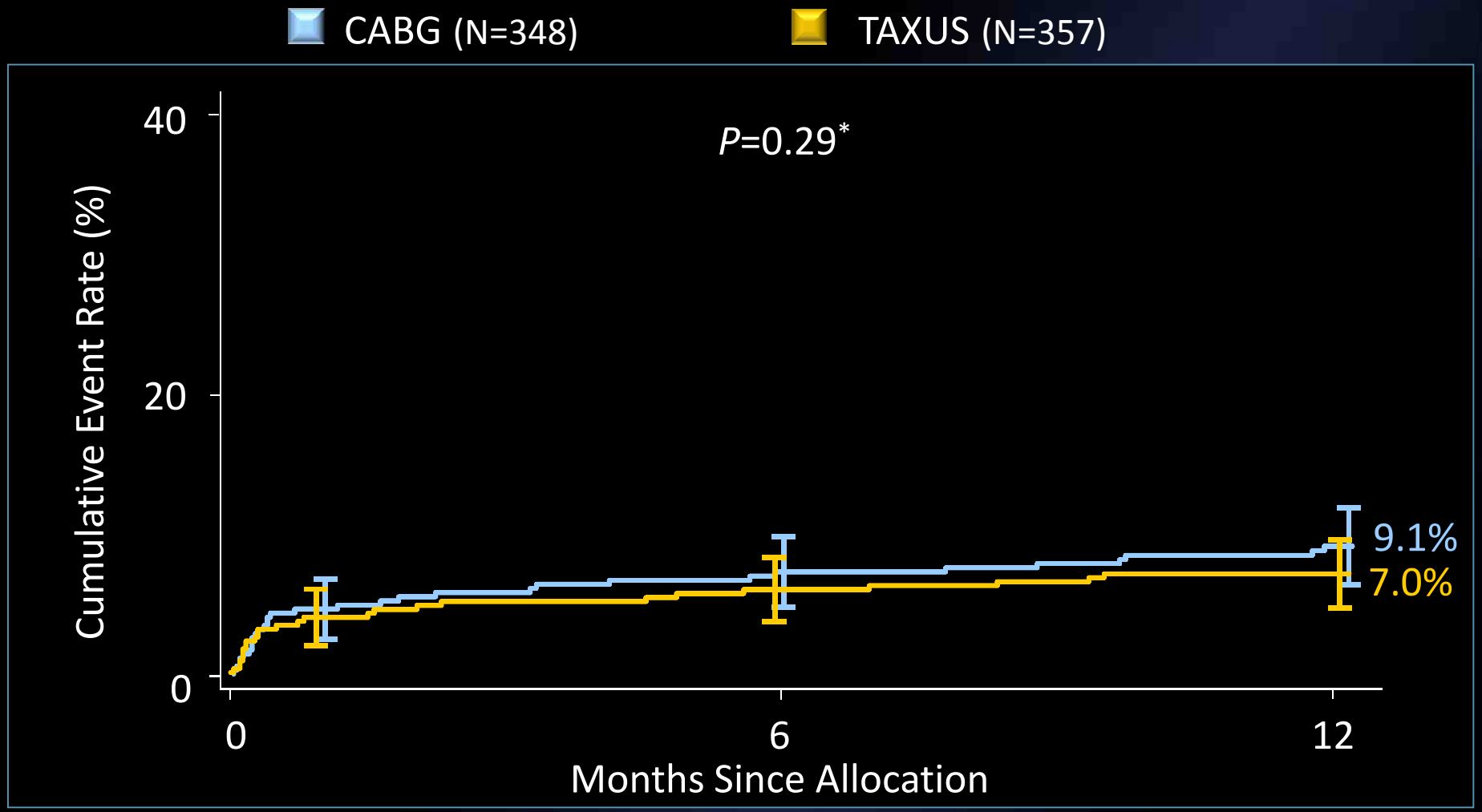

Event rate ± 1.5 SE, *Fisher exact test

ITT population

Serruys PW. TCT 2008

# Death/CVA/MI to 12 Months

## *Left Main Subset*



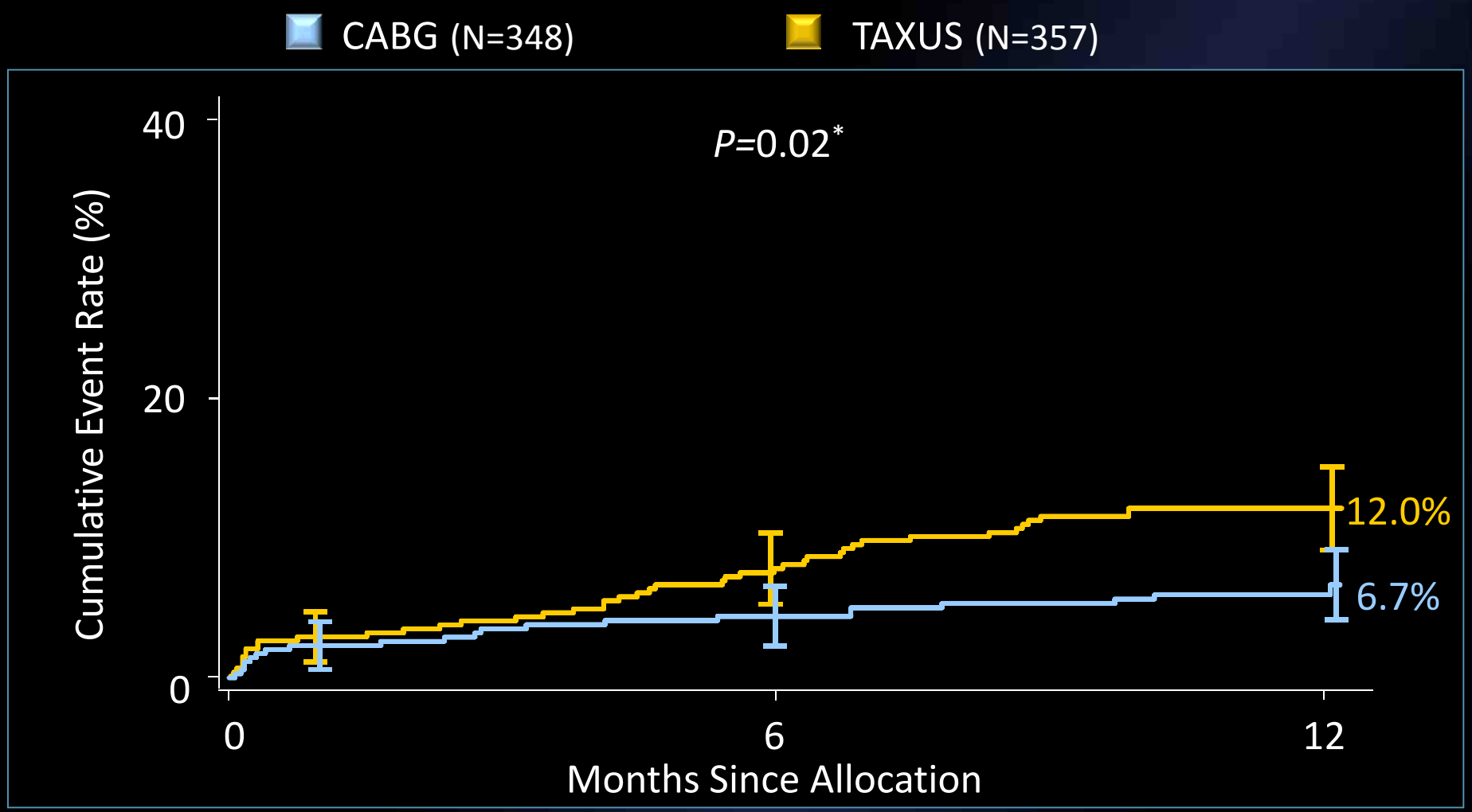

Event rate ± 1.5 SE, *Fisher exact test

ITT population

Serruys PW. TCT 2008

# Revascularization* to 12 Months

## *Left Main Subset*



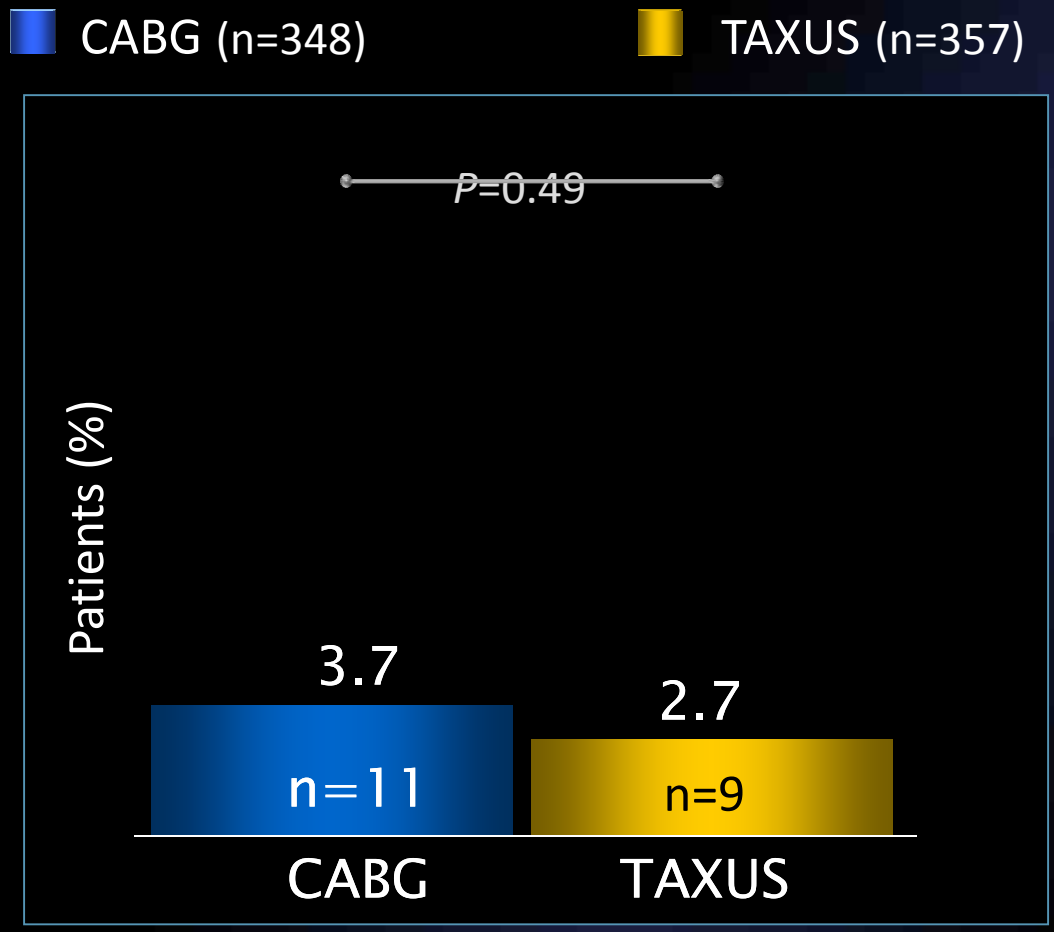

Event rate ± 1.5 SE, *Fisher exact test

*Any revascularization (PCI or CABG); ITT population

Serruys PW. TCT 2008

# Symptomatic Graft Occlusion & Stent Thrombosis to 12 Months

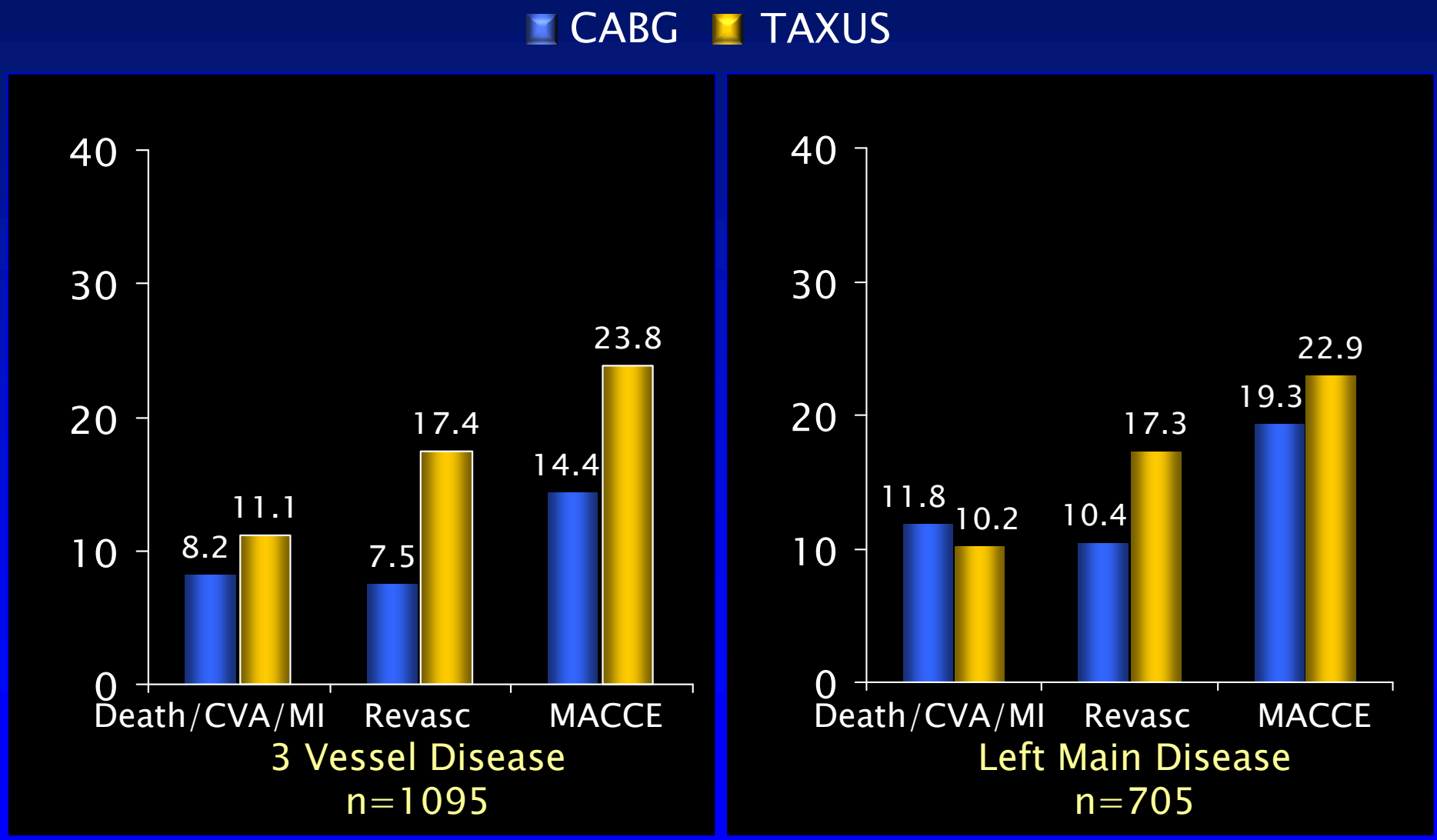
## *Left Main Subset*




Serruys PW. TCT 2008

ITT population

# SYNTAX : 2 Year Outcomes in 3VD and LM Subgroups

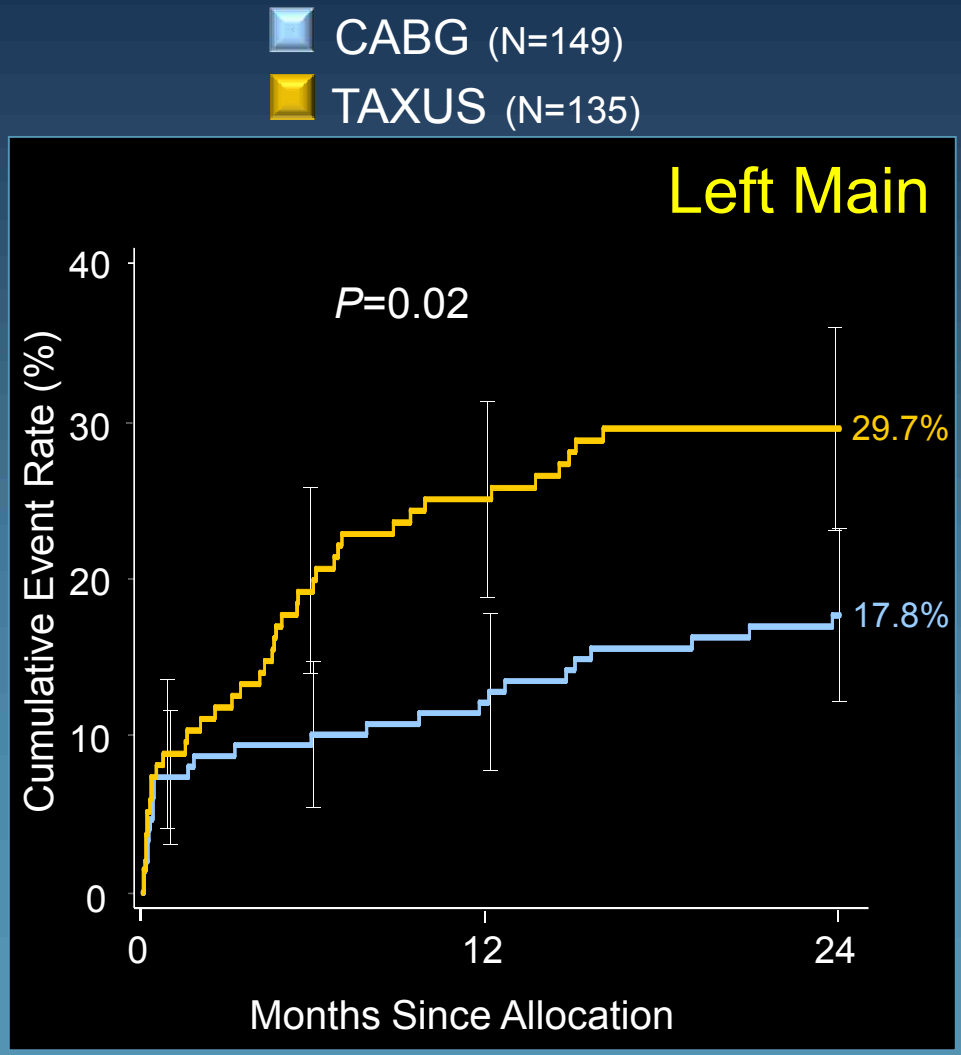



Time-to Event; Log-rank *P* value

ITT population

# SYNTAX: MACCE to 2 Years by SYNTAX Score Tercile *Left Main*

## *SYNTAX Score ≥33*



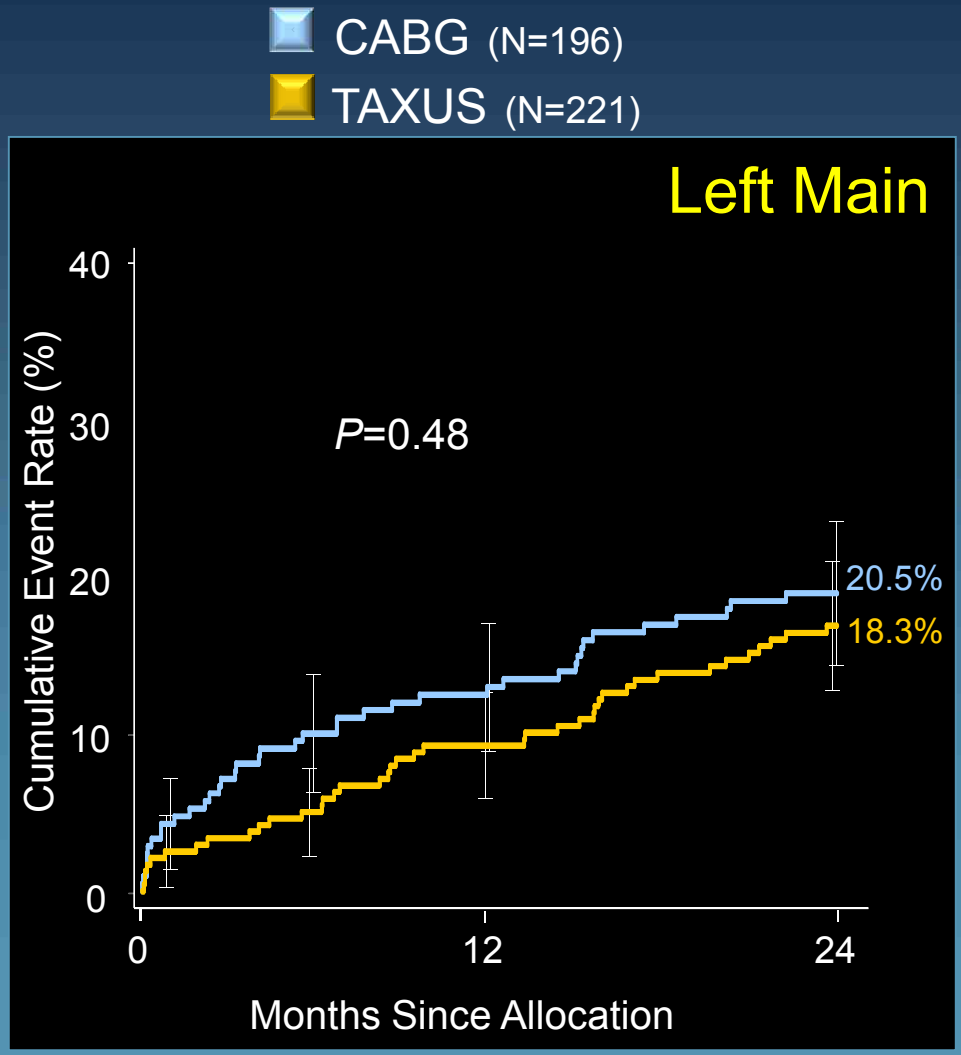

| | CABG | PCI | *P*-value |
|---|---|---|---|
| Death | 4.1% | 10.4% | 0.04 |
| CVA | 4.2% | 0.8% | 0.08 |
| MI | 6.1% | 8.4% | 0.48 |
| Death, CVA or MI | 11.5% | 15.6% | 0.32 |
| Revasc. | 9.2% | 21.8% | 0.003 |

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

Site-reported data; ITT population

# SYNTAX: MACCE to 2 Years by SYNTAX Score Tercile *Left Main*

## *SYNTAX Scores 0–32*




| | CABG | PCI | *P*–value |
|---|---|---|---|
| Death | 7.9% | 2.7% | 0.02 |
| CVA | 3.3% | 0.9% | 0.09 |
| MI | 2.6% | 3.8% | 0.59 |
| Death, CVA or MI | 12.1% | 6.9% | 0.06 |
| Revasc. | 11.4% | 14.3% | 0.44 |

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

Site-reported Data; ITT population

# Impact of Current Studies

- Surgeons (and others) believe CABG is superior, since the primary endpoint of SYNTAX favored surgery
- Interventionalists (and others) believe unprotected LM DES is reasonable in selected patients, offering advantages of less morbidity, fewer strokes and a shorter hospitalization and return to work/ADL with a modest rate of increased revascularization
  - Guidelines committee has advanced PCI to Class IIb (Focused Update 2009)
  - PCI in unprotected LM disease is likely to become much more widely practiced
  - ⇨ Clinical equipoise

# Why was the SYNTAX LM trial not definitive?

- The LM subgroup of SYNTAX was markedly underpowered for the "hard" endpoints of death, MI, or stroke (or even MACCE)
- Both PCI and CABG were suboptimal in SYNTAX

| PCI | CABG |
| --- | --- |
| Multiple strategies were used for the distal bifurcation | Complete arterial revasc 19% |
| Infrequent use of IVUS and FFR | Bilateral IMAs 28% |
| Minimal staging | No touch aortic surgery not emphasized |
| Good stent, but not the best | Complete revasc rates low |
| | Long waiting period to CABG |
| | Suboptimal post CABG medical Rx |

# Do we really need another randomized trial of PCI vs. CABG for LM disease?

- **YES: SYNTAX leaves many questions unanswered**

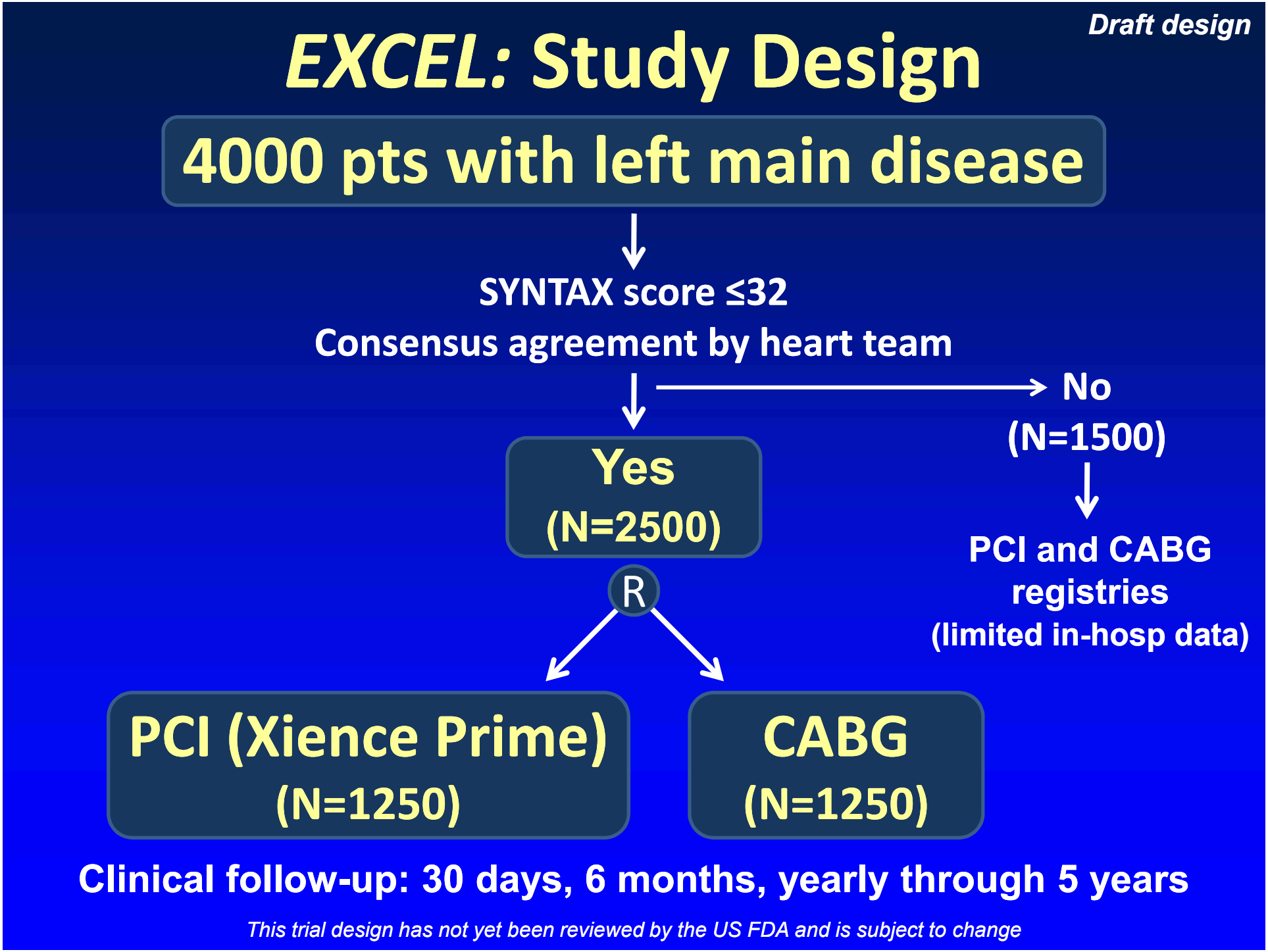
1) SYNTAX suggests (but doesn't prove) that:
   - PCI and CABG for LM ds. have similar rates of death/MI/stroke
   - PCI may be acceptable or superior for certain LM subsets
2) Could the results be further improved with a better DES?
3) What is the optimal approach to the distal bifurcation?
4) Could IVUS and/or FFR improve outcomes?

# 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: D or MI or CVA
- ~2500 randomized pts

*Draft design*

# *EXCEL:* Study Design




*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*

# *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: 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
- Data Safety and Monitoring Board
  - Lars Wallentin, Chair
- Academic Research Organizations
  - Cardiovascular Research Foundation and Cardialysis
- Sponsor: Abbott Vascular

# *EXCEL:* Status

- After 11 months of formal preparation the protocol is nearly finalized
- The site selection process is underway
- FDA pre-IDE meeting is scheduled for this month and global regulatory filings are being prepared
- First patient enrolled: 3rd Quarter 2010