



## Debate: Treatment of Multivessel disease

Interventionalist Perspective:  
the Treatment Pathway was shifted

Alaide Chieffo, Antonio Colombo

*S. Raffaele Hospital and EMO Centro  
Cuore Columbus, Milan, Italy*

## DES vs. Coronary Artery Bypass Grafting in Multivessel Coronary Disease: New York State Registry

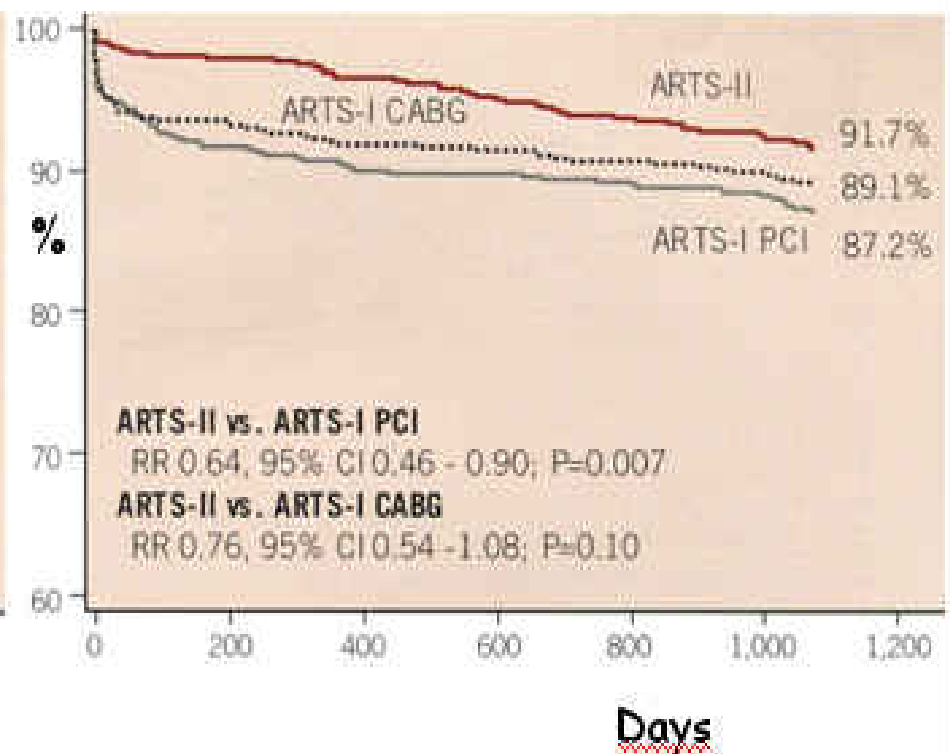
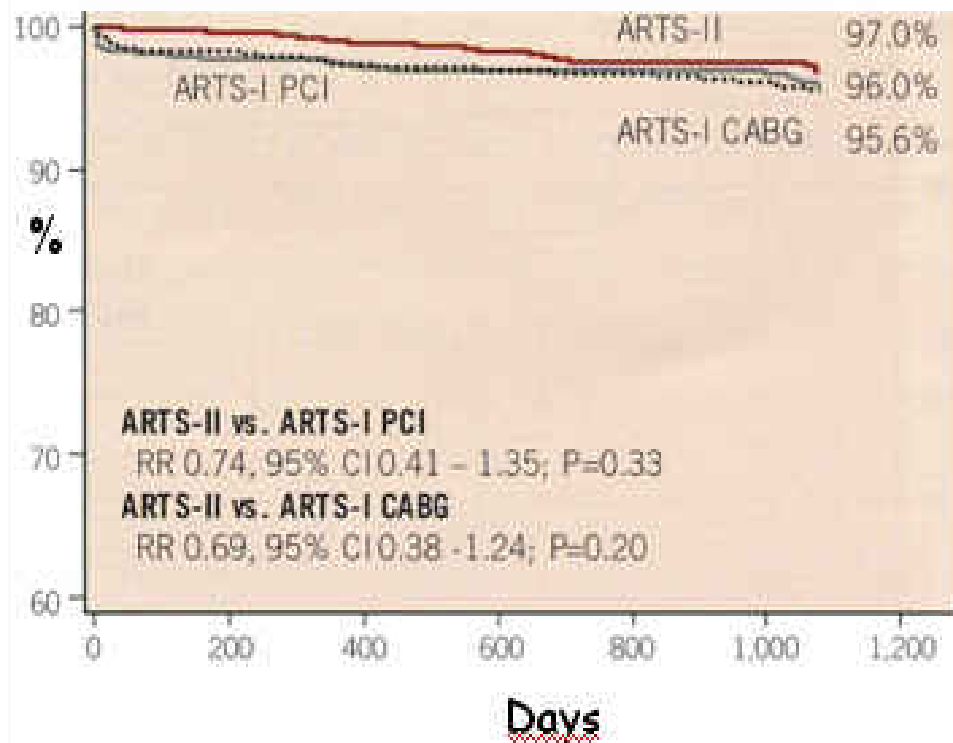
18-Month Follow-up	CABG	DES	P Value
<b>Pts. with 3-vessel disease</b>			
Survival, %	94	93	0.03
Survival free of MI, %	92	90	<0.001
<b>Pts. with 2-vessel disease</b>			
Survival, %	96	95	0.003
Survival free of MI, %	94	92	<0.001



# 3 Years survival outcome

All Cause  
Survival

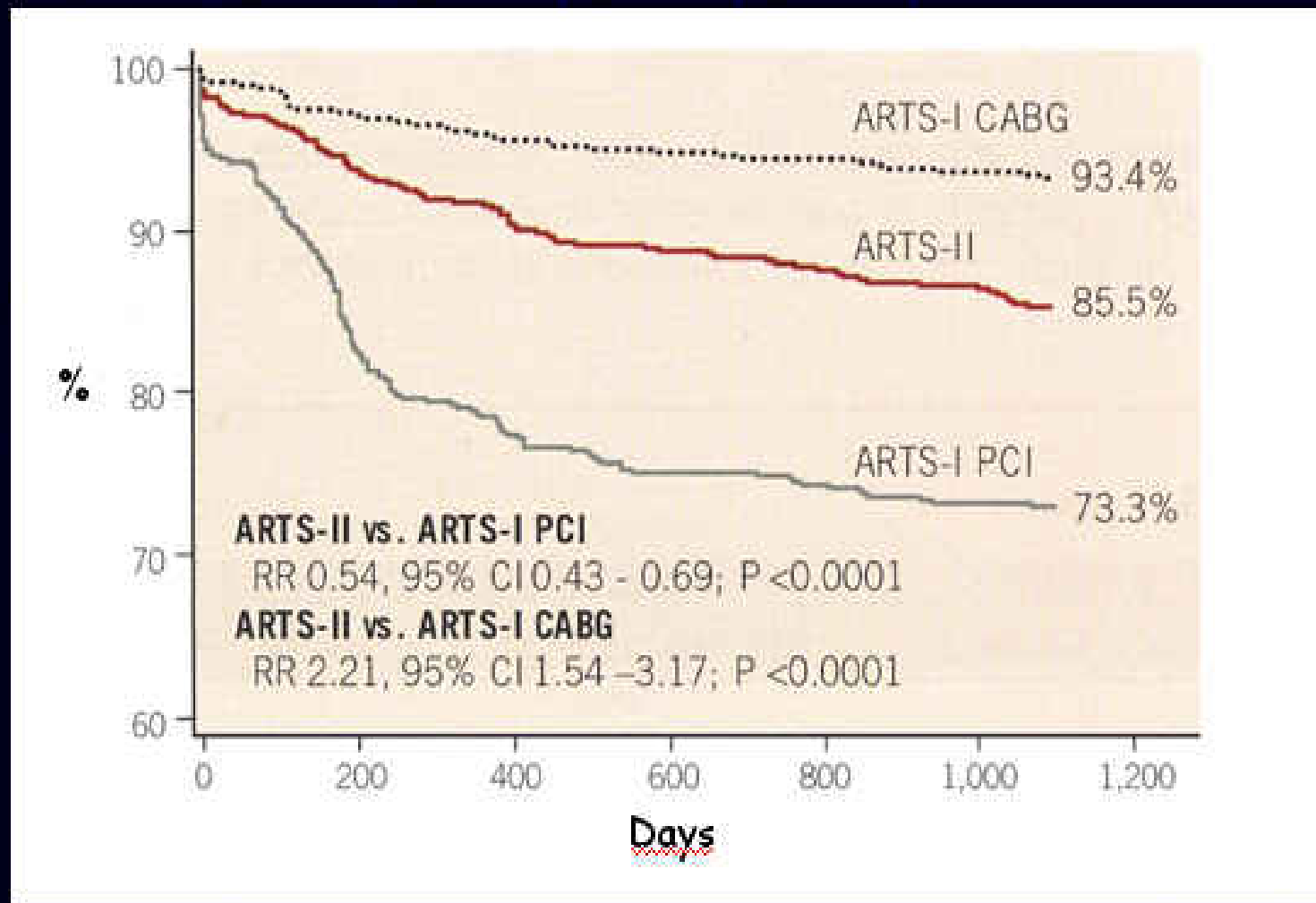
Freedom from All Cause  
Death, CVA or MI



## ARTS I-II Kaplan-Meier curves

# 3 Years survival outcome

## Freedom from Repeat Revascularization



# Meta-analysis of PCI vs. CABG for Multivessel Disease

5-year patient-level analysis of ARTS, SoS, ERACI-II, and MASS-II

Events at 5 Years	PCI (n = 1,518)	CABG n = 1,533)	HR (95% CI)	P Value
Death	8.5%	8.2%	0.95 (0.73-1.23)	NS
Stroke	3.1%	3.6%	1.16 (0.73-1.83)	NS
MI	7.3%	7.6%	0.91 (0.68-1.23)	NS
Repeat Revascularization	29.0%	7.9%	0.23 (0.18-0.29)	<0.001
Death, Stroke, MI, or Repeat Revasc	39.2%	23.0%	0.53 (0.45-0.61)	<0.001



## CABG vs PCI in MV

a collaborative analysis of individual patient data from 10 randomised trials.

N= 7812 pts

Median follow-up of 5.9 years (IQR 5.0-10.0),

	PCI (n = 3923)	CABG n = 3889)	HR (95% CI)	P Value
Death	16%	15%	0.91 (0.82-1.02)	0.12

In patients **with diabetes** (CABG, n=615; PCI, n=618), mortality was lower in the CABG group (HR 0.70, 0.56-0.87); mortality was similar in patients **without diabetes** (HR 0.98, 0.86-1.12; p=0.014 for interaction).

**Patient age** modified the effect of treatment on mortality, with hazard ratios of 1.25 (0.94-1.66) in patients younger than 55 years, 0.90 (0.75-1.09) in patients aged 55-64 years, and 0.82 (0.70-0.97) in patients 65 years and older (p=0.002 for interaction).

*Hlatky et al Lancet 2009*

# SYNTAX Trial Design

62 EU Sites + 23 US Sites

Heart Team (surgeon & interventionalist)

Amenable for both treatment options

Amenable for only one treatment approach

Stratification:  
LM and Diabetes

*Randomized Arms*  
N=1800

*Two Registry Arms*  
N=1275

CABG  
N=897

vs

TAXUS<sup>®</sup>  
N=903

CABG  
N=1077

PCI  
N=198

DM  
28.5%

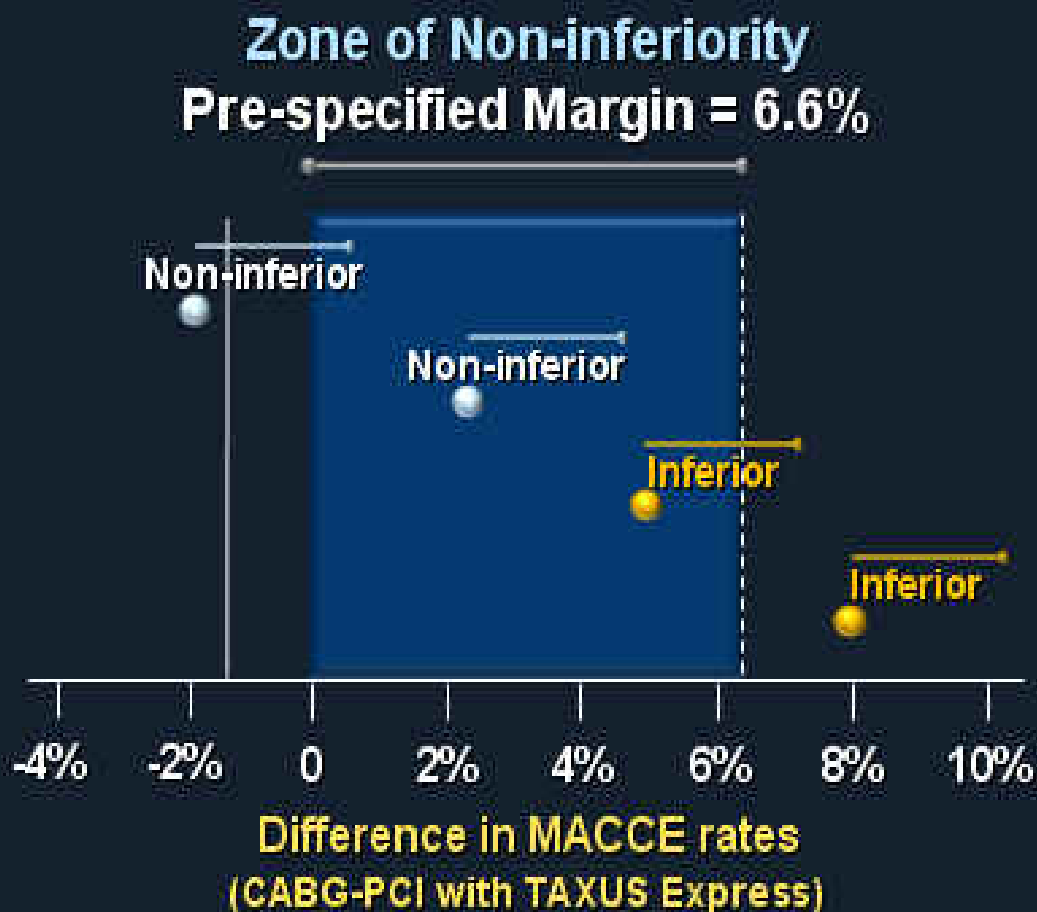
Non DM  
71.5%

DM  
28.2%

NonDM  
71.8%

TAXUS Express

# SYNTAX: Primary Endpoint (12 Month MACCE): Non-inferiority to CABG



● Difference in MACCE rates

— Upper 1-sided 95% confidence intervals



# SYNTAX: Patient Characteristics (I)

## Randomized Cohort

<i>Patient-based</i>	<b>CABG</b> N=897	<b>TAXUS</b> N=903
Age, mean $\pm$ SD (y)	65.0 $\pm$ 9.8	65.2 $\pm$ 9.7
Male, %	78.9	76.4
BMI, mean $\pm$ SD	27.9 $\pm$ 4.5	28.1 $\pm$ 4.8
Diabetes, %	28.5	28.2
Hypertension, %	77.0	74.0
Hyperlipidemia, %	77.2	78.7
Current smoker, %	22.0	18.5
Prior MI, %	33.8	31.9
Unstable angina, %	28.0	28.9
Additive EuroSCORE,	3.8 $\pm$ 2.7	3.8 $\pm$ 2.6
Total Parsonnet score,	8.4 $\pm$ 6.8	8.5 $\pm$ 7.0

# SYNTAX: Patient Characteristics (II)

## Randomized Cohort

<i>Patient-based</i>	<b>CABG N=897</b>	<b>TAXUS N=903</b>
<b>Total SYNTAX Score</b>	<b>29.1 ±11.4</b>	<b>28.4 ±11.5</b>
<b>Diffuse disease or small vessels, %</b>	<b>10.7</b>	<b>11.3</b>
<b>No. lesions, mean ± SD</b>	<b>4.4 ±1.8</b>	<b>4.3 ±1.8</b>
<b>3VD only, %</b>	<b>66.3</b>	<b>65.4</b>
<b>Left main, any, %</b>	<b>33.7</b>	<b>34.6</b>
<b>Left Main only</b>	<b>3.1</b>	<b>3.8</b>
<b>Left Main + 1 vessel</b>	<b>5.1</b>	<b>5.4</b>
<b>Left Main + 2 vessel</b>	<b>12.0</b>	<b>11.5</b>
<b>Left Main + 3 vessel</b>	<b>13.5</b>	<b>13.9</b>
<b>Total occlusion, %</b>	<b>22.2</b>	<b>24.2</b>
<b>Bifurcation, %</b>	<b>73.3</b>	<b>72.4</b>
<b>Trifurcation, %</b>	<b>10.6</b>	<b>10.7</b>

# Procedural Characteristics CABG Randomized Cohort



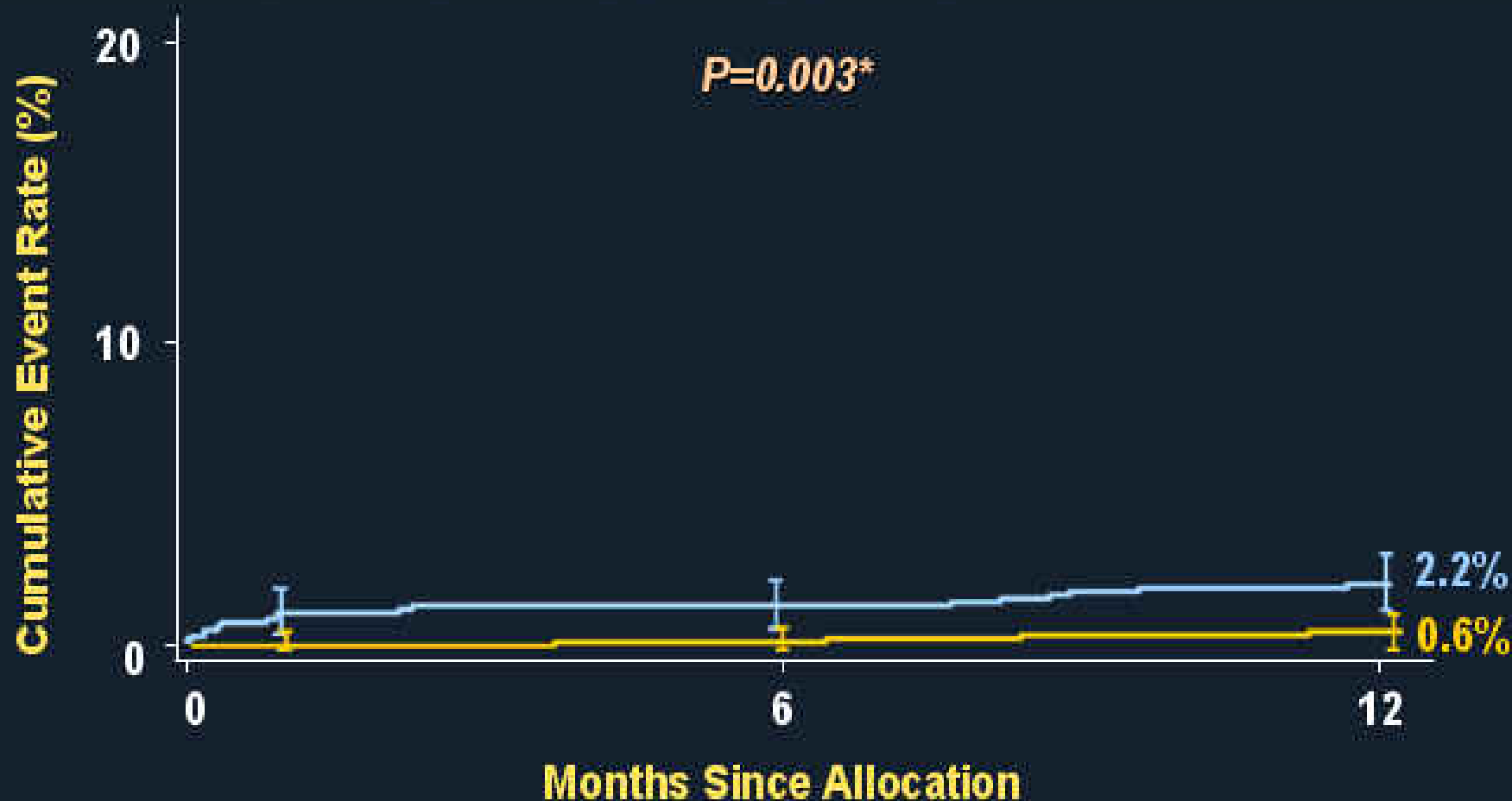
	<b>CABG N=897</b>
Off-pump surgery, %	15.0
Graft revascularization, %	
At least one arterial graft	97.3
Arterial graft to LAD	95.6
<u>LIMA+venous</u>	78.1
Double LIMA/RIMA	27.6
<b>Complete arterial revascularization</b>	<b>18.9</b>
Radial artery	14.1
Venous graft only	2.6
Grafts per patient, mean $\pm$ SD	2.8 $\pm$ 0.7
<u>Distal anastomosis/pt</u> , mean $\pm$ SD	3.2 $\pm$ 0.9

# SYNTAX: CVA to 12 Months



CABG (n=897)

TAXUS (n=903)



Event Rate  $\pm$  1.5 SE. \*Fisher's Exact Test

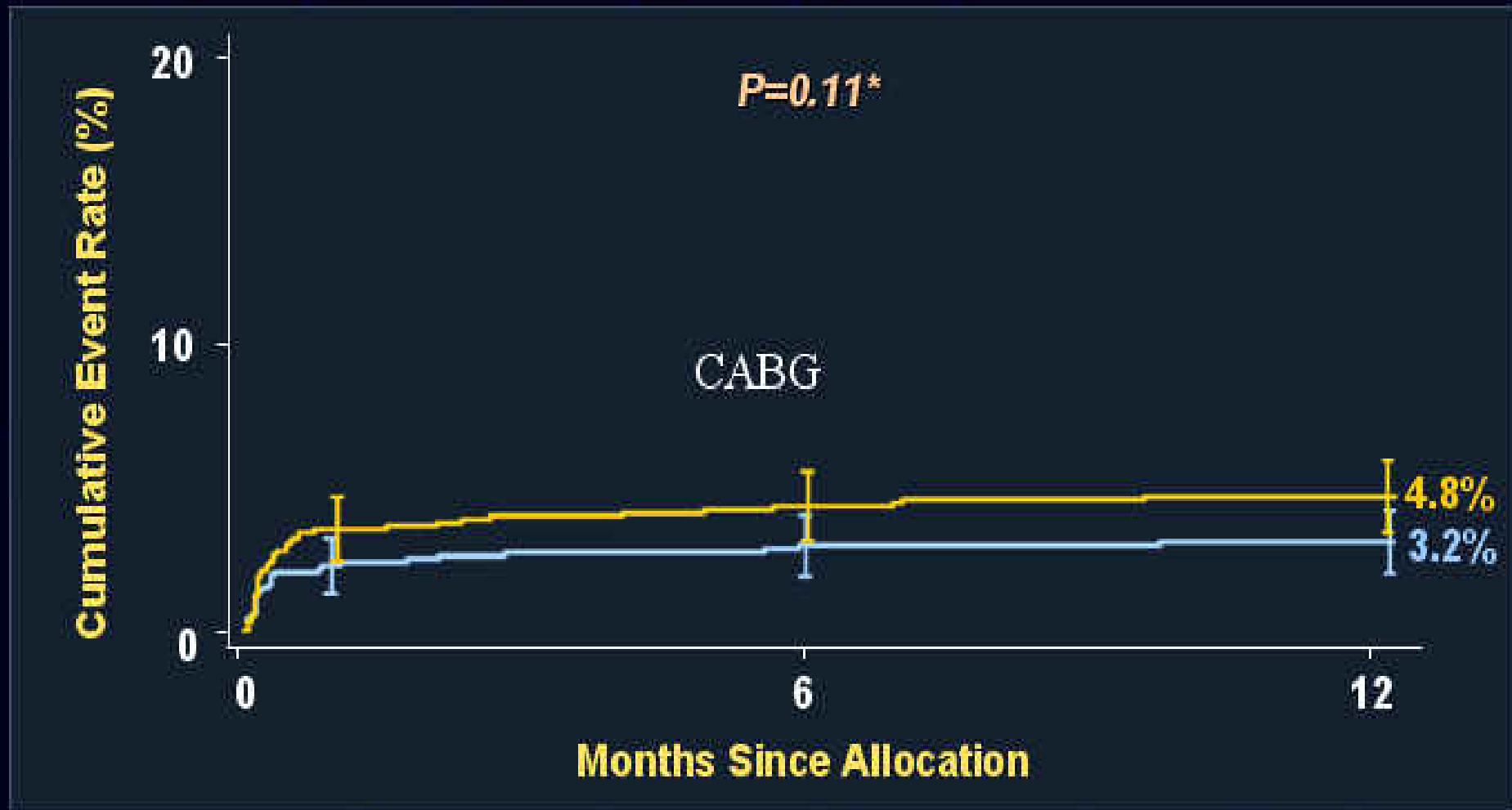
*Serruys et al N Engl J Med 2009 Mar 5;360(10):961-72*



# SYNTAX: MI to 12 Months

■ CABG (n=897)

■ TAXUS (n=903)

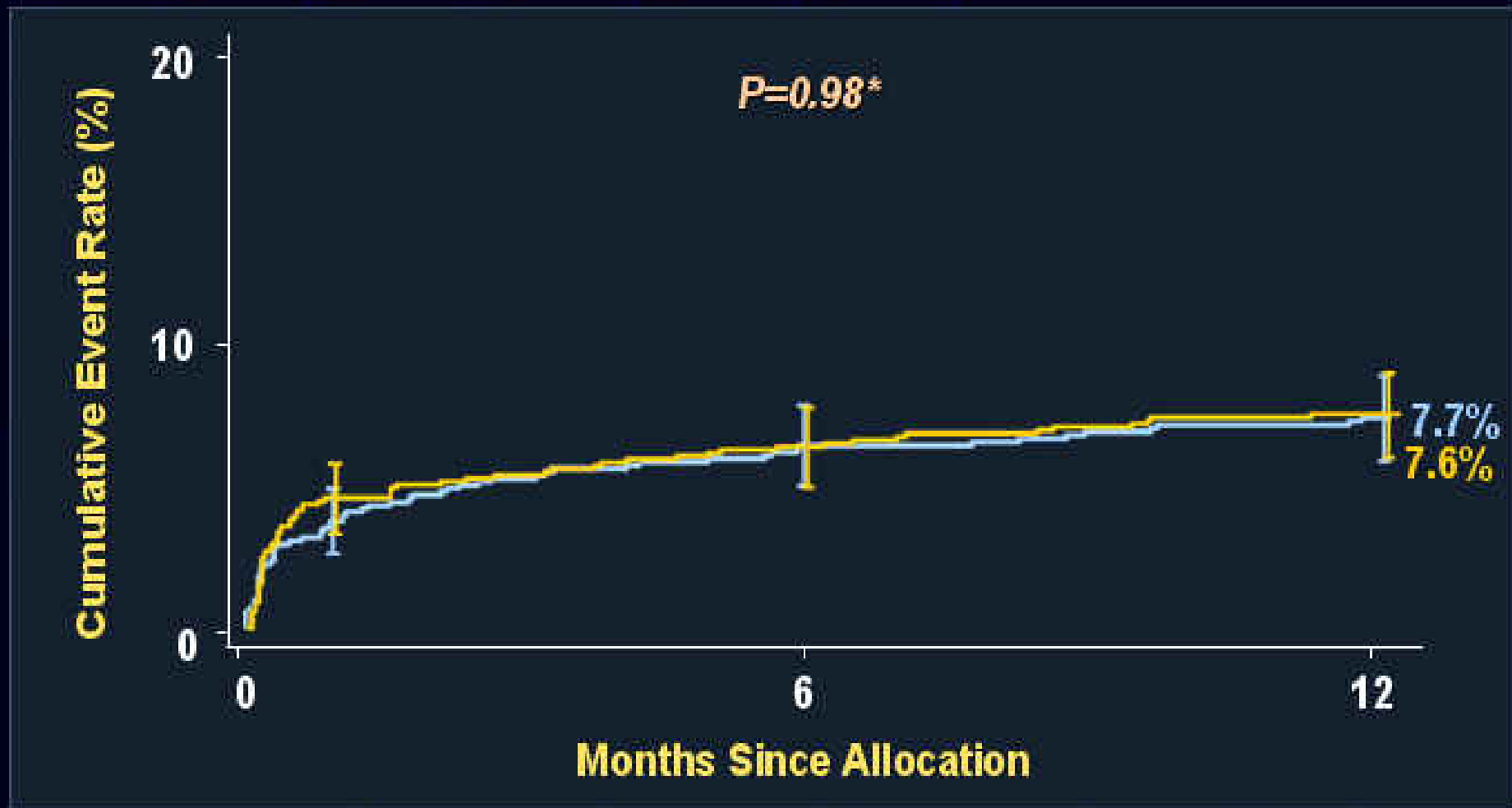


Event Rate  $\pm$  1.5 SE. \* Fisher's Exact Test

# SYNTAX: All-Cause Death/CVA/MI

■ CABG (n=897)

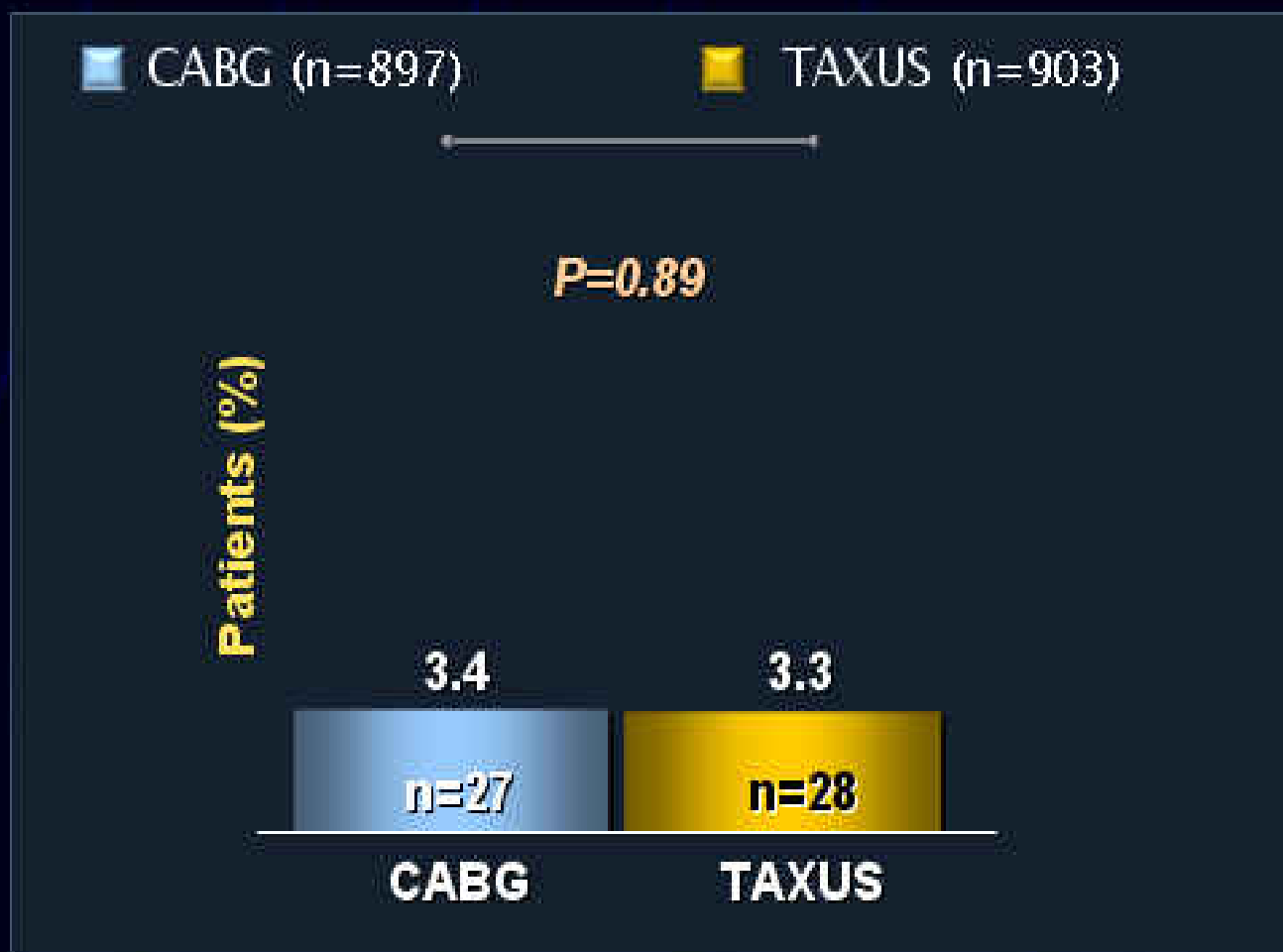
■ TAXUS (n=903)



Event Rate  $\pm$  1.5 SE. \* Fisher's Exact Test



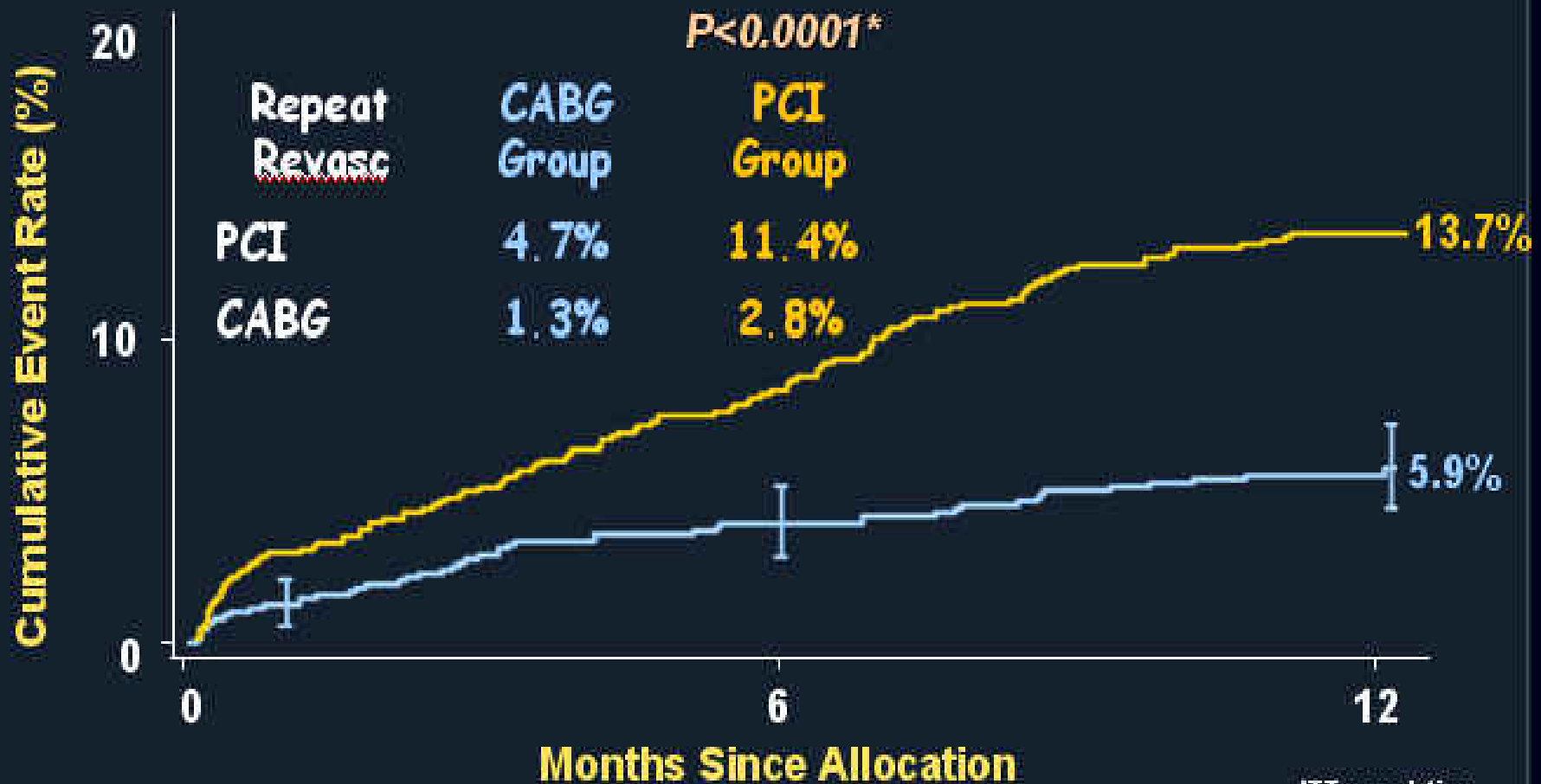
# SYNTAX: Symptomatic Graft Occlusion & Stent Thrombosis to 12 Months



# SYNTAX: Repeat Revascularization to 12 Months

■ CABG (n=897)

■ TAXUS (n=903)



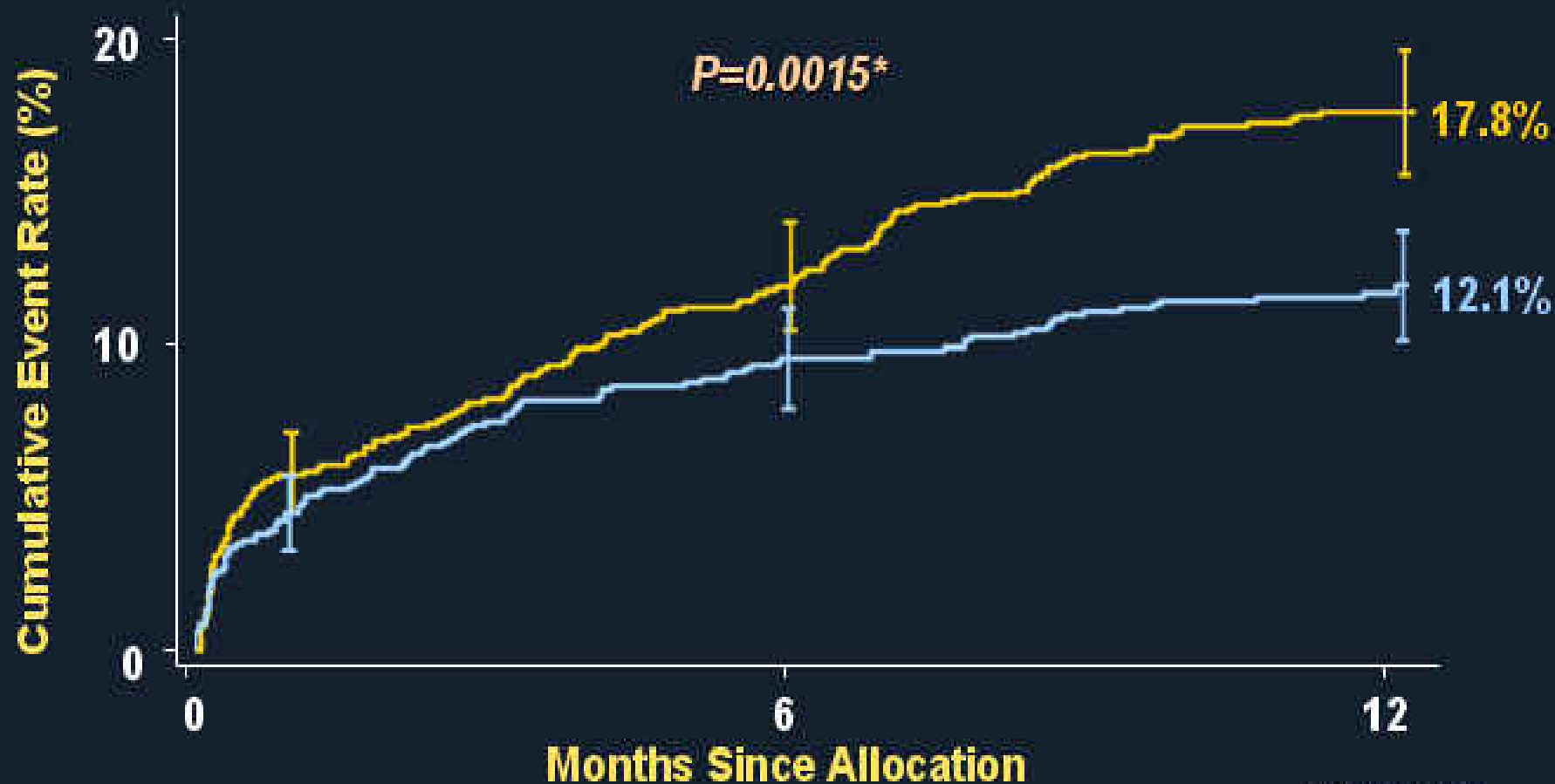
Event Rate  $\pm$  1.5 SE. \* Fisher's Exact Test *Serruys et al N Engl J Med 2009 Mar 5;360(10):961-72*



# SYNTAX: MACCE to 12 Months

■ CABG (n=897)

■ TAXUS (n=903)



ITT population

Event Rate  $\pm$  1.5 SE. \*Fisher's Exact Test

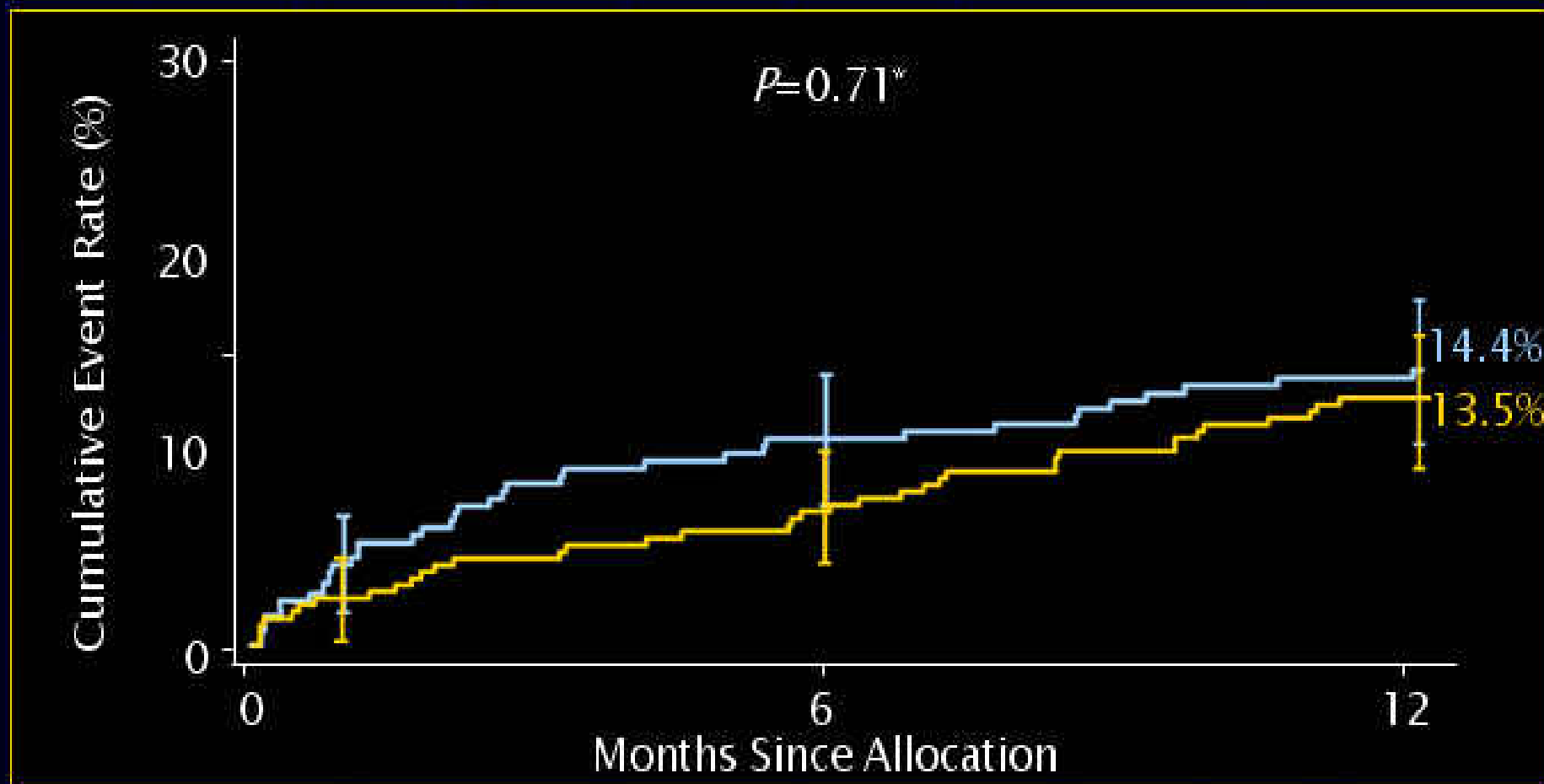
*Serruys et al N Engl J Med 2009 Mar 5;360(10):961-72*



# MACCE to 12 months vs SYNTAX Score: Low scores (0-22)

CABG (N=274)

TAXUS (N=299)



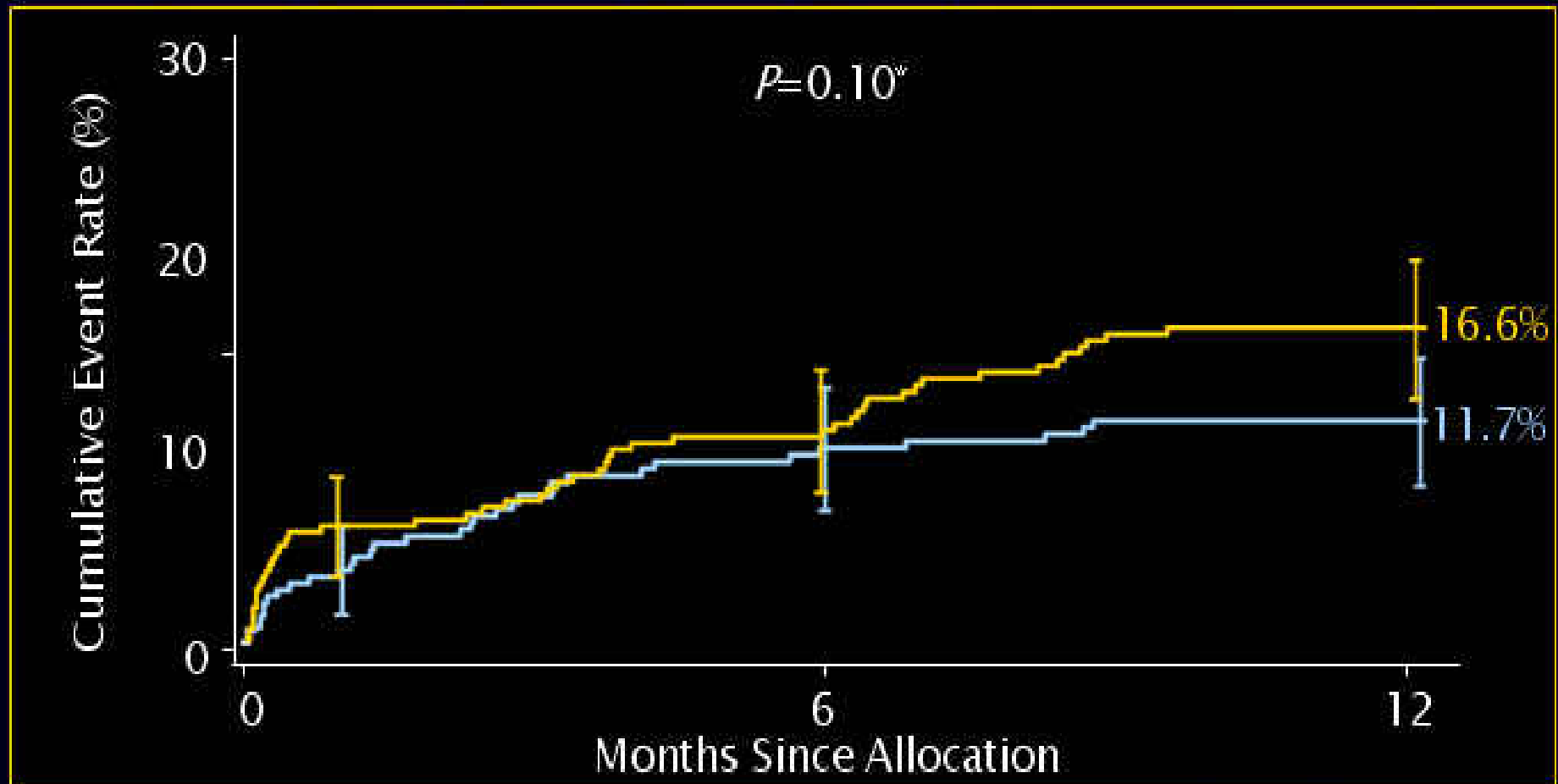
Event Rate  $\pm$  1.5 SE; \*chi square test; raw SYNTAX score for illustrative purposes only

RCT ITT pts; site-reported data

## MACCE to 12 months vs SYNTAX Score: Intermediate scores (23-32)

■ CABG (N=300)

■ TAXUS (N=310)



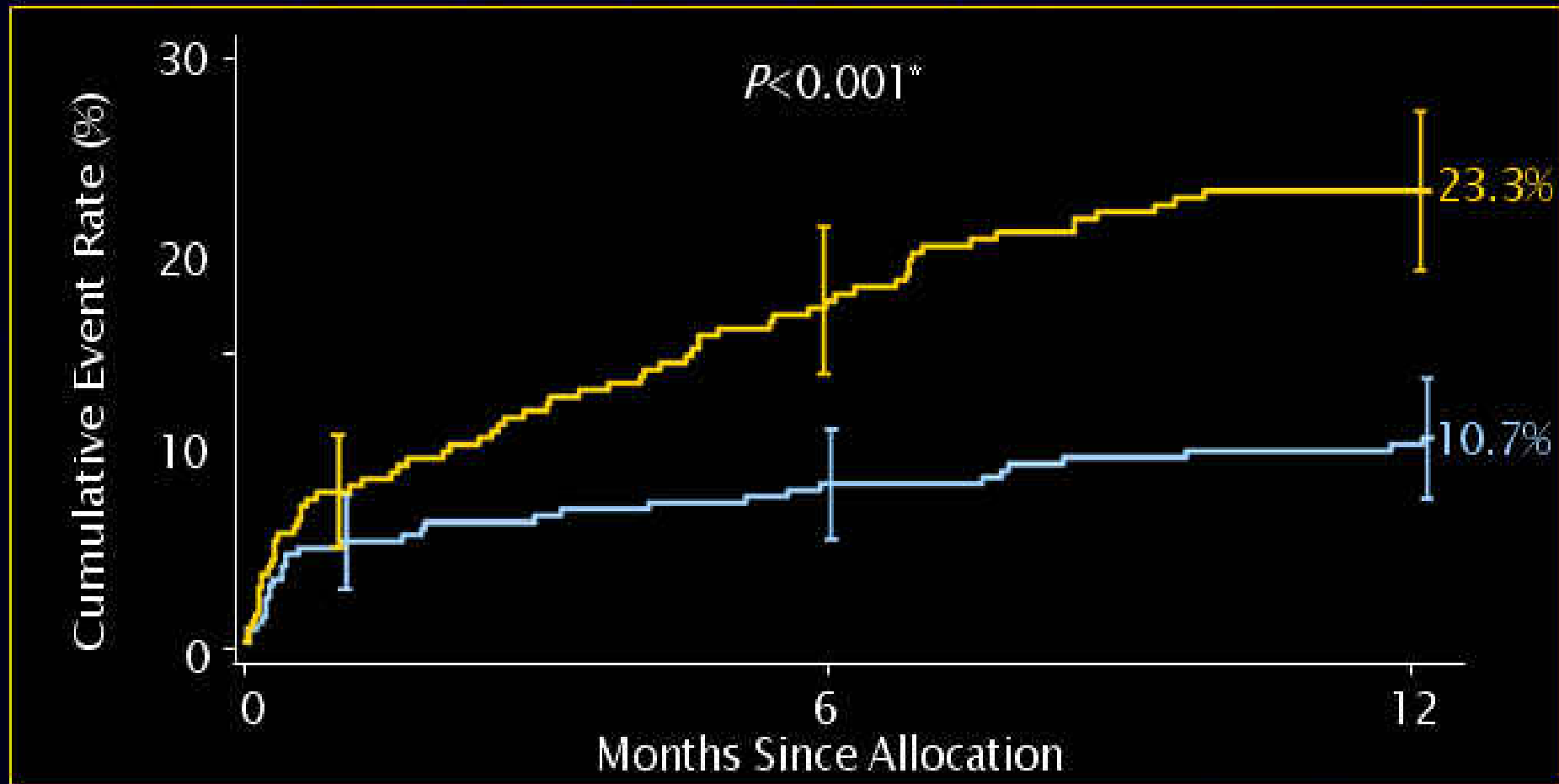
Event Rate  $\pm$  1.5 SE; \*chi square test; raw SYNTAX score for illustrative purposes only

RCT ITT pts; site-reported data

# MACCE to 12 months vs SYNTAX Score: High scores ( $\geq 33$ )

■ CABG (N=316)

■ TAXUS (N=290)

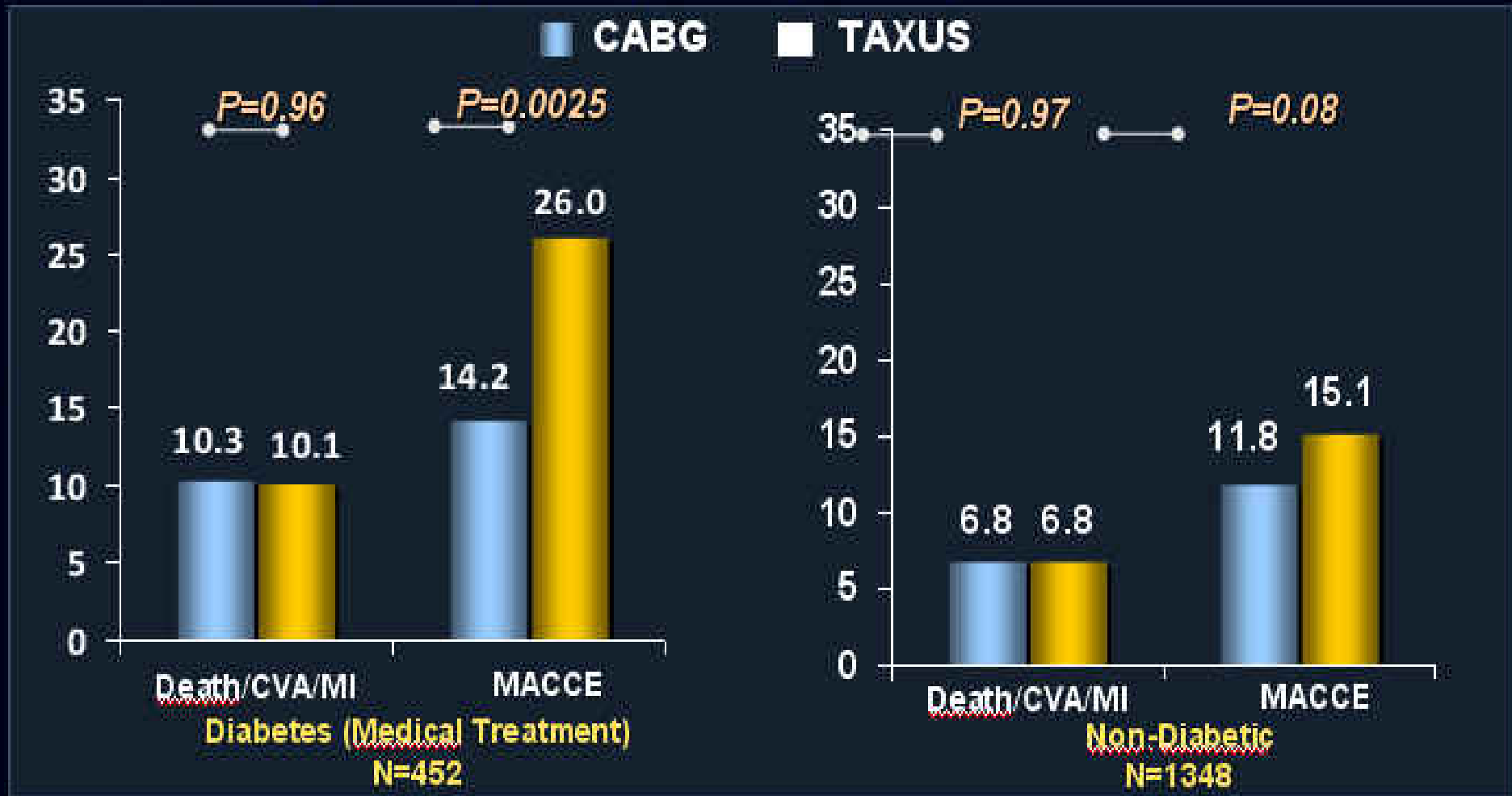


Event Rate  $\pm$  1.5 SE; \*chi square test; raw SYNTAX score for illustrative purposes only

RCT ITT pts; site-reported data



# SYNTAX: Outcome According to Diabetic Status



# Coronary Artery Revascularization in Diabetes— The CARDia Trial.

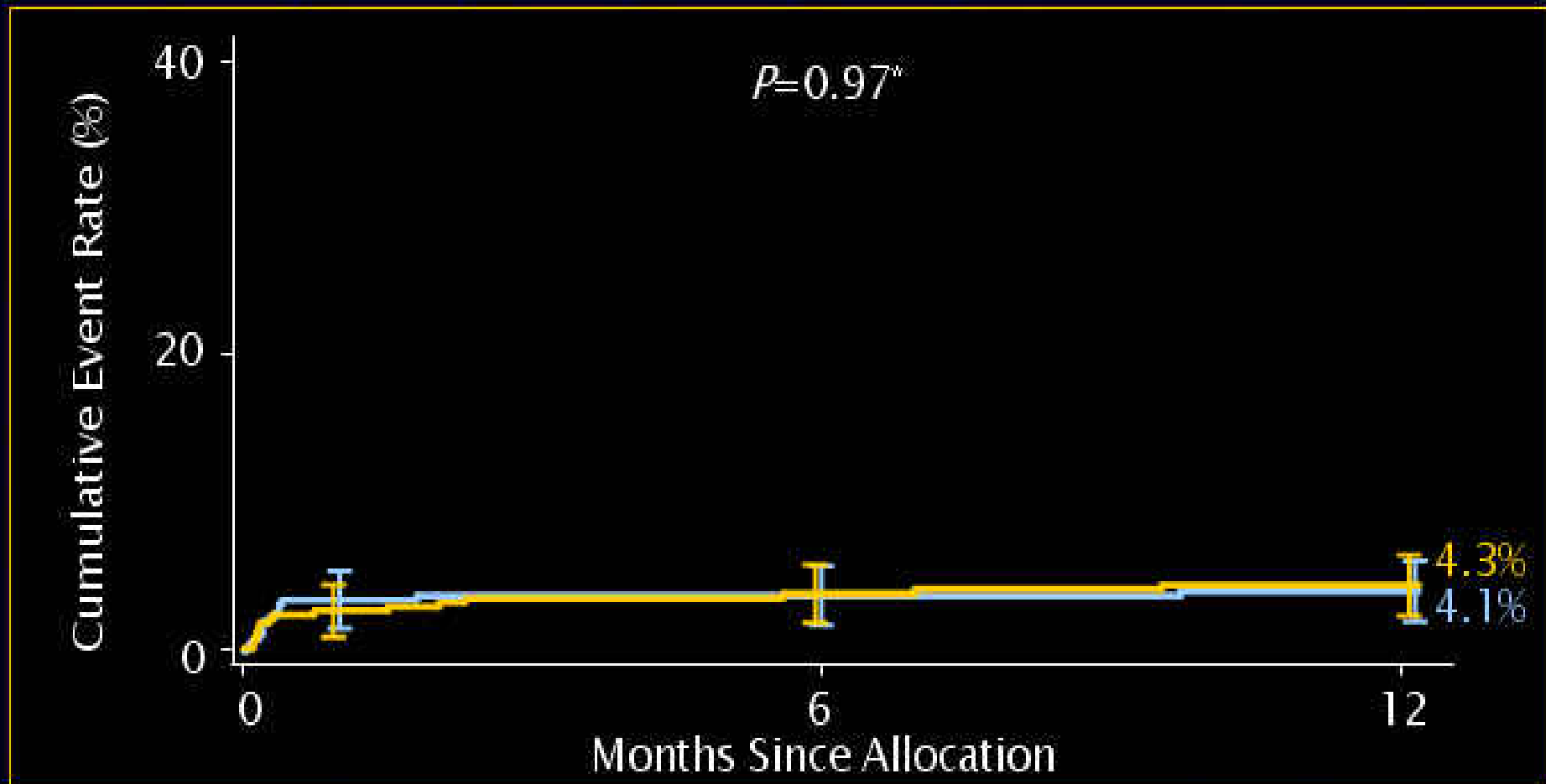
**510 diabetic patients with multivessel disease or complex single-vessel disease  
randomized to either CABG or PCI (71% DES).**

<b>CABG vs. DES</b>	<b>CABG n=245</b>	<b>PCI n=179</b>	<b>P Value</b>
Death	3.3%	3.9%	0.723
Nonfatal stroke	2.5%	0%	0.041
Death, MI, stroke (primary endpoint)	10.2%	10.1%	0.98
Death, MI, stroke and repeat revascularization	11.0%	15.1%	0.217
Further revascularization at 1 Year	2.0%	7.3%	0.013

# Myocardial Infarction to 12 Months Left Main Subset

CABG (N=348)

TAXUS (N=357)



Event rate  $\pm$  1.5 SE, Fisher exact test

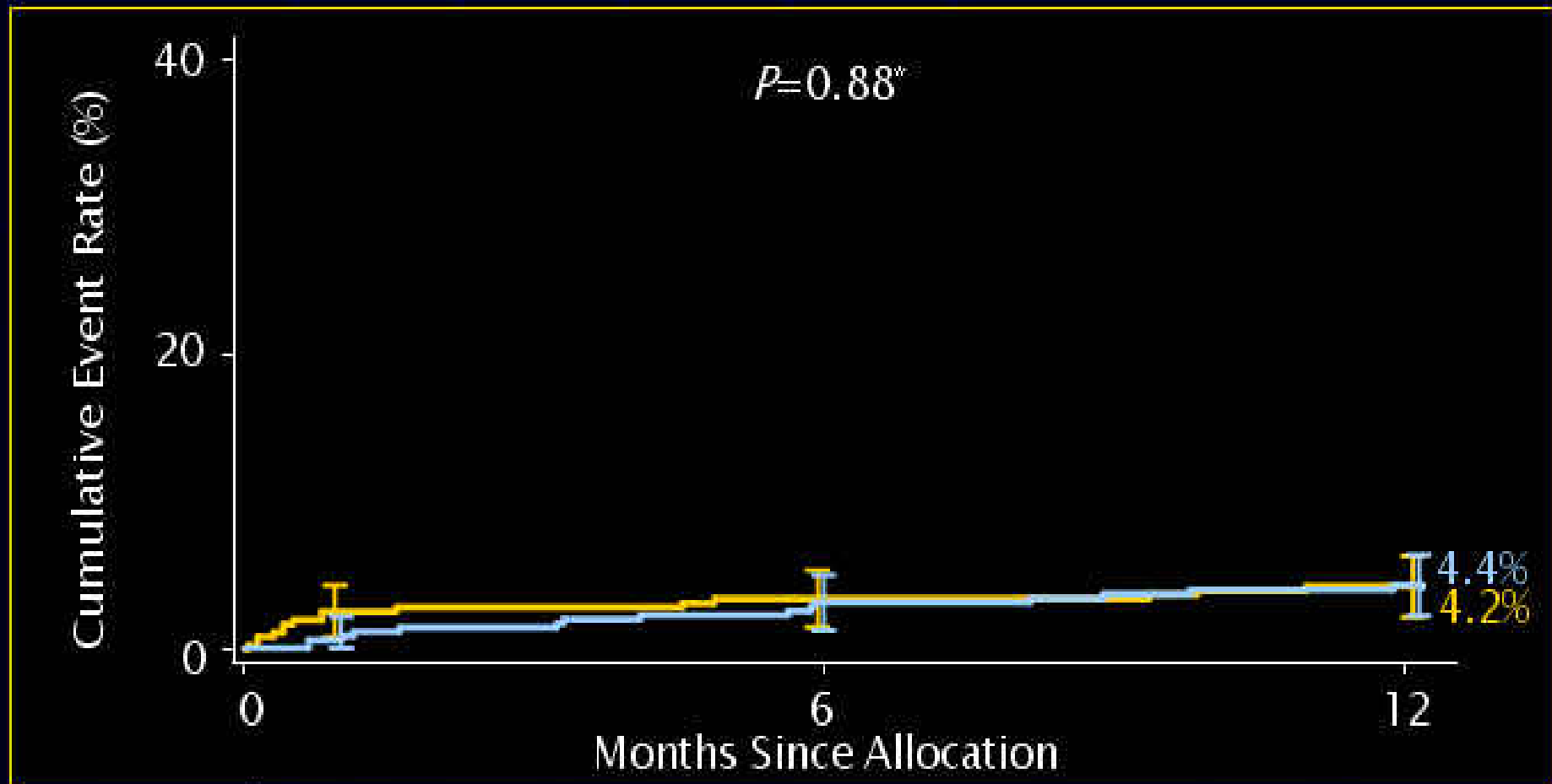
ITT population

# Death (All-cause) to 12 Months

## Left Main Subset

■ CABG (N=348)

■ TAXUS (N=357)



Event rate  $\pm$  1.5 SE, \*Fisher exact test

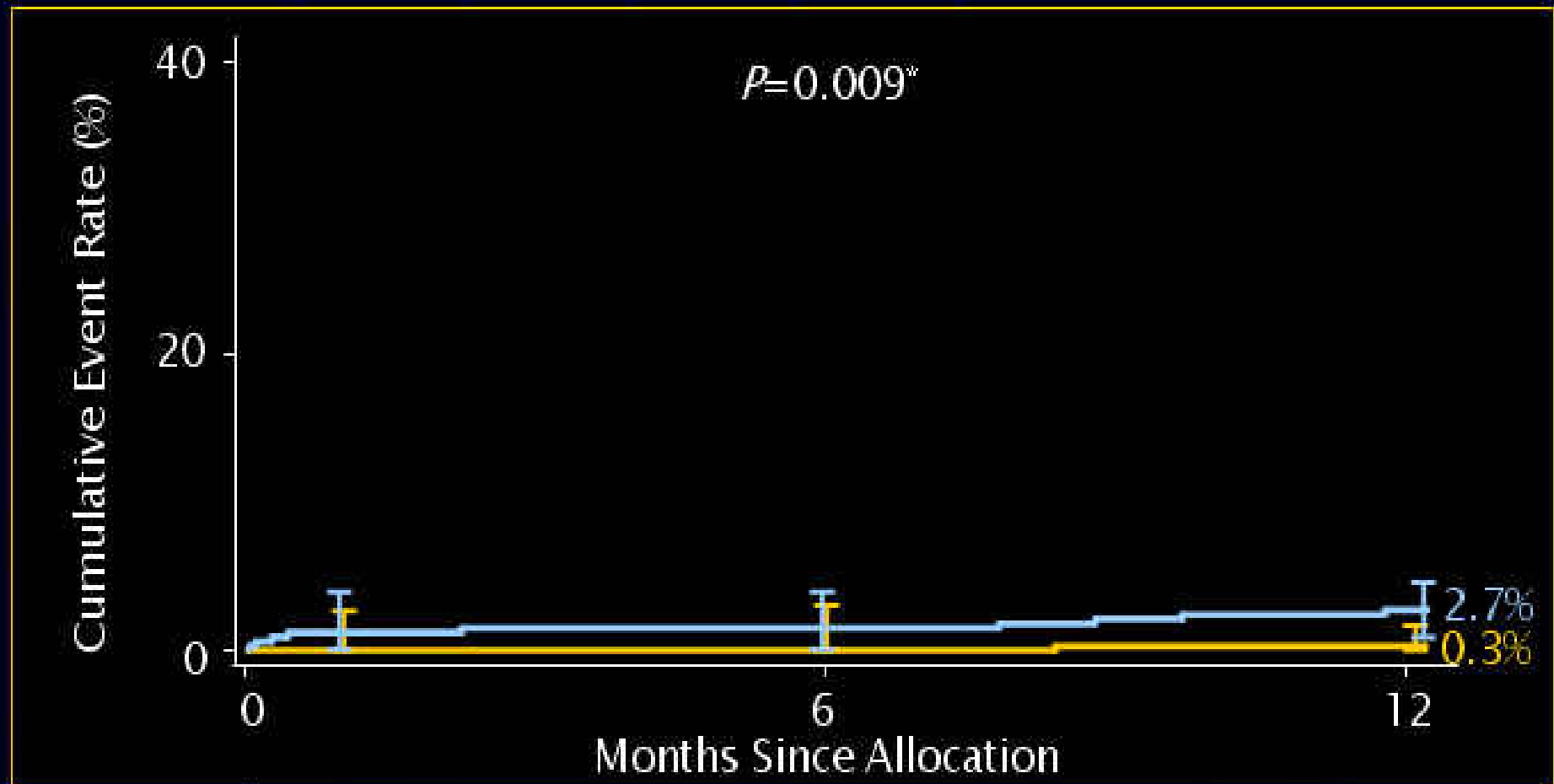
ITT population



# CVA (Stroke) to 12 Months Left Main Subset

■ CABG (N=348)

■ TAXUS (N=357)



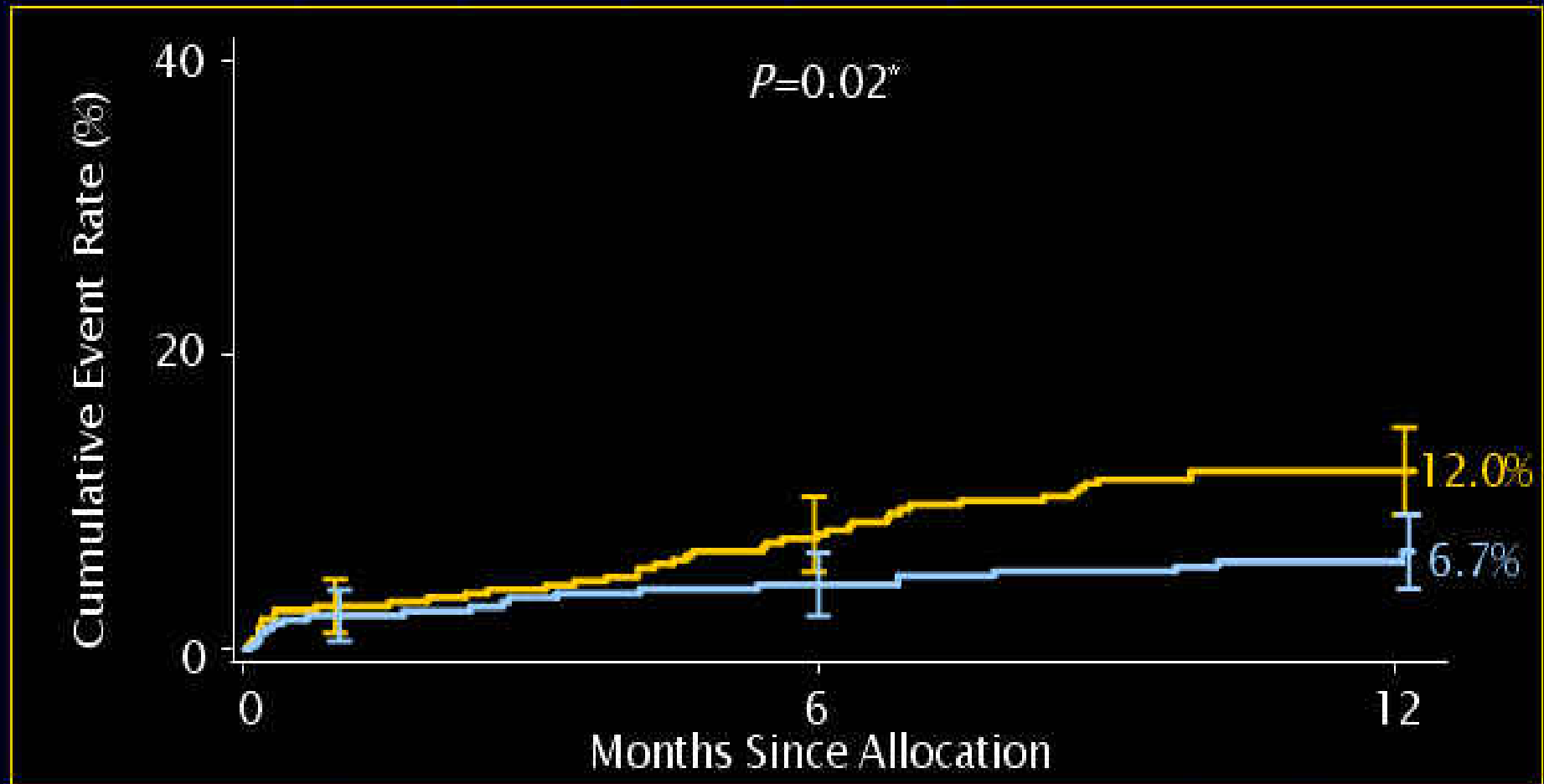
Event rate  $\pm$  1.5 SE, \*Fisher exact test

ITT population

# Revascularization\* to 12 Months *Left Main Subset*

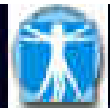
■ CABG (N=348)

■ TAXUS (N=357)



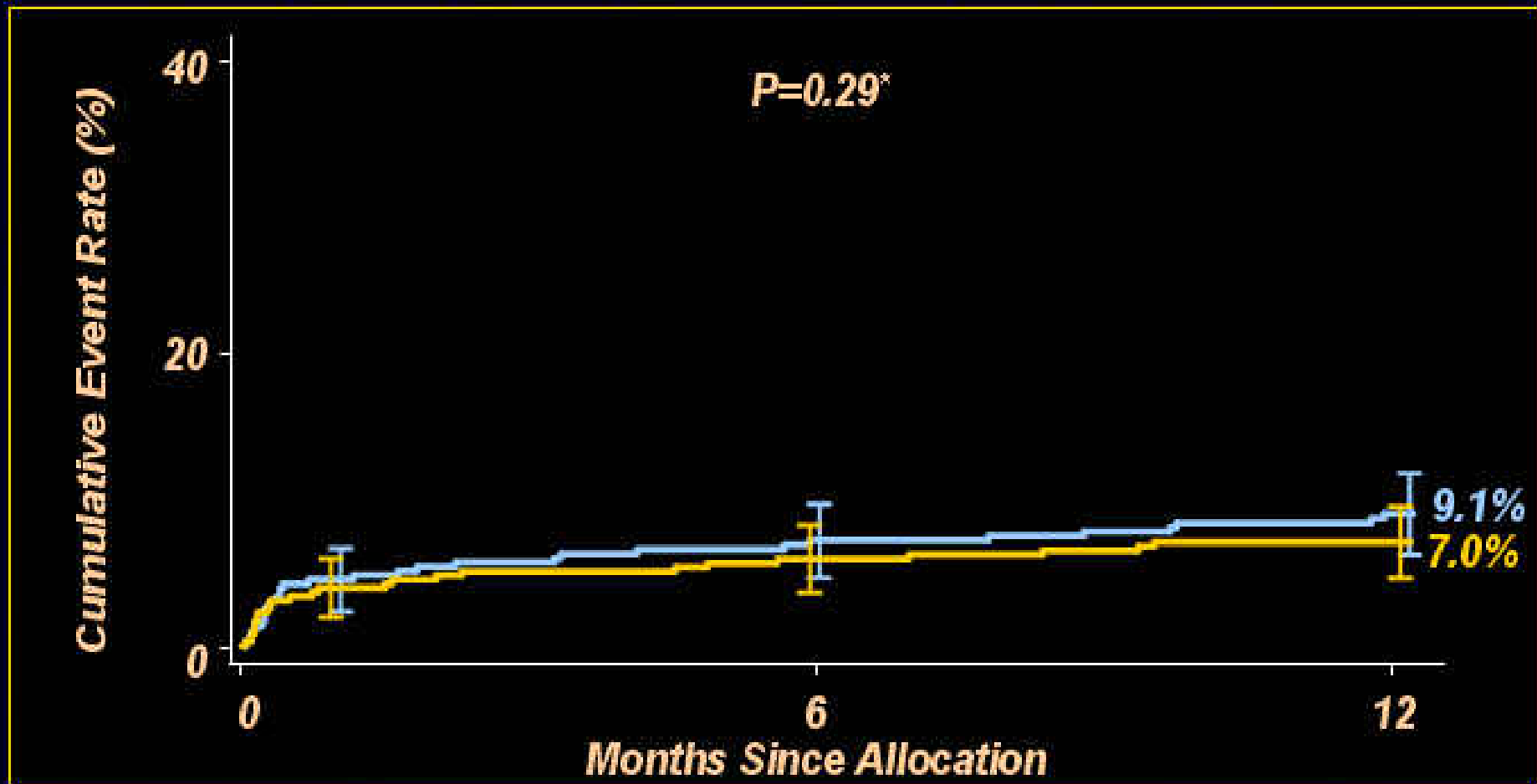
Event rate  $\pm$  1.5 SE, \*Fisher exact test

\*Any revascularization (PCI or CABG); ITT population



# Death/CVA/MI to 12 Months SYNTAX Left Main Subset

CABG (N=348)      TAXUS (N=357)

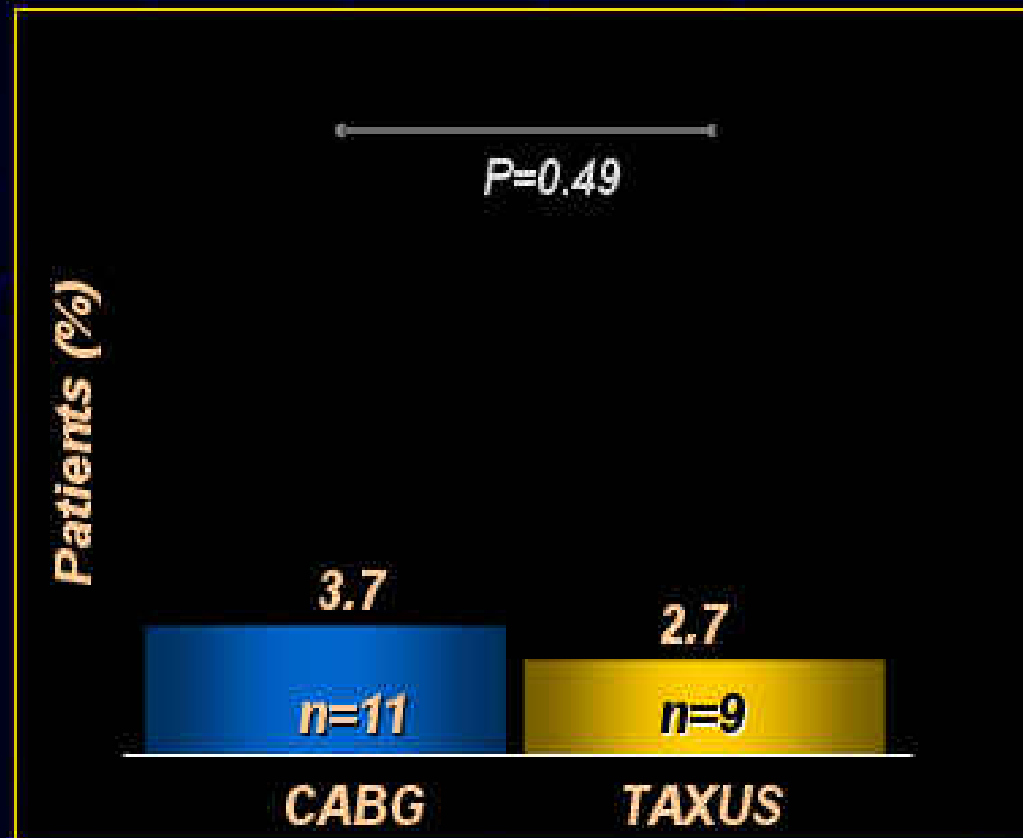


Event rate  $\pm$  1.5 SE, Fisher exact test

ITT population

# Symptomatic Graft Occlusion & Stent Thrombosis to 12 Months Left Main Subset

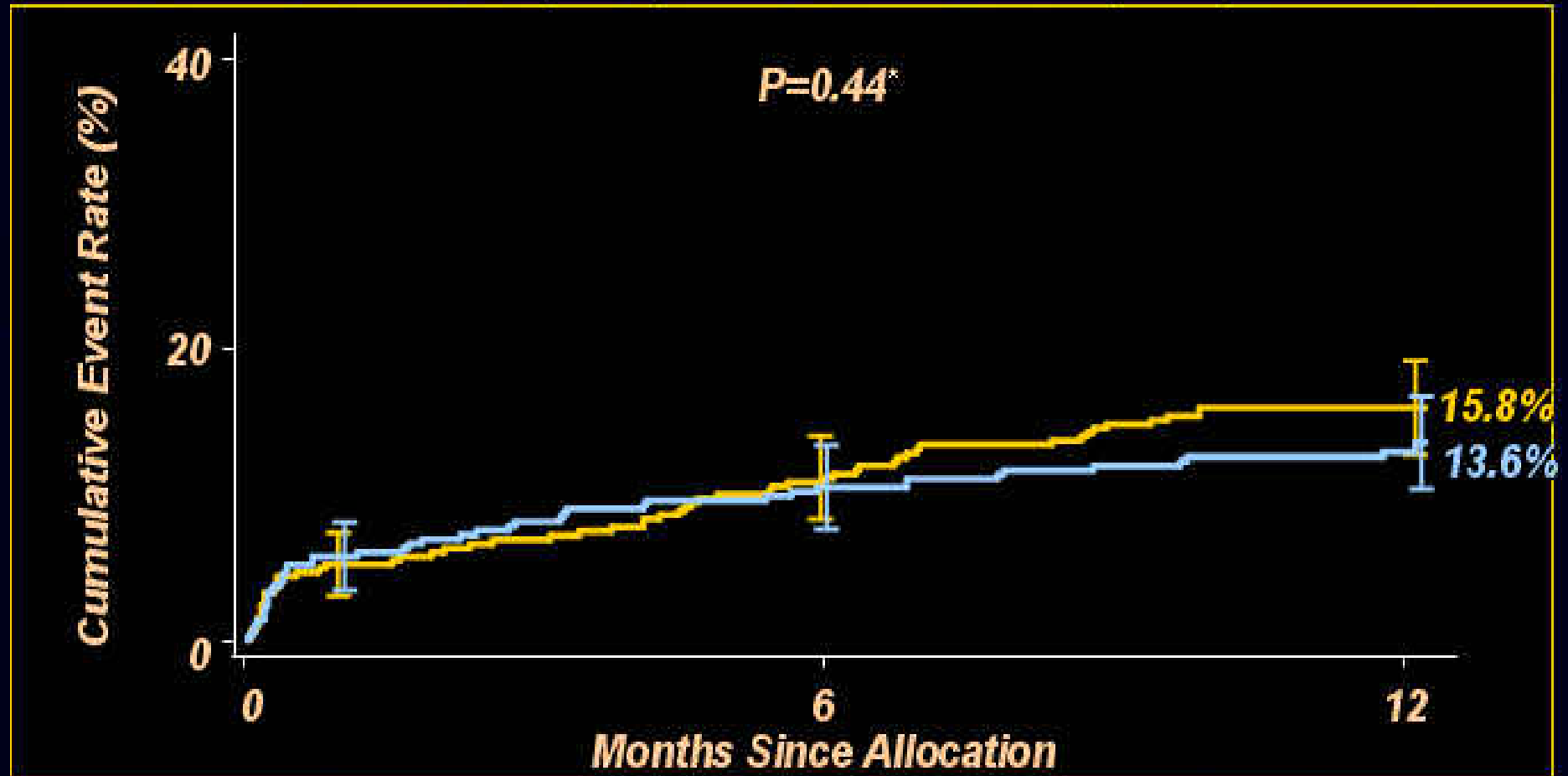
**CABG (n=348)**      **TAXUS (n=357)**



# MACCE to 12 Months

## Left Main Subset

■ CABG (N=348)      ■ TAXUS (N=357)



Event rate  $\pm 1.5$  SE, Fisher exact test

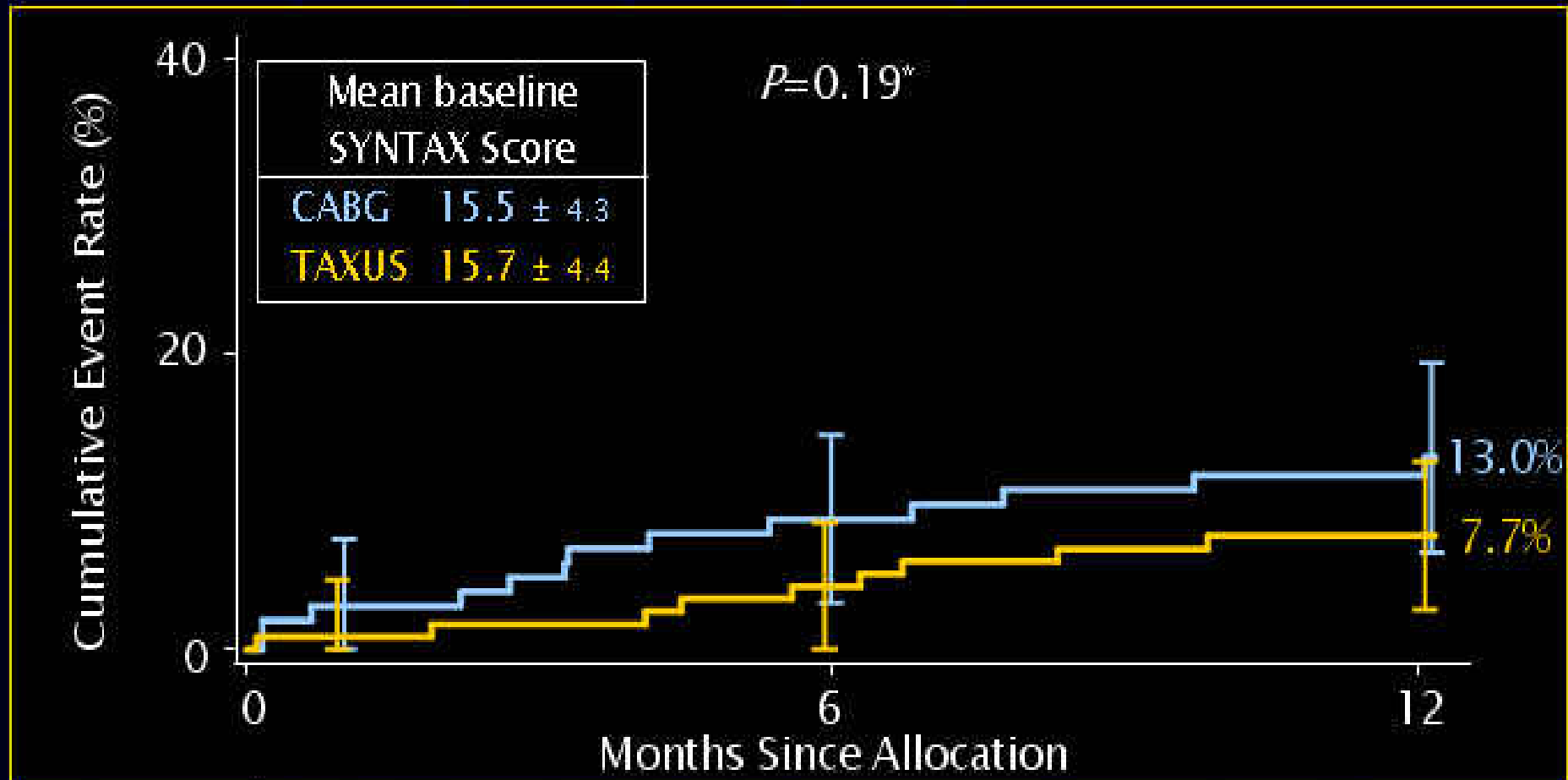
ITT population

# MACCE to 12 Months by SYNTAX Score Tertile

## Low Scores (0-22) LM Subset

■ CABG (N=103)

■ TAXUS (N=118)



Event rate ± 1.5 SE, Fisher exact test

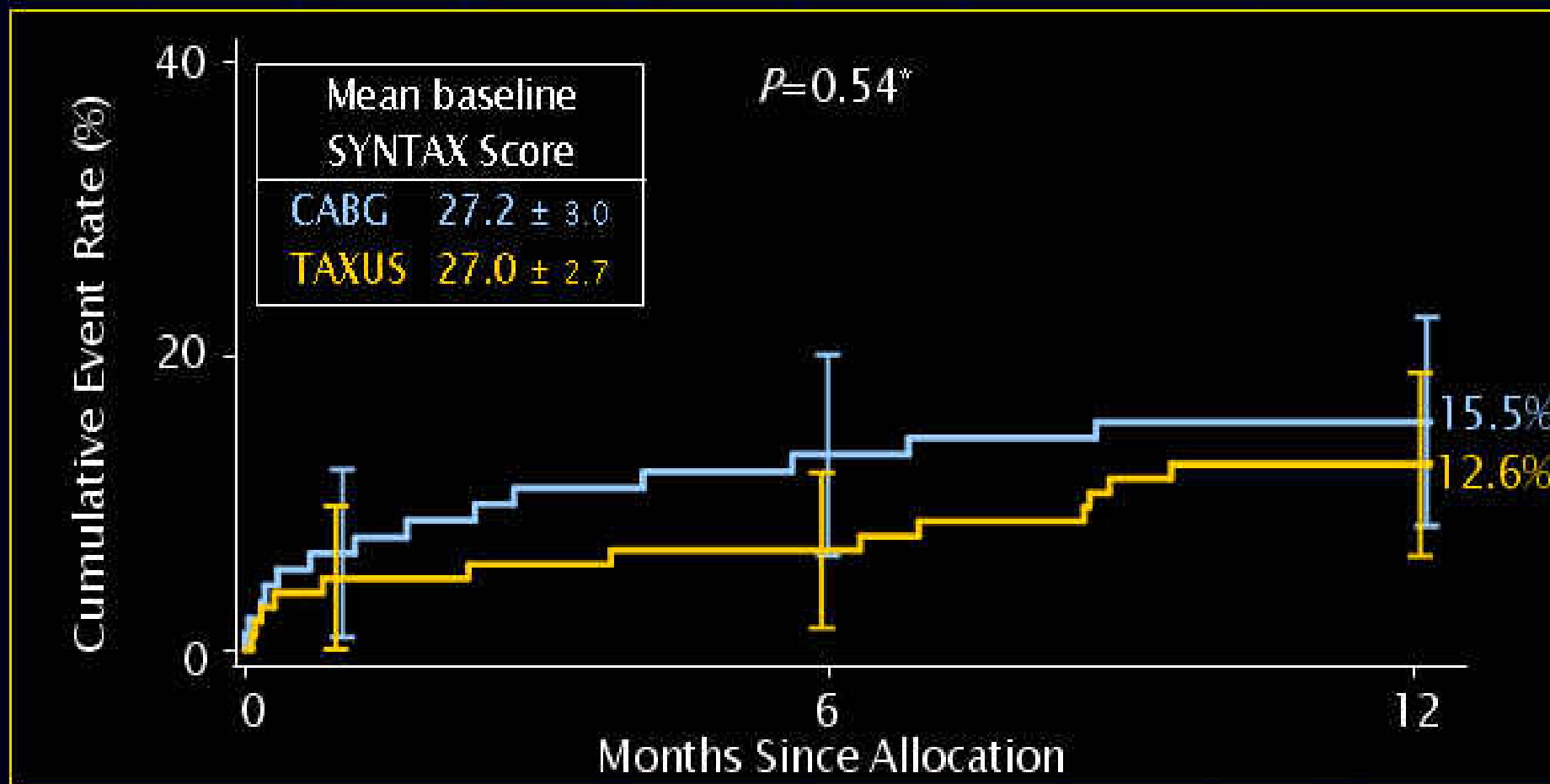
Calculated by core laboratory; ITT population

# ACCE to 12 Months by SYNTAX Score Tertile

*Intermediate Scores (23-32) LM Subset*

■ CABG (N=92)

■ TAXUS (N=195)



Event rate ± 1.5 SE, \*\*Fisher exact test

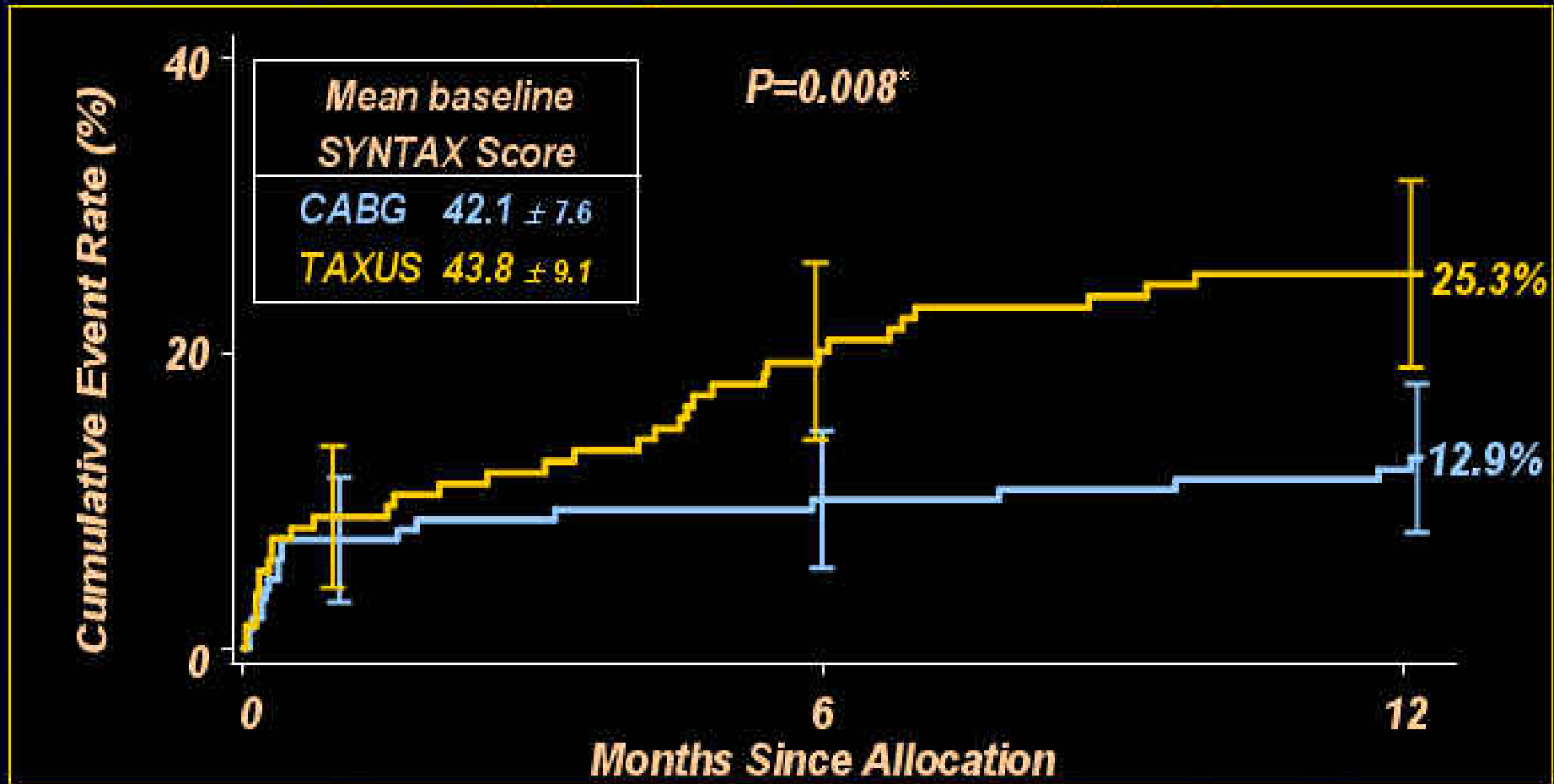
Calculated by core laboratory; ITT population



# MACCE to 12 Months by SYNTAX Score Tertile

High Scores ( $\geq 33$ ) Left Main Subset

■ CABG (N=150)      ■ TAXUS (N=135)



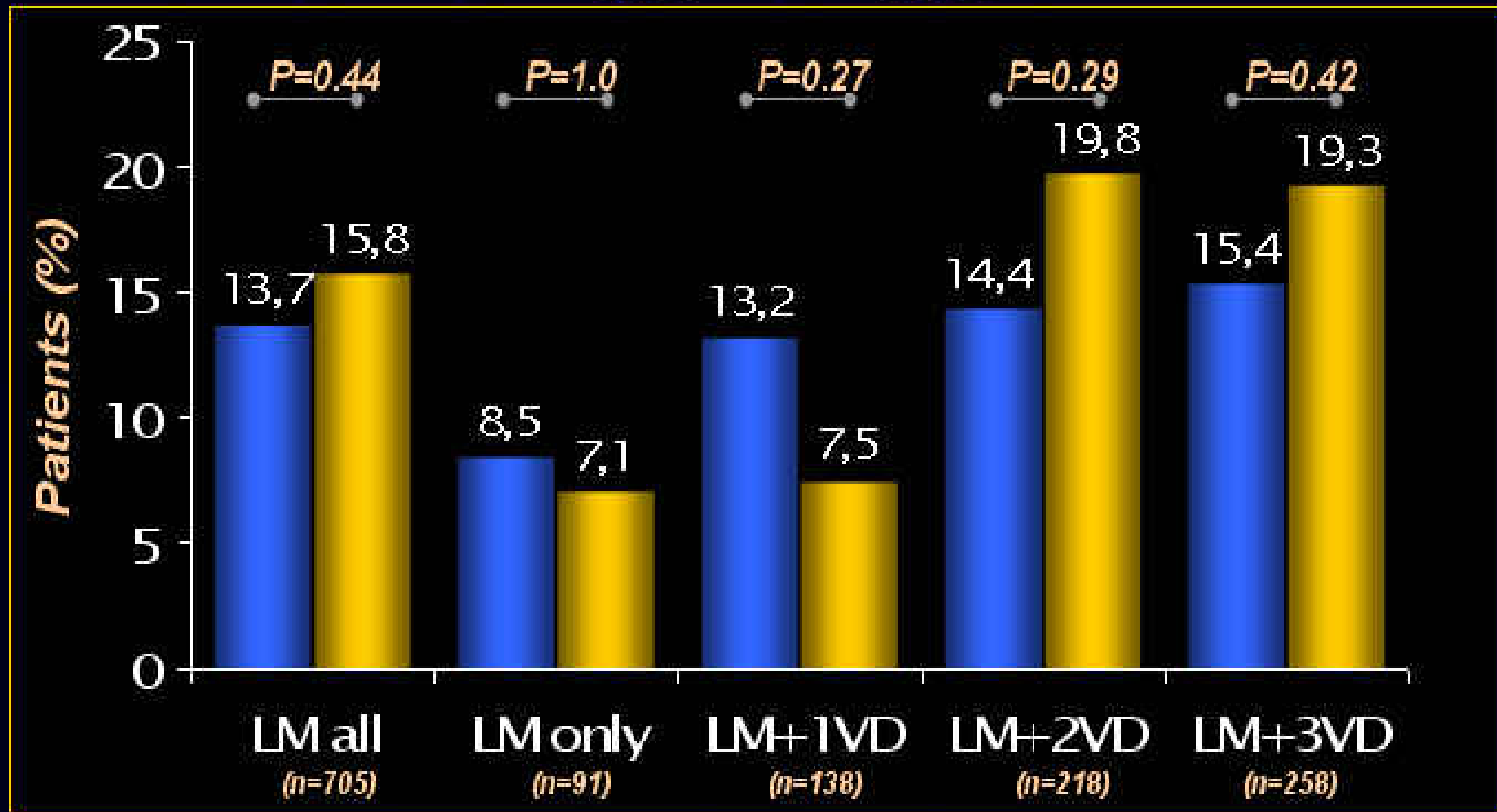
Event rate  $\pm$  1.5 SE, Fisher exact test



# Overall MACCE at 12 Months

## Left Main Subset

CABG TAXUS



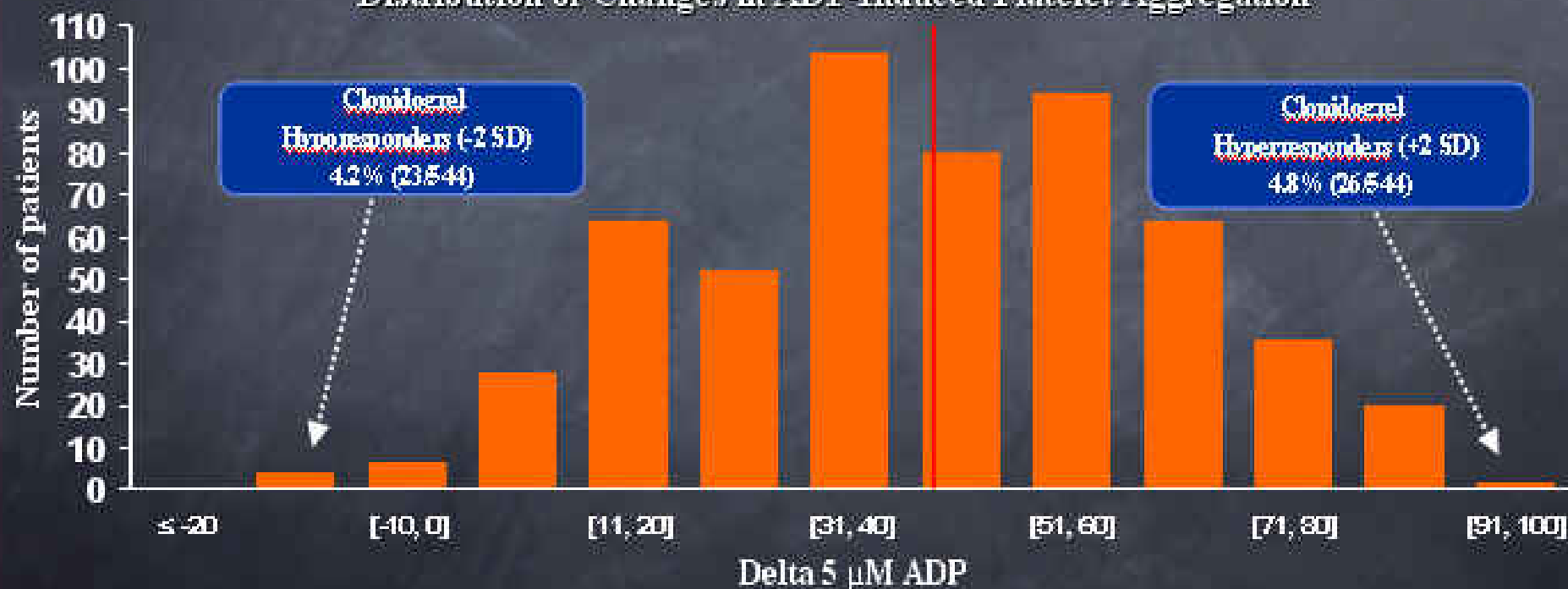
# CAN WE IMPROVE OUR RESULTS ?

- Optimizing DAT responsiveness
- IVUS guidance
- NEW DES

# Patient-to-Patient Variability in Anti-platelet Responsiveness

This retrospective analysis demonstrates a marked variability in subject's response after standard dosing of the anti-platelet agent clopidogrel (N=544)

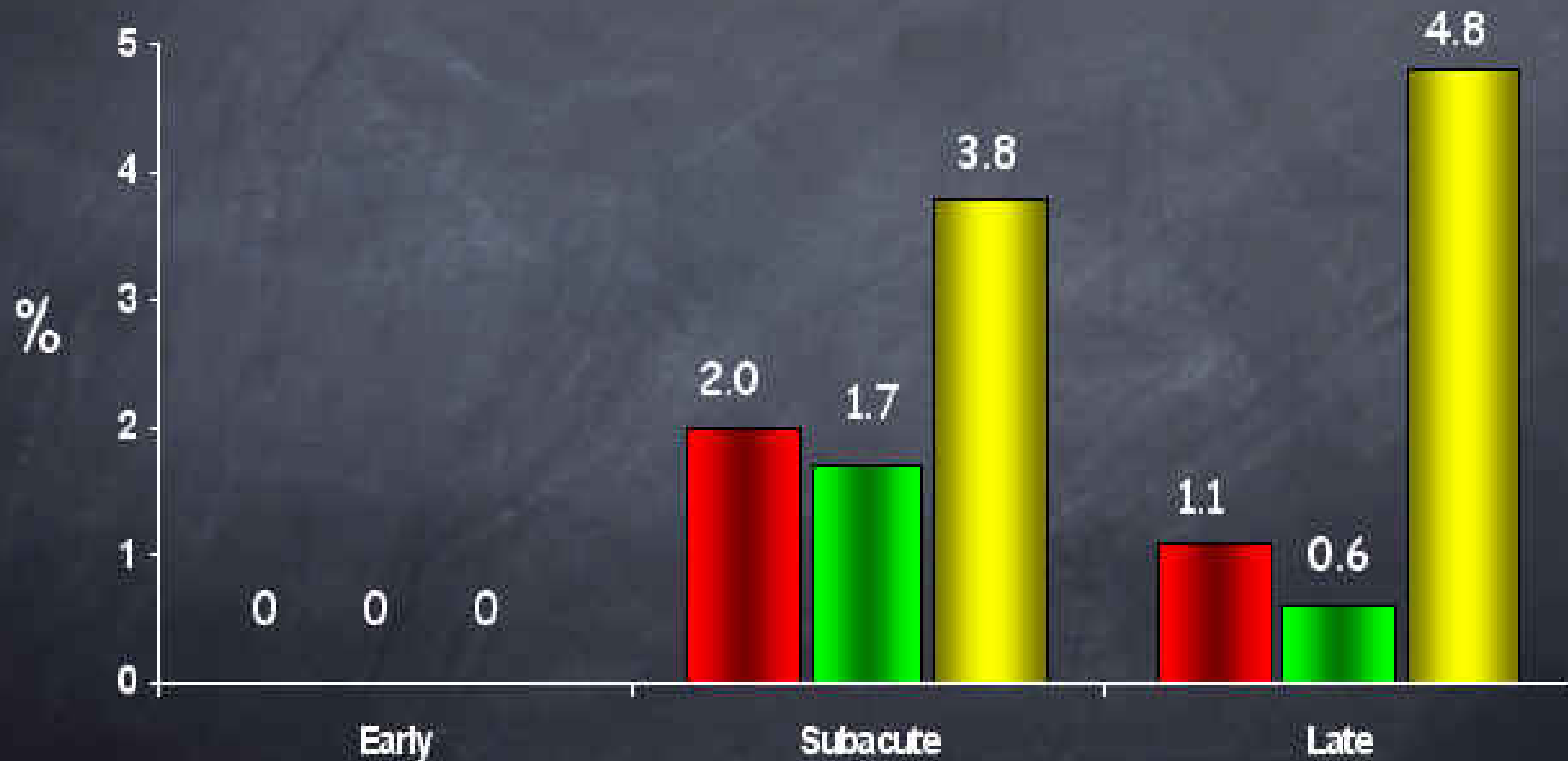
Distribution of Changes in ADP-Induced Platelet Aggregation



ADP = adenosine diphosphate; SD = standard deviation.  
Serebruany et al. *J Am Coll Cardiol*. 2005;45:246.

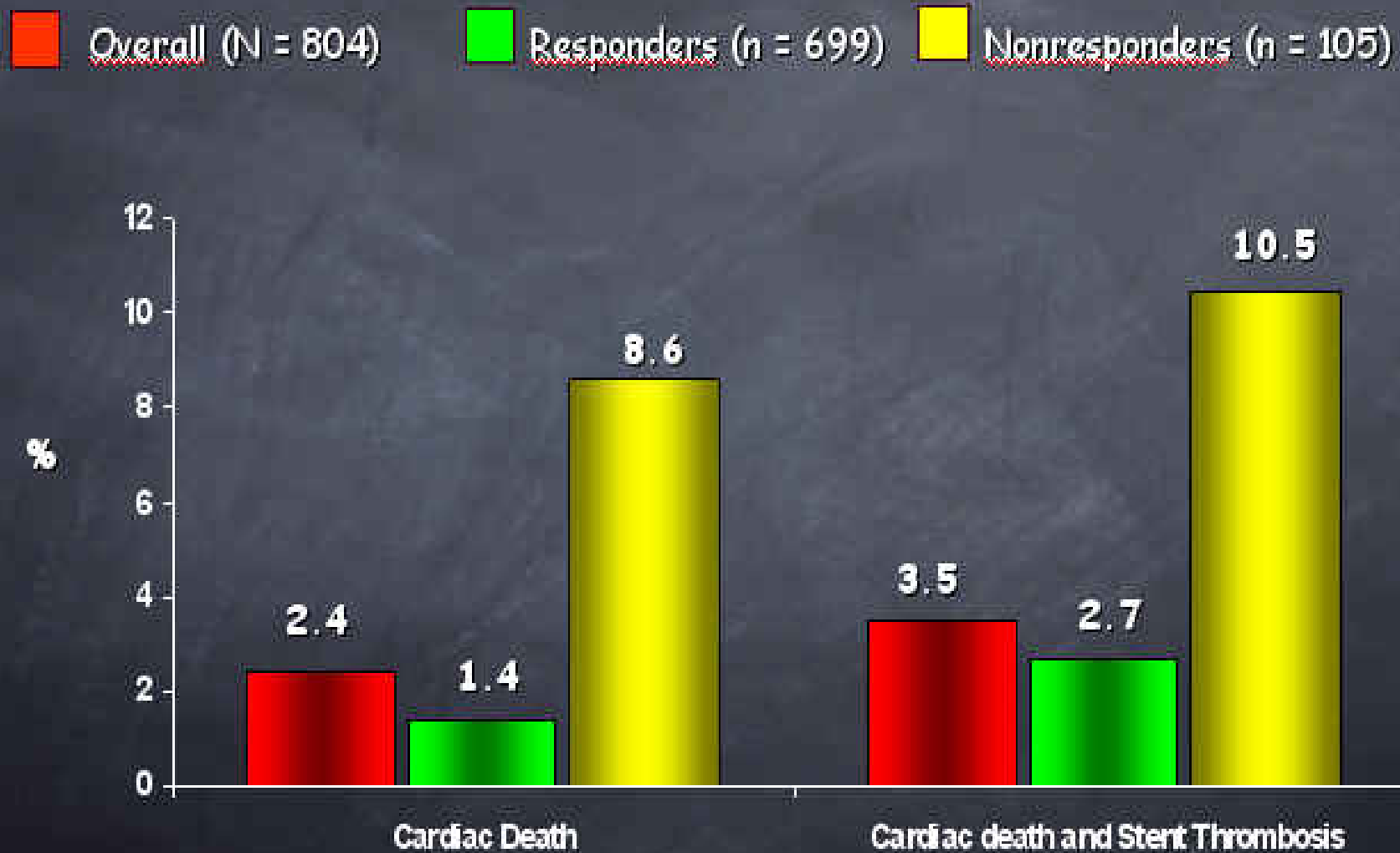
## RECLOSE timing of stent thrombosis

Overall (N = 804)    Responders (n = 699)    Nonresponders (n = 105)





## RE-CLOSE cardiac mortality with and without stent thrombosis (secondary endpoint)



# Prasugrel versus Clopidogrel

13,608 patients

	Prasugrel	Clopidogrel
BMS	48%	47%
DES	47%	47%
ST (ARC d+prob)	1.1%	2.4%

**BMS HR 0.52 (95% CI 0.35 - 0.77) P < 0.001**

**DES HR 0.43 (95% CI 0.28 - 0.66) P < 0.001**

## Prasugrel versus Clopidogrel

### Primary End point

Cardiovascular Death + MI + Stroke 14 months

	<u>Prasugrel</u>	<u>Clopidogrel</u>	<u>Risk reduction</u>
BMS (6,461 pts)	10%	12.2%	20%
DES(6,383 pts)	9.4%	11.6%	18%

# DES Strut and Polymer Thickness

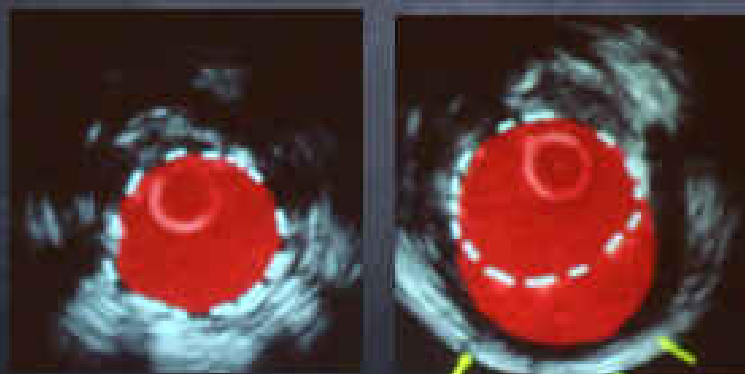
3.0 mm diameter, 500x magnification

Cypher®	TAXUS® Express	Endeavor™	XIENCETM V
			
<p>Strut Thickness 140 <math>\mu\text{m}</math></p> <p>Polymer Thickness 12.6 <math>\mu\text{m}</math></p> <p>Total 152.6 <math>\mu\text{m}</math></p>	<p>Strut Thickness 132 <math>\mu\text{m}</math></p> <p>Polymer Thickness 16.0 <math>\mu\text{m}</math></p> <p>Total 148.0 <math>\mu\text{m}</math></p>	<p>Strut Thickness 91 <math>\mu\text{m}</math></p> <p>Polymer Thickness 5.3 <math>\mu\text{m}</math></p> <p>Total 96.3 <math>\mu\text{m}</math></p>	<p>Strut Thickness 81 <math>\mu\text{m}</math></p> <p>Polymer Thickness 7.6 <math>\mu\text{m}</math></p> <p>Total 88.6 <math>\mu\text{m}</math></p>



## IVUS guidance during stent implantation

- Dante Pazzanese experience:
- 195 pts treated with Cypher or Taxus and IVUS follow-up
- Late incomplete apposition in 10 pts, 5.1%

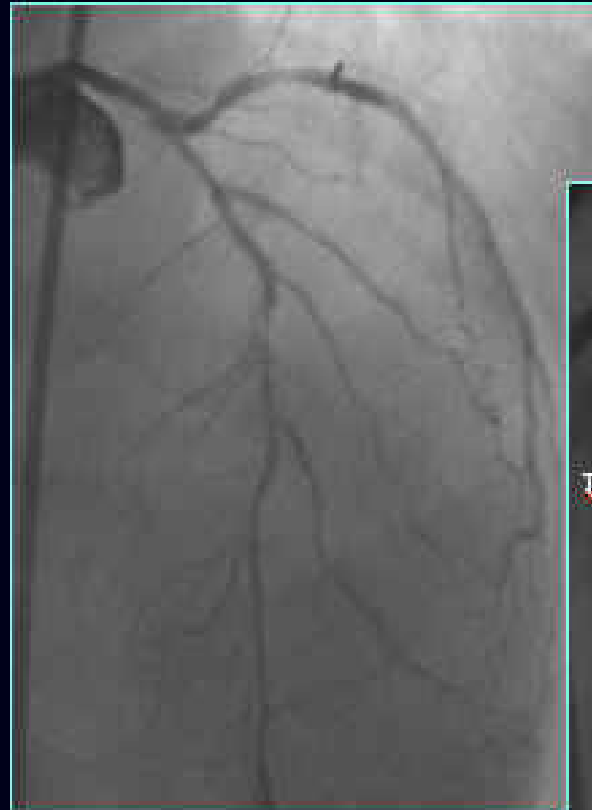


20% of pts with  
Late malapposition had  
Stent thrombosis

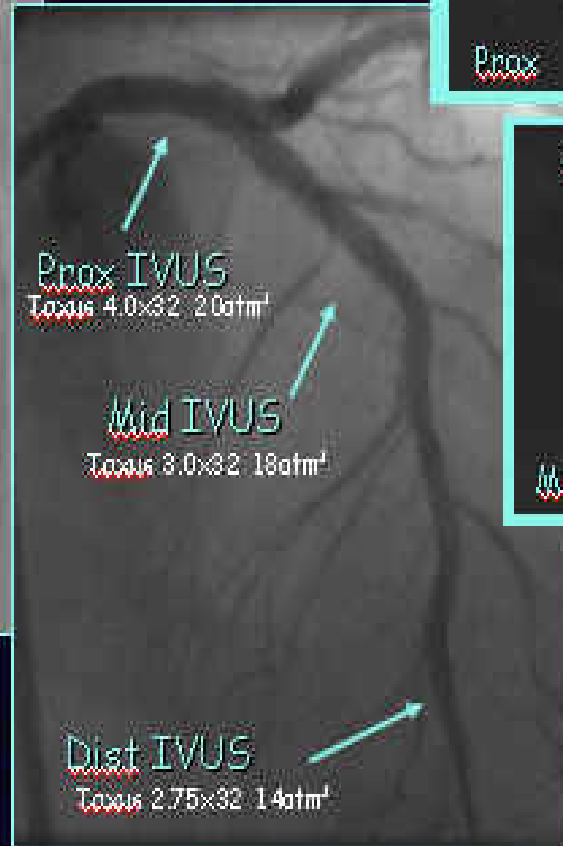
Can better stent implantation affect risk of late ST ?



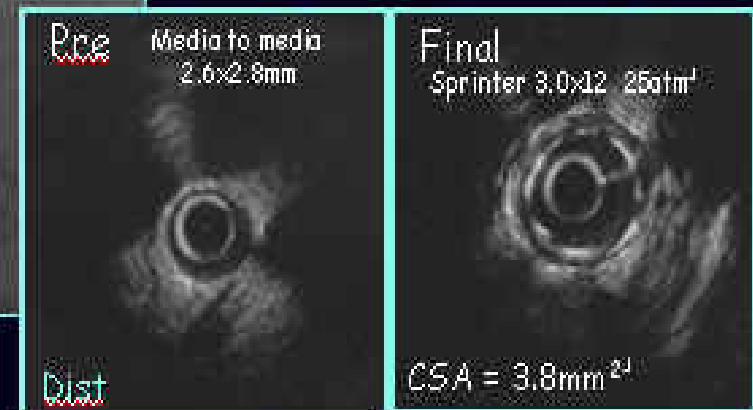
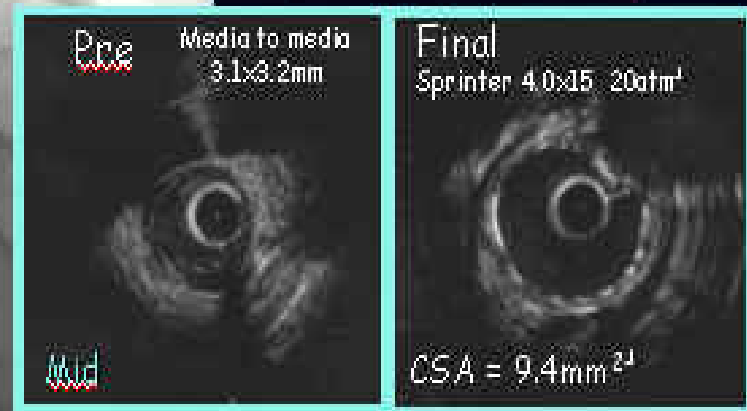
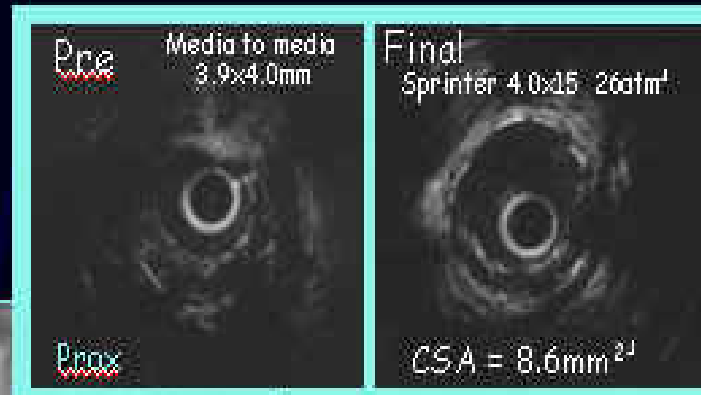
## Vessel sizing



**Baseline**



**Final Result**



# Conclusions I

- PCI in MVD is comparable to CABG in the composite end point of MI+CVE+death, still an advantage in favor of CABG is present in terms of repeated revascularizations>>>primary end-point of non inferiority in MACCE at 1 year not met in SYNTAX trial.
- The extent of disease evaluated with SYNTAX Score is important in order to assess the optimal therapy in MVD.
- Evaluation of DAT responsiveness, new antiplatelet agents, IVUS guidance and new DES could be helpful in improving our results.

## Conclusions II

- PCI in ULMCA is comparable to CABG in terms of MACCE. Results from SYNTAX should be interpreted as hypothesis generating (lack of statistical power). Conclusive information about the optimal treatment of LMCA will come only from prospective, randomized trial comparing CABG vs PCI with extended follow-up at least until 5 years.
- Further informations on optimal treatment of MVD in diabetes will come FREEDOM trial