

# Left Main Revascularization and the EXCEL Trial

## Evolution of Science, Method and Clinical Trial Design

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# Disclosure

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

<u>Affiliation/Financial Relationship</u>	<u>Company</u>
Grant/Research Support	Abbott Vascular, Boston Scientific, Medtronic CardioVascular
Consulting Fees/Honoraria	Boston Scientific Corporation, Medtronic CardioVascular, Micell Technologies, Biotronik, Thoratec
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

# Left Main Percutaneous Revascularization

## *Historical Perspective of Evidence, Anecdote and Misperception*

- Historical studies with balloon angioplasty or bare-metal stents reported at best inconsistent intermediate-term success and at worst unacceptably high rates of restenosis-related complications manifested as repeat revascularization or even sudden cardiac death<sup>1</sup>
- Early discouraging reports were confounded by poor patient selection and still-evolving procedural technique
- 2005 AHA/ACC/SCAI guidelines recommended against UPLM percutaneous revascularization as an optional therapy in individuals eligible for CABG (Class III) and support the indication with a still uncertain benefit (Class IIb) only in circumstances of excessive surgical risk<sup>2</sup>

<sup>1</sup>Kandzari et al. JACC 2009; <sup>2</sup>Smith et al. JACC 2006

# ULM PCI in the United States

## Trends in Performance and Outcome, 2004–2008

ULM PCI performed in 4.3% of patients in CathPCI Registry from 2004-2008 (N=5,627/131,004)

Annualized rates from 2004-2008 stagnant

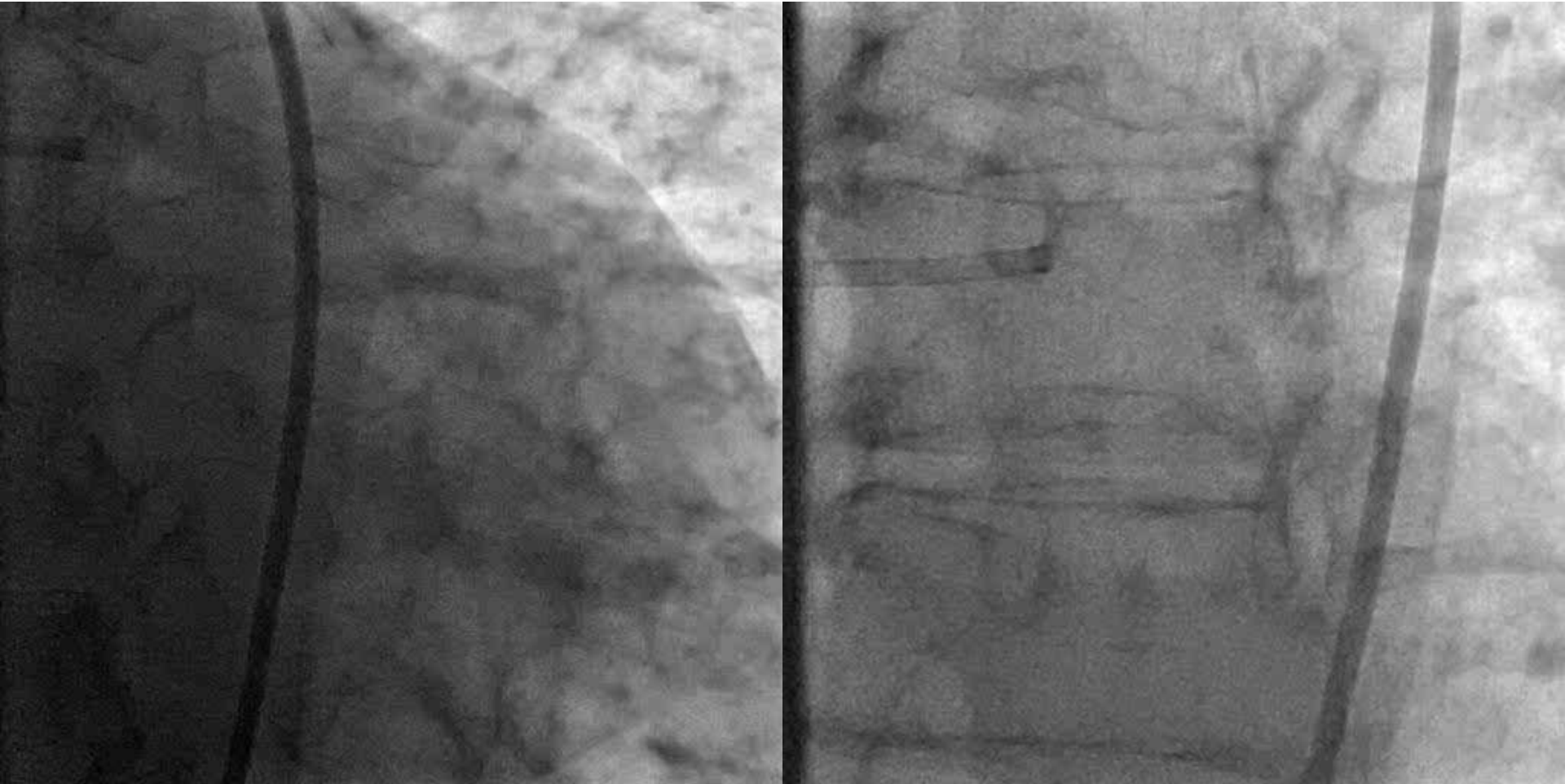
In-hospital mortality: 2.9% to 45.1%

By 30 months, 57.9% of Medicare-linked cohort ( $\geq 65$  years, N=2,765) experienced death (42.7%), MI (8.2%), or repeat revascularization (17.5%)

DES had lower 30-month mortality vs BMS (HR 0.84, 95% CI 0.73-0.96), but similar composite of major adverse events (HR 0.95, 95% CI 0.84-1.06)

# Then and Now: Left Main Revascularization 2014

58 yo male with diabetes, HTN; SYNTAX Score 25



# 2011 ACC/AHA PCI Guidelines

LM or Complex CAD

Heart Team Approach

Calculation of STS and SYNTAX Scores

I C

IIa B

# 2011 ACC/AHA PCI Guidelines

## LM Subset By Anatomy, Risk and Predicted Outcome

– Anatomy with a low risk of procedural complications and a high likelihood of good long-term outcome (SYNTAX score of  $\leq 22$ , ostial or trunk left main CAD), AND

IIa B

*Current guidelines do not address the much larger population of patients with low to intermediate complexity disease and who are eligible for CABG and PCI*

intermediate to high likelihood of good long-term outcome (low-intermediate SYNTAX score of  $< 33$ , bifurcation left main CAD), AND

– Characteristics predict increased surgical risk (moderate-severe COPD, disability from prior stroke, or prior cardiac surgery; STS-predicted risk of operative mortality  $> 2\%$ )

IIb B

Unfavorable anatomy for PCI and good candidates for CABG

III B

# 2013 Appropriateness Criteria

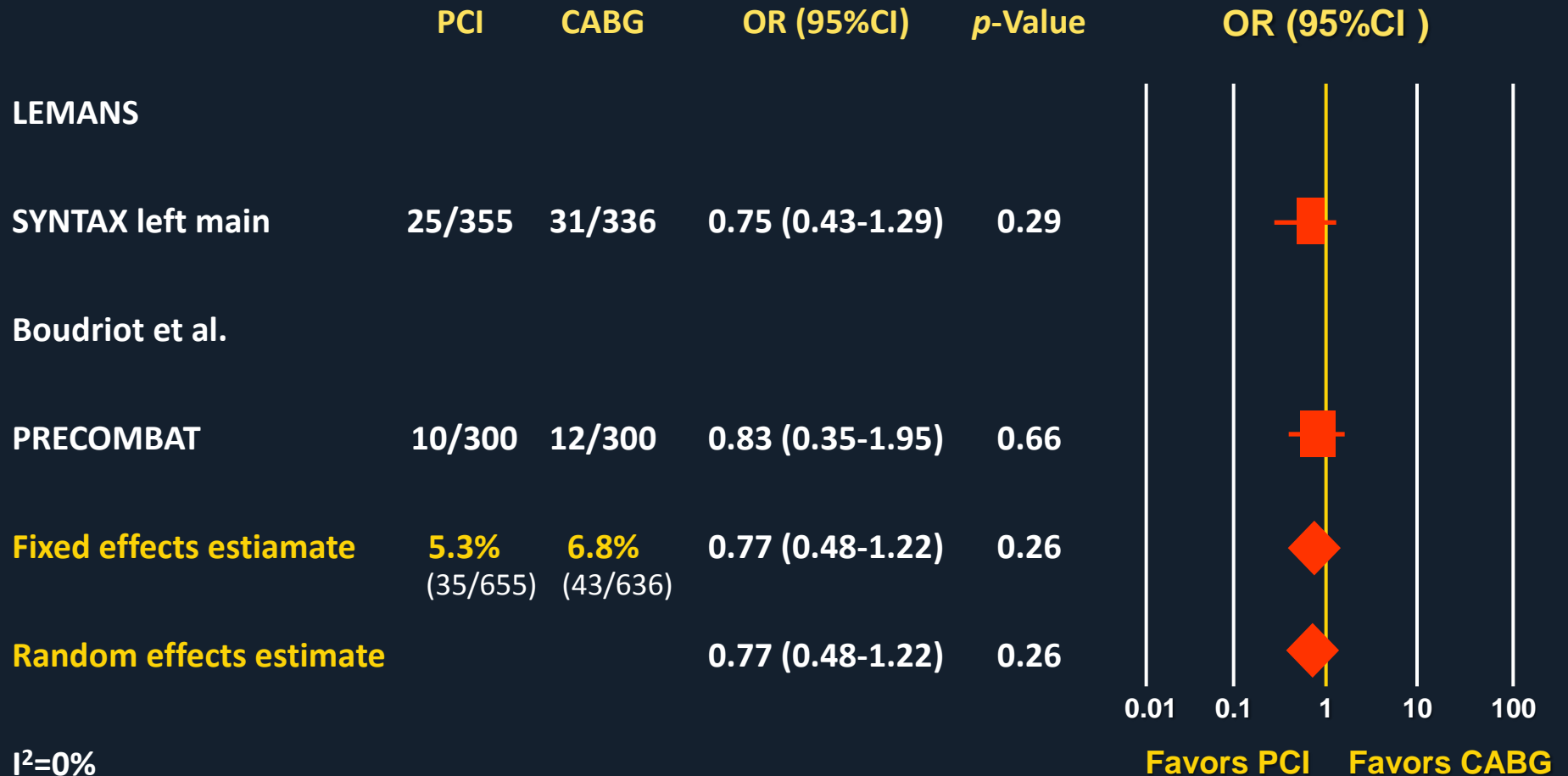
	CABG	PCI
Two-vessel CAD with proximal LAD stenosis	A	A
Three-vessel CAD with low CAD burden ( <i>ie</i> , three focal stenoses, low SYNTAX score)	A	A
Three-vessel CAD with intermediate to high CAD burden ( <i>ie</i> , multiple diffuse lesions, presence of CTO or high SYNTAX score)	A	M
Isolated left main stenosis	A	M
Left main stenosis and additional CAD with low CAD burden ( <i>ie</i> , 1- to 2-vessel additional involvement, low SYNTAX score)	A	M
Left main stenosis and additional CAD with intermediate to high CAD burden ( <i>ie</i> , three vessel involvement, presence of CTO or high SYNTAX score)	A	R



# PCI vs. CABG for Left Main Disease

## Meta-analysis of 4 RCTs, 1,611 Patients

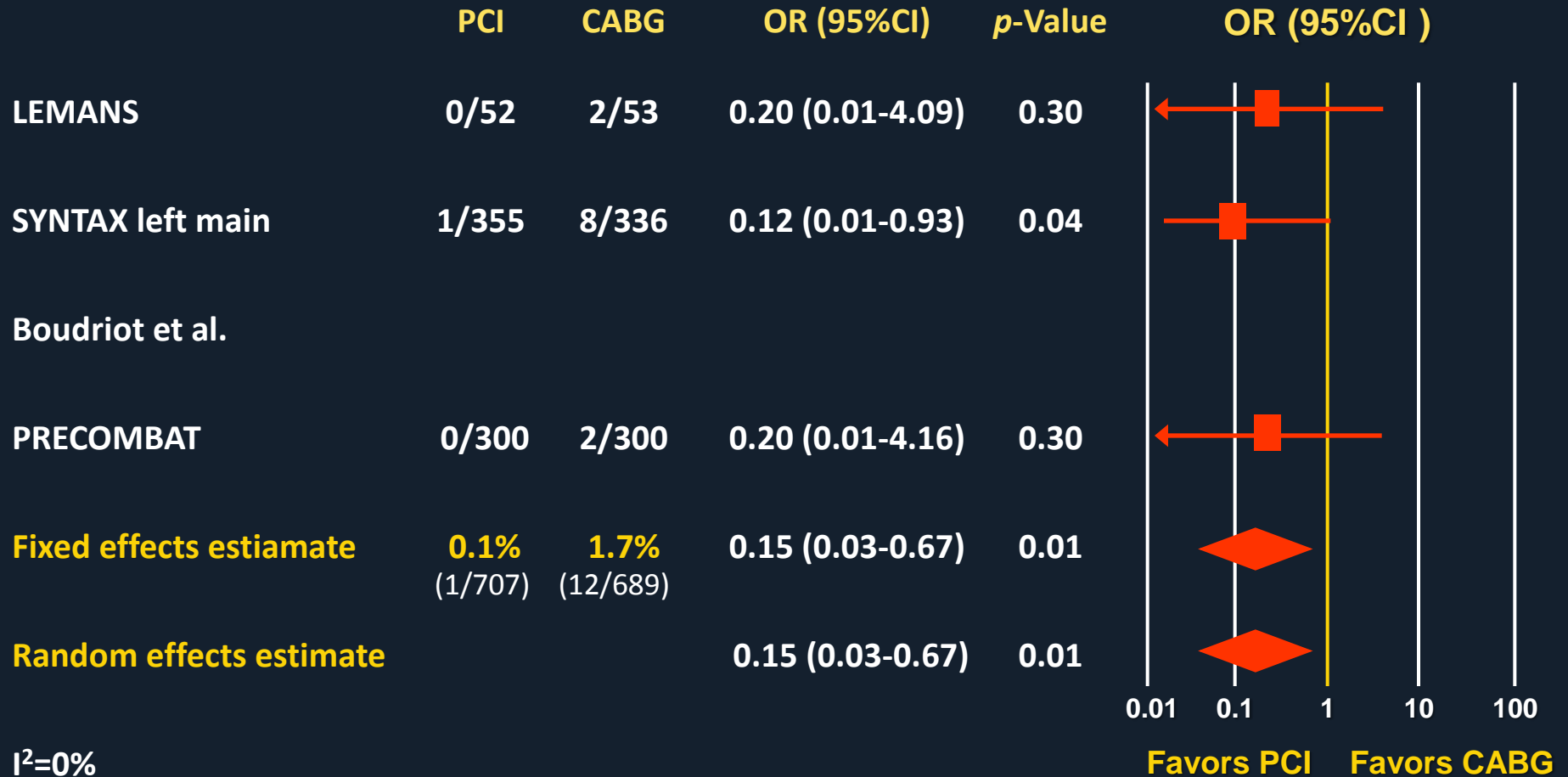
1 Year Death/MI/Stroke



# PCI vs. CABG for Left Main Disease

## Meta-analysis of 4 RCTs, 1,611 Patients

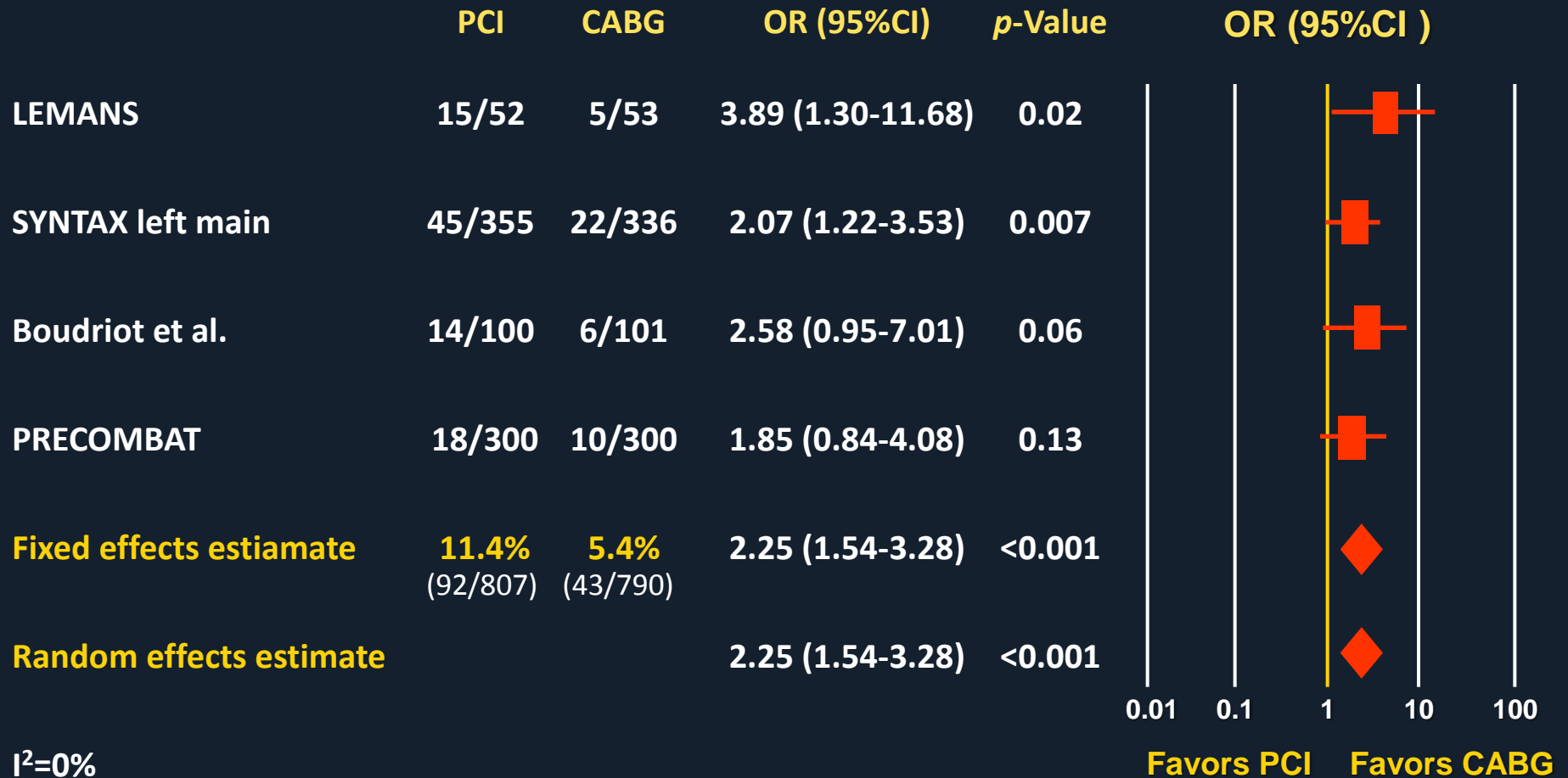
### 1 Year Stroke



# PCI vs. CABG for Left Main Disease

## Meta-analysis of 4 RCTs, 1,611 Patients

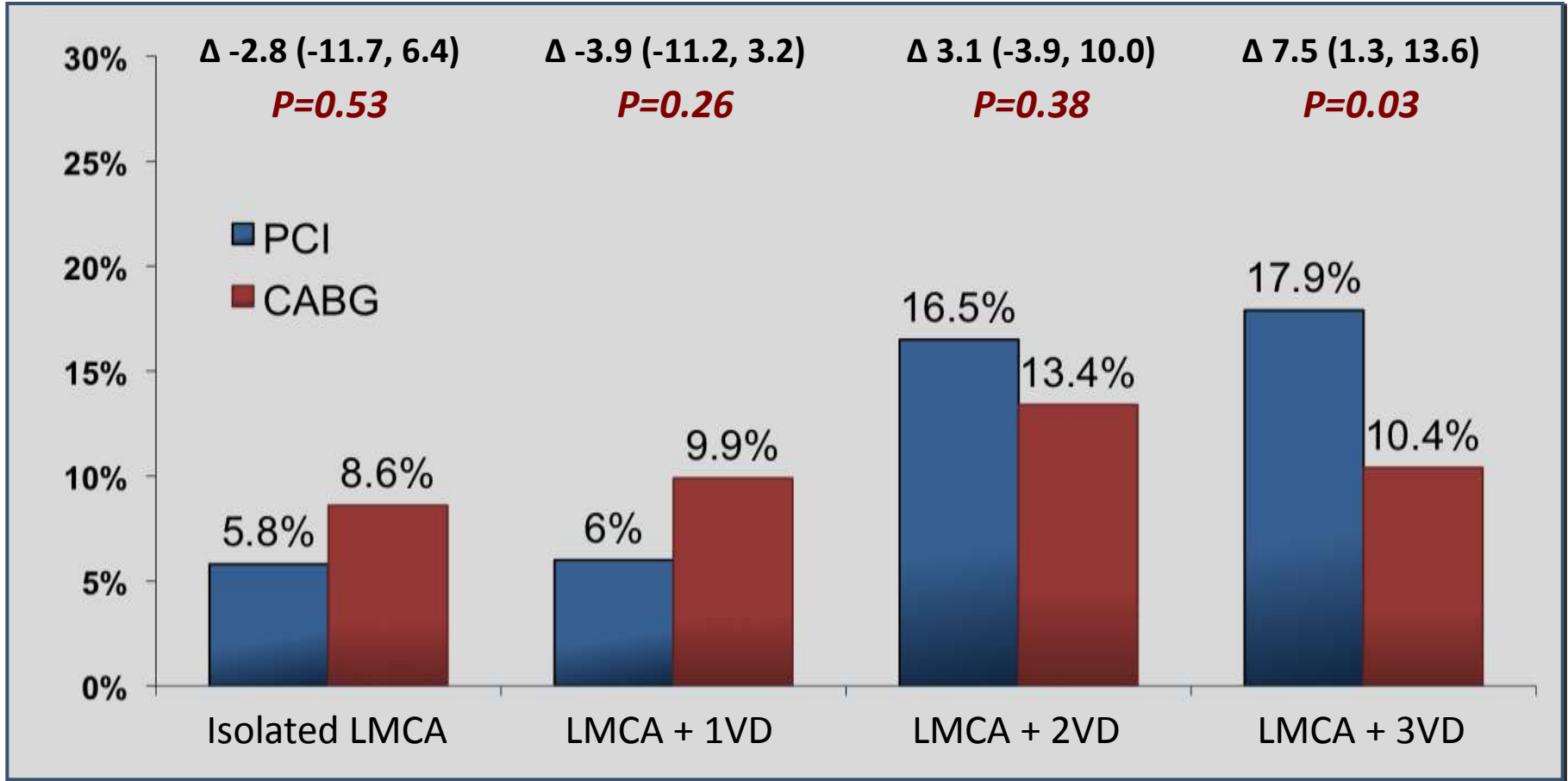
### 1 Year Repeat Revascularization



# PCI vs. CABG for Left Main Disease

## Meta-analysis of 4 RCTs, 1,611 Patients

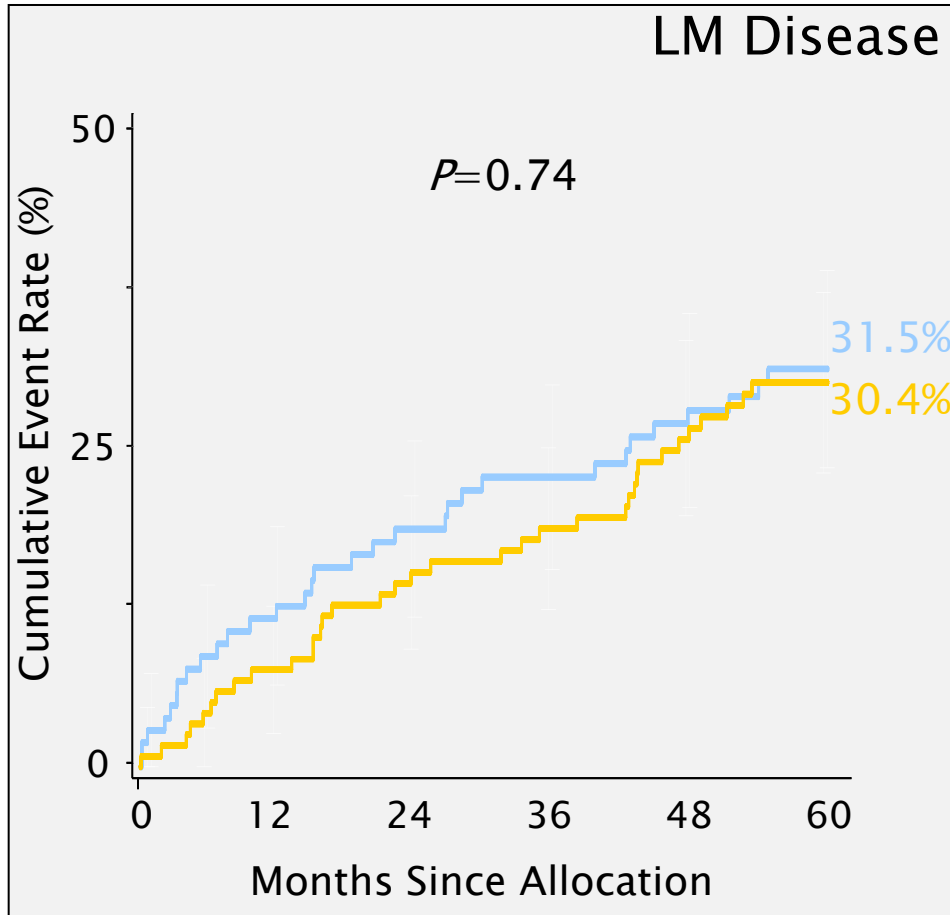
1 Year MACCE



# MACCE to 5 Years by SYNTAX Score Tercile

## LM Subset Low Scores 0-22

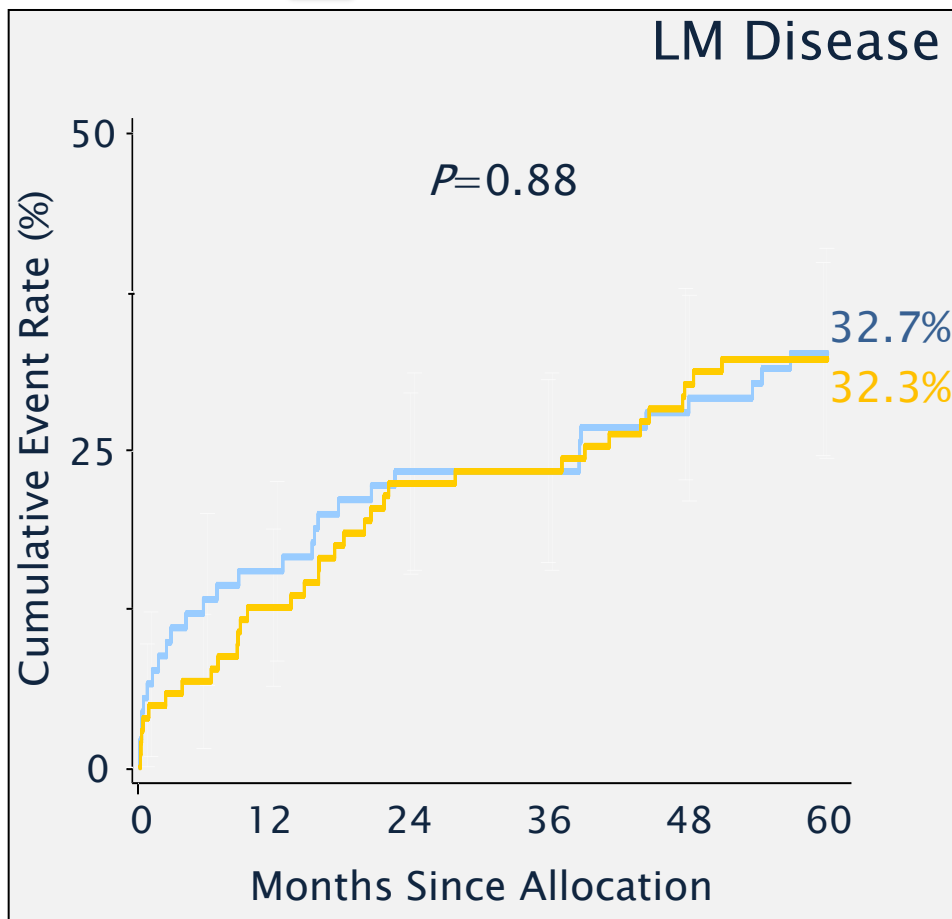
■ CABG (N=104)  
■ TAXUS (N=118)



	CABG	PCI	Pvalue
Death	11.3% >	7.0%	0.28
CVA	4.1% >	1.8%	0.28
MI	3.1% <	6.2%	0.32
Death, CVA or MI	15.2% >	13.9%	0.71
Revasc.	20.3% <	23.0%	0.65

# MACCE to 5 Years by SYNTAX Score Tercile LM Subset Intermediate Scores 23–32

■ CABG (N=92)  
■ TAXUS (N=108)



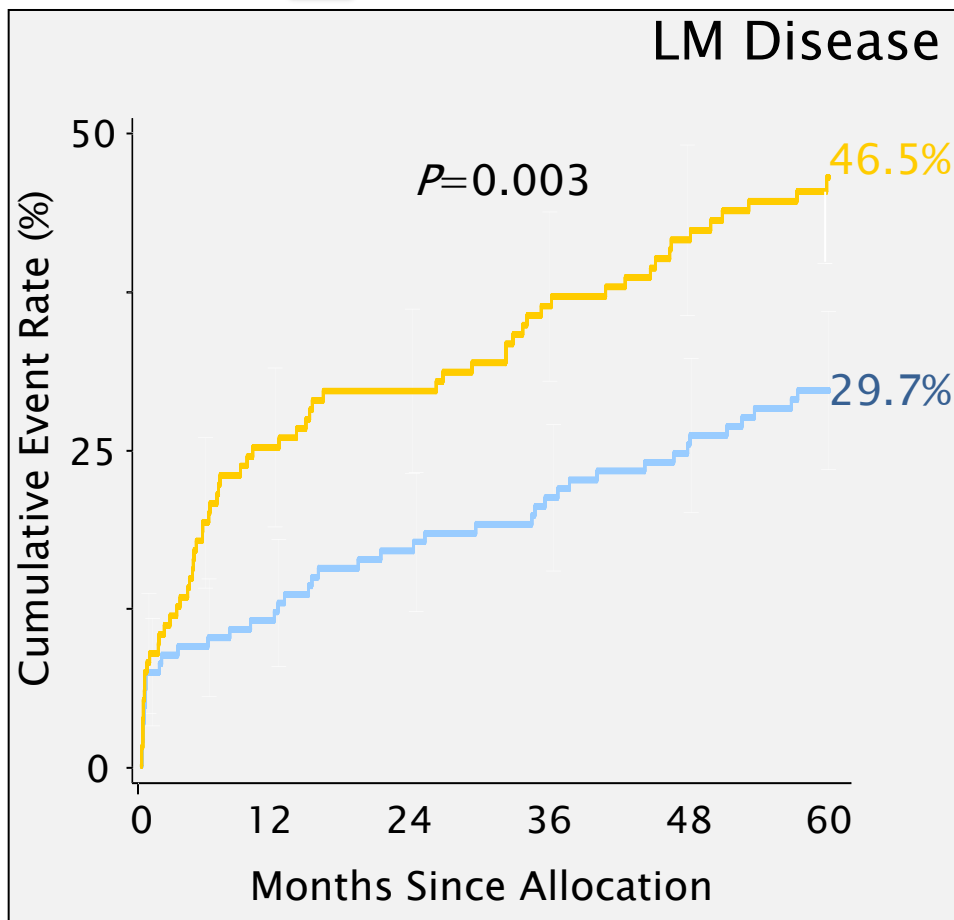
	CABG	PCI	Pvalue
Death	19.3% >	8.9%	0.04
CVA	3.6% >	1.0%	0.23
MI	4.6% <	6.0%	0.71
Death, CVA or MI	24.9% >	15.7%	0.11
Revasc.	16.6% <	22.2%	0.40

Cumulative KM Event Rate  $\pm$  1.5 SE; log-rank  $P$  value reported Data; ITT population  
Serruys P. TCT2012

# MACCE to 5 Years by SYNTAX Score Tercile

## LM Subset High Scores $\geq 33$

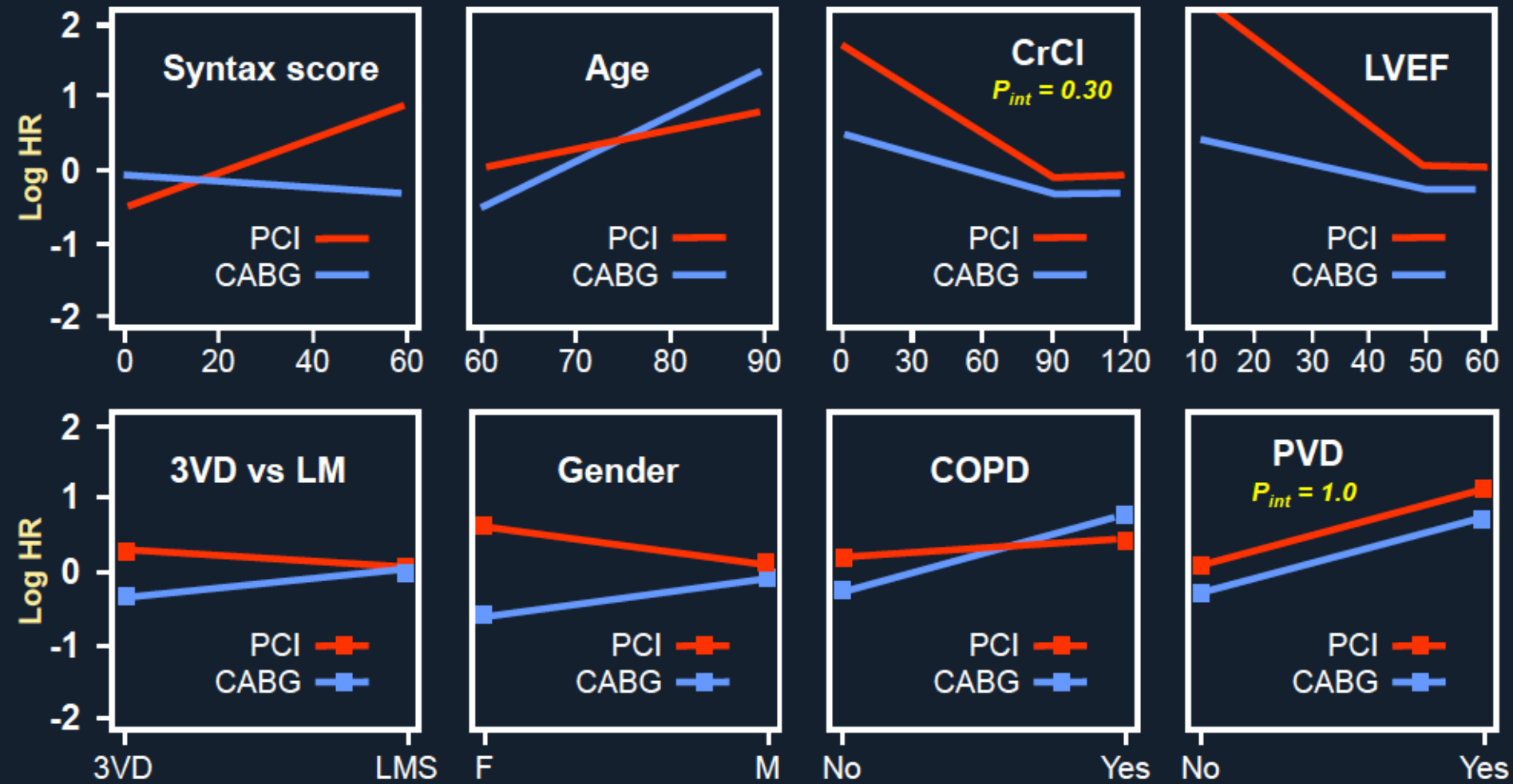
■ CABG (N=149)  
■ TAXUS (N=135)



	CABG	PCI	Pvalue
Death	14.1%	< 20.9%	0.11
CVA	4.9%	> 1.6%	0.13
MI	6.1%	< 11.7%	0.13
Death, CVA or MI	22.1%	< 26.1%	0.40
Revasc.	11.6%	< 34.1%	<0.001

# SYNTAX Score II

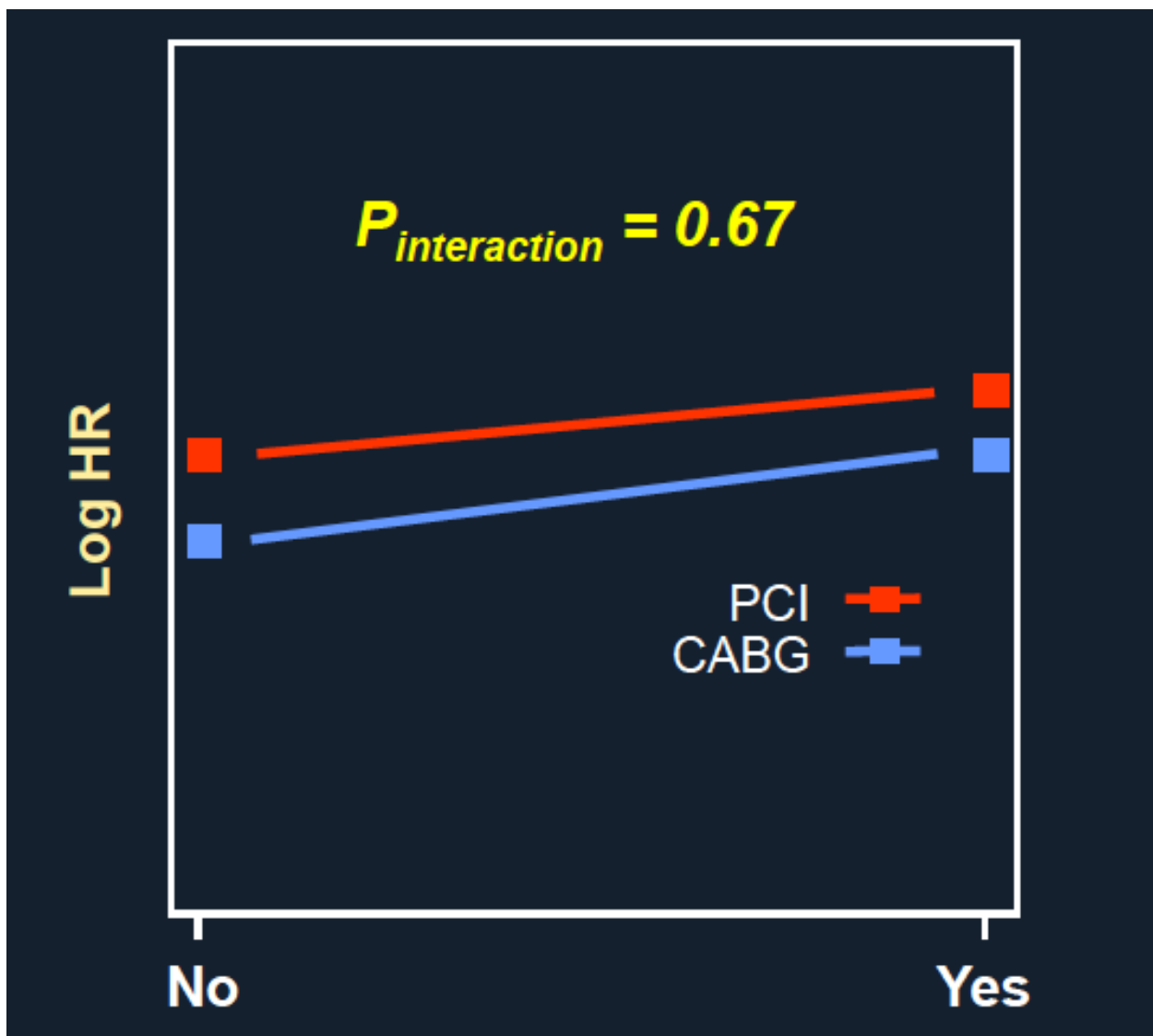
## CABG vs PCI Interactions





# SYNTAX Score II

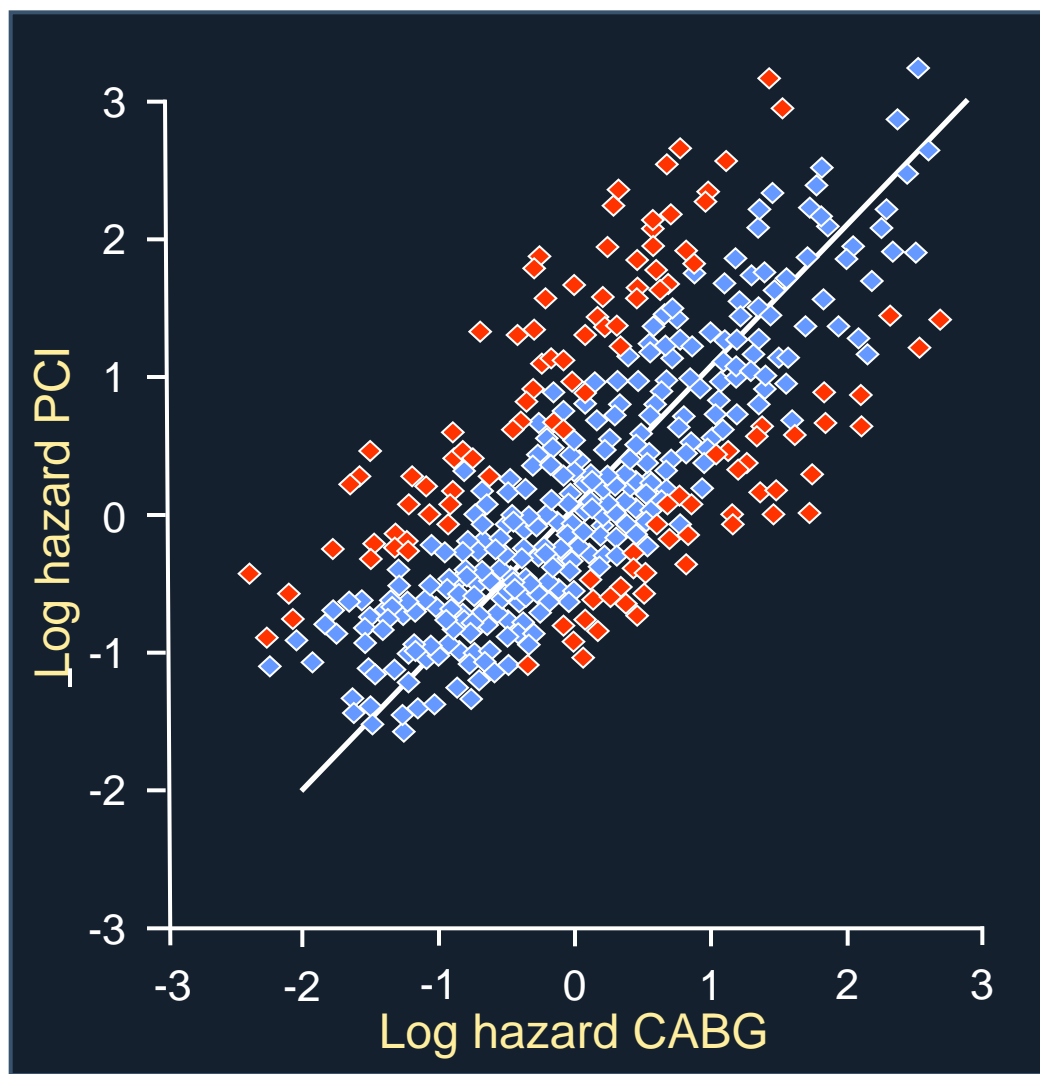
## Impact of Diabetes



*Diabetes was not an independent predictor or mortality or MACE for PCI or CABG and had a negative interaction term*

# SYNTAX Score II

## CABG vs PCI Interactions in LM Cohort



### CABG Favored

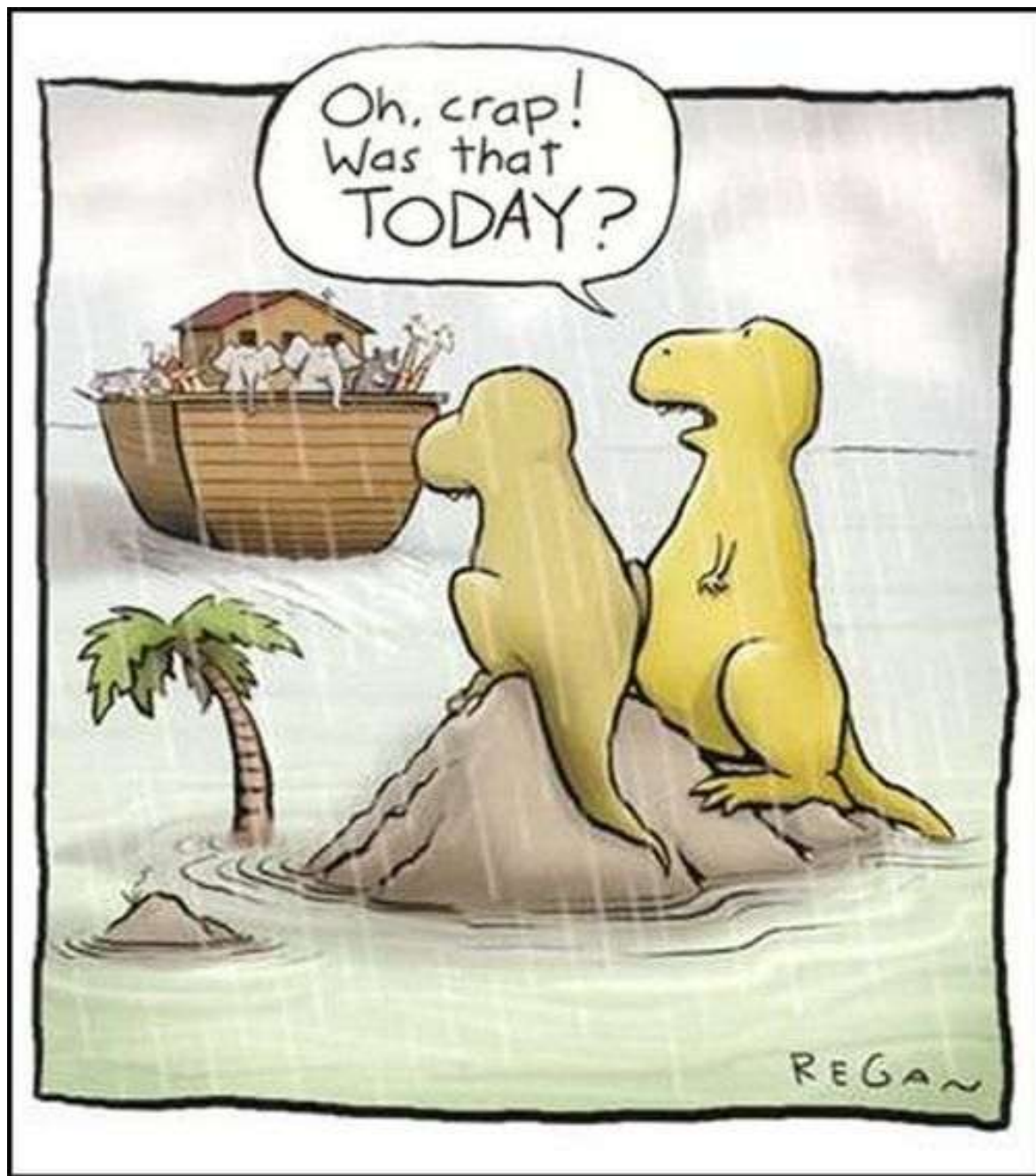
Overall 50.1%  
>95% CI 11.5%

### PCI Favored

Overall 49.9%  
>95% CI 8.8%

***79.7% lie within 95% CI***

Oh, crap!  
Was that  
TODAY?



# NOBLE

## Nordic-Baltic-British Left Main Revascularization Study

26 EU Sites

1200 pts with left main disease and  
 $\leq 3$  'non-complex' additional lesions

Randomize

Approx 1,000/1,200 pts enrolled  
March 1, 2014

DES

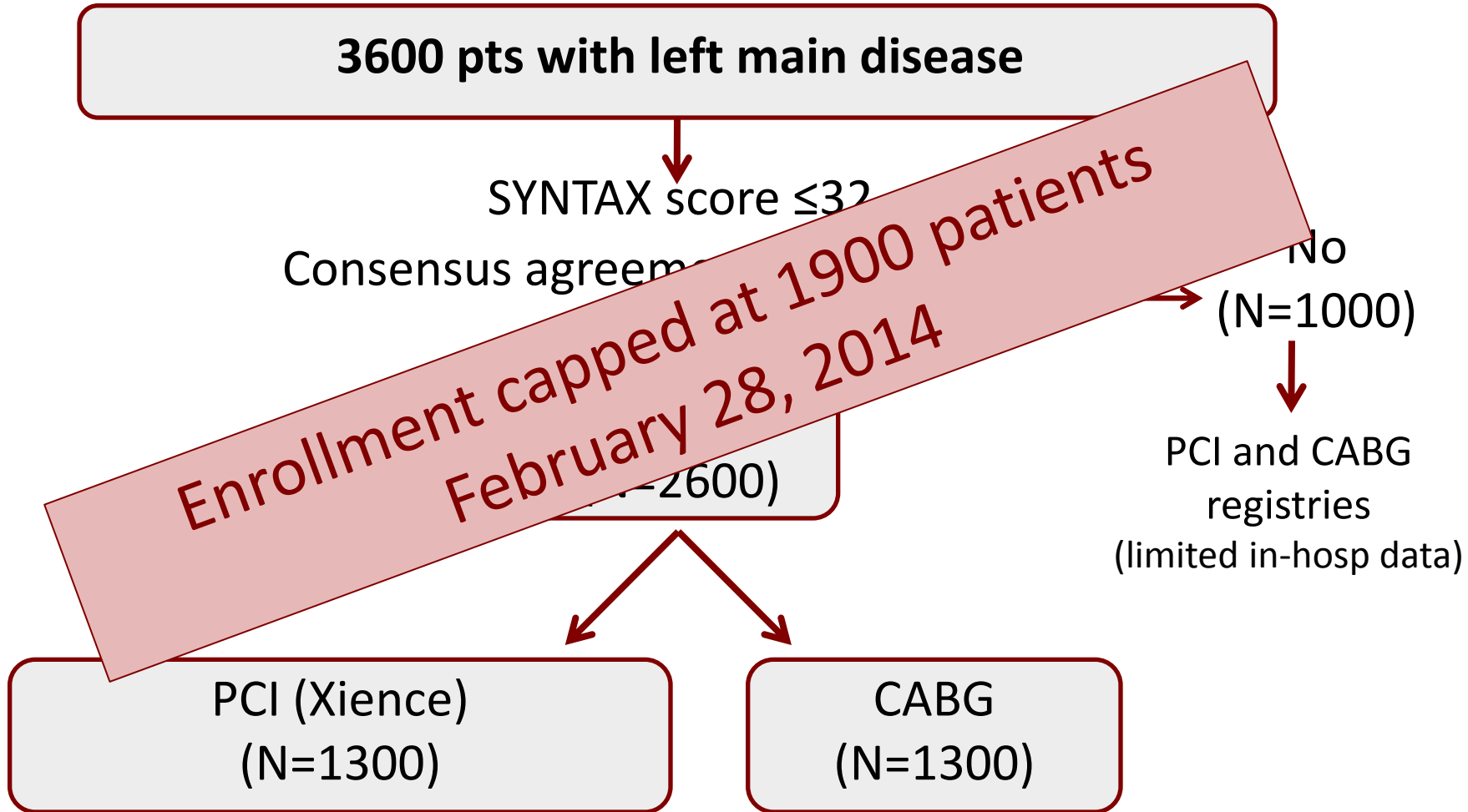
CABG  
(N=600)

Primary Endpoint: Death, MI, stroke or new  
revascularization at 2 years

# EXCEL

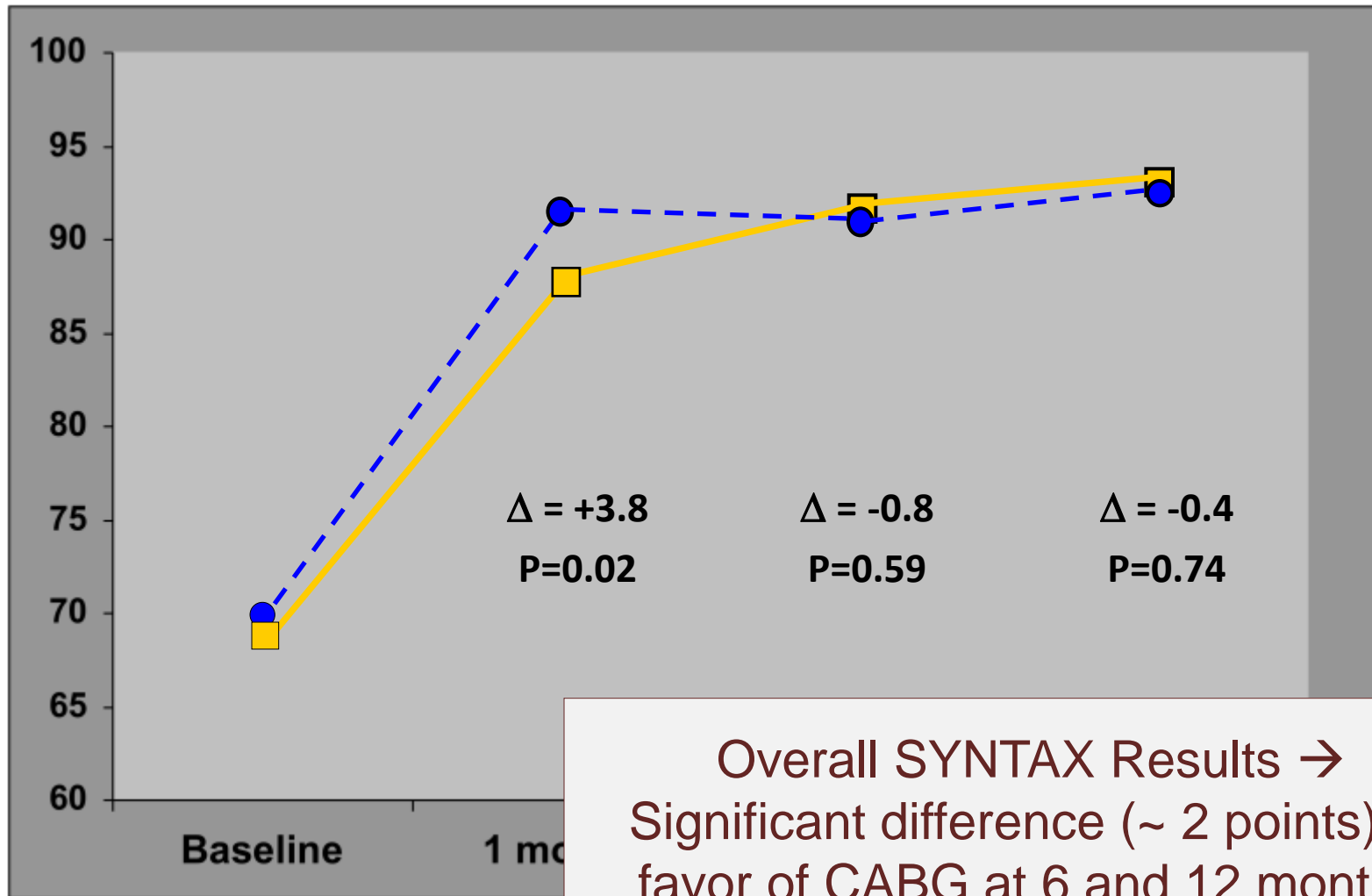
## Evaluation of Xience Prime versus CABG for Effectiveness of Left Main Revascularization

126 Sites in 17 Countries



Primary Endpoint: Death, MI or stroke at median follow-up 3 years

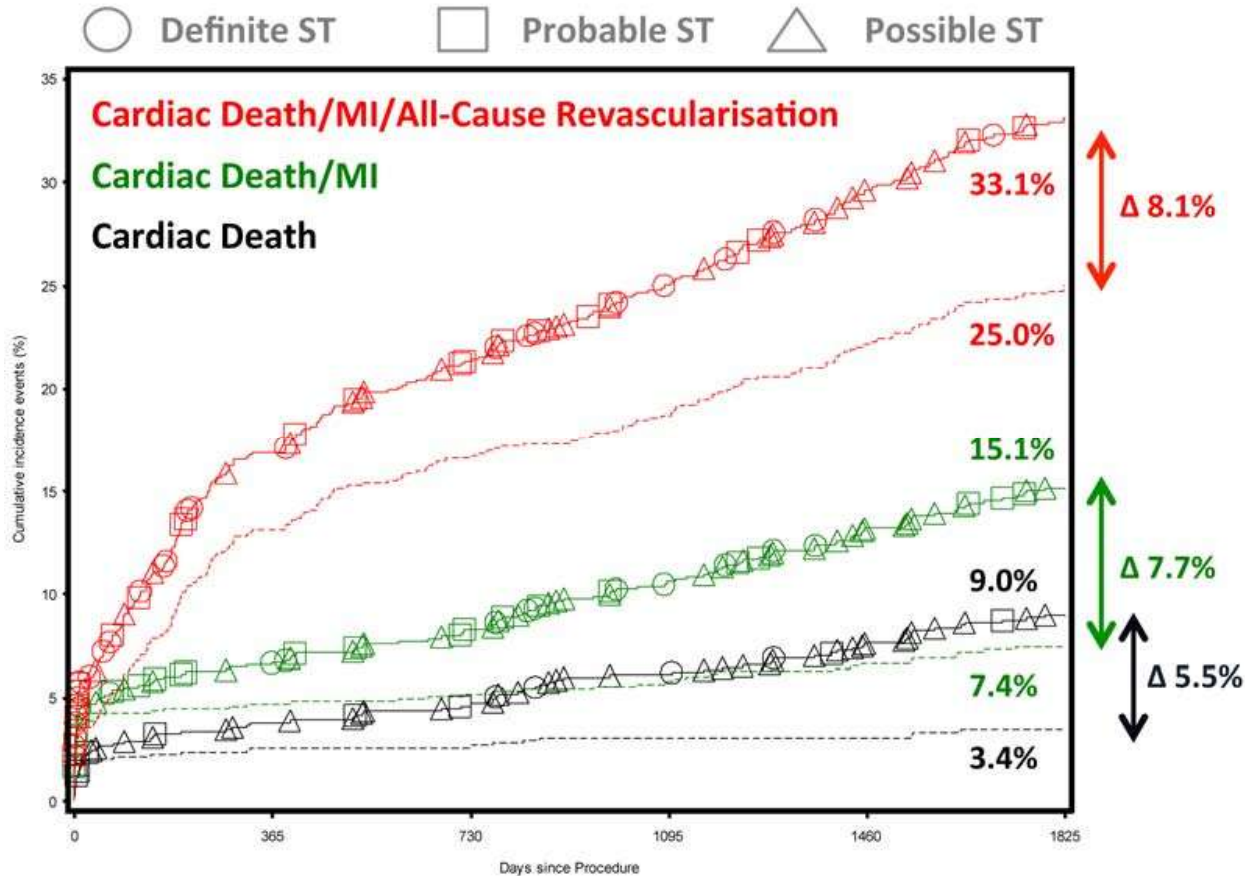
# SYNTAX LM Primary QOL Endpoint: SAQ-Angina Frequency



# Opportunities for Improvement

## Outcomes Attributable to Stent Thrombosis in SYNTAX Trial

*SYNTAX 5 yr Def/Prob ST 10.4% with 19.4% attributed to LM segment*



Δ5.1% for def/prob

Δ3.8% for def/prob

Δ1.5% for def/prob

*ΔCardiac Mortality (CABG-PCI) in SYNTAX: 3.7%*

# Core Laboratory vs Site SYNTAX Score Piedmont Experience

N=106

	Core Lab SS	Site SS	Difference
Min	11	10	0
Max	48	32	20
Mean	25.2	23.4	5.1
SD	8.0	6.6	5.1

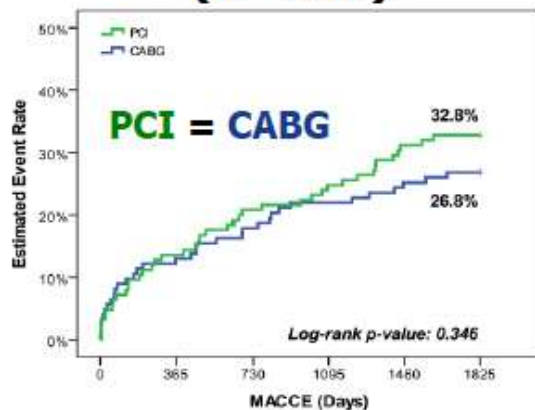
Cases over 33	18	17.6%
Cases over 33 with >5 pt difference	13	



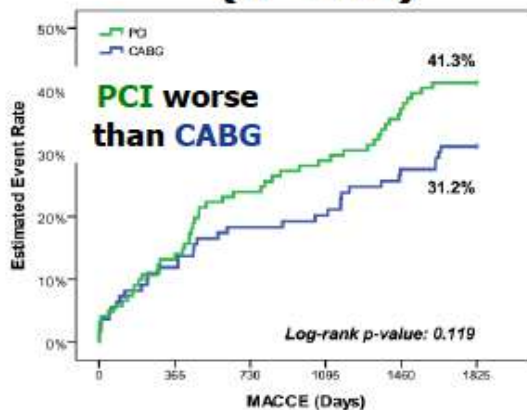
# MACCE in LM Cohort Based on Site SYNTAX Score

Subgroups using traditional cut-off values derived from the Syntax trial (0-22, 23-32,  $\geq 33$ )

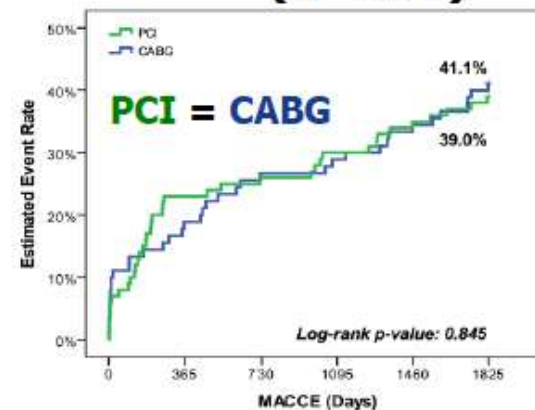
**Low**  
(n=266)



**Interm**  
(n=245)

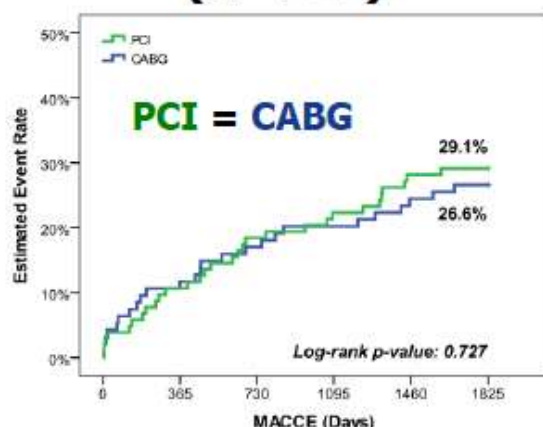


**High**  
(n=194)

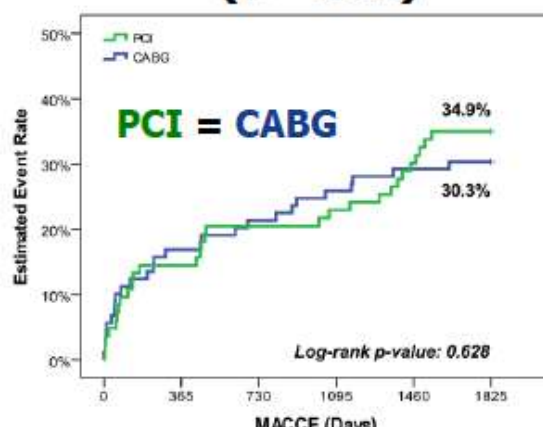


Subgroup using new tertiles (0-19, 20-27,  $\geq 28$ )

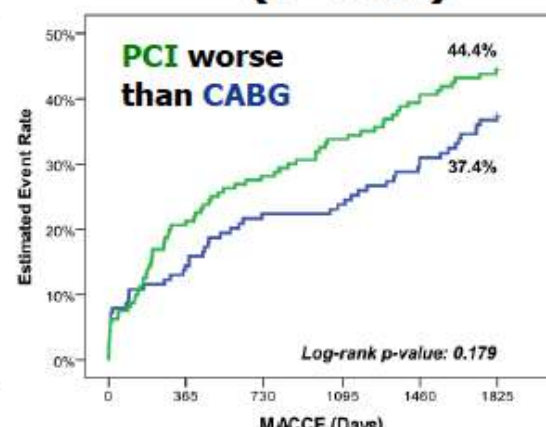
**Low**  
(n=211)



**Interm**  
(n=182)



**High**  
(n=312)



# LM Revascularization and EXCEL in Perspective

- › SYNTAX and like trials suggest a role for both PCI and CABG in overlapping subgroups with LM disease
  - › Especially relevant for pts with low/intermediate SYNTAX score
- › Practicality of application and validity of newer risk scores that incorporate clinical demographics is evolving
- › Elements of contemporary trials do encourage expansion of PCI strategy (*eg*, hard endpoints, cost/QOL) but guidelines-directed therapy and AUC remain restrictive
- › EXCEL represents an opportunity to advance LM revascularization guidance, inform/resolve diabetic dilemma, and examine factors related to quality of life, recovery
- › EXCEL (and NOBLE) will address whether LM PCI is non-inferior to CABG among pts with low to intermediate complexity disease

**EXCEL Results Expected 2016**