Revascularization in Multivessel CAD
PCI vs. CABG

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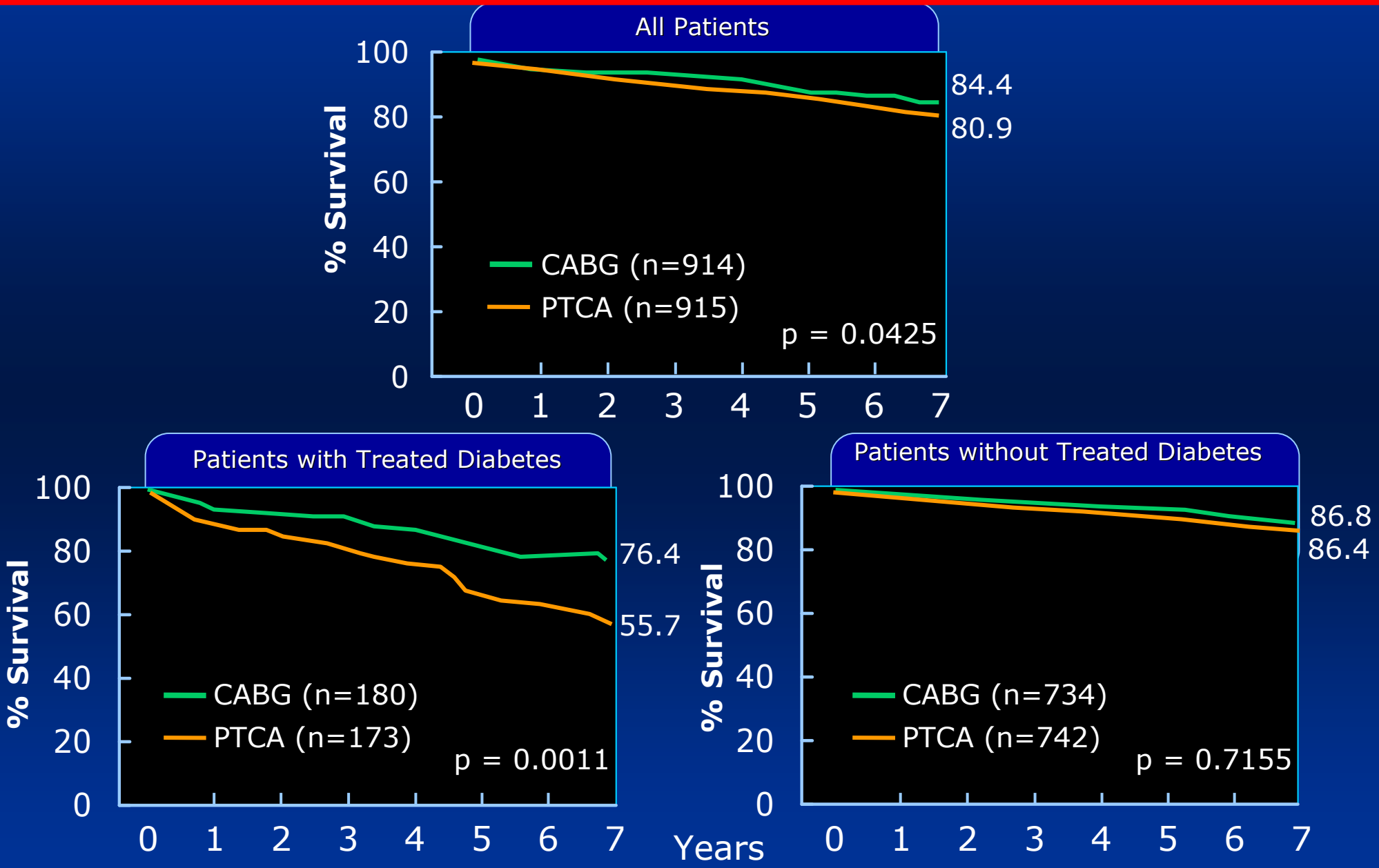
7-year Survival in BARI Trial

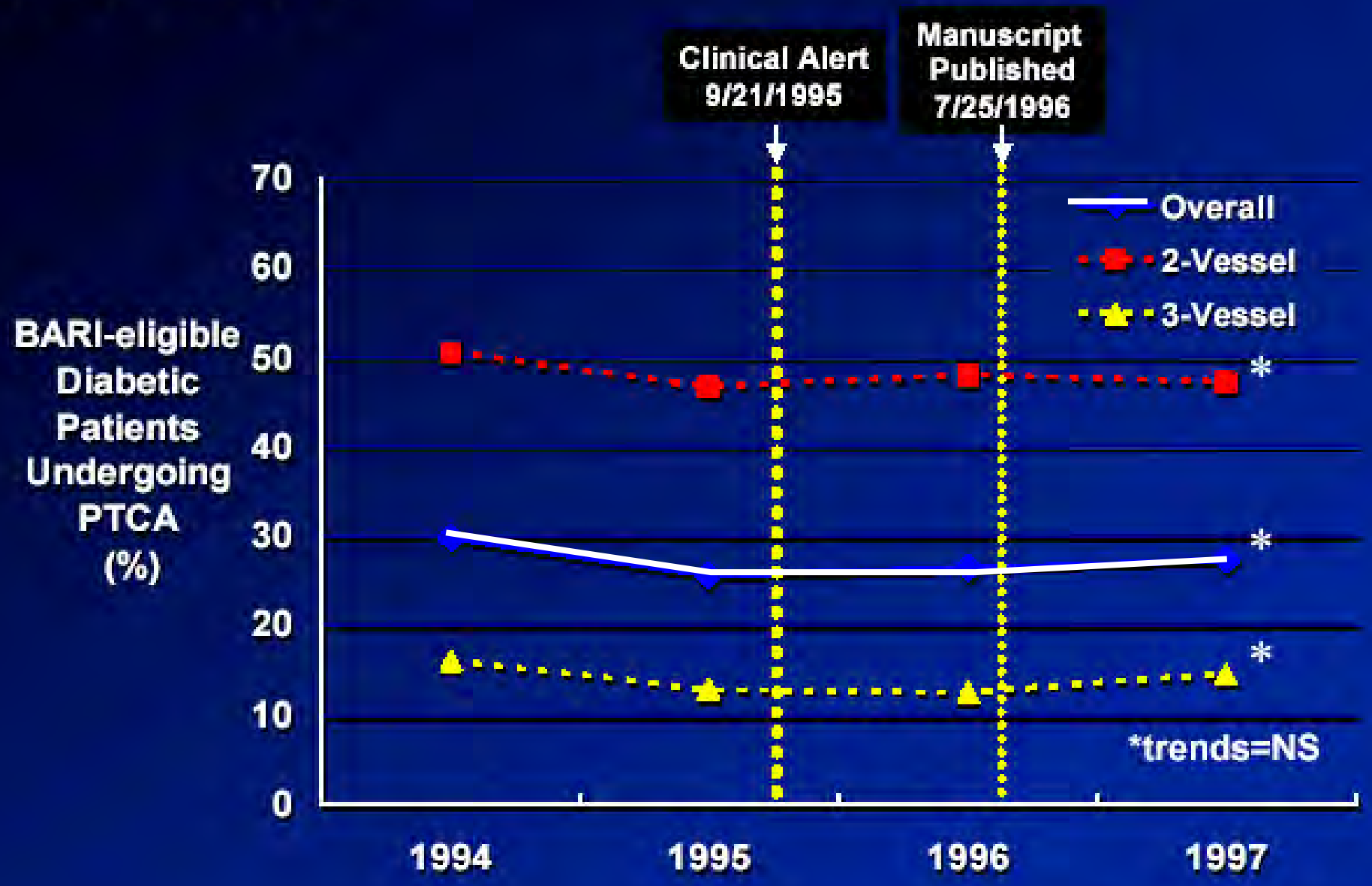


BARI Investigators. NEJM 1996 and JACC 2000

BARI – Conclusion Diabetic Patients

- Clinical alert to physicians by the NHLBI (National Heart, Lung and Blood Institute)
  - CABG is the better revascularization alternative in diabetic patients with multivessel disease suitable for both PTCA and CABG
- However

Revascularization trends before and after BARI



McGuire et al, Circ 2003; 107: 1864-187.

מה השתנה מאז מחקר BARI

- Surgical Technique
  - Arterial grafts, Off pump etc.
- PCI Technique
  - BMS, DES, Adjunct pharmacology
- Medical Treatment
  - Statins, Antihypertensives, Antidiabetics, Antiplatelets etc.

מה מהשינויים הנ"ל משמעותי ביותר בהקשר לתוצאות BARI?

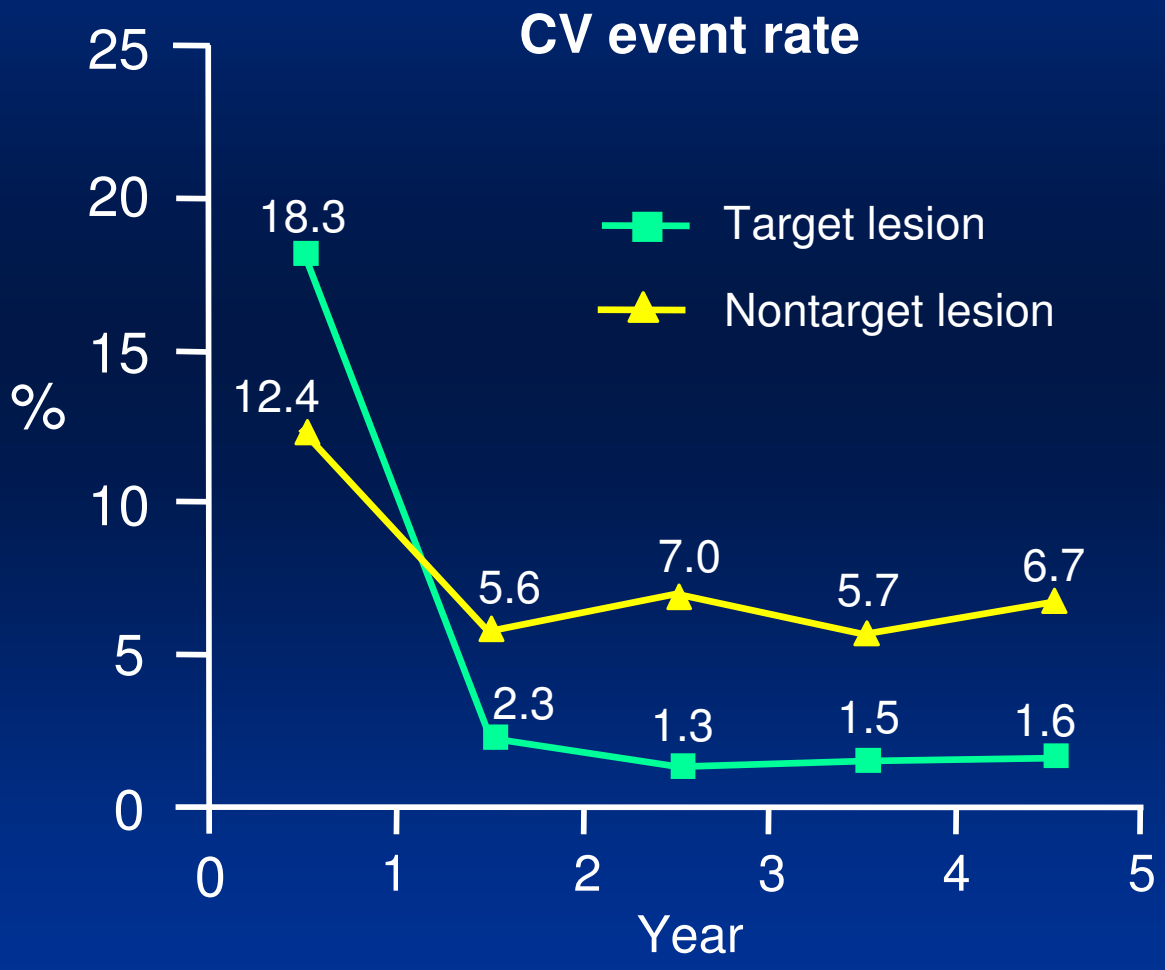
ארועים חוזרים לאחר רווסקולריזציה מוצלחת
PCI or CABG

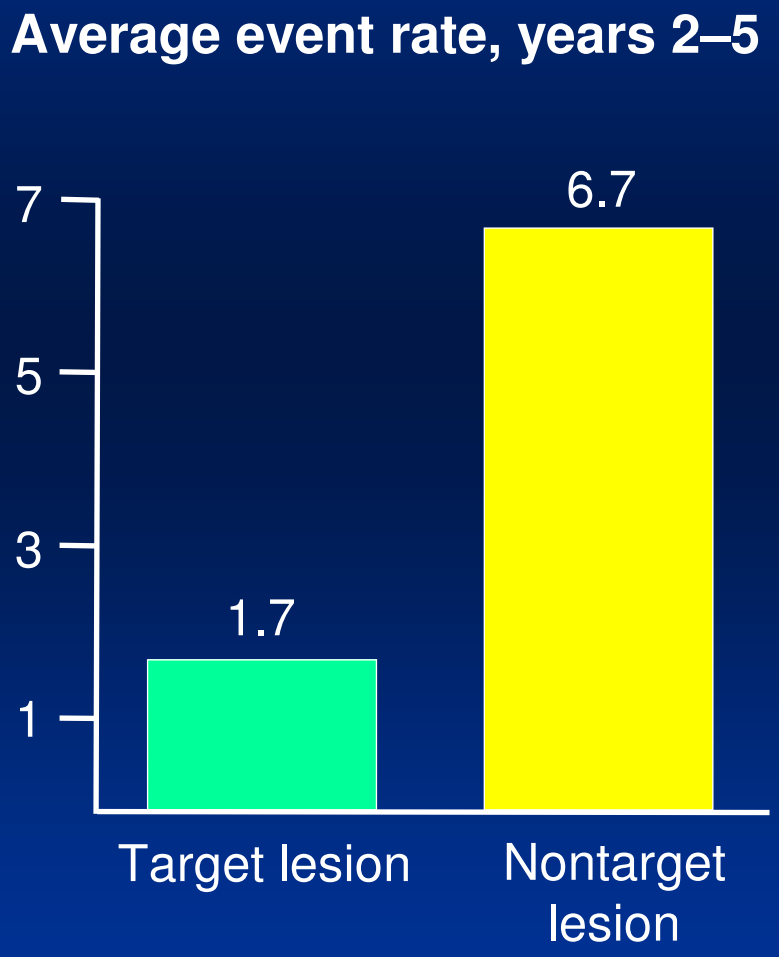
- בטווח הקצר - כשנה
  - רסטנוזיס / טרומבוזיס אחרי PCI
  - חסימת שתל לאחר ניתוח

- בטווח הארוך
  - כשלון מעקפים לאחר CABG
  - פרוגרסיה של הטרשת

Disease progression in non-stented lesions causes most late CV events

N = 1228 in 2nd-generation coronary stent trials*





*Non-drug eluting stents

Cutlip DE et al. *Circulation*. 2004;110:1226-30.

ארועים חוזרים לאחר רווסקולריזציה <u>מוצלחת</u>
PCI or CABG

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המשמעותי ביותר לטווח הארוך – טיפול תרופתי

CABG vs. PCI: Randomized Trial Results Summary

- CABG has NO clear death/MI benefit over PCI in patients suitable for either
- CABG historically showed benefit over PCI in repeat revascularization

Superior Treatment Modality

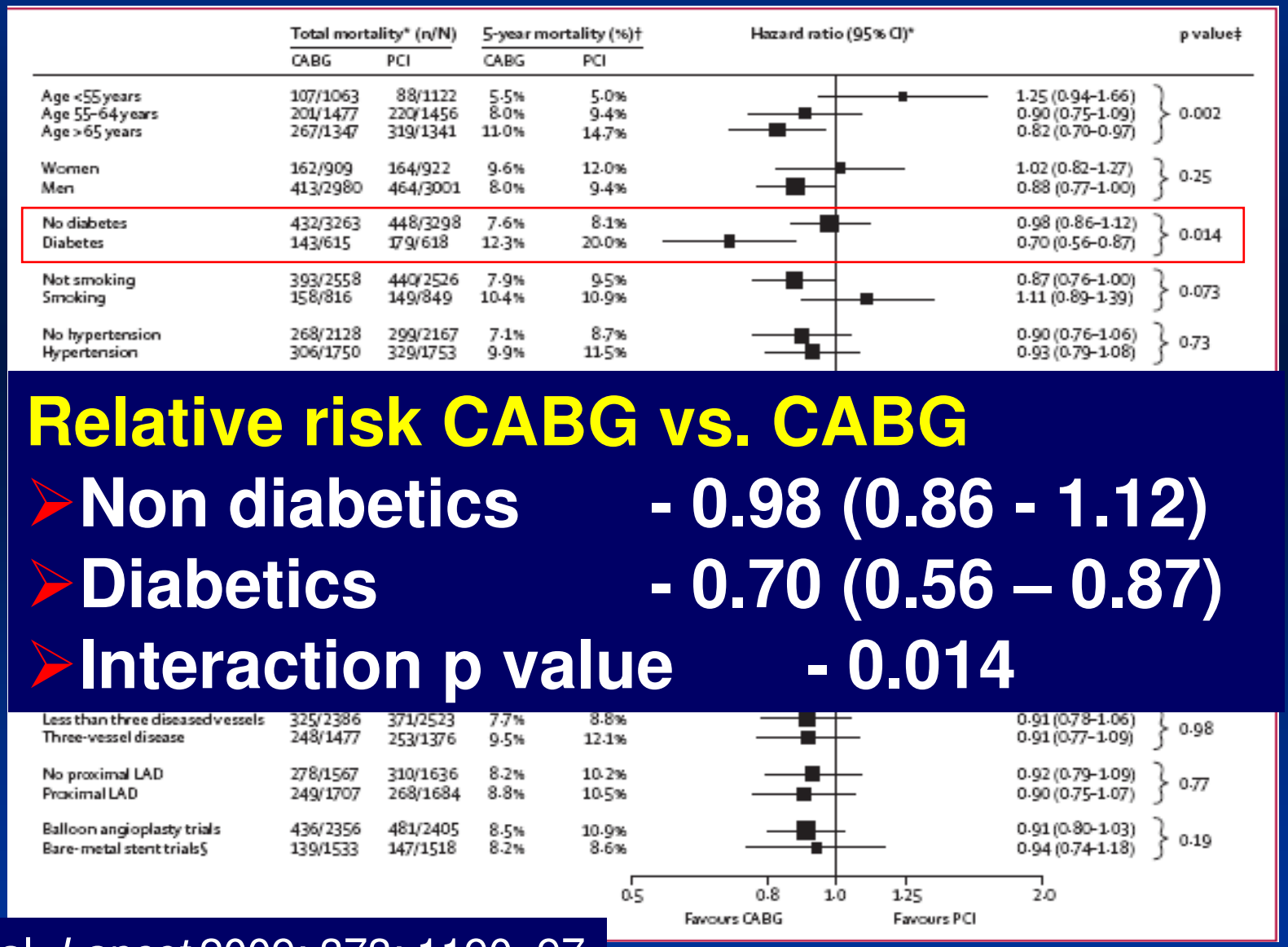
CABG | PCI | No difference

	Trial	Clinical Parameters: Mortality & MI	Clinical Parameters: Angina Relief	Clinical Parameters: Repeat Revascularization
POBA	GABI	PCI	PCI	CABG
	EAST	No difference	CABG	CABG
	RITA	No difference	CABG	CABG
	ERACI	No difference	CABG	CABG
	CABRI	No difference	CABG	CABG
	BARI	No difference	n/a	CABG
BMS	MASS-2	CABG (MI)	n/a	CABG
	AWESOME	No difference	No difference	CABG
	ERACI-2	PCI	n/a	CABG
	SoS	CABG (Mortality)	CABG	CABG
	ARTS	No difference	n/a	CABG

Source references listed in appendix

5 year Mortality of CABG vs. PCI:

a collaborative analysis of individual patient data from ten randomised trials



	Total mortality* (n/N)		5-year mortality (%)†		Hazard ratio (95% CI)*	p value‡
	CABG	PCI	CABG	PCI		
Age <55 years	107/1063	88/1122	5·5%	5·0%	1·25 (0·94–1·66)	
Age 55–64 years	201/1477	220/1456	8·0%	9·4%	0·90 (0·75–1·09)	0·002
Age >65 years	267/1347	319/1341	11·0%	14·7%	0·82 (0·70–0·97)	
Women	162/909	164/922	9·6%	12·0%	1·02 (0·82–1·27)	0·25
Men	413/2980	464/3001	8·0%	9·4%	0·88 (0·77–1·00)	
No diabetes	432/3263	448/3298	7·6%	8·1%	0·98 (0·86–1·12)	0·014
Diabetes	143/615	179/618	12·3%	20·0%	0·70 (0·56–0·87)	
Not smoking	393/2558	440/2526	7·9%	9·5%	0·87 (0·76–1·00)	0·073
Smoking	158/816	149/849	10·4%	10·9%	1·11 (0·89–1·39)	
No hypertension	268/2128	299/2167	7·1%	8·7%	0·90 (0·76–1·06)	0·73
Hypertension	306/1750	329/1753	9·9%	11·5%	0·93 (0·79–1·08)	
Less than three diseased vessels	325/2386	371/2523	7·7%	8·8%	0·91 (0·78–1·06)	0·98
Three-vessel disease	248/1477	253/1376	9·5%	12·1%	0·91 (0·77–1·09)	
No proximal LAD	278/1567	310/1636	8·2%	10·2%	0·92 (0·79–1·09)	0·77
Proximal LAD	249/1707	268/1684	8·8%	10·5%	0·90 (0·75–1·07)	
Balloon angioplasty trials	436/2356	481/2405	8·5%	10·9%	0·91 (0·80–1·03)	0·19
Bare-metal stent trials§	139/1533	147/1518	8·2%	8·6%	0·94 (0·74–1·18)	

0·5 0·8 1·0 1·25 2·0

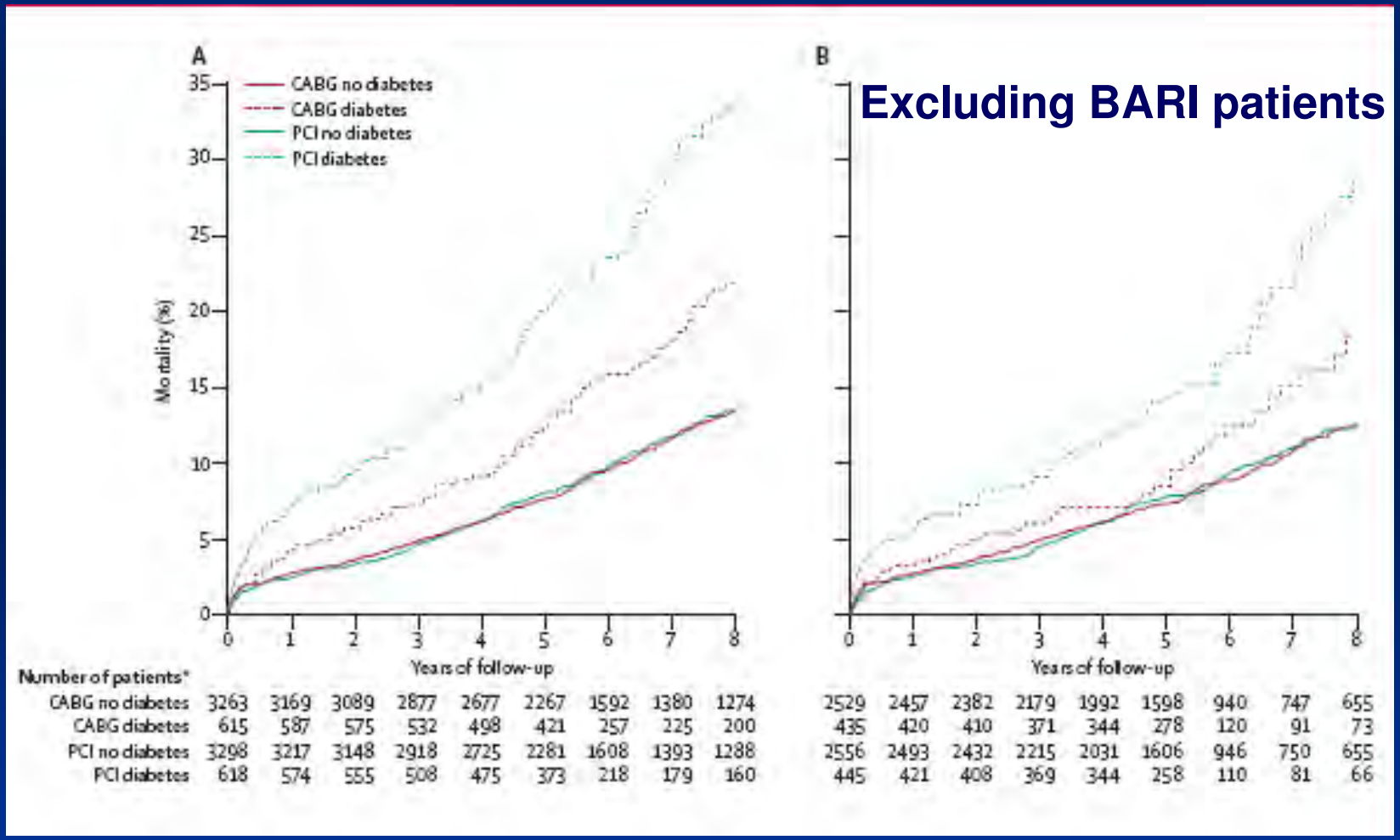
Favours CABG Favours PCI

Relative risk CABG vs. CABG

- Non diabetics - 0.98 (0.86 - 1.12)
- Diabetics - 0.70 (0.56 – 0.87)
- Interaction p value - 0.014

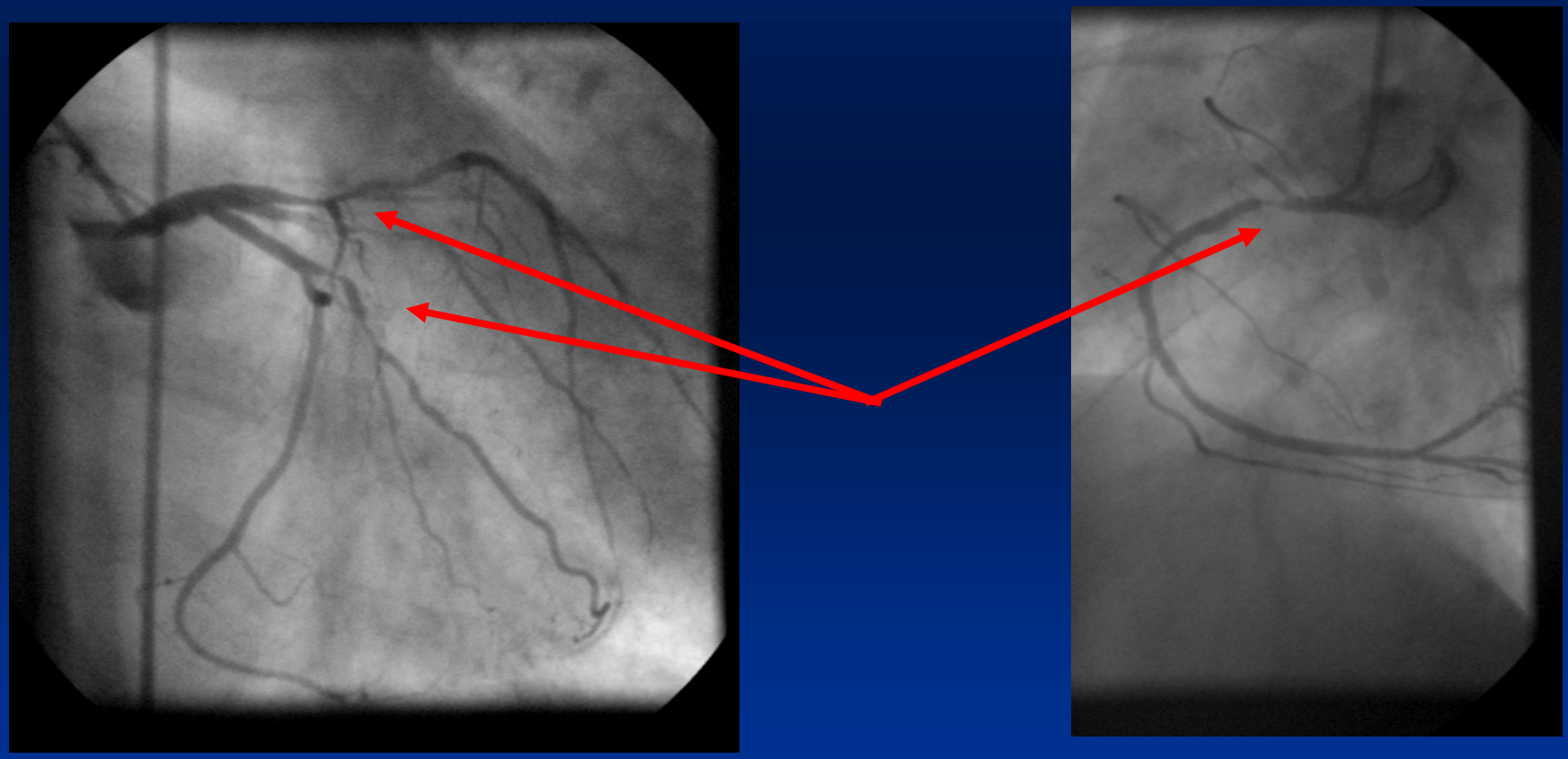
Hlatky et al. *Lancet* 2009; 373: 1190–97

Mortality of CABG vs. PCI: a collaborative analysis of individual patient data from ten randomised trials

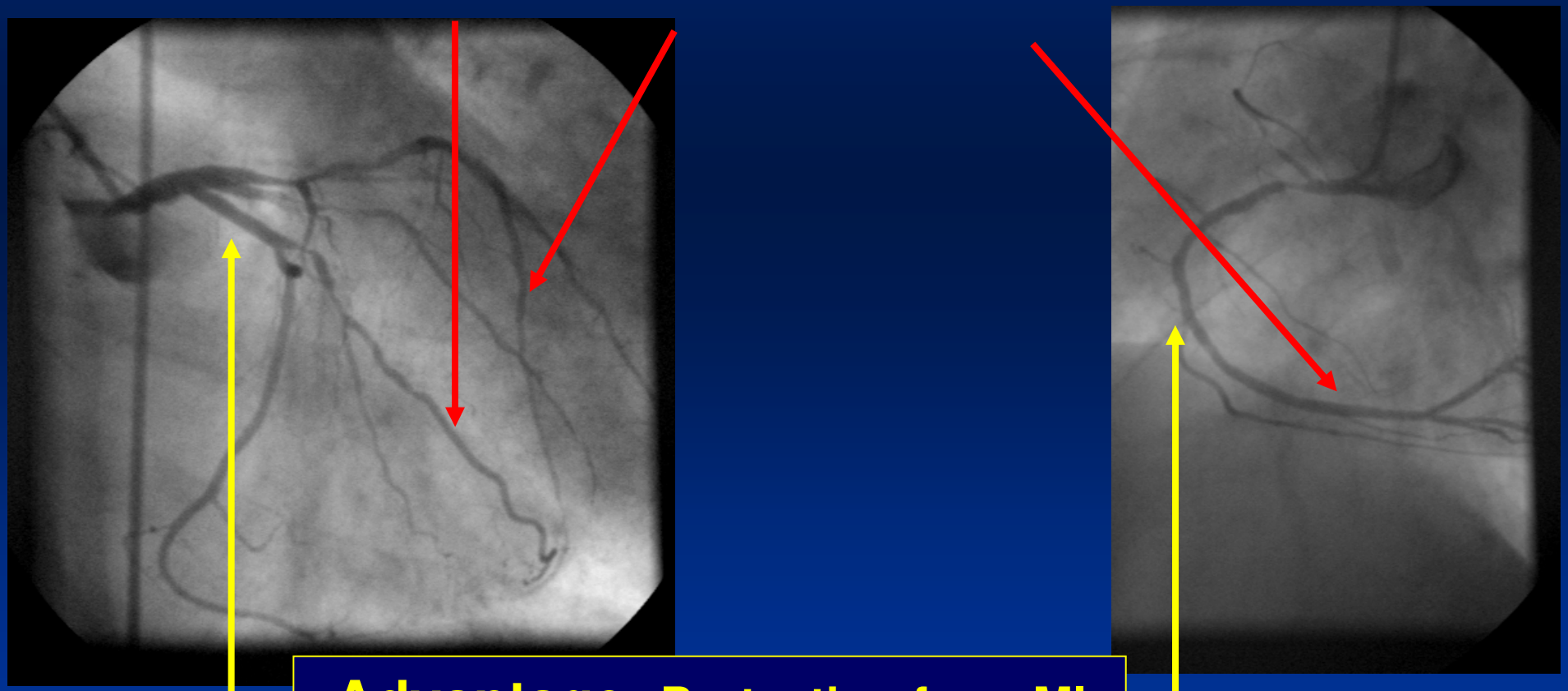


Hlatky et al. *Lancet* 2009; 373: 1190–97

Proximal Triple Vessel Disease in a Diabetic Patient

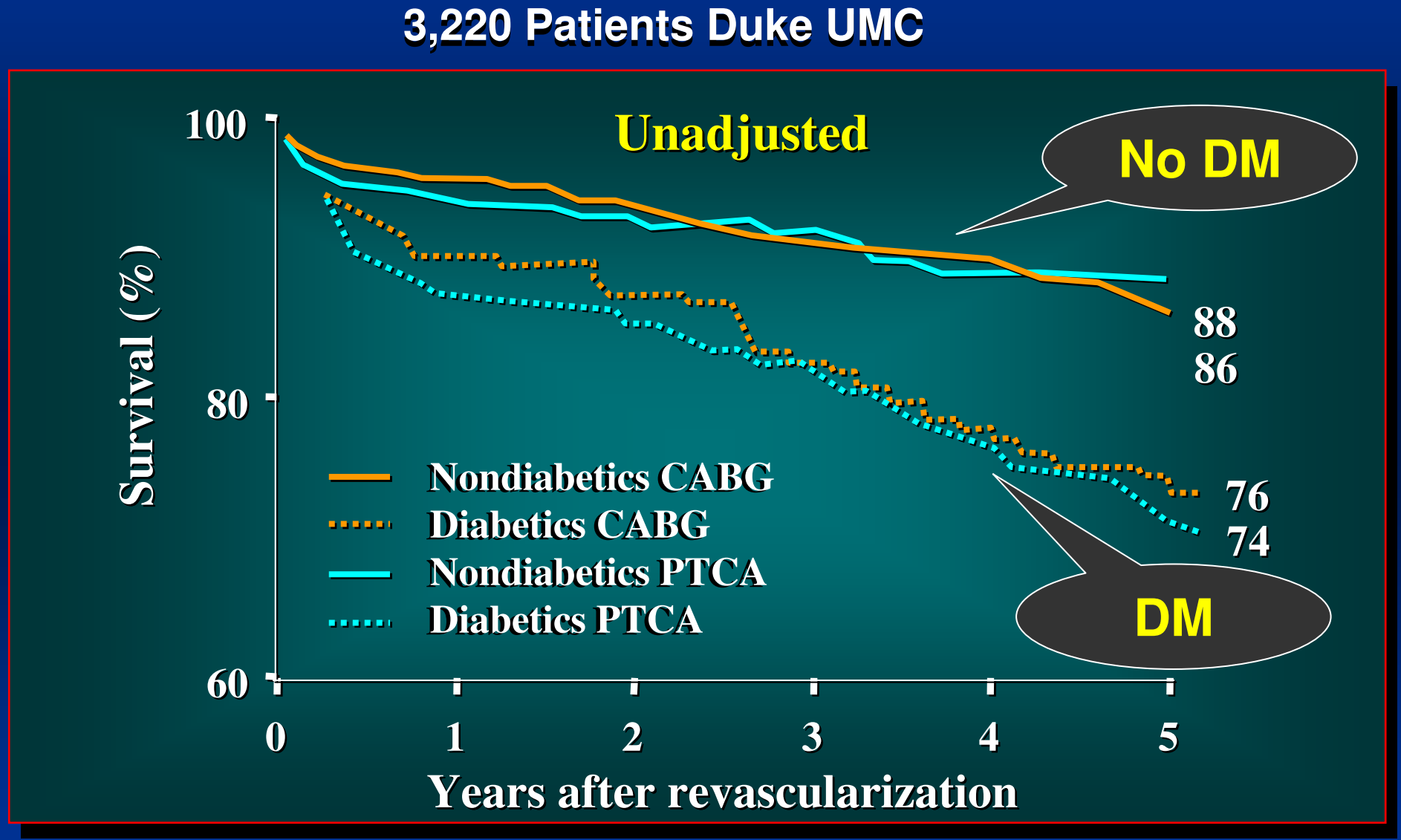


Standard therapy – CABG with 3 grafts



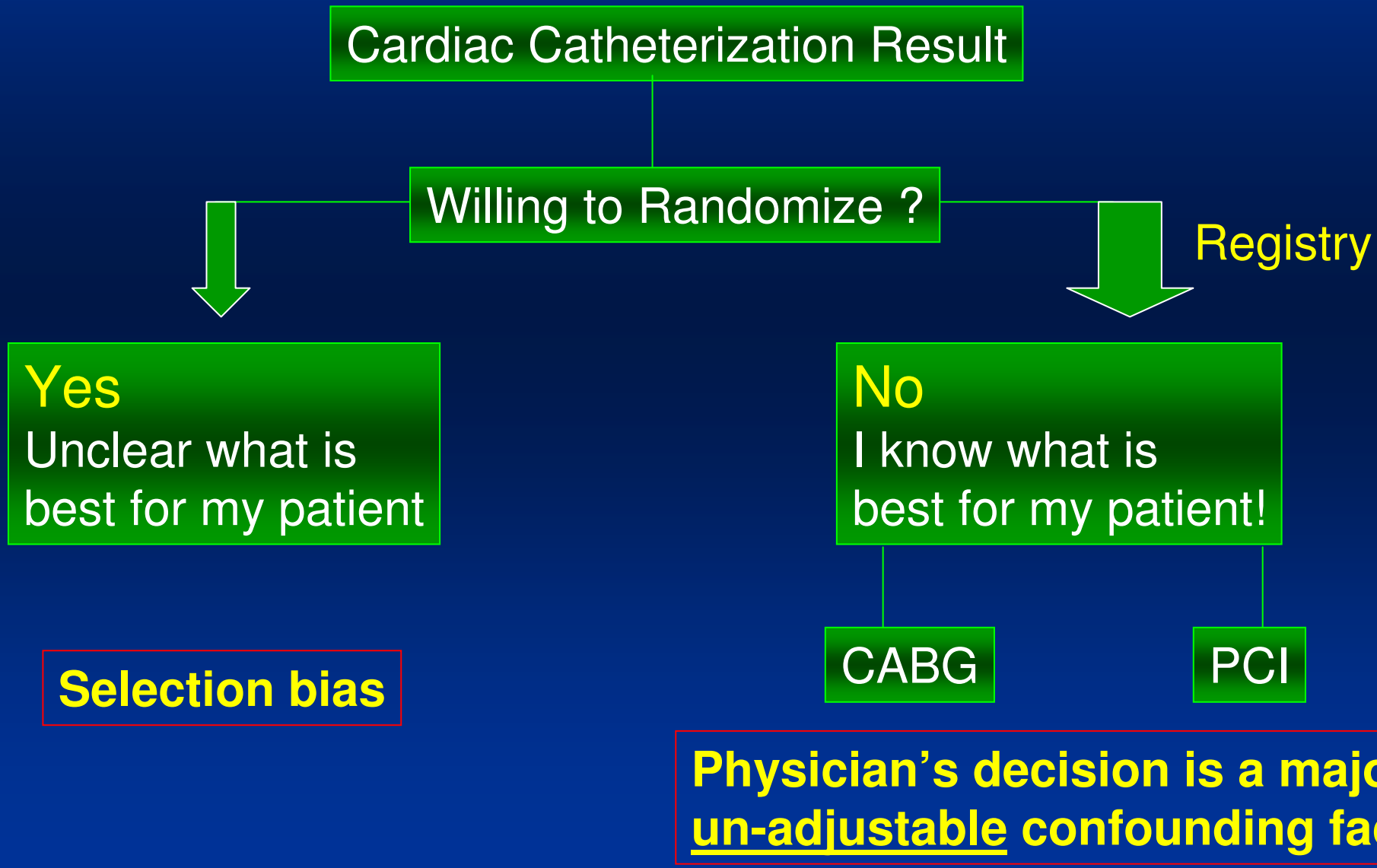
Advantage: Protection from MI and death from new lesions

Coronary Revascularization in Patients with Multivessel Disease – Registry Data



Barsness: Circulation, 1998

Randomized Trials and Registries



New-York Revascularization Registry

- **Included**:
  - New York residents with **multivessel** coronary artery disease
- **Excluded**:
  - previous revascularization, left main disease, acute myocardial infarction
- The study group comprised:
  - 37,212 - CABG
  - 22,102 - PCI

Hannan et al. NEJM 2005, 352:2174-2183

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Stenting (N=22,102)	CABG (N=37,[illegible]12)	P Value
Demographic characteristics			
Age (% of patients)			<0.001
<50 yr	11.7	7.3	
50–59 yr	22.3	19.7	
60–69 yr	28.0	30.7	
70–79 yr	27.3	33.9	
≥80 yr	10.8	8.5	
Median age (yr)	65	67	<0.001
Sex (% of patients)			<0.001
Male	68.6	70.9	
Female	31.4	29.1	
Hispanic ethnicity (% of patients)	6.3	5.6	0.001
Race (% of patients)			<0.001
White	87.0	89.2	
Black	6.4	5.5	
Other	6.7	5.3	
Coexisting conditions or other risk factors			
Ejection fraction (% of patients)			<0.001
<20%	0.7	1.8	
20–29%	3.1	7.3	
30–39%	8.0	14.9	
≥40%	81.5	74.1	
Data missing	6.8	2.0	
Median ejection fraction (%)	53	50	<0.001
Previous myocardial infarction	27.4	25.0	<0.001
1–7 days	22.8	16.3	<0.001
≥8 days	4.6	8.7	
Stroke	4.4	6.9	<0.001
Carotid or cerebrovascular disease	3.5	14.0	<0.001
Aortoiliac disease	2.9	4.6	<0.001
Femoral or popliteal disease	3.6	8.7	<0.001
Hemodynamic instability	0.5	0.7	0.001
Shock	0.1	0.2	0.16
Cardiopulmonary resuscitation	0.1	0	0.01
Electrocardiographic evidence of left ventricular hypertrophy	7.4	11.5	<0.001
Congestive heart failure	11.4	19.5	<0.001
Current admission	7.0	12.3	
Before this admission	4.4	7.2	
Malignant ventricular arrhythmia	1.3	1.8	<0.001
Chronic obstructive pulmonary disease	5.9	16.4	<0.001
Diabetes	25.3	33.2	<0.001
Renal failure	2.2	3.4	<0.001
Requiring dialysis	1.0	1.4	
Creatinine >2.5 mg/dl	1.2	2.0	
No. of diseased vessels (% of patients)†			<0.001
2	80.4	30.7	
3	19.6	69.3	

* Because of rounding, percentages may not total 100. To convert values for creatinine to micromoles per liter, multiply by 88.4.
† Diseased vessels were defined by the presence of stenosis of at least 70 percent.

Baseline Criteria

	stenting	CABG	
No. of diseased vessels (% of patients)†			<0.001
2	80.4	30.7	
3	19.6	69.3	

Double Vessel Disease:

- ✓PCI - 17770
- ✓CABG - 11424

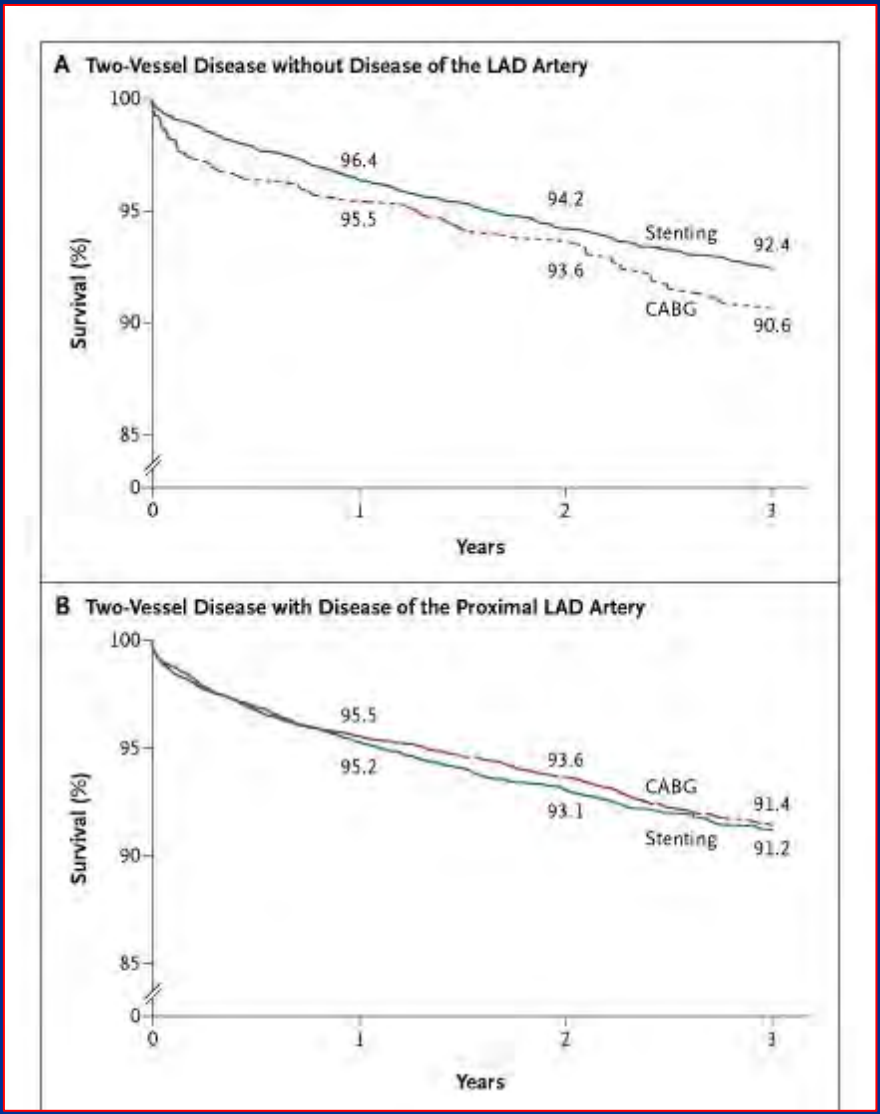
Triple Vessel Disease:

- ✓PCI - 4331
- ✓CABG - 25788

Not included:

Dementia, activity level, etc.

NY Registry: Patients with Double Vessel Disease - Survival



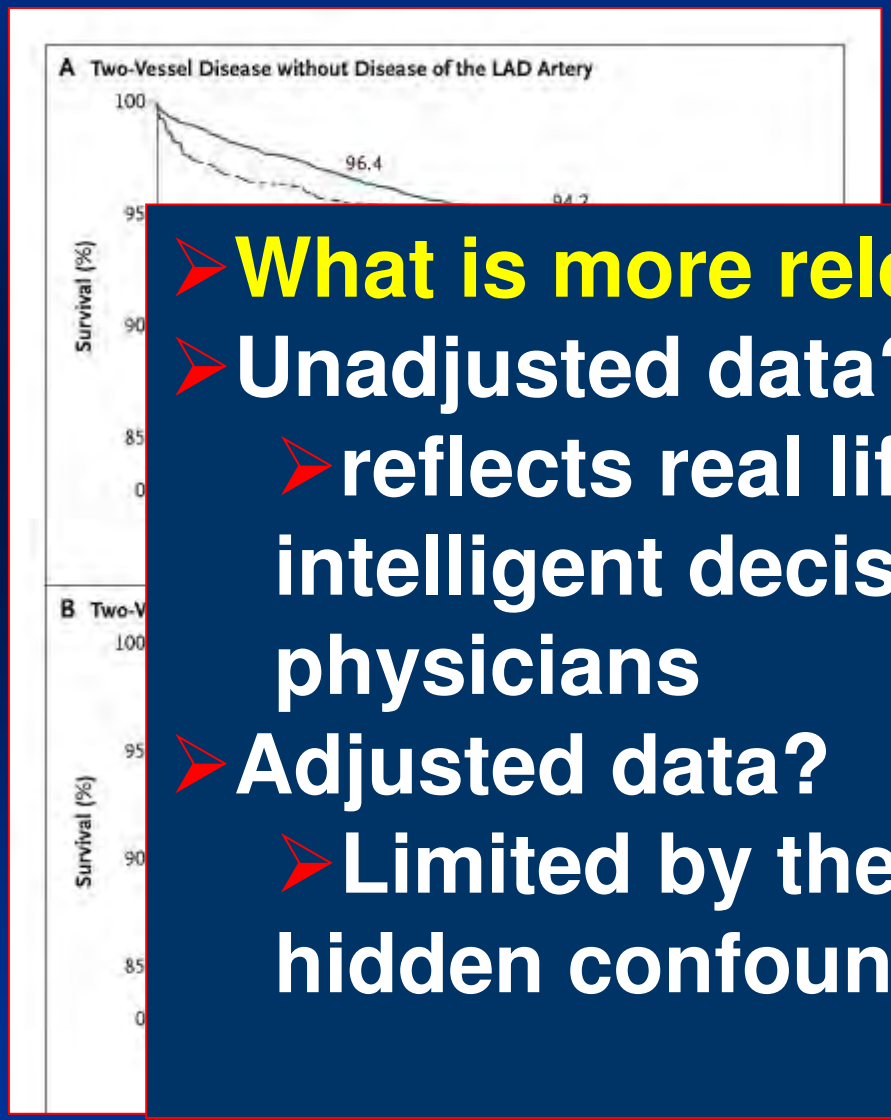
<u>Unadjusted</u> data: 2 vessel CAD:

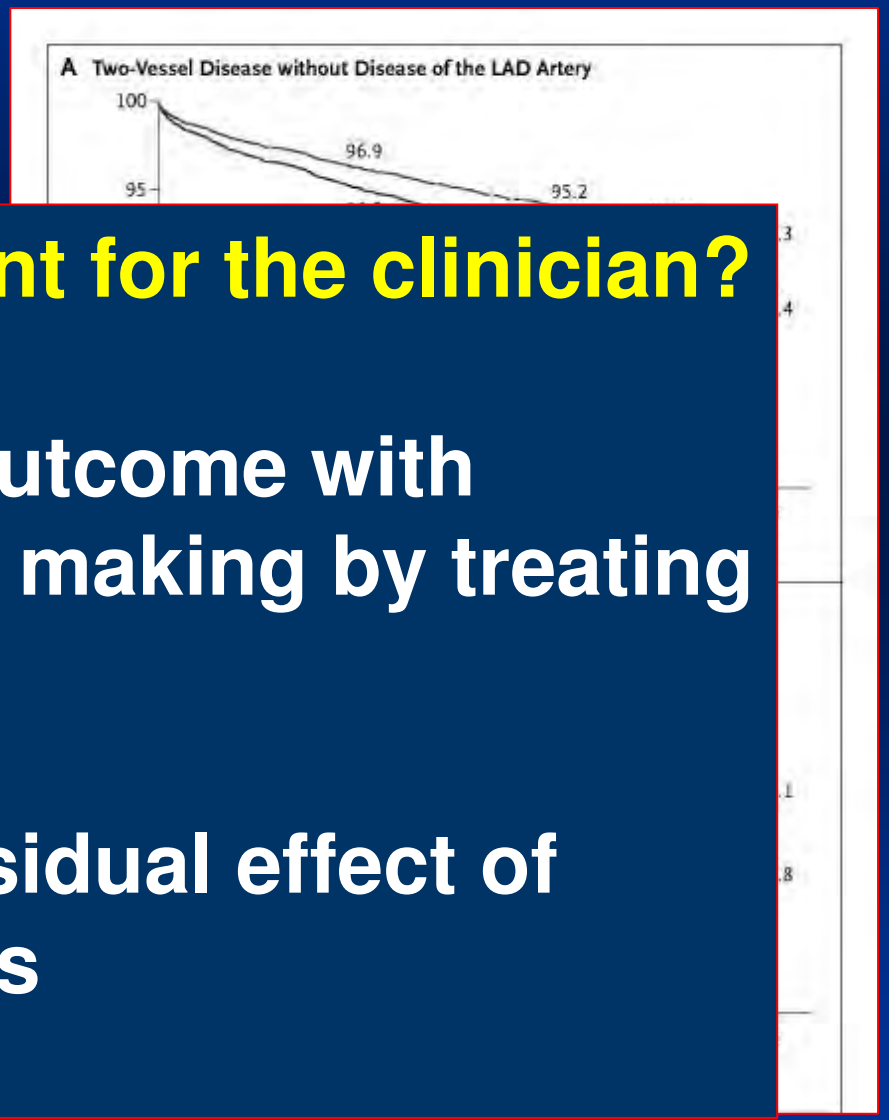
- Advantage of PCI over CABG without LAD involvement
- Similar PCI and CABG outcome with proximal LAD

However

- Groups are different and statistical adjustment is required

NY Registry: Survival of Patients with Double Vessel Disease





- What is more relevant for the clinician?
- Unadjusted data?
  - reflects real life outcome with intelligent decision making by treating physicians
- Adjusted data?
  - Limited by the residual effect of hidden confounders

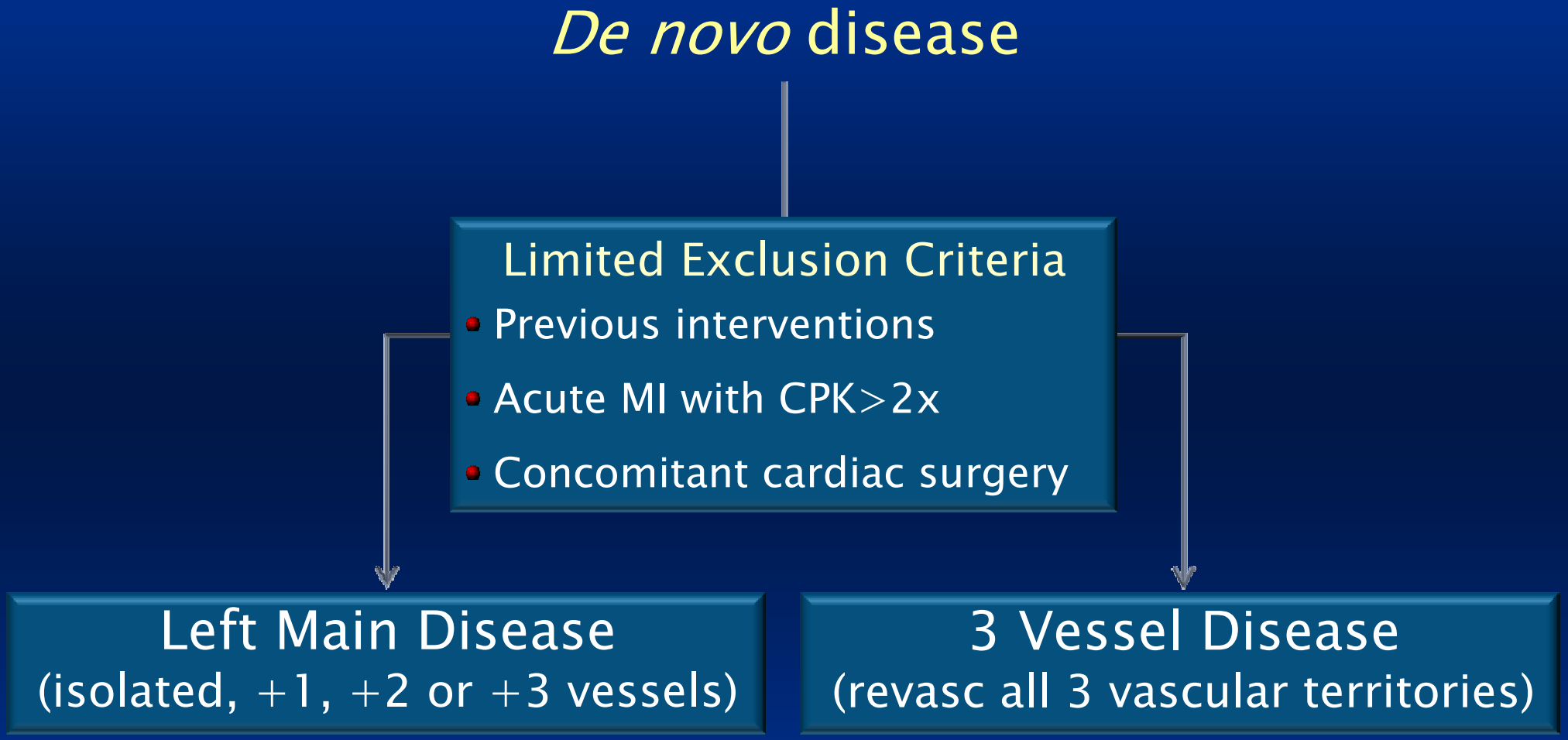
Unadjusted

Adjusted

מחקר SYNTAX – רקע

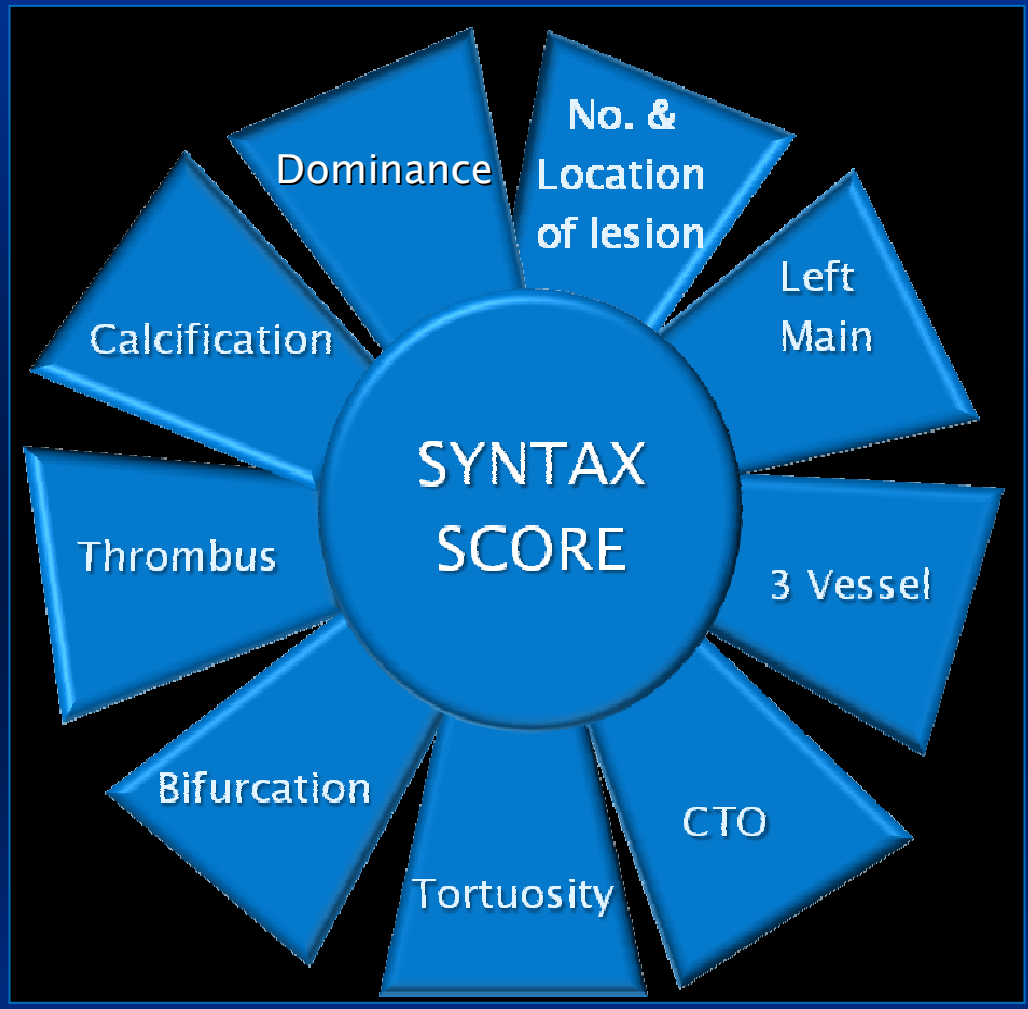
- During the present decade, major developments in CABG (e.g. off-pump technique, less invasive approach, increased arterial revascularization and optimal perioperative care).
- In PCI (e.g. improved technique, stent design, guide wires, anti-platelet therapy, and drug-eluting stents) have made it important to reassess the respective values of the two revascularization techniques in an all-comers population as seen by the surgeon and the interventional cardiologist in their daily practice.

SYNTAX Eligible Patients



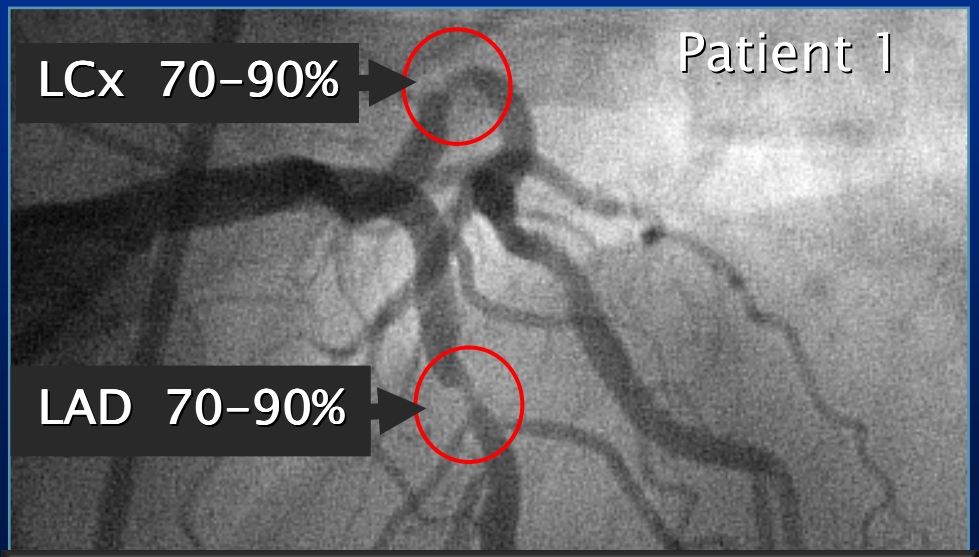
Patient Profiling – SYNTAX Score

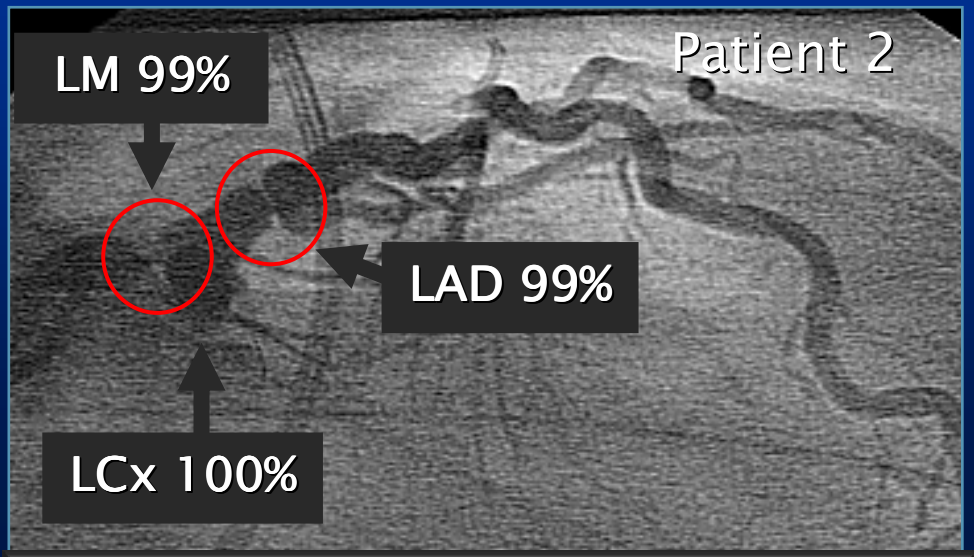
- ההיקף החומרה והמורכבות של המחלה הכלילית אופיינו באמצעות ה score .
- לערך זה יש כמובן משמעות בעיקר בהקשר לפרוצדורת ה PCI
  - הצלחה מיידית וסיבוכים
- יש לערך משמעות גם בהקשר להיקף המחלה הטרשתית
  - תוצאות לטווח ארוך



BARI classification of coronary segments
Leaman score, Circ 1981;63:285-299
Lesions classification ACC/AHA , Circ 2001;103:3019-3041
Bifurcation classification, CCI 2000;49:274-283
CTO classification, J Am Coll Cardiol 1997;30:649-656

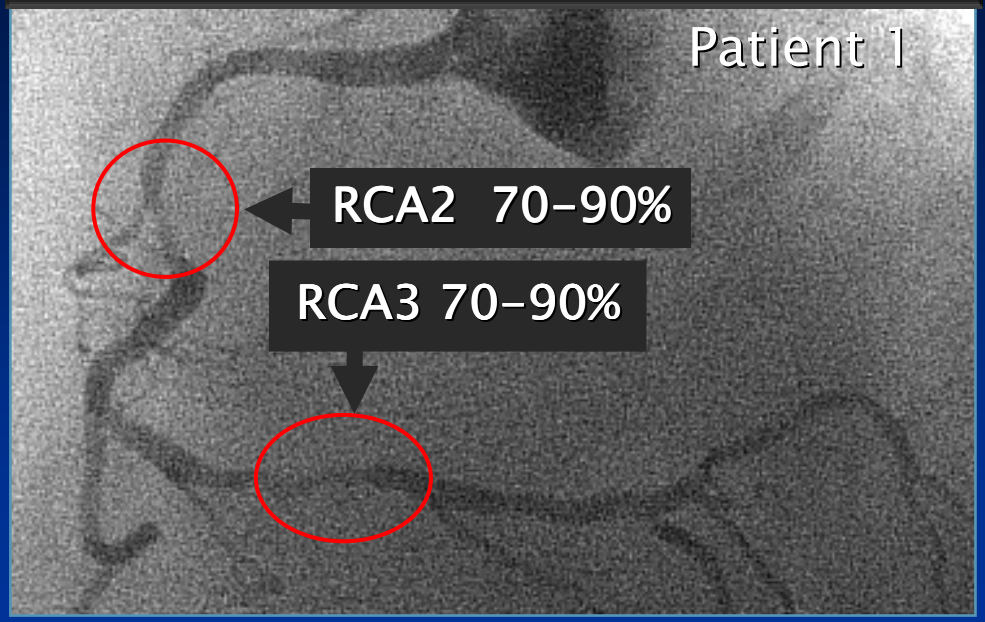
There is '3-vessel disease' and '3-vessel disease'

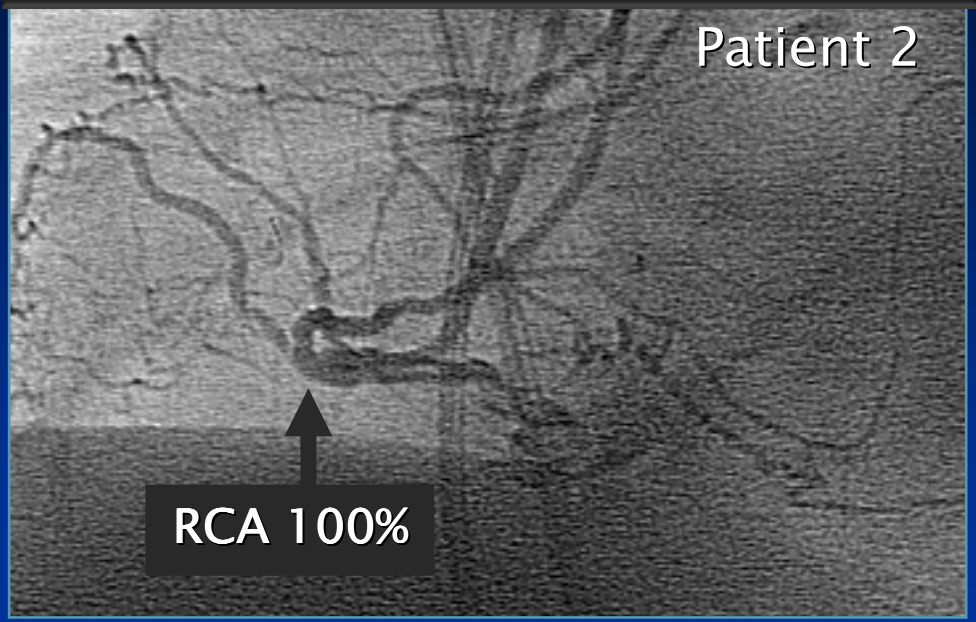




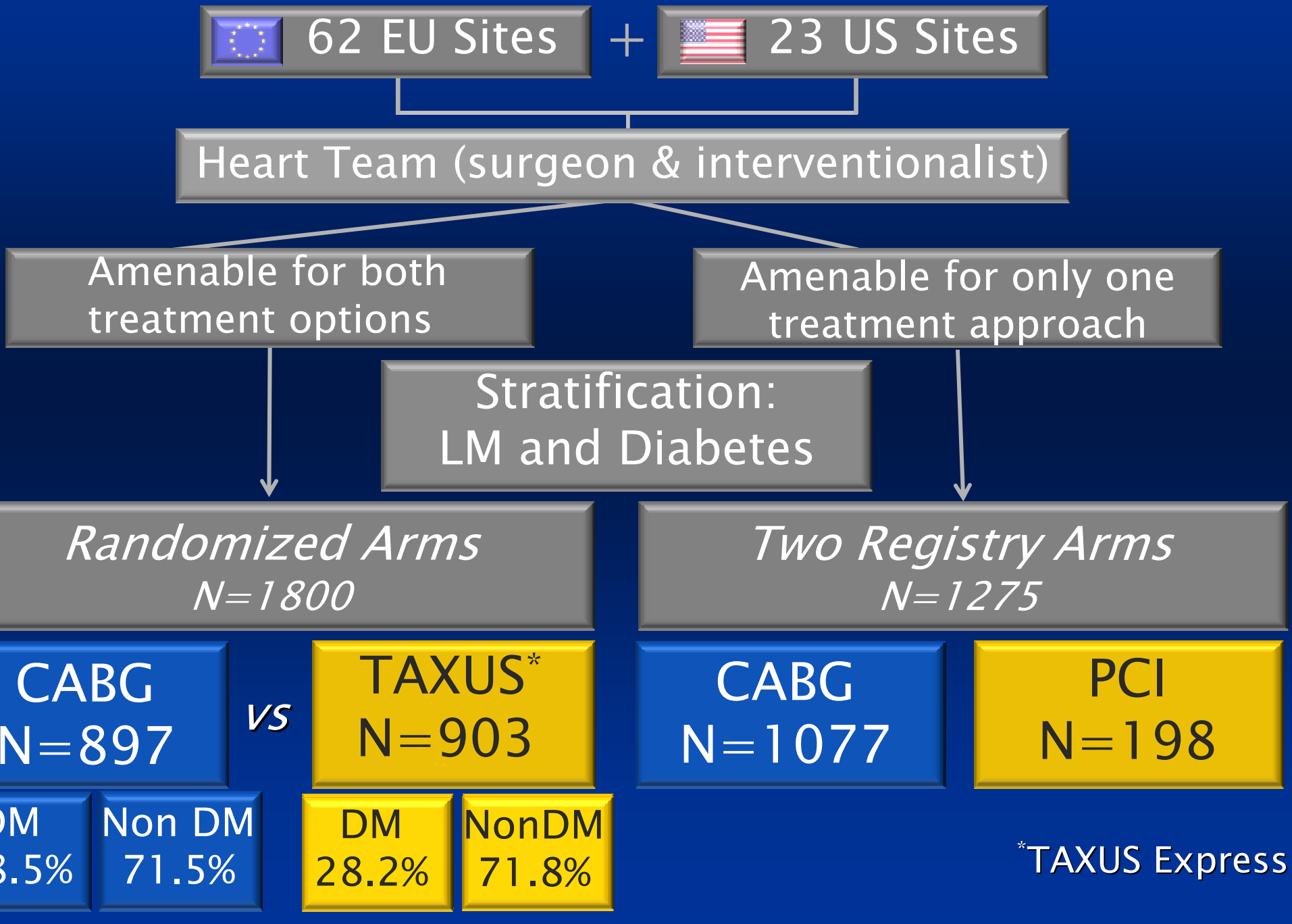
SYNTAX SCORE 21

SYNTAX SCORE 52





SYNTAX Trial Design



- האם כל מה שמוגדר כ MACCE הינו באמת בעל אותו משקל?
- האם בעיני החולה:
  - עלית טרופונין שקולה לארוע מוחי?
  - PCI חוזר שקול לארוע מוחי?
  - כמה PCI חוזרים מוכן החולה לעבור ובלבד שלא לחוות אירוע מוחי משמעותי

- MACCE is defined as:
  - All cause Death
  - Cerebrovascular Accident (CVA/Stroke)
  - Documented Myocardial Infarction (ARC definition)
  - Any Repeat Revascularization (PCI and/or CABG)
- All events CEC Adjudicated

*ARC MACCE definition Circ 2007; 115:2344-2351

Patient Characteristics (I)
Randomized Cohort

	CABG N=897	TAXUS N=903	*P* value
Age, mean ± SD (y)	65.0 + 9.8	65.2 + 9.7	0.55
Male, %	78.9	76.4	0.20
BMI, mean + SD	27.9 + 4.5	28.1 + 4.8	0.37
Diabetes, %	28.5	28.2	0.89
Hypertension, %	77.0	74.0	0.14
Hyperlipidemia, %	77.2	78.7	0.44
Current smoker, %	22.0	18.5	0.06
Prior MI, %	33.8	31.9	0.39
Unstable angina, %	28.0	28.9	0.67
Additive EuroSCORE, mean + SD	3.8 + 2.7	3.8 + 2.6	0.78
Total Parsonnet score , mean + SD	8.4 + 6.8	8.5 + 7.0	0.76

Patient Characteristics (II)
Randomized Cohort

Patient-based	CABG N=897	TAXUS N=903	*P* value
Total SYNTAX Score	29.1 +11.4	28.4 +11.5	0.19
Diffuse disease or small vessels, %	10.7	11.3	0.69
No. lesions, mean + SD	4.4 +1.8	4.3 +1.8	0.44
3VD only, %	66.3	65.4	0.70
Left main, any, %	33.7	34.6	0.70
Left Main only	3.1	3.8	0.46
Left Main + 1 vessel	5.1	5.4	0.78
Left Main + 2 vessel	12.0	11.5	0.72
Left Main + 3 vessel	13.5	13.9	0.78
Total occlusion, %	22.2	24.2	0.33
Bifurcation, %	73.3	72.4	0.67
Trifurcation, %	10.6	10.7	0.92

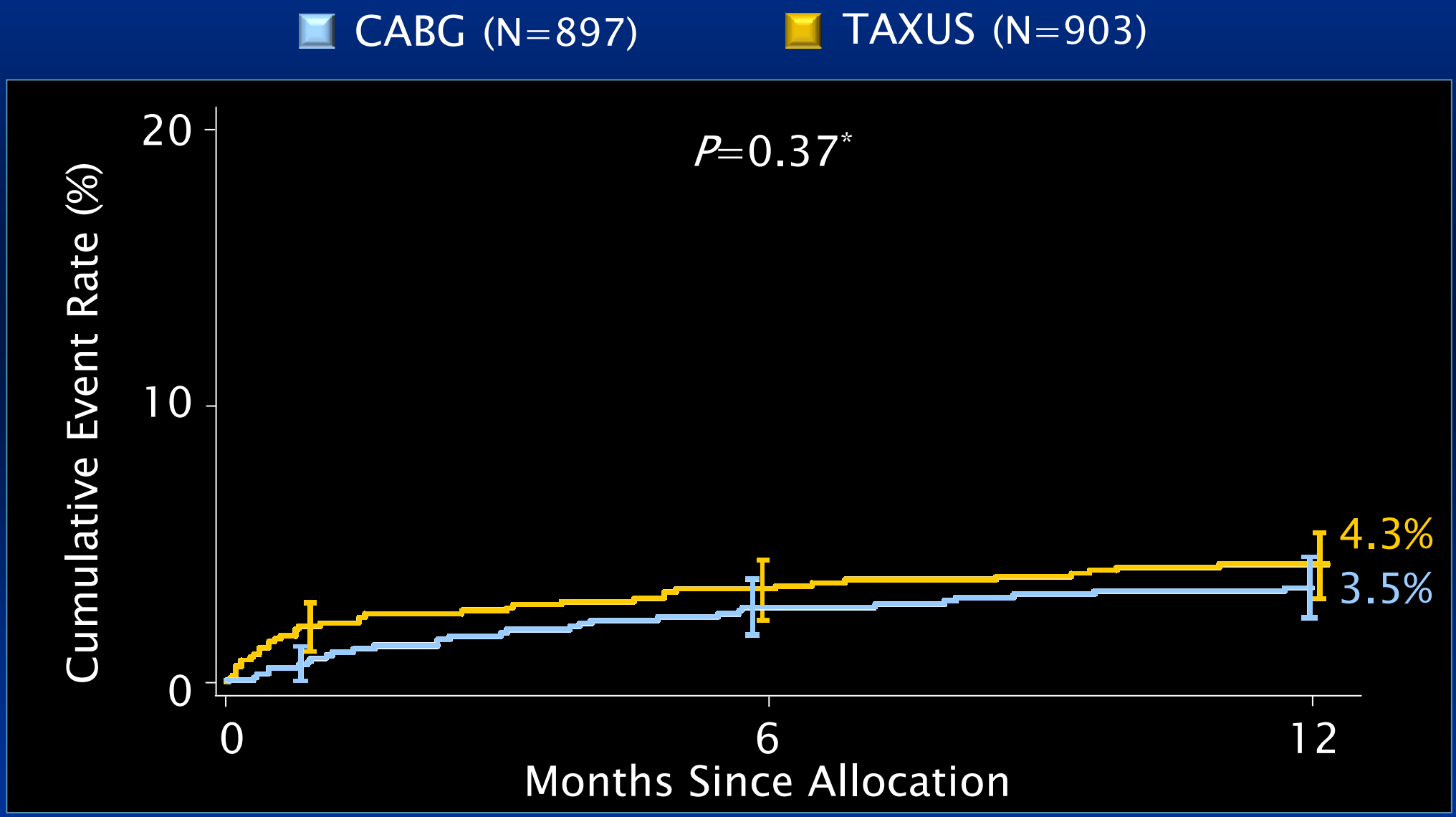
Procedural Characteristics
PCI Randomized Cohort

Patient-based	TAXUS N=903
Staged procedure, %	14.1
Lesions treated/pt, mean + SD	3.6 + 1.6
No. stents implanted, mean + SD	4.6 ± 2.3
Total length implanted, mm + SD	86.1 ± 47.9
Range, mm	8 – 324
Long stenting (>100 mm), %	33.2

Procedural Characteristics
CABG Randomized Cohort

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

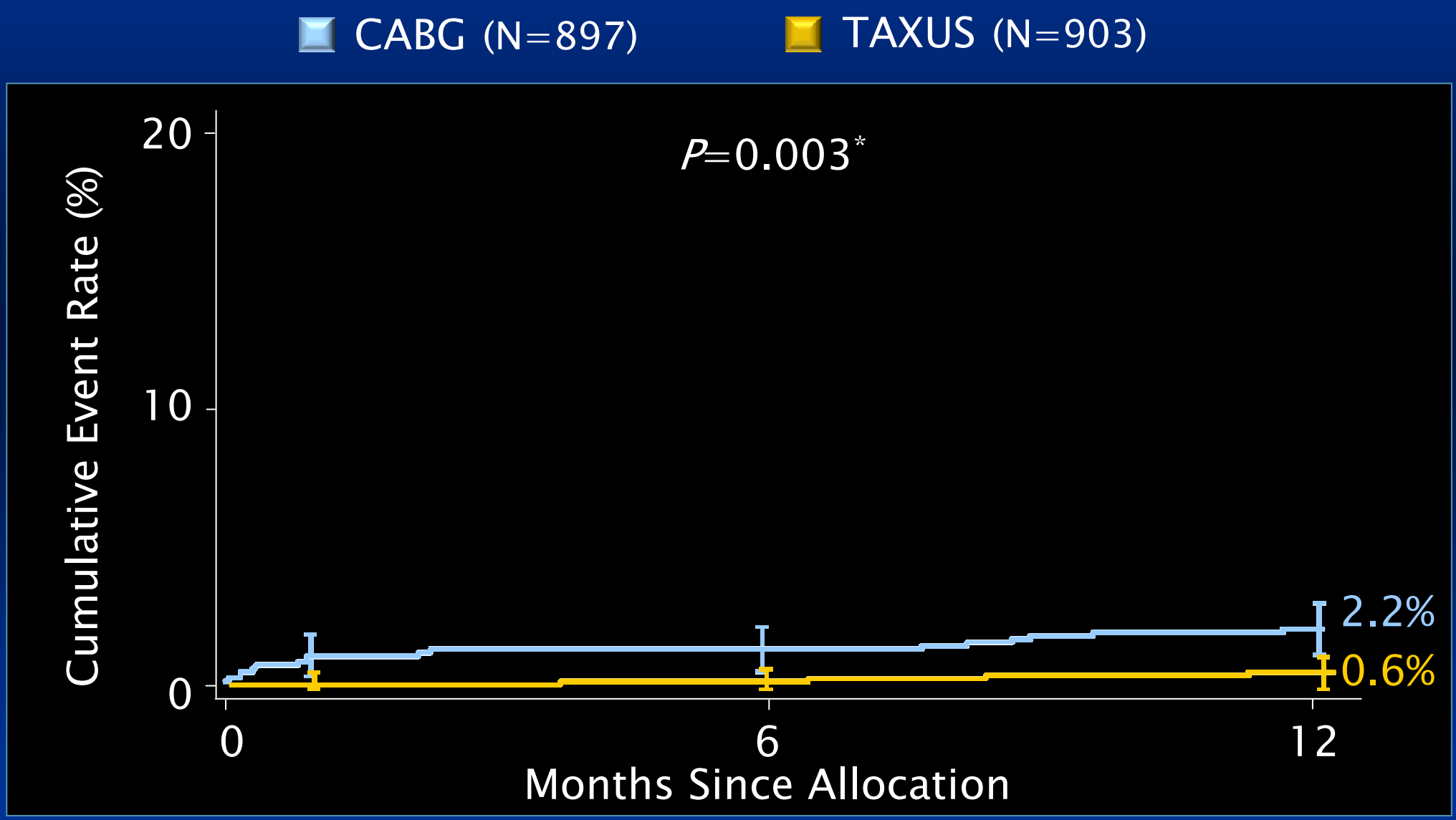
All-Cause Death to 12 Months



Event Rate + 1.5 SE. *Fisher's Exact Test

ITT population

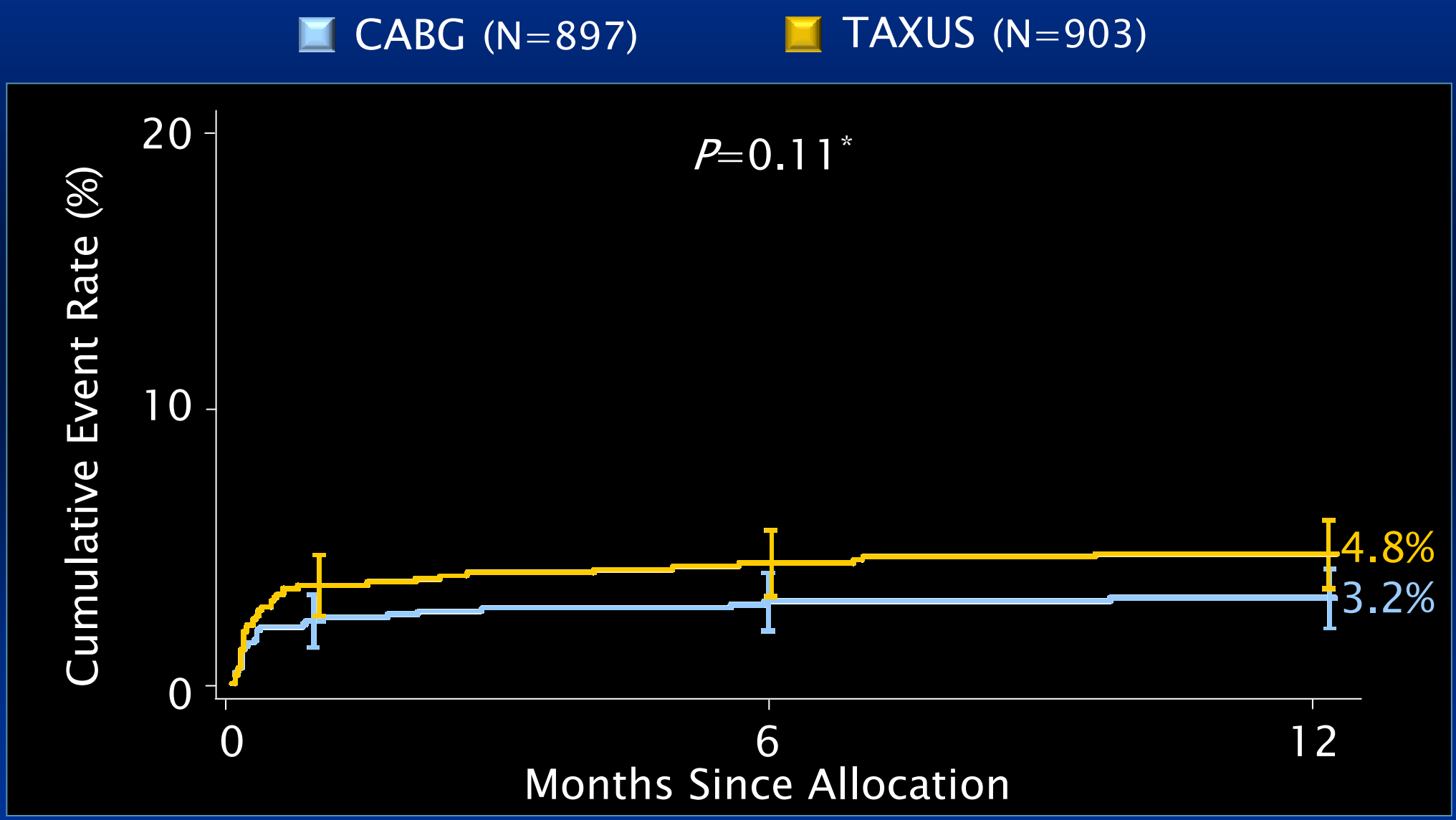
CVA to 12 Months



Event Rate + 1.5 SE. *Fisher's Exact Test

ITT population

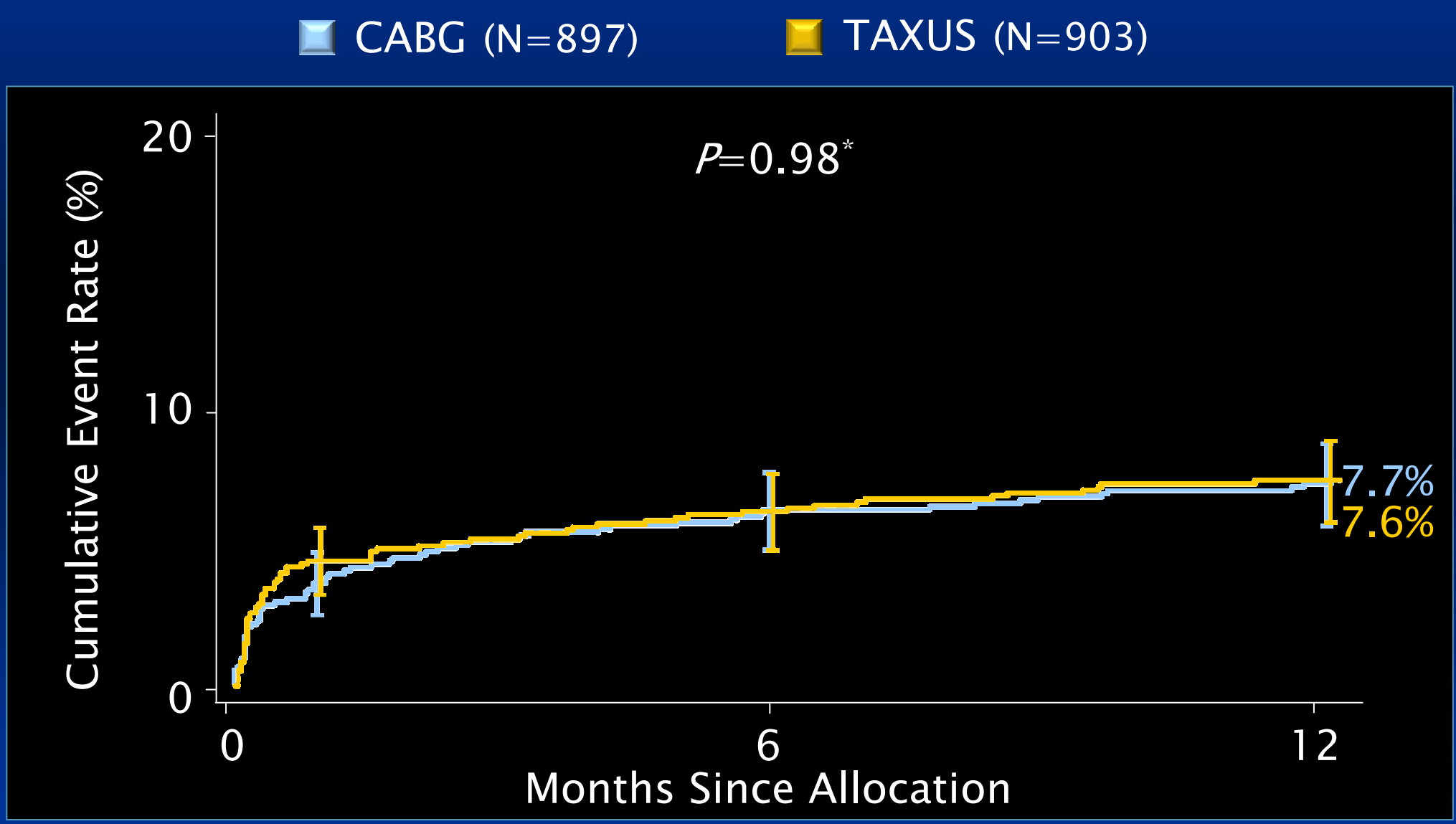
Myocardial Infarction to 12 Months



Event Rate + 1.5 SE. *Fisher's Exact Test

ITT population

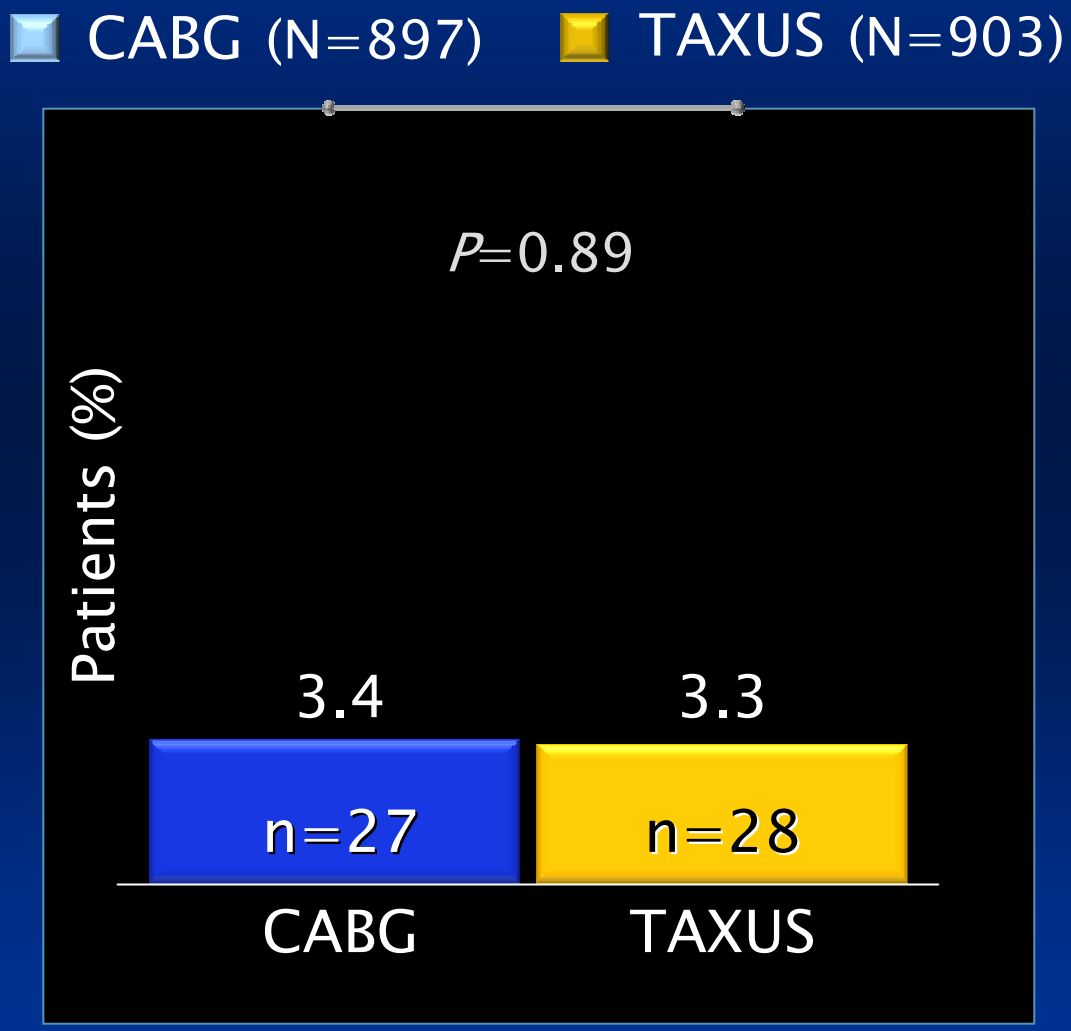
All-Cause Death/CVA/MI to 12 Months



Event Rate + 1.5 SE. *Fisher's Exact Test

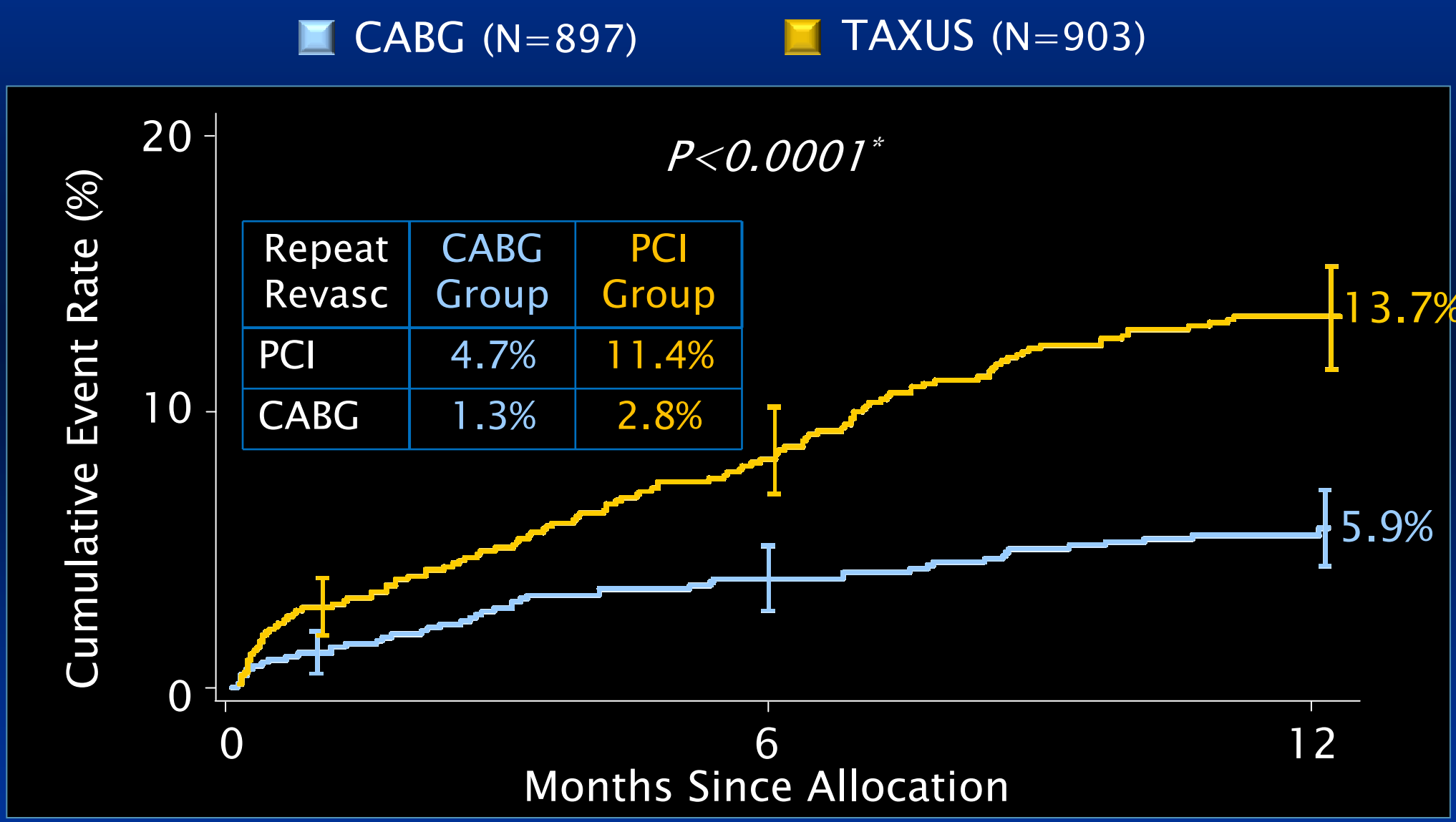
ITT population

Symptomatic Graft Occlusion & Stent Thrombosis to 12 Months



ITT population

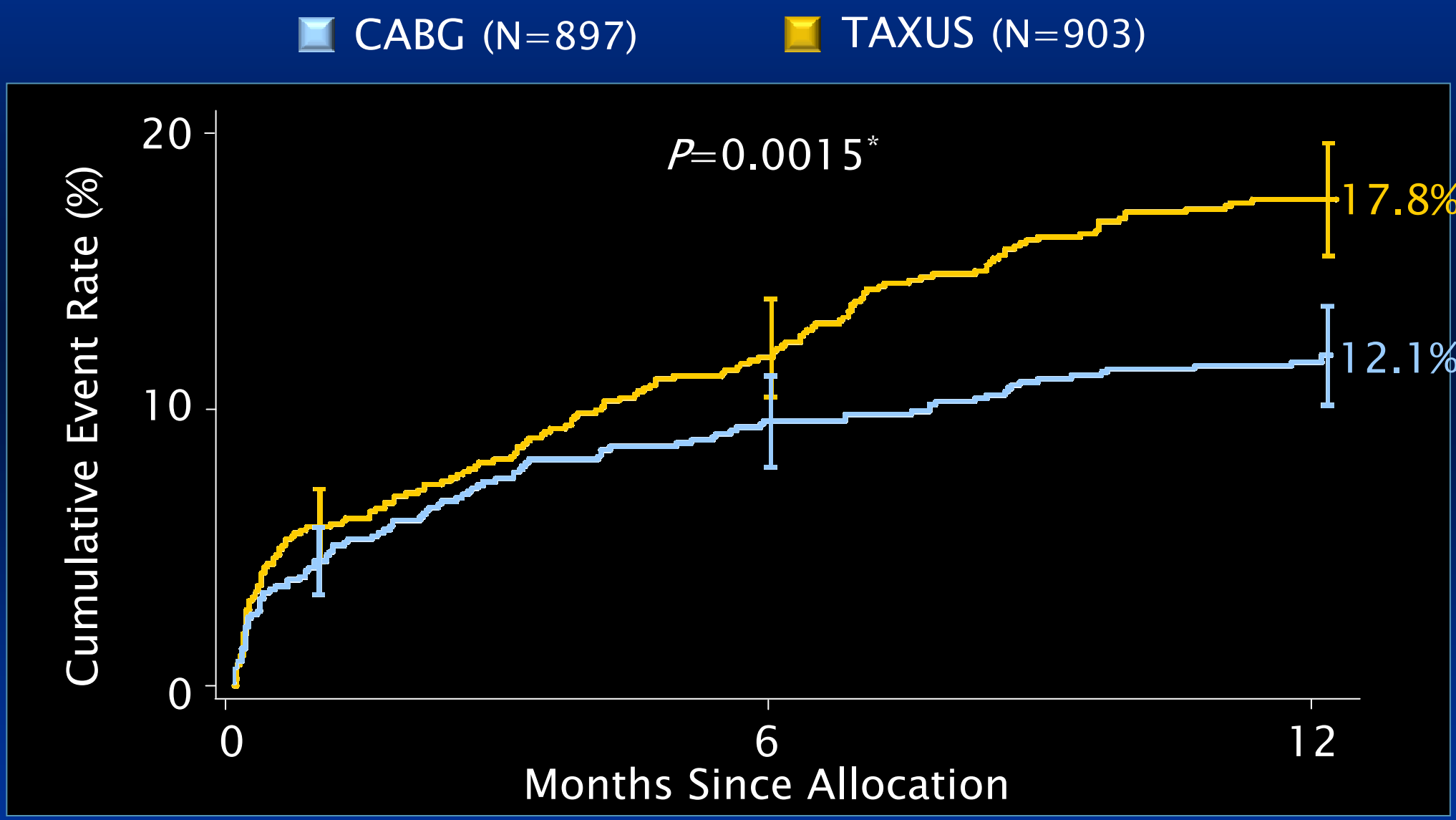
Repeat Revascularization to 12 Months



Event Rate + 1.5 SE. *Fisher's Exact Test

ITT population

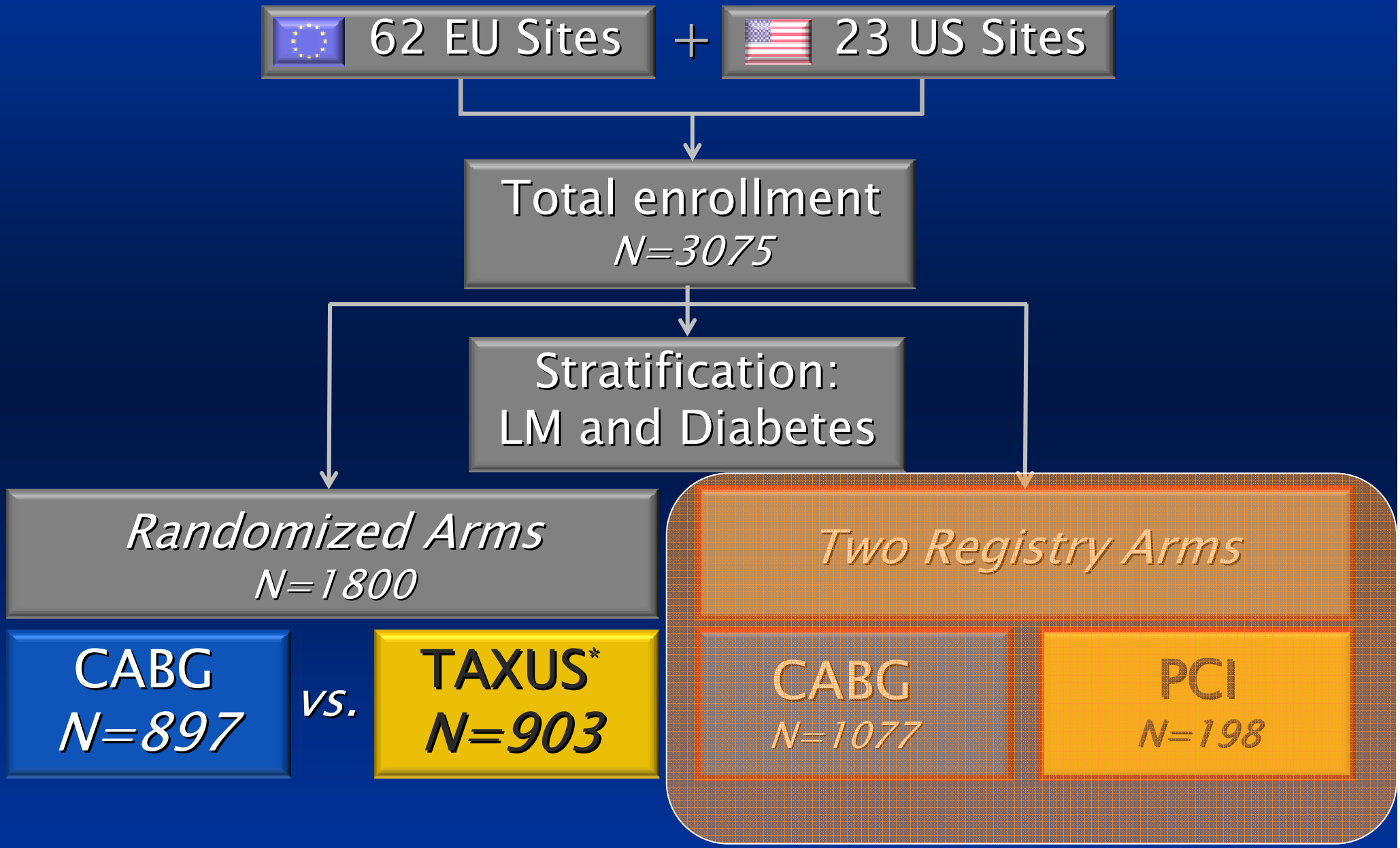
MACCE to 12 Months – Study Endpoint



Event Rate + 1.5 SE. *Fisher's Exact Test

ITT population

SYNTAX Trial Design



*TAXUS Express

Reasons for Registry Allocation

PCI Registry- CABG ineligible due to:

- Co-morbidities (70.7%)
- No graft material (9.1%)
- Small or poor quality of distal vessel (1.5%)
- Patient refused CABG (5.6%)
- Other (13.1%)

CABG Registry- PCI ineligible due to:

- Complex anatomy (70.9%)
- Untreatable CTO (22.0%)
- Unable to take anti-platelet medications (0.9%)
- Patient refused PCI (0.5%)
- Other (5.7%)

Procedural Characteristics

Notable Differences: PCI RCT + Registry

	TAXUS RCT* n=903	PCI Reg n=192
Staged Procedure, %	14.1	13.0
Bi/trifurcation lesions treated, %	24.8	64.4
Lesions treated, mean+SD	3.6 + 1.6	2.5 + 1.3
Stents implanted, mean+SD	4.6 + 2.3	3.1 + 1.8
Total length implanted, mm	86.1 + 47.9	58.5 + 41.2
Range, mm	8.0–324.0	8.0–252.0
Long stenting (>100 mm), %	33.2	12.2

*For descriptive purposes only; no statistical comparisons done

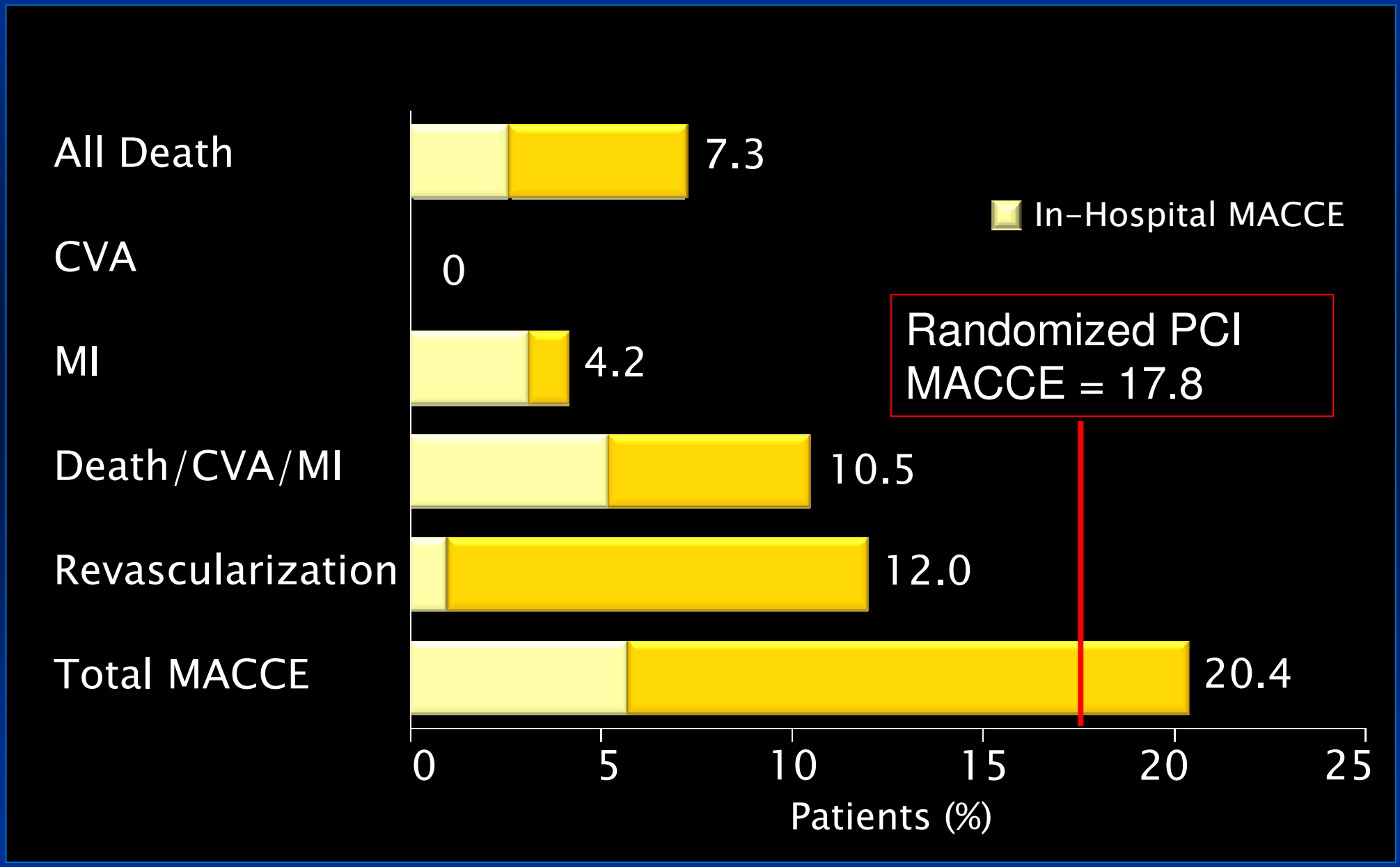
Procedural Characteristics

Notable Differences CABG RCT + Registry

Procedure-related	CABG RCT* n=897	CABG Reg n=644
Off-pump surgery, %	15.0	18.6
Graft revascularization, %		
At least one arterial graft	97.3	96.7
Arterial graft to LAD	95.6	94.7
LIMA + venous	78.1	85.1
Double LIMA/RIMA	27.6	16.1
Complete arterial revascularization	18.9	11.2
Venous graft only	2.6	3.3
Grafts per patient, mean +SD	2.8 + 0.7	3.0 + 0.9
Distal anastomoses, mean +SD	3.2 + 0.9	3.5 + 1.0

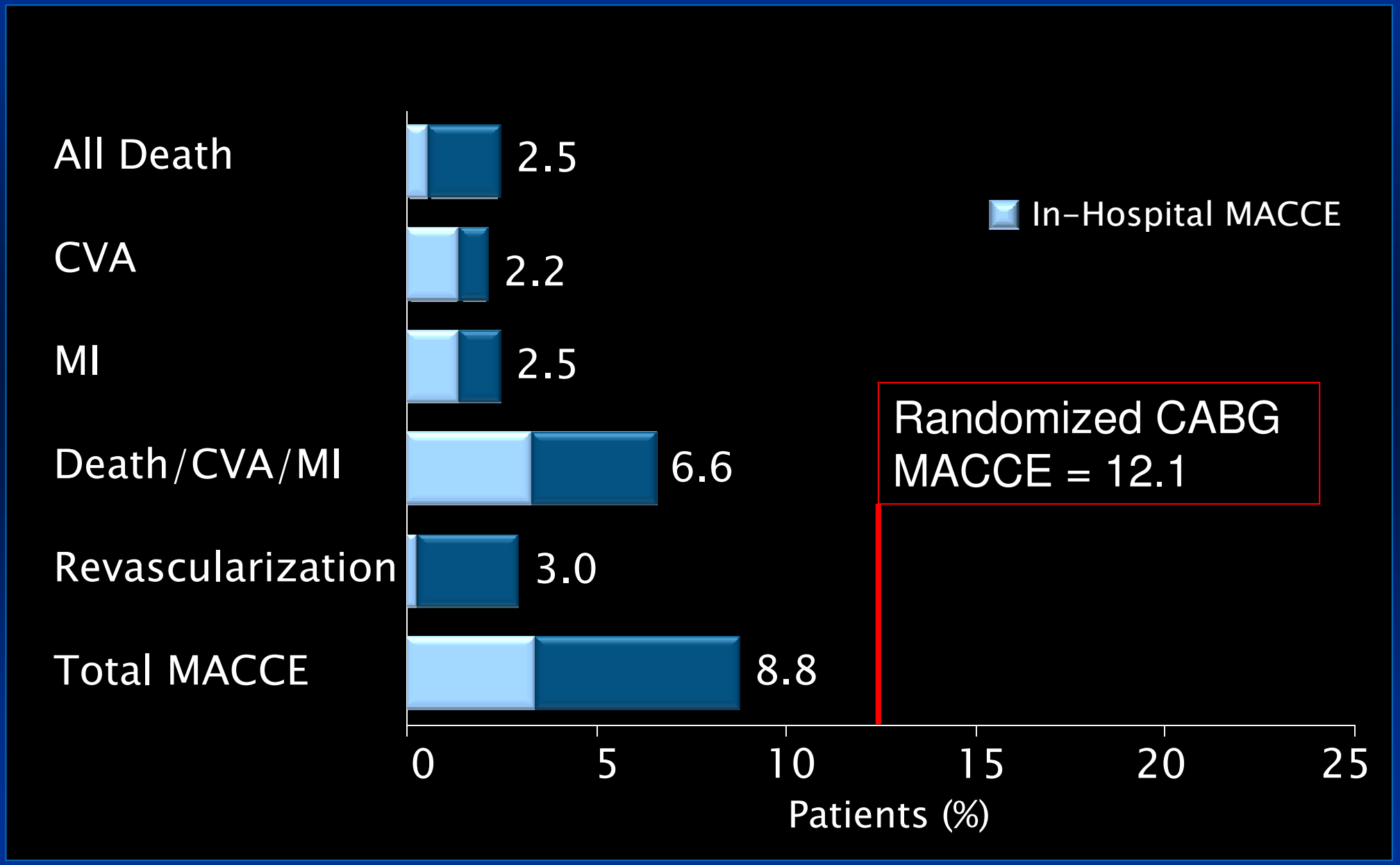
*For descriptive purposes only; no statistical comparisons done

12 Month MACCE Rates
PCI Registry (N=192)



Per-protocol population

12 Month MACCE Rates
CABG Registry (N=644)

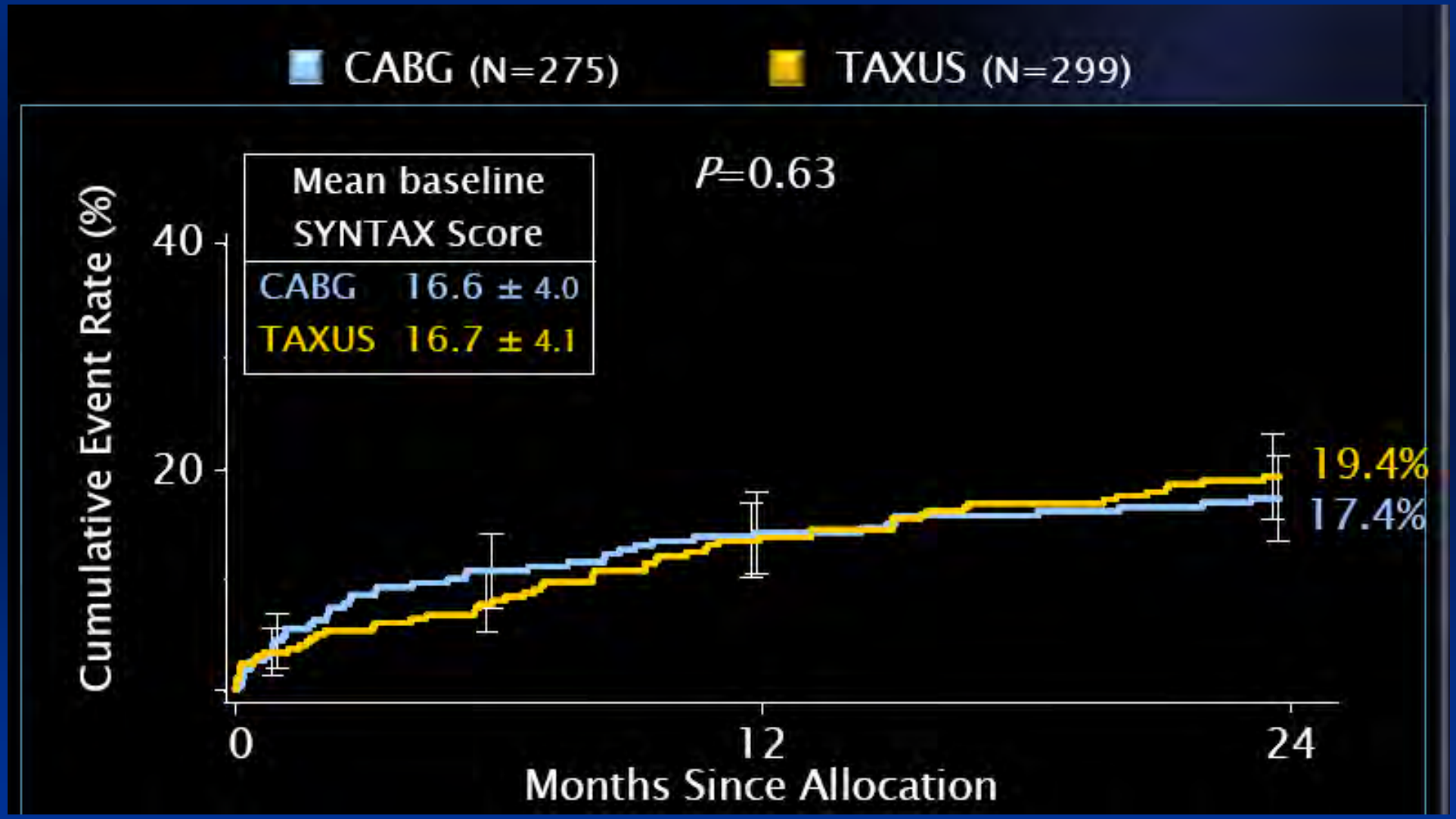


Per-protocol population

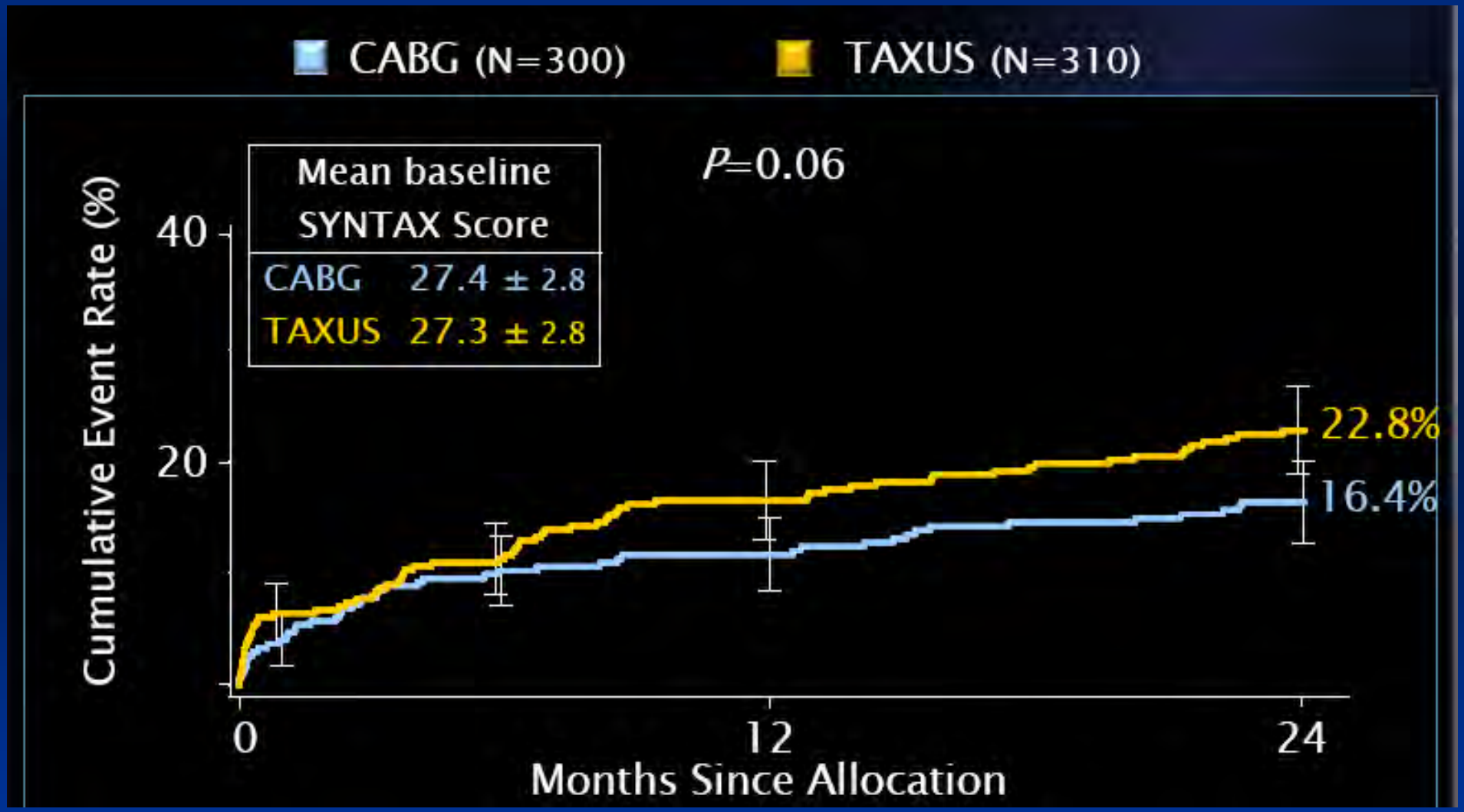
אנליזה של תת-קבוצות
Randomized Cohort

- SYNTAX Score
  - נמוך, בינוני, גבוה
- סוכרת
  - תסמונת מטבולית, סוכרת (ללא ועם אינסולין)

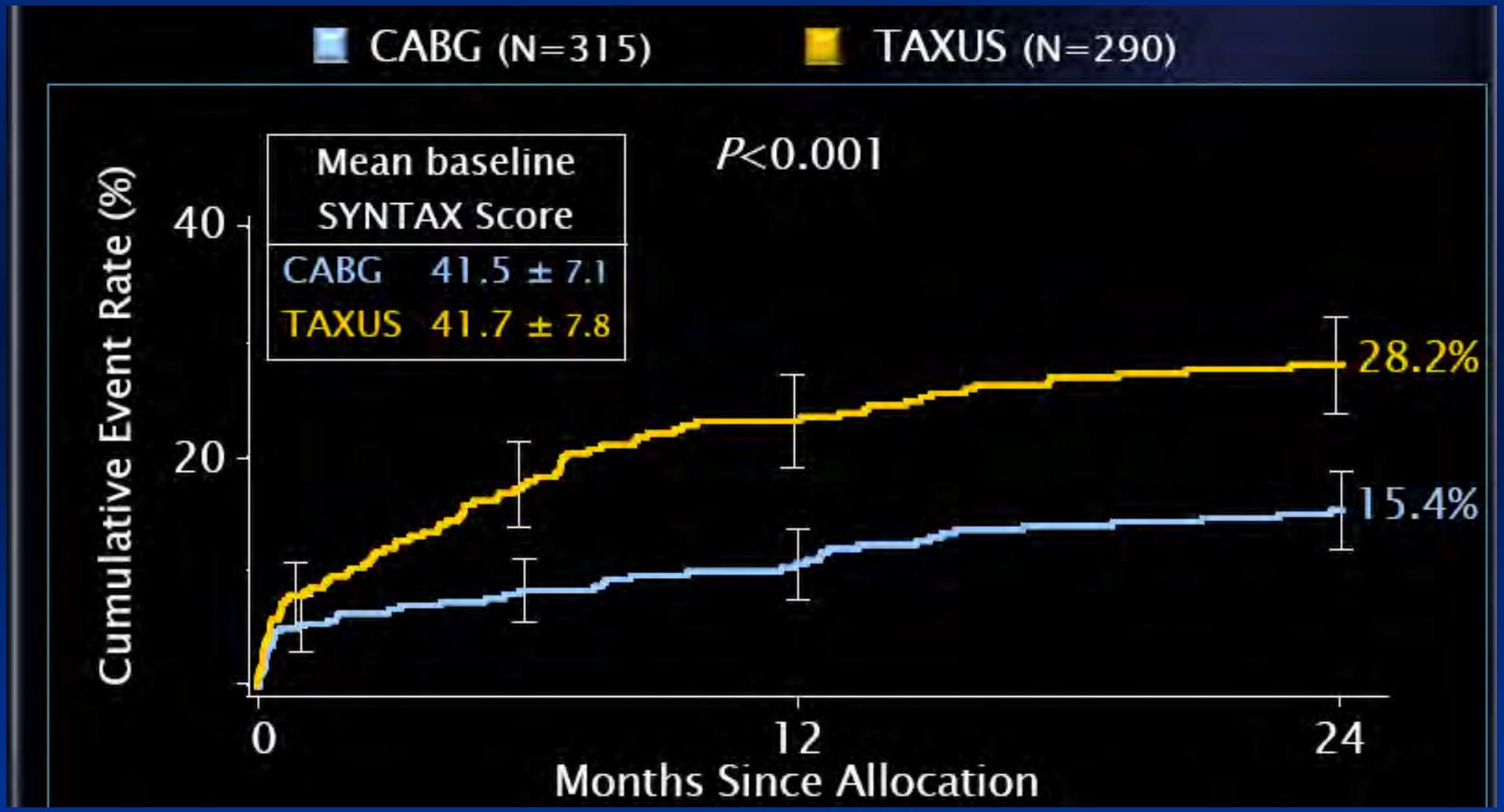
MACCE at 2 years:
Low SYNTAX score (0-22)



MACCE at 2 years: Intermediate SYNTAX score (23-32)

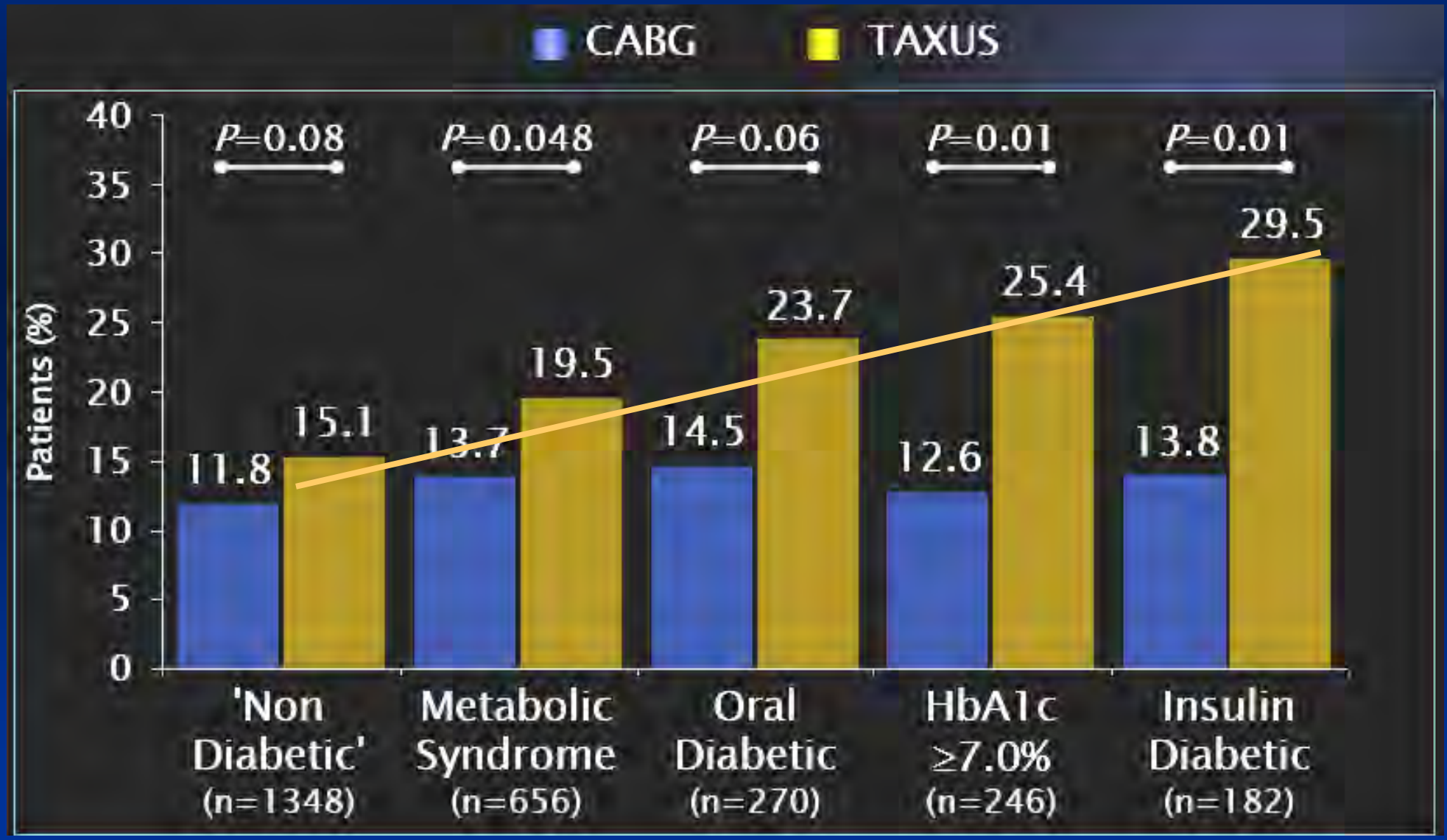


MACCE at 2 years:
High SYNTAX score (> 33)



SYNTAX: 12 months MACE Rate

Superiority of CABG increases with increase in metabolic abnormality

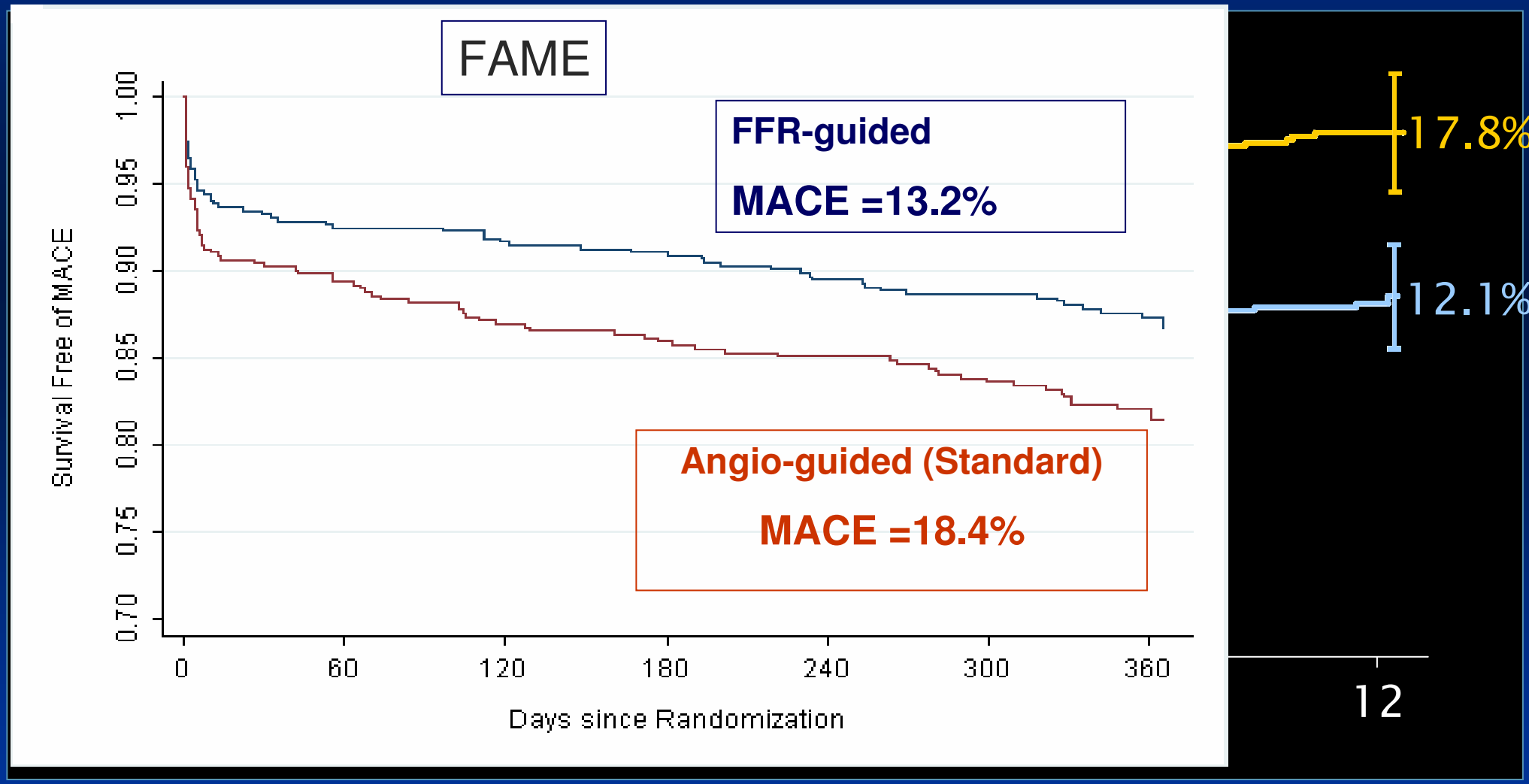


מסקנה

- ההבדל בתוצאות לטובת CABG יותר מודגש ככל ש:
  - החומרה האנטומית של המחלה הכלילית קשה יותר SYNTAX Score
  - ההפרעה המטבולית של החולה (תסמונת מטבולית, סוכרת וכו') קשה יותר
- ההסבר קשור בכך שלניתוח מעקפים (לא ל PCI) יש אפקט מגן מפני התוצאה הקשורה בהתקדמות המחלה הטרשתית
  - היצרויות פרוקסימליות לאנסטומוזה
- מדגיש את הצורך בטיפול תרופתי אינטנסיבי למכלול החולים הנזקקים לרווסקולריזציה

MACCE to 12 Months – Study Endpoint

CABG (N=897) TAXUS (N=903)



Event Rate + 1.5 SE. *Fisher's Exact Test

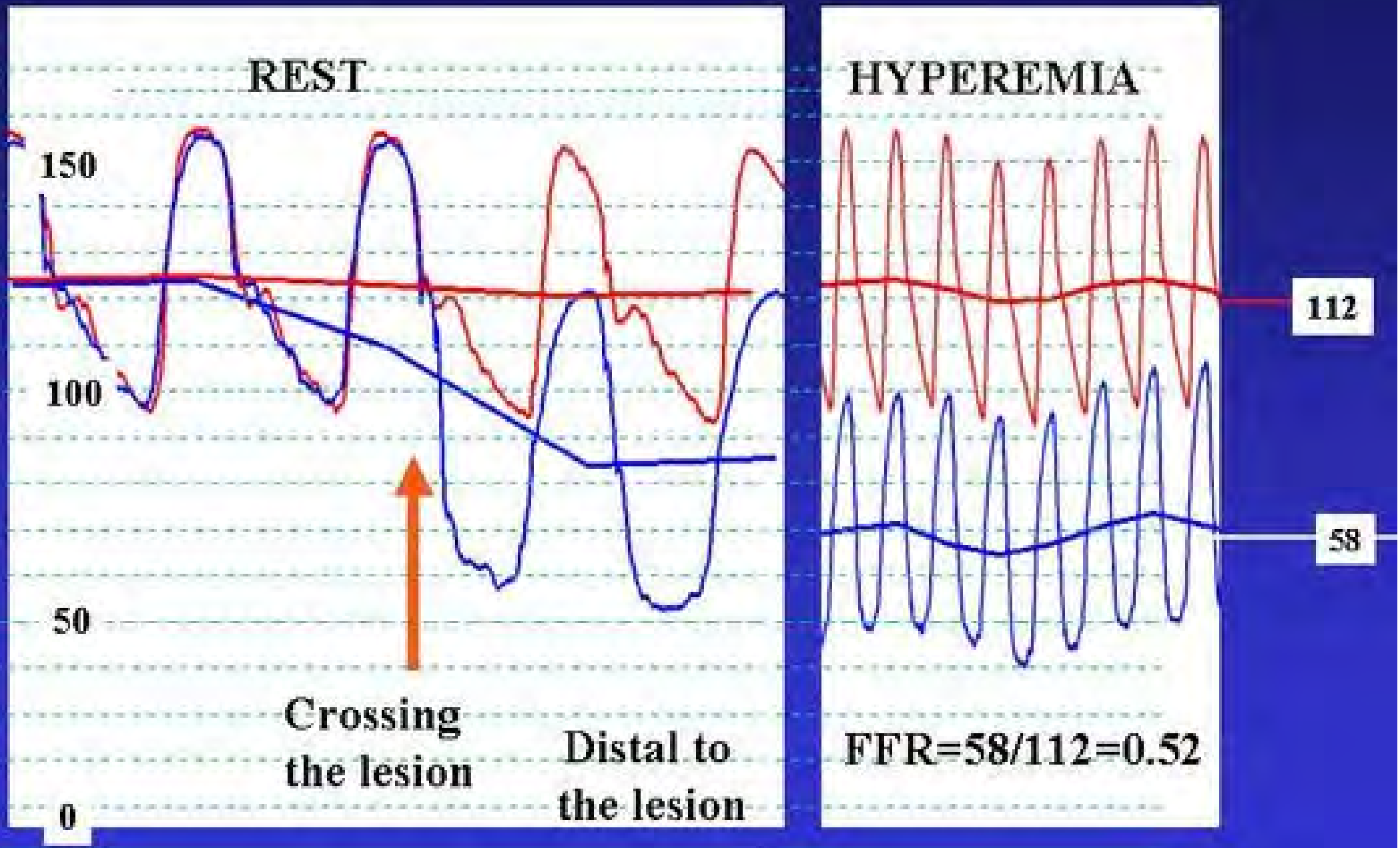
ITT population

הערכת לזיה כלילית
אנטומיה או פונקציה?

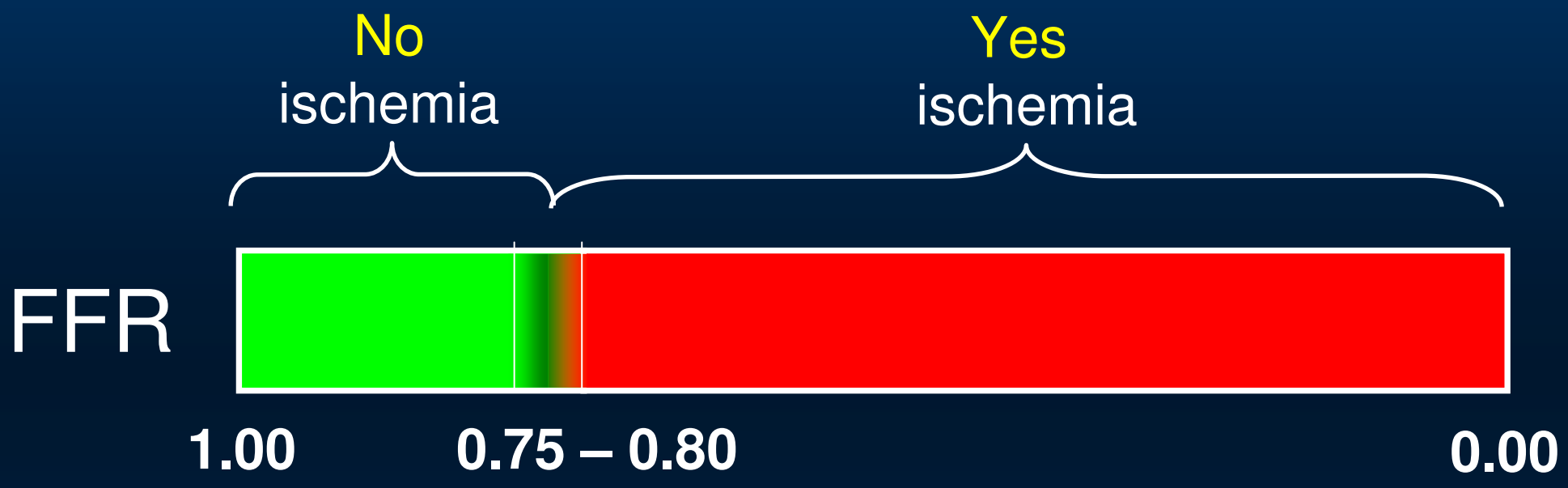
היפותזה

- התועלת / נזק בהקשר ל PCI היא תוצאה של שווי משקל בין
  - מניעת נזק הקשור לאיסכמיה הנגרמת כתוצאה מנוכחות ההיצרות
  - נזק הנגרם כתוצאה מסיבוכי הפעולה
    - מיידיים ומאוחרים יותר
- הרחבת היצרויות שאינן גורמות להפרעה בזרימה אינה מומלצת
  - מחקר DEFER

Fractional Flow Reserve in Clinical Practice



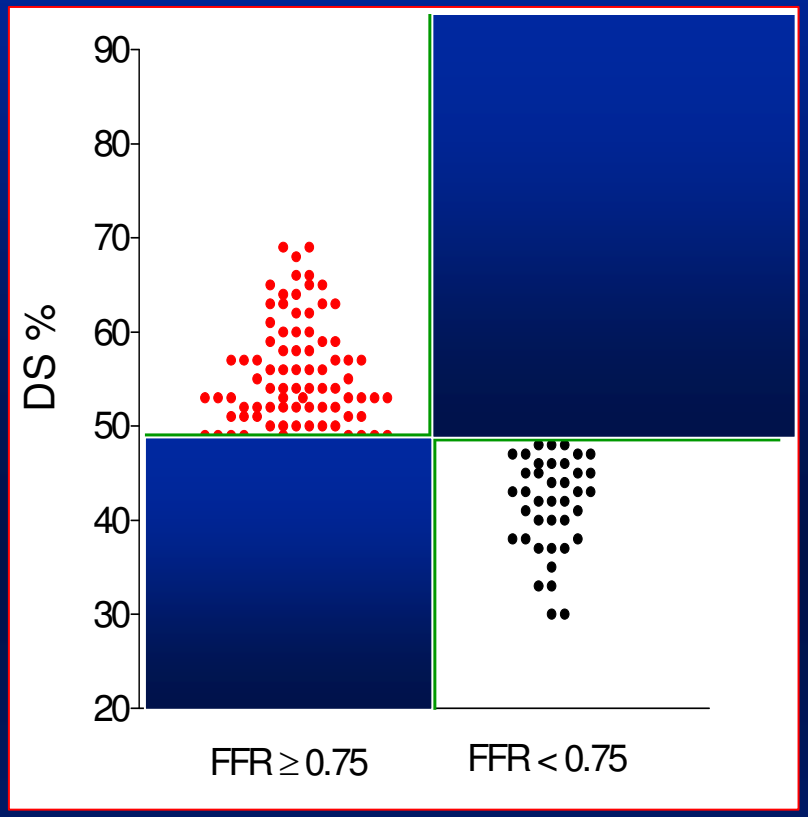
FFR threshold for ischemia



FFR < 0.75 → inducible ischemia (spec. 100 %)
FFR > 0.75 → no inducible ischemia (sens. 90 %)

Pijls, De Bruyne et al, NEJM 1996

Diameter Stenosis versus FFR



- Diameter stenosis is the main determinant of coronary stenosis

However

- Resistance is also influenced by lesion length and the 3D morphology of the stenosis

- Anatomical assessment is not accurate enough to determine physiological significance
- Coronary angiography provides only the anatomical data

FAME study: HYPOTHESIS

FFR guided Percutaneous Coronary Intervention (PCI) in multivessel disease, is superior to current angiography guided PCI

FLOW CHART

Patient with stenoses ≥ 50% in at least 2 of the 3 major epicardial vessels

Indicate all stenoses ≥ 50% considered for stenting

Randomization

Angiography-guided PCI

Stent all indicated stenoses

FFR-guided PCI

Measure FFR in all indicated stenoses

Stent only those stenoses with FFR ≤ 0.80

1-year follow-up

FAME study: Baseline Characteristics (2)

	ANGIO-group N=496	FFR-group N=509	P-value
# indicated lesions per patient	2.7±0.9	2.8±1.0	0.34
Reference diameter (mm)	2.5±0.6	2.5±0.7	0.81
% stenosis severity	61±17	60±18	0.24
MLD (mm)	1.0±0.4	1.0±0.5	0.35
50-70% narrowing, No (%)	550 (41)	624 (44)	-
70-90% narrowing, No (%)	553 (41)	530 (37)	-
90-99% narrowing, No (%)	207 (15)	202(14)	-
Total occlusion, No (%)	40 (3)	58 (4)	-
Patients with ≥1 total occlusion (%)	7.5	10.6	0.08

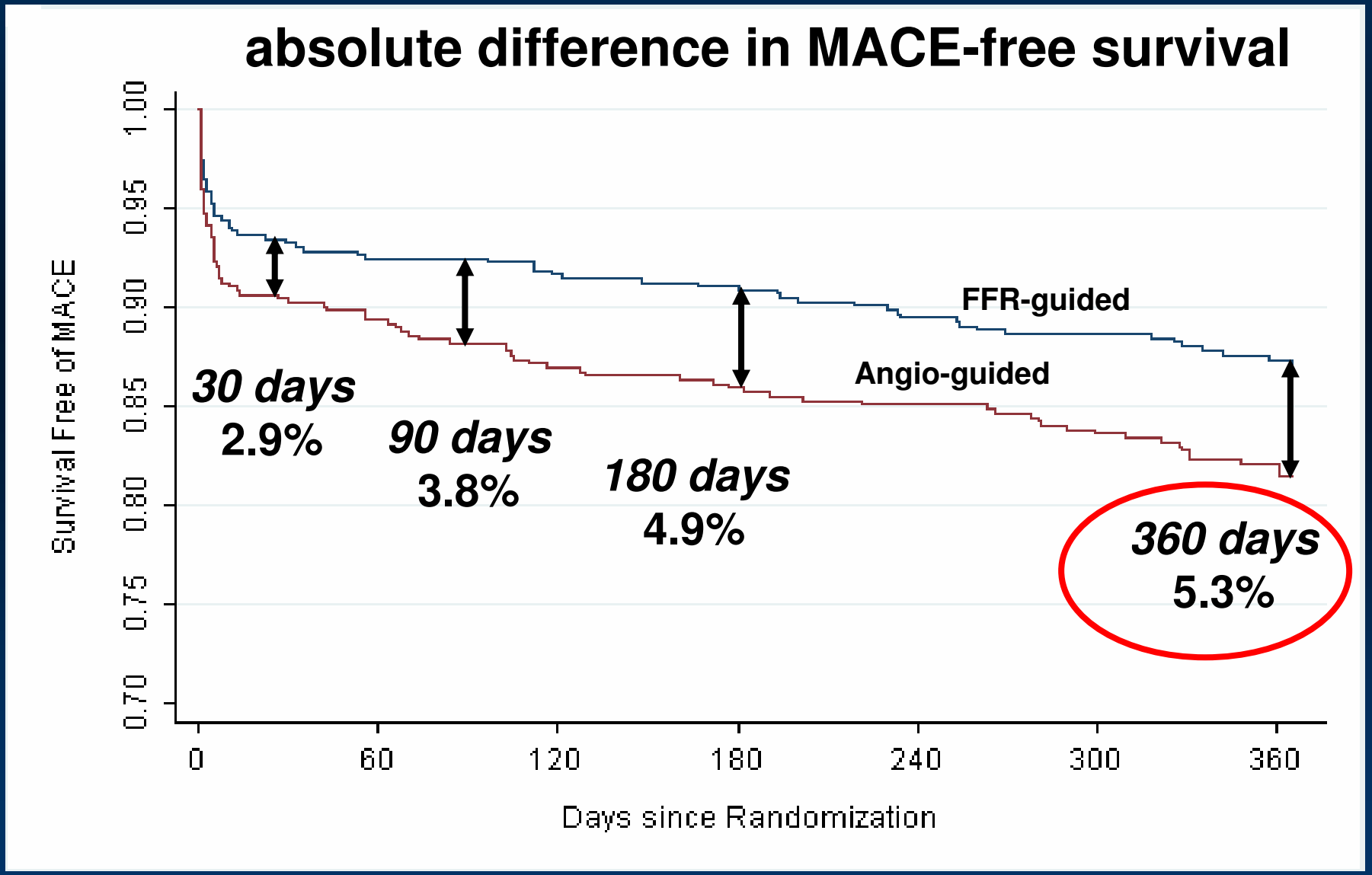
FAME study: Procedural Results (1)

	ANGIO-group N=496	FFR-group N=509	P-value
# indicated lesions per patient	**2.7 ± 0.9**	**2.8 ± 1.0**	0.34
FFR results			
Lesions succesfully measured, No (%)	-	**1329 (98%)**	-
Lesions with FFR ≤ 0.80 ,No (%)	-	**874 (63%)**	-
Lesions with FFR > 0.80 ,No (%)	-	**513 (37%)**	-

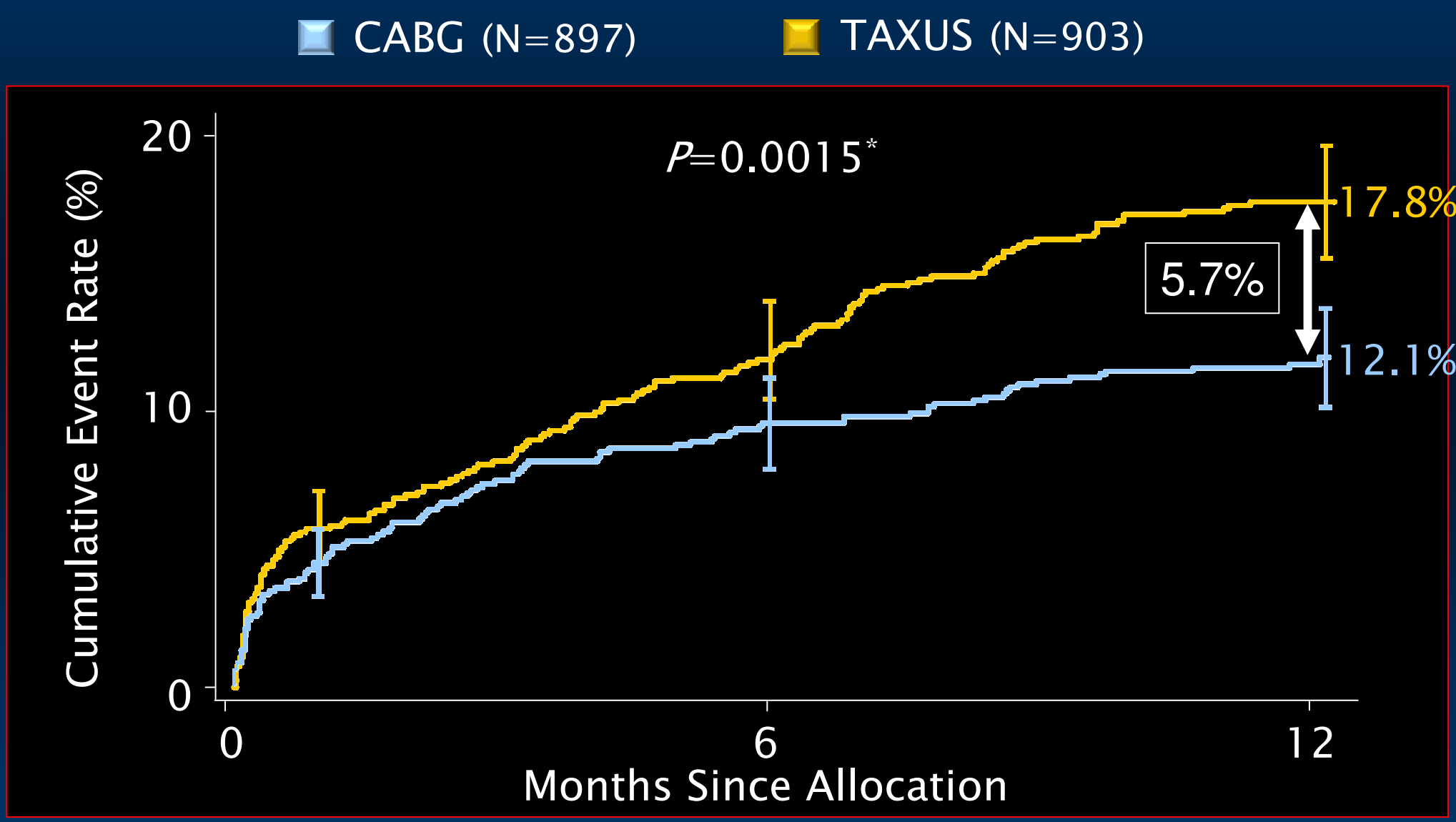
FAME study: Procedural Results (1)

	ANGIO-group N=496	FFR-group N=509	P-value
# indicated lesions per patient	**2.7 ± 0.9**	**2.8 ± 1.0**	0.34
FFR results			
Lesions succesfully measured, No (%)	-	**1329 (98%)**	-
Lesions with FFR ≤ 0.80 ,No (%)	-	**874 (63%)**	-
Lesions with FFR > 0.80 ,No (%)	-	**513 (37%)**	-
stents per patient	**2.7 ± 1.2**	**1.9 ± 1.3**	<0.001
Lesions succesfully stented (%)	**92%**	**94%**	-
DES, total, No	**1359**	**980**	-

FAME study: Event-free Survival



SYNTAX: MACCE to 12 Months – Study Endpoint



Event Rate + 1.5 SE. *Fisher's Exact Test

ITT population

PCI vs. CABG: המחקר הבא

- PCI בהנחיית FFR תוך שימוש בסטנטים מצופים מהדור החדש
- CABG – שימוש נרחב ברווסקולריזציה עורקית
- ? משמעות FFR בהקשר לרווסקולריזיה כירורגית

Coronary Revascularization
Daily Practice

- Mode of revasculaization in a specific patient is determined by
  - Physician's preference (clinical judgment)
    - Age, coronary anatomy, LV function, Comorbidities
    - Clinical trials results
      - Registry and randomized trials
  - Patient's preference
- Physicians will rarely follow recommendations that are against their clinical judgment

תודה