Composite Endpoints In Clinical Trials

C. Michael Gibson, M.S., M.D.

Harvard Medical School

Chairman, PERFUSE Study Group

Founder and Chairman, WikiDoc & WikiPatient, The World's Open Source Textbook of Medicine Viewed 896 Million Times A Year

What is a Composite Endpoint?

- Endpoint that combines several outcomes
  - Sub-components
- Components are typically directionally related (e.g. death/MI)
  - But may not be “equal” in severity and definitions can vary across trials
- May be related to the final outcome (death) but *mechanisms can be different*
  - Death/MI/bleeding
  - Death/MI/TVR

Composite Endpoints

- **We need them**
  - **Individual outcomes lack statistical power**
  - **But this can be abused**
- **We sometimes dislike them**
  - **Components vary in their clinical importance**
  - **Treatment effect varies across components**
- **May actually *lose* power by using a composite endpoint!!!**

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Composite Outcomes in Published CV Trials

- **304 trials in 14 journals in 2000-2006**

- ***73% had composite as primary endpoint, median 3 components***

death	98%
myocardial infarction	92%
reintervention	54%
stroke	32%
angina	10%
hospitalization	12%
cardiac failure	9%

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Lim et al Ann Int Med 2008

Composite Endpoints: Take Care
RITA 3 Trial

	Intervention	vs Conservative
Patients	895	915
Deaths	26	23
After 4 months MIs	30	34
Refractory angina	39	85
Death, MI or refractory angina (primary endpoint)	86 (9.6%)	133 (14.5%)

Overall p=0.001

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Fox K et al. Lancet 2002; 360(9335): 743-51

TYPHOON trial

DES vs. BMS in primary PCI

primary endpoint: cardiac death, MI, TVR by 1 year

	sirolimus (N=355)	control (N=377)	
primary	26	51	P=.004
cardiac death	7	5	
myocardial infarction	4	5	
TVR	20	48	

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c/o S. Pocock

2 Primary Stent Endpoints (at 12 Months)

1) Ischemia-driven TLR*

and

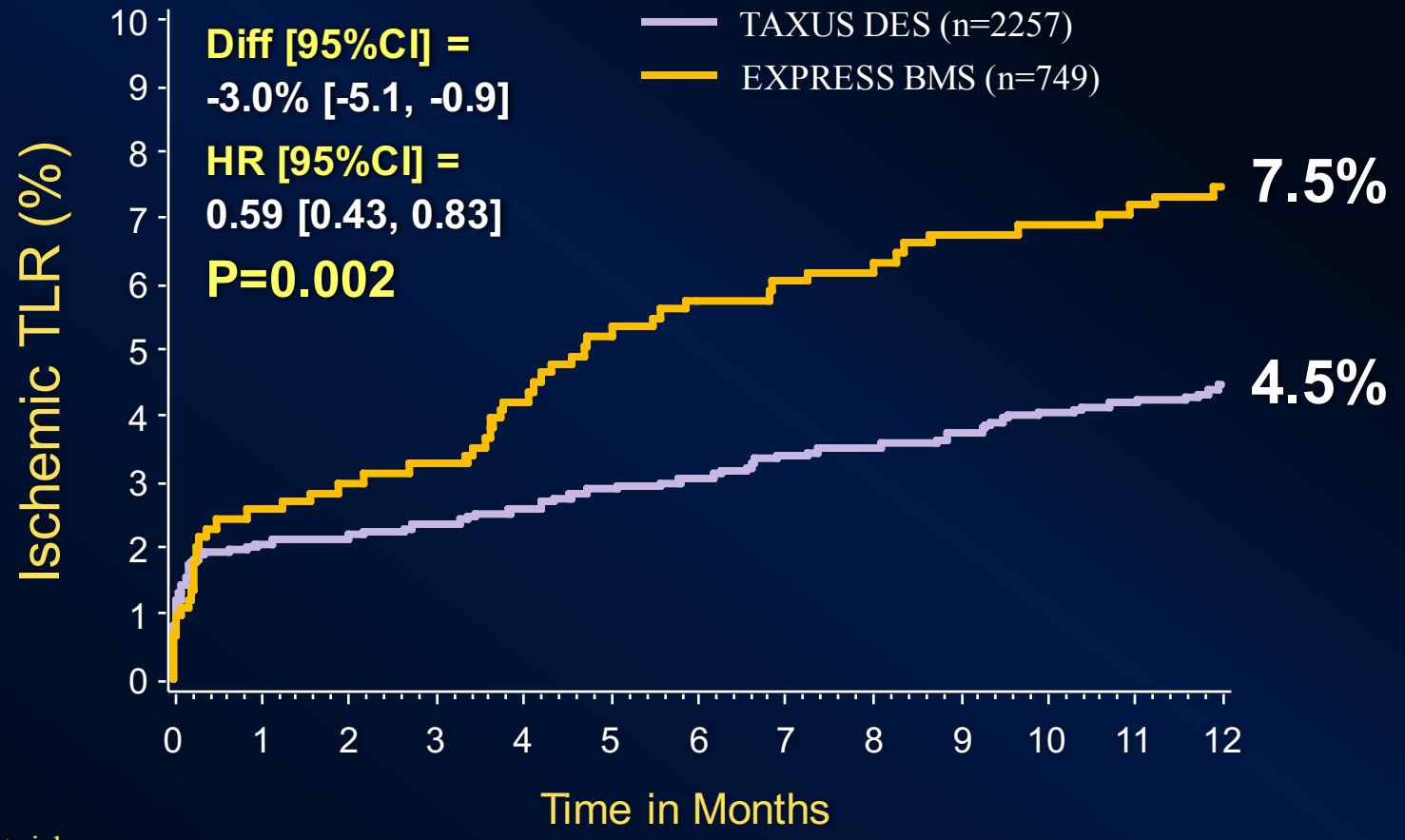
2) Composite Safety MACE = All cause death, reinfarction, stent thrombosis (ARC definite or probable)**, or stroke

Major Secondary Endpoint (at 13 Months)

Binary angiographic restenosis

* Related to randomized stent lesions (whether study or non study stents were implanted); ** In randomized stent lesions with ≥1 stent implanted (whether study or non study stents)

Primary Efficacy Endpoint: Ischemic TLR



Number at risk					
TAXUS DES	2257	2132	2098	2069	1868
EXPRESS BMS	749	697	675	658	603

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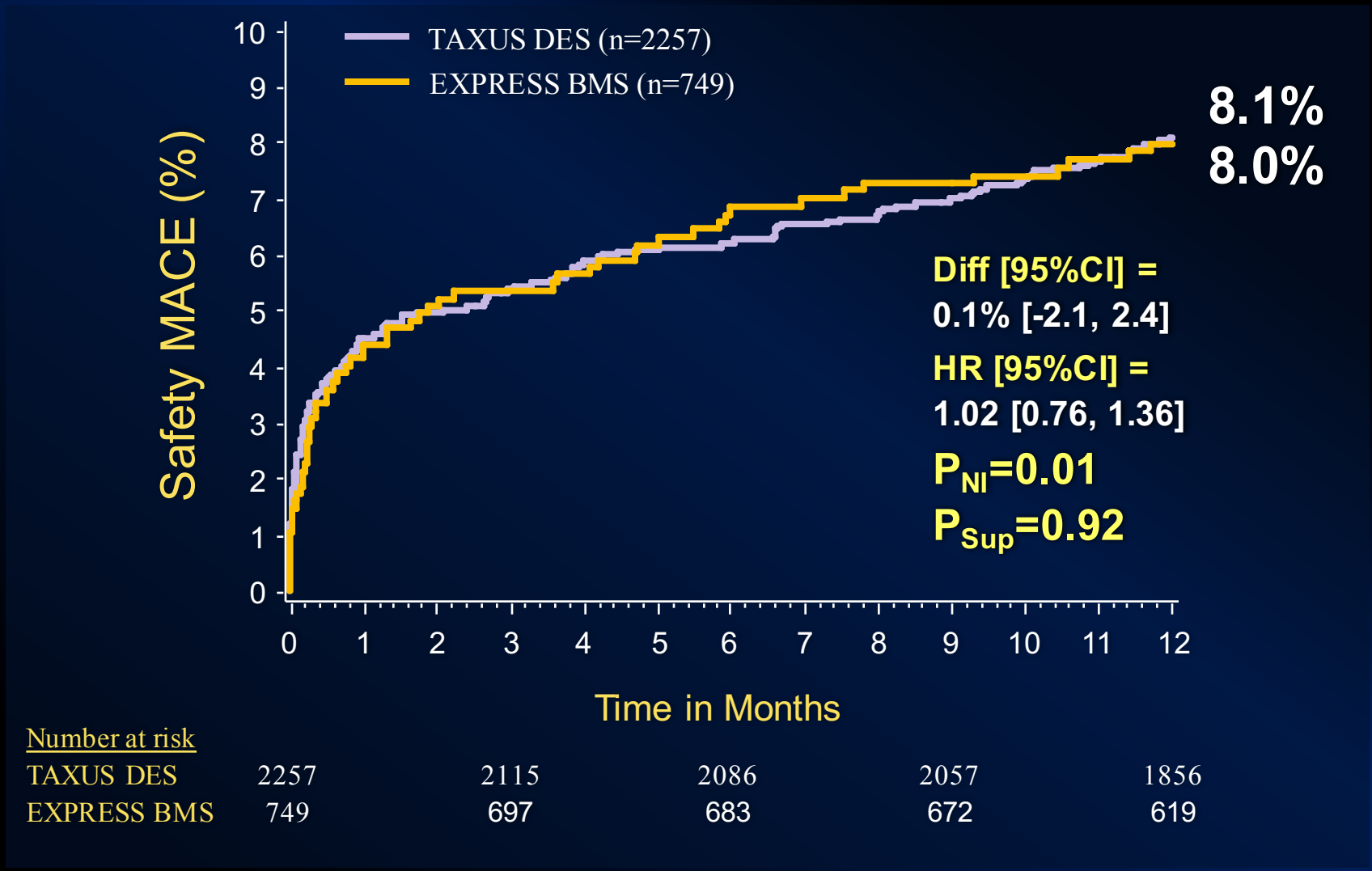
Primary Safety Endpoint: Safety MACE*



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* Safety MACE = death, reinfarction, stroke, or stent thrombosis

HORIZONS-AMI trial

Primary efficacy: target lesion revascularization at 1 year

Composite safety: death, reinfarction, stroke, stent thrombosis

	TAXUS stent (N=2257)	**bare-metal stent** (N=749)	
TLR	4.5%	7.5%	P=.002
Composite safety	8.1%	8.0%	P=.92

Separate re-intervention from major clinical concerns

Non-inferiority re safety, components "equally flat"

SYNTAX: PCI vs. CABG

"SYNTAX fails to show non-inferiority for DES"

1800 patients with left main/3 vessel disease

Primary Endpoint of MACCE:

Composite of death, stroke, MI repeat revascularisation

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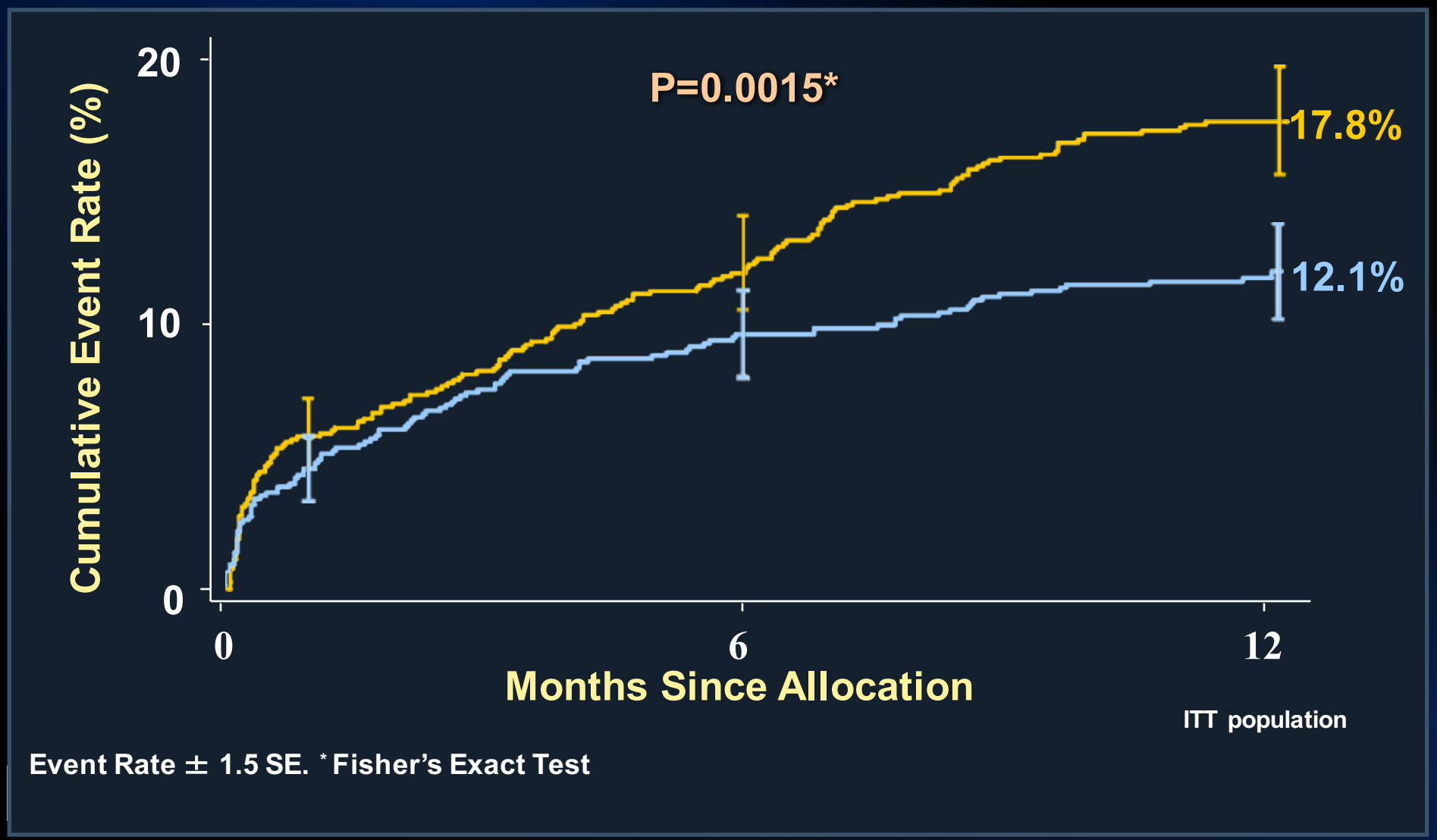
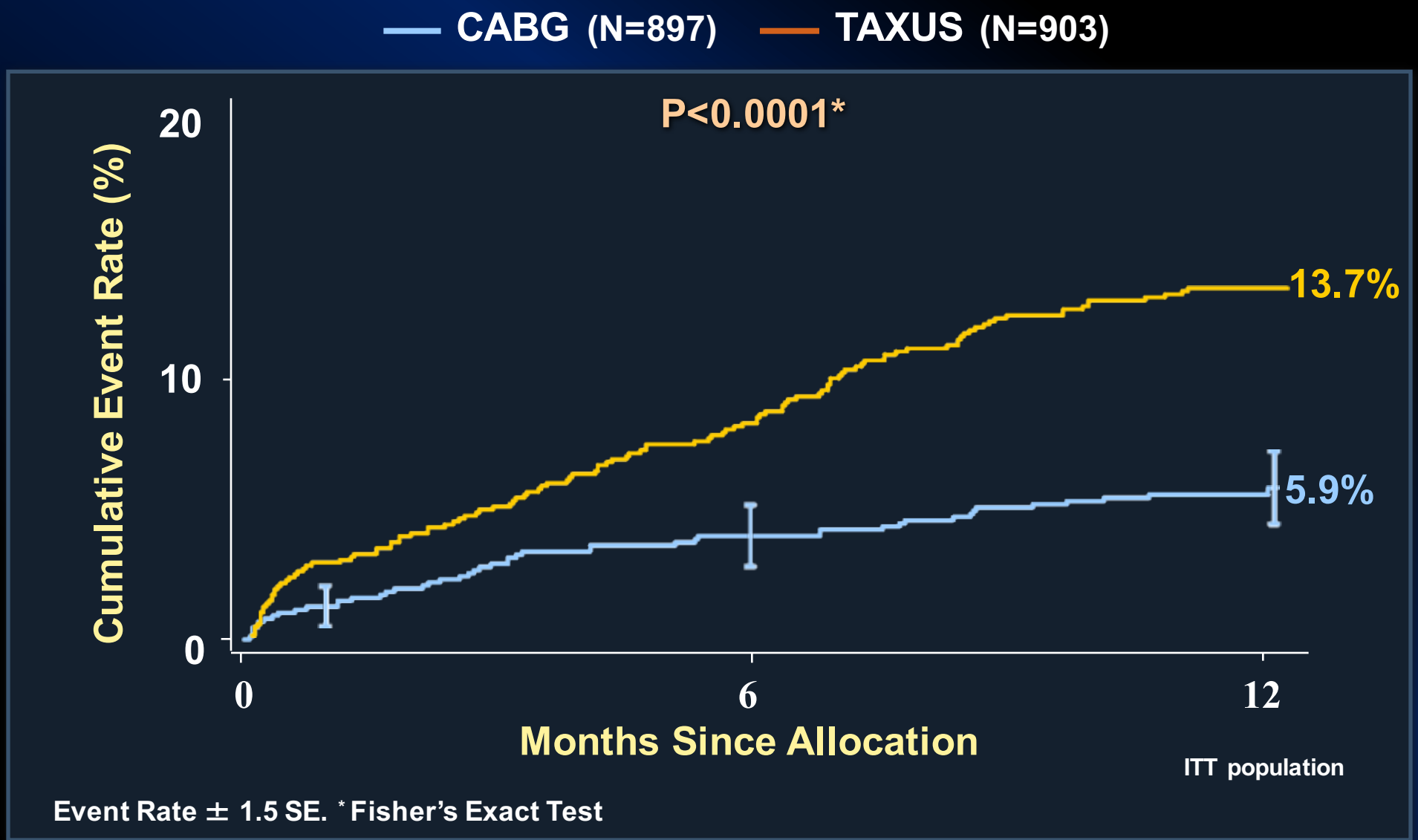
MACCE to 12 Months

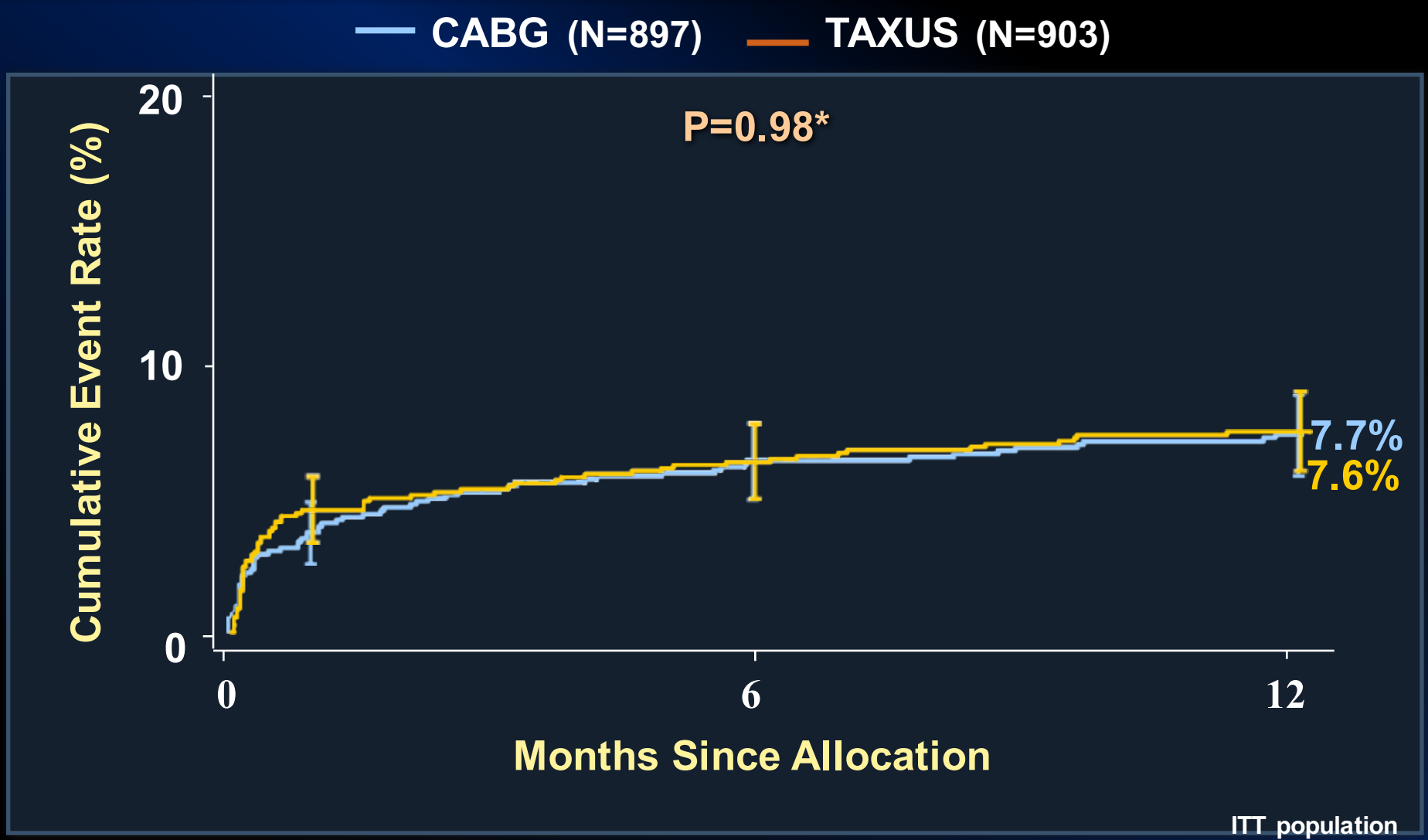


Event Rate ± 1.5 SE. * Fisher's Exact Test

Repeat Revascularization to 12 Months



All-Cause Death/CVA/MI to 12 Months



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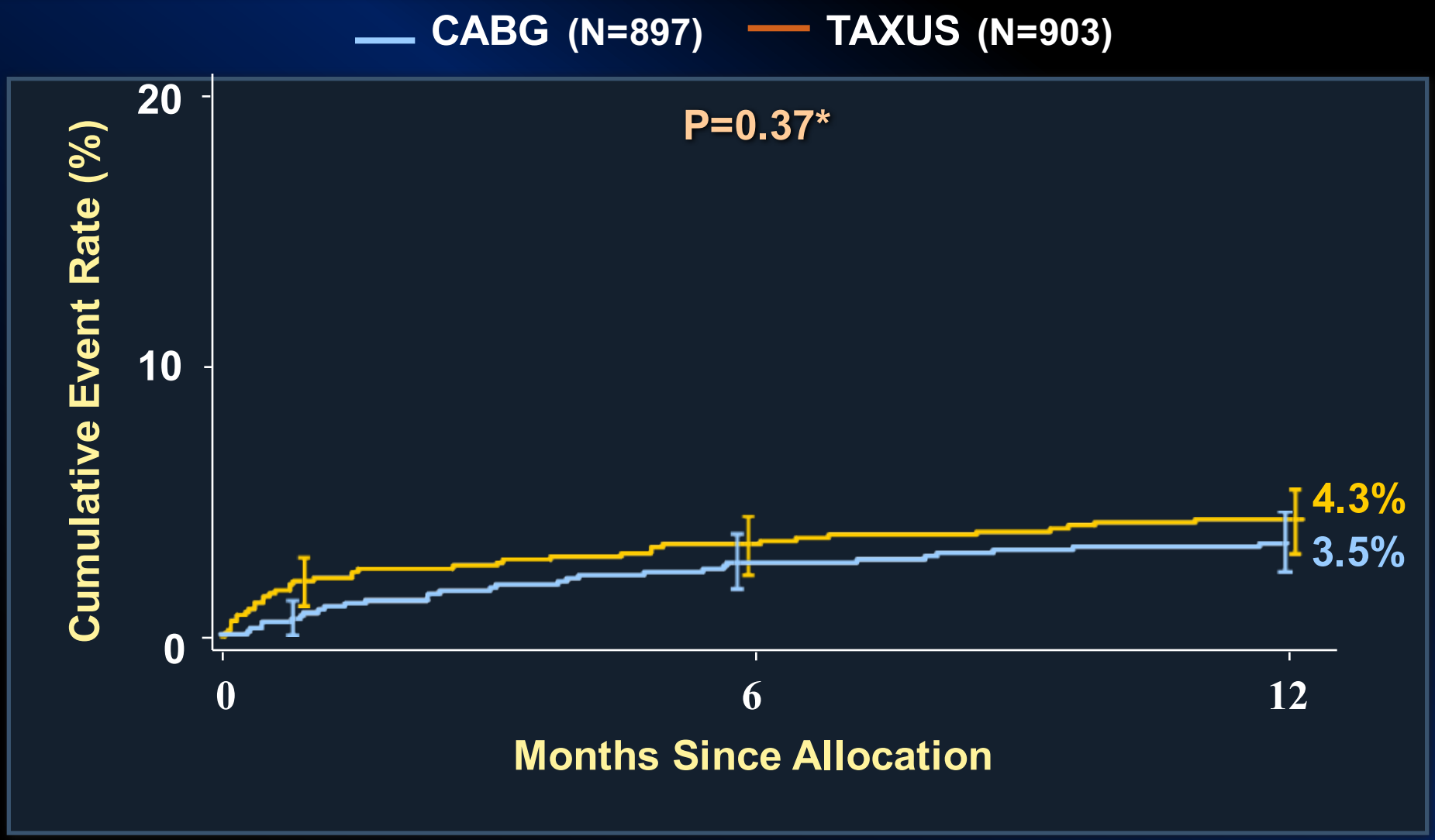
Event Rate ± 1.5 SE. * Fisher's Exact Test

All-Cause Death to 12 Months



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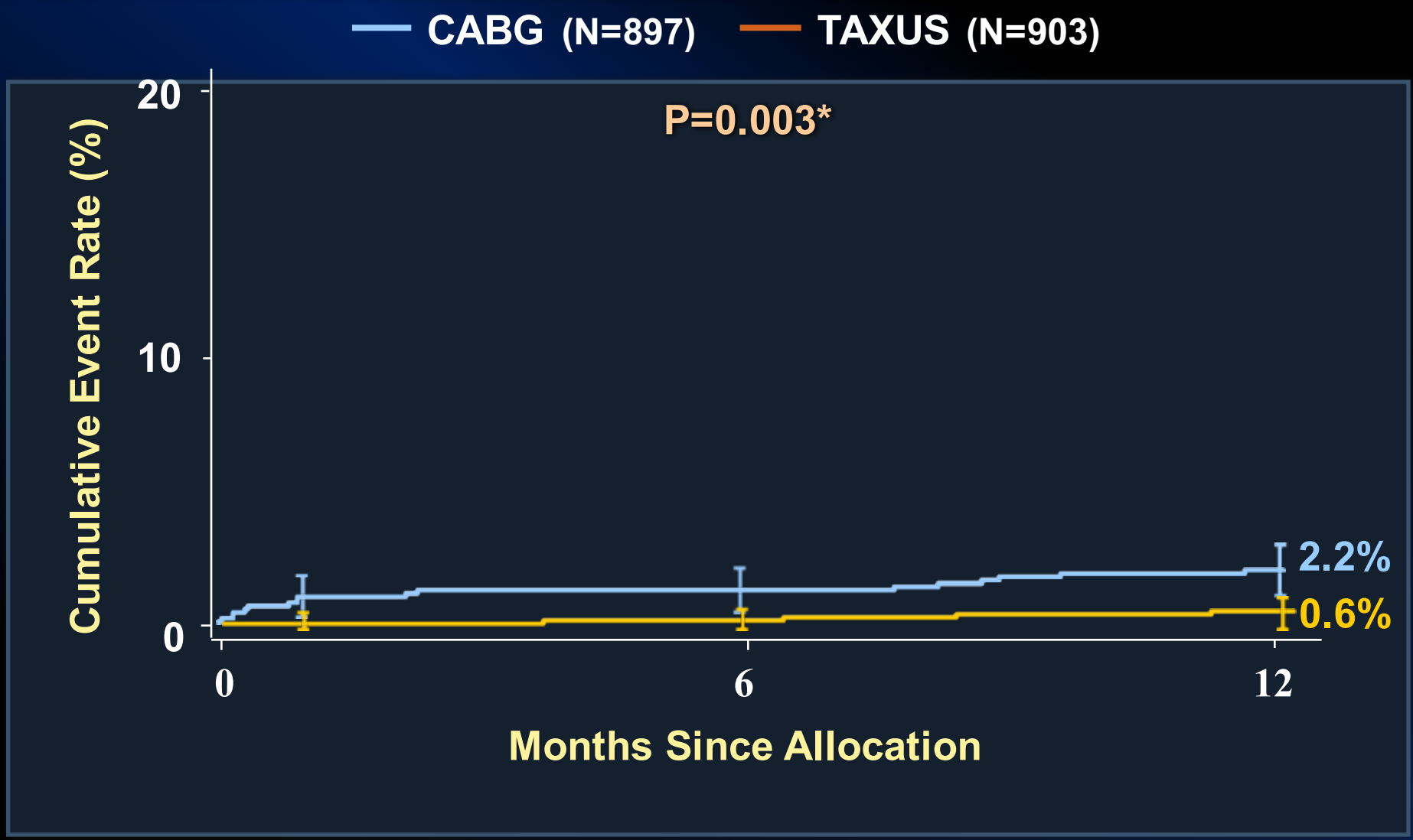
ITT population

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

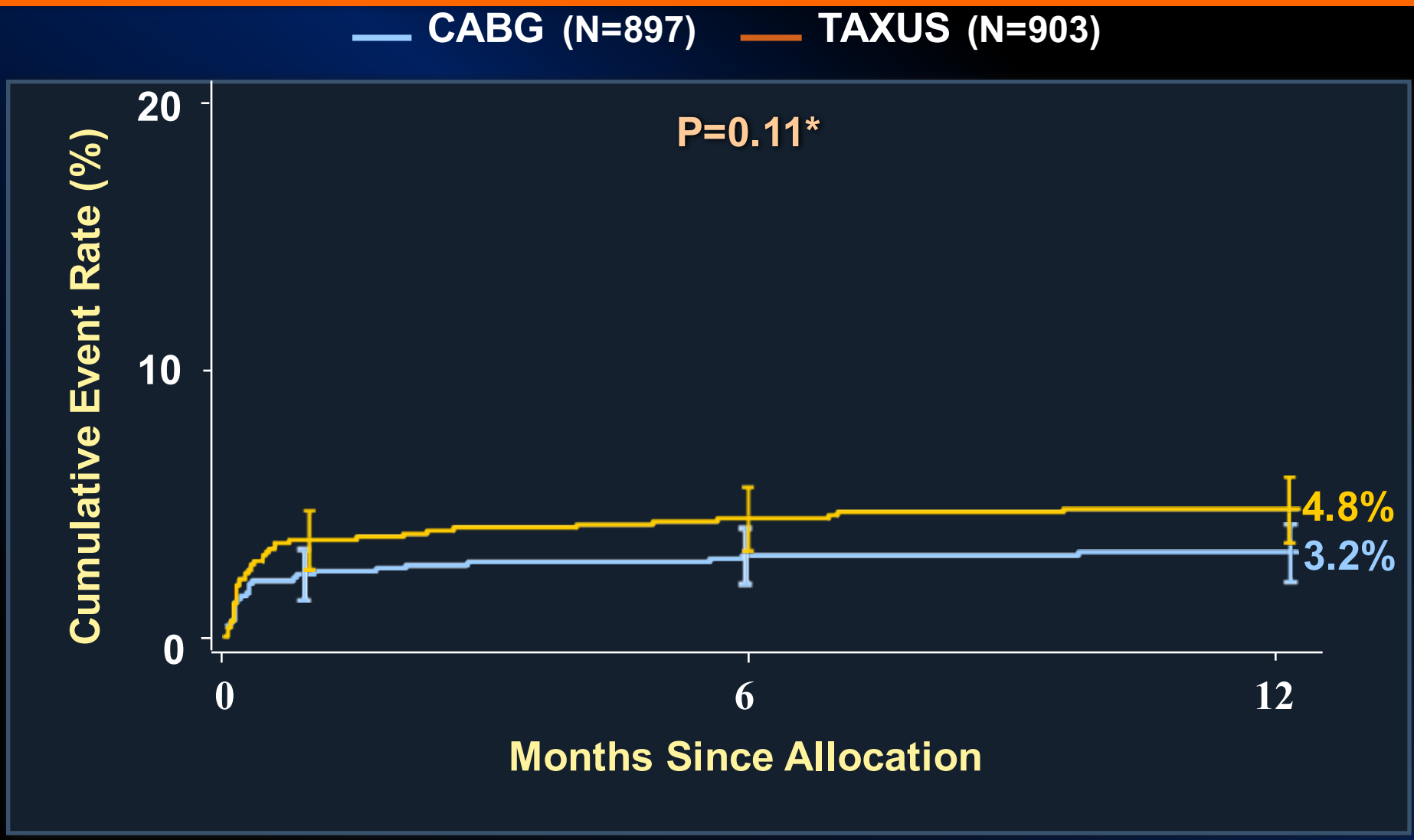
CVA to 12 Months



ITT population

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

Myocardial Infarction to 12 Months



ITT population

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

SYNTAX Summary

- Composite MACCE (death/MI/stroke/revasc) driven by greater repeat revascularization alone
  - Death/MI/Stroke rates virtually identical
- Composite death/MI/stroke had offsetting components
  - Higher MI with PCI
  - Higher stroke with CABG
- What about other differences not captured in the composite?

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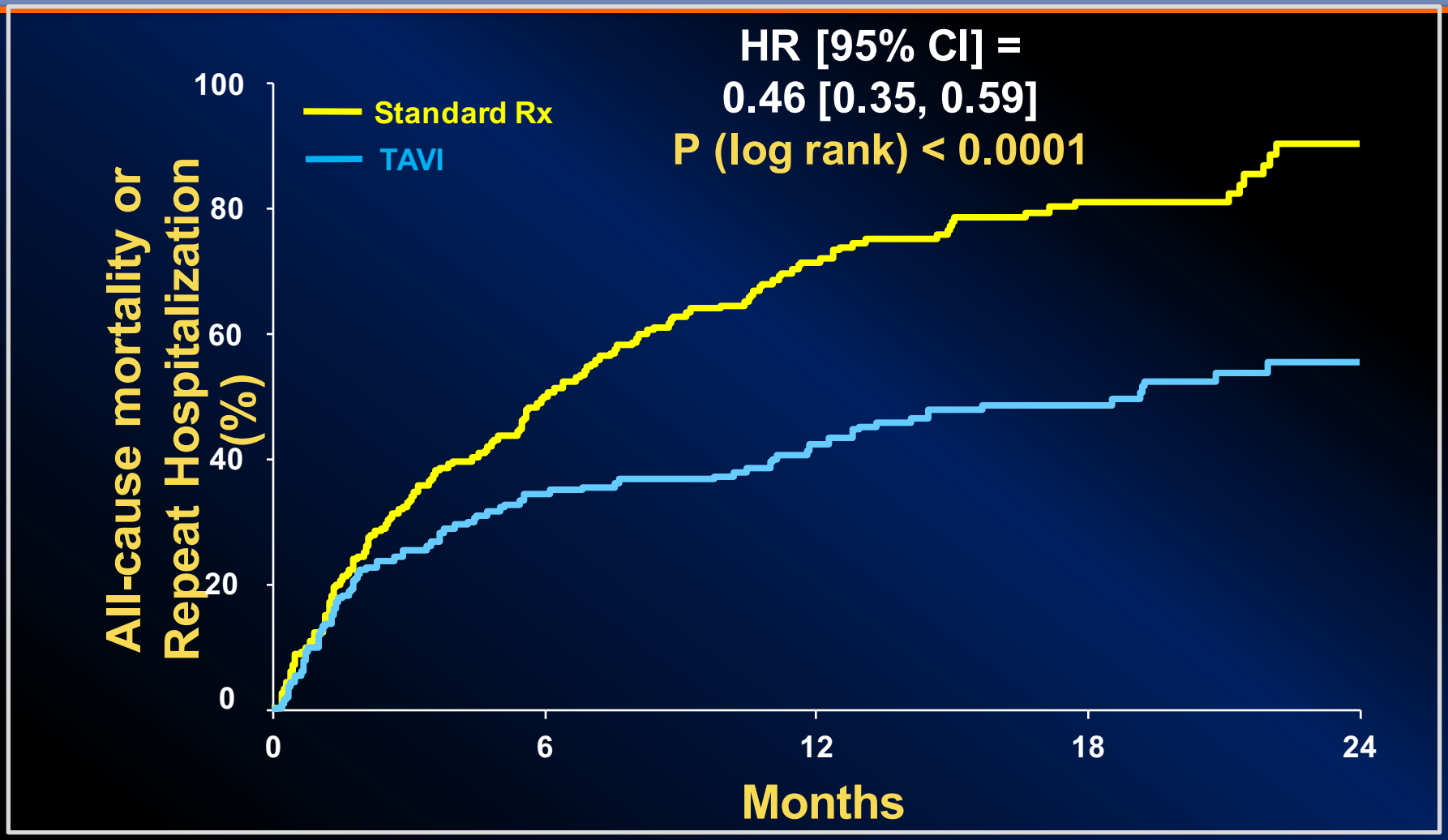
PARTNER Endpoints

- *PRIMARY: All-cause mortality over the duration of the study*
  - Superiority test (two-sided), 85% power to detect a difference, α = 0.05, sample size = 350 total patients

- *CO-PRIMARY: Hierarchical composite of all-cause mortality and repeat hospitalization*
  - Non-parametric method described by Finkelstein and Schoenfeld (multiple pair-wise comparisons)
  - > 95% power to detect a difference, α = 0.05

Mortality or Repeat Hosp



Numbers at Risk					
TAVI	179	117	102	56	22
Standard Rx	179	121	49	23	4

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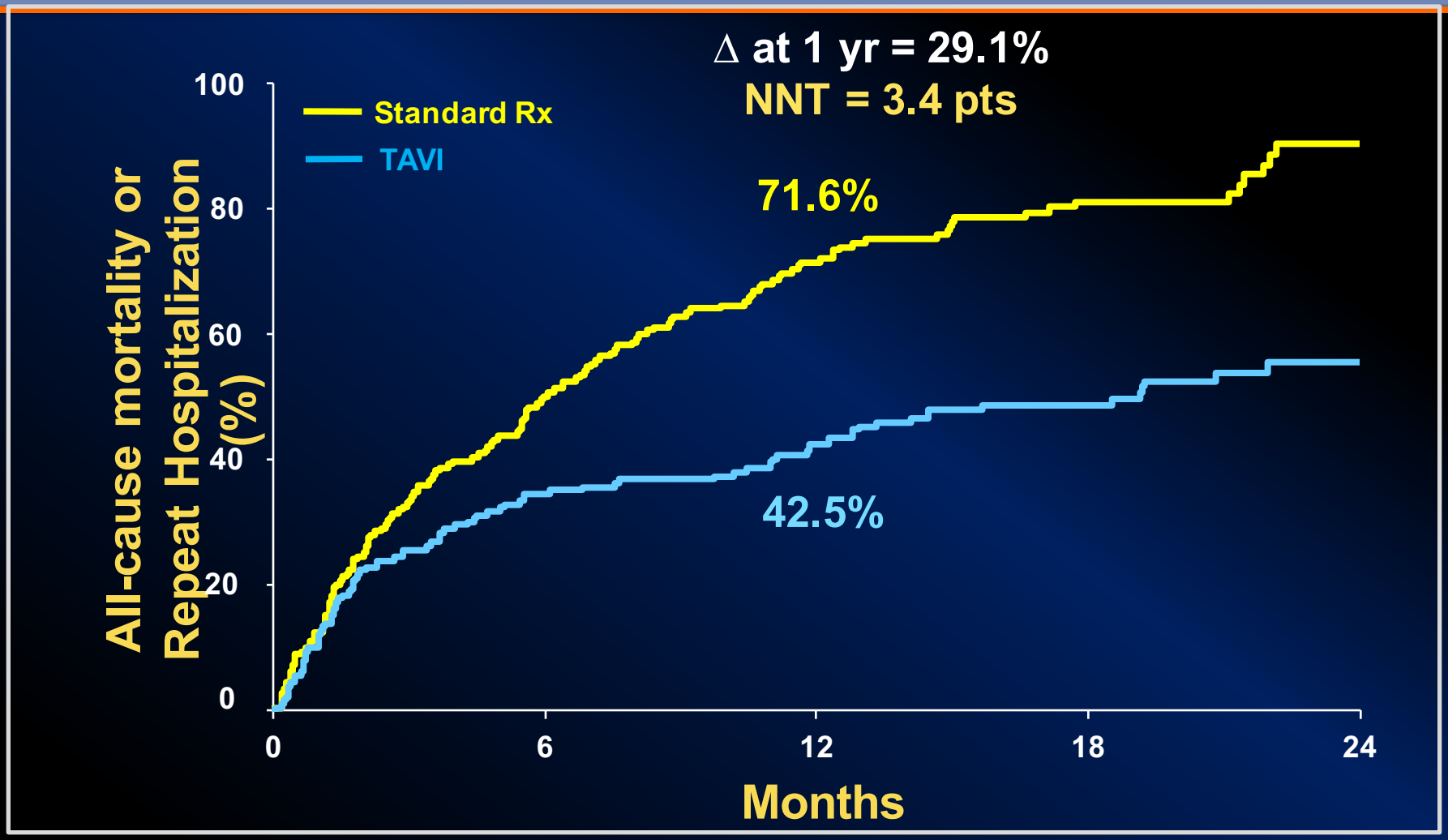

Numbers at Risk					
TAVI	179	117	102	56	22
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Finklestein & Schoenfeld Analysis (hierarchical multiple pair-wise comparison)

- *Compare, at random, every TAVI patient with every Standard Rx patient;* 179 x 179 (32,041) patient pairs, which did better?
- *#1, compare "time to death"*
  - 72% chance that we know who died first
  - If so, 63% chance that Standard Rx patient died first and 37% chance that TAVI patient died first
- *#2, if necessary, compare "time to repeat hospitalization"*
  - 17% chance that we know who had repeat hosp first
  - If so, 75% chance that Standard Rx patient had repeat hosp first and 25% chance that TAVI patient had repeat hosp first

PARTNER: Win Ratio Analysis

Compare every TAVI pt with Standard pt:
Total no. of pairs: 179 x 179 = 32041

Death w TAVI 1st		8498	LOSE
Death w standard 1st		14466	WIN
Hosp survivor w TAVI 1st	1345	LOSE	
Hosp survivor w standard 1st		3979	WIN
None of the above		3753	TIE

Win Ratio = Pairs with TAVI win / Total Number of pairs
Win ratio for composite: 1.87 (95% CI 1.35-2.54)

Pocock et al Eur Heart J 2011

Weighting Components of Composites

- Endpoint Weights
  - *Can discount less important outcomes (e.g. a TLR is worth some fraction of a non-fatal NQWMI)*
- But from whose perspective?
- Outside of QOL / Cost-Effectiveness analyses, there is poor guidance on how to weigh endpoints
- Issues of interpretability

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Summary: Composite Endpoints

- Advantages
  - *May provide* gain in statistical power
  - Simple summary of several outcomes
- Disadvantages
  - Can be clinically difficult to interpret
  - May be a mixed bag of “hard” and “softer” outcomes
  - Combined outcomes of varying importance
    - Often no clear way to “weigh” these outcomes

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Summary

- **Composite primary endpoints are of value**
  - When no single component dominates
  - Statistical power may be increased
  - Provides a global summary of treatment effect

- **Composite primary endpoints have problems**
  - What components to include?
  - Components vary in clinical importance
  - Treatment effect varies across components
  - Results often misinterpreted

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