OPTIMIZE: A Prospective, Randomized Trial *of 3 Months Versus 12 Months* of Dual Antiplatelet Therapy with the *Endeavor Zotarolimus-Eluting Stent*

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On behalf of the OPTIMIZE Trial Investigators

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Disclosure Statement of Financial Interest

Fausto Feres, MD

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

Affiliation/Financial Relationship	Company
• Consulting Fees/Honoraria	• Biosensors, Eli Lilly, Medtronic

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Background

- **Current recommendations for antithrombotic therapy after drug-eluting stent (DES) implantation *include prolonged dual antiplatelet therapy* (DAPT).**
- **However, *the impact of such a regimen* for all patients receiving a specific DES system remains unclear based on scientific evidence available to date.**

Levine GN, et al. *Circulation*. 2011;124:e574-651
Wijns W, et al. *Eur Heart J*. 2010;31(20):2501-55

DAPT Post-DES

- ***Premature DAPT discontinuation*** **has been determined to be one of the most powerful predictors of thrombotic events after first generation DES.**

- **Also, several other issues have been identified with prolonged DAPT, *including bleeding, compliance, and cost.***

Iakovou I, et al. *JAMA*. 2005;293:2126–30
Bhatt DL, et al. *NEJM*. 2006;354:1706-17

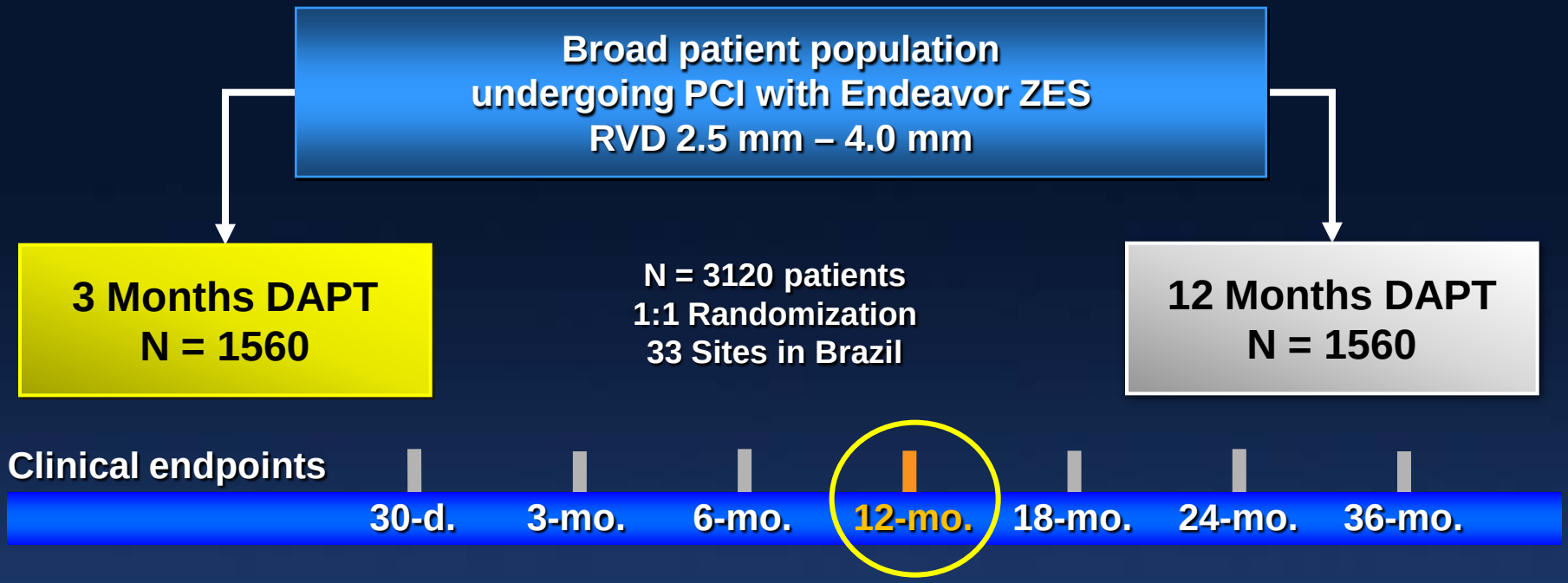
Objective

- The Endeavor® zotarolimus-eluting stent (E-ZES) has demonstrated (very) ***long-term efficacy and safety***, despite short duration DAPT (3 months) in the majority of studies.

- Therefore, we sought to investigate the safety and clinical impact of ***short-term (3 months) DAPT with E-ZES*** in daily clinical practice.

Feres F. et al, *Am Heart J*. 2012;164:810-6

Study Design



Primary Endpoint: NACCE (Death / MI / Stroke / Major Bleeding) at 12 months

Secondary Endpoints: ARC defined ST, TVR, TLR, MACE, DAPT compliance, and major bleeding (REPLACE-2 & GUSTO definitions)

NACCE = Net Adverse Clinical and Cerebral Events
MACE is composed of Death, MI, Emergent CABG, TLR

Feres F. et al, *Am Heart J.* 2012;164:810-6

Patient Eligibility Criteria

Inclusion Criteria

- Stable or unstable angina, or recent MI*
- ≥ 1 coronary lesion suitable for PCI with E-ZES
- Native vessel ≥ 2.50 mm in diameter with stenosis > 50%

*Formal recommendation to not enroll patients with ACS and positive biomarker at index procedure.

Exclusion Criteria

- Primary or rescue PCI for STEMI
- Lesion located in SVG
- Previous PCI with DES
- PCI in non-target lesion with BMS <6 months (ISR allowed)

Feres F. et al, *Am Heart J.* 2012;164:810-6

Study Organization

Principal Investigator
Fausto Feres

Steering Committee
Fausto Feres (Chair)
Deepak L. Bhatt
Roberto Botelho
Ricardo A. Costa
Spencer King
Martin Leon
Manuela Negoita

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Cardiovascular Research Center, Sao Paulo, Brazil
Angiographic Core Laboratory
Clinical Events Committee
Data Management
Data Monitoring
Statistical Analysis

Sponsors
Cardiovascular Research Center, Sao Paulo, Brazil
Medtronic Comercial Ltda, Sao Paulo, Brazil

33 Clinical Sites in Brazil

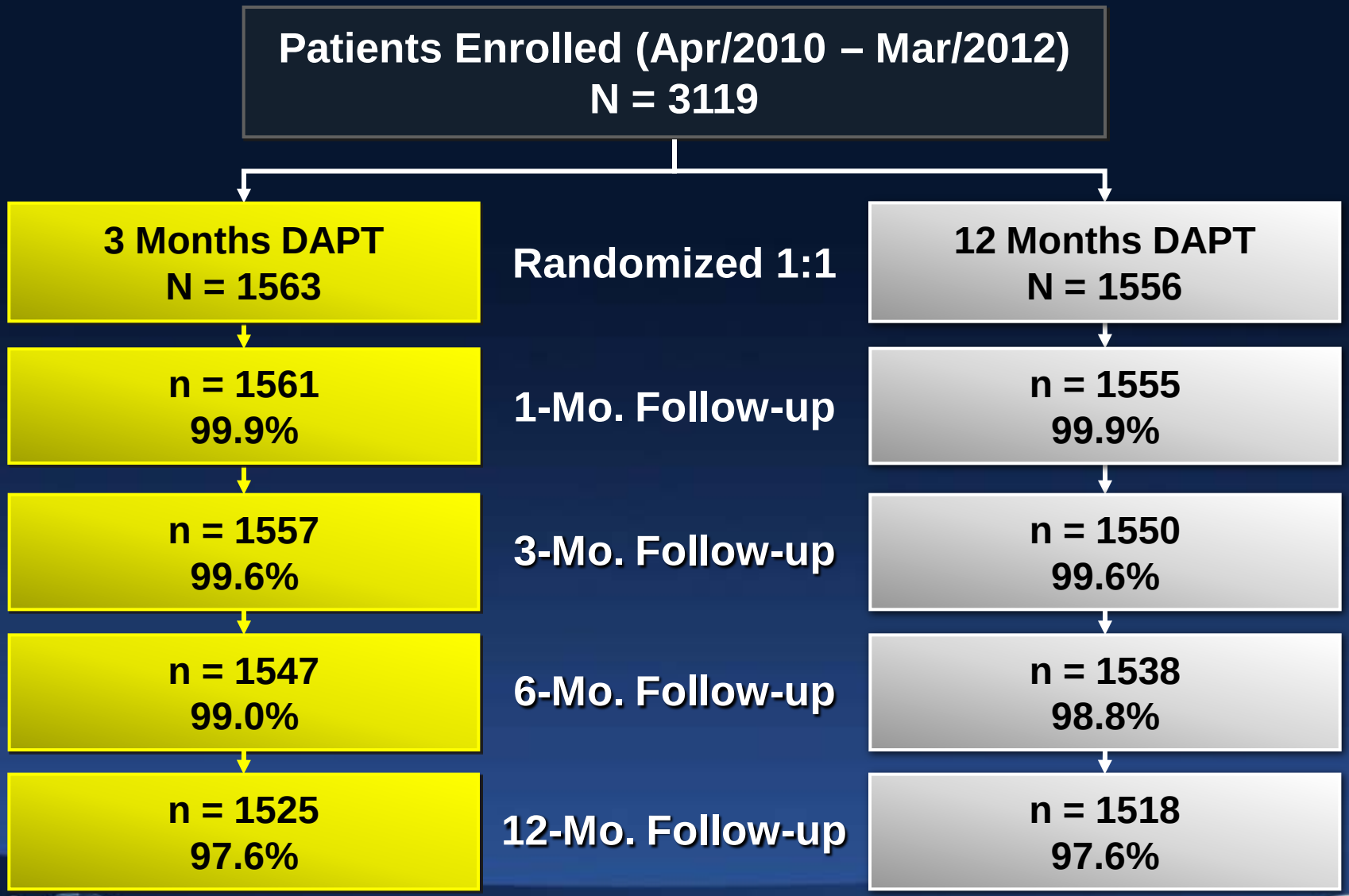
1st Investigator Meeting

2009

Statistical Power Calculation

- ***Non-inferiority analysis*** **by Intention-to-Treat (ITT)**
- **Primary endpoint: *NACCE* (Net Adverse Clinical and Cerebral Events) defined as death by any cause, MI, stroke, or major bleeding at 12 months**
- **Assumptions:**
  - **Expected NACCE at 12 months in the long-term DAPT group = 9%**
  - **Delta (δ) = 2.7%**
  - **Statistical power = 80%**
  - **Alpha level (one-sided) = 5% (0.05)**
- **A minimum of 1,404 patients in each group would be necessary to demonstrate non-inferiority for the primary endpoint**
- **Considering lost to follow-up of 10%, sample size increased by ~10% to total = *1,560 patients in each group***

Patient Flow Chart



Baseline Characteristics

OPTIMIZE

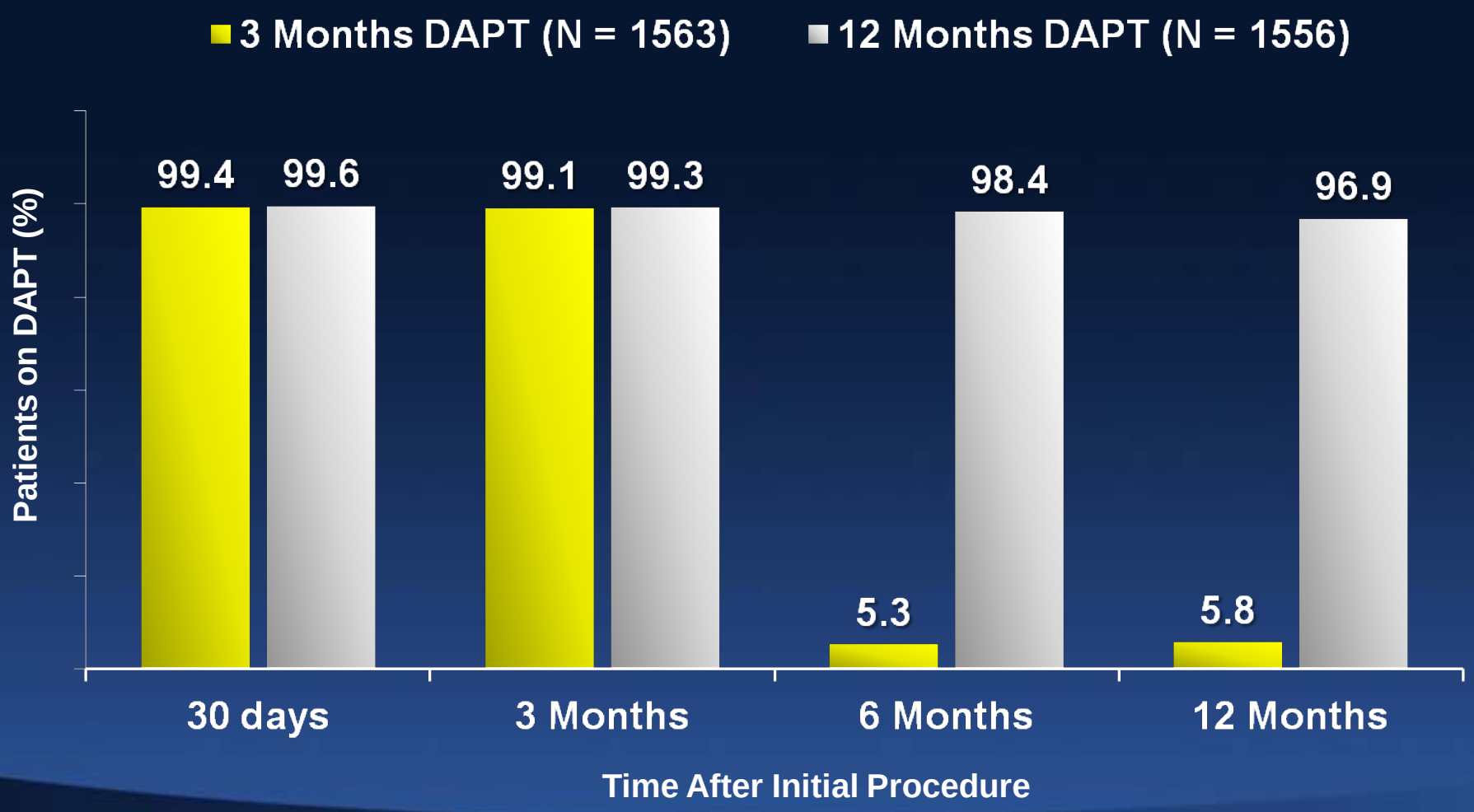
Variable (%)	*3 Months DAPT N = 1563*	*12 Months DAPT N = 1556*	*P-Value*
Age (yr)	61.3± 10.4	61.9 ± 10.6	0.13
Female	36.5	36.9	0.84
Diabetes mellitus	35.4	35.3	0.93
Insulin dependent	10.2	10.4	0.92
Hypertension	86.4	88.2	0.15
Hyperlipidemia	63.2	63.7	0.80
Current smoker	18.6	17.3	0.36
Family history of CAD	41.3	42.8	0.42
Renal insufficiency	7.4	5.8	0.08
Prior MI	34.6	34.8	0.90
Prior PCI	20.9	19.1	0.20
Prior CABG	7.1	8.2	0.24
Silent ischemia	8.6	9.2	0.55
Stable angina	59.8	58.6	0.47
Recent ACS (≤30 days)	31.6	32.3	0.72

Lesion Characteristics

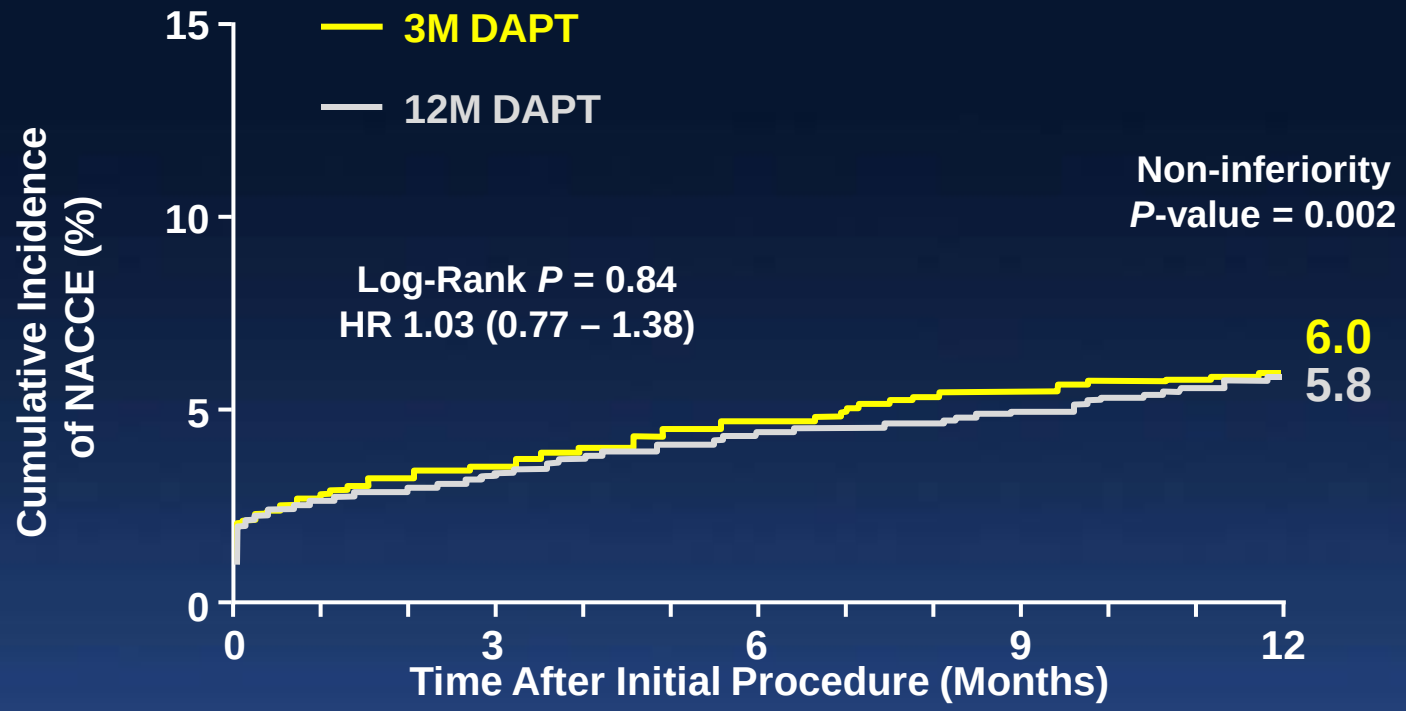
Variable	*3 Months DAPT N = 1563*	*12 Months DAPT N = 1556*	*P-Value*
Number of Lesions	**2058**	**2062**	
Target lesion coronary artery (%)			
LAD	47.9	46.6	0.38
LCx	23.4	24.3	0.49
RCA	27.6	27.7	0.92
Unprotected Left Main	1.2	1.5	0.42
ACC/AHA lesion class type C (%)	**37.0**	**37.4**	**0.80**
Pre-TIMI flow grade <3 (%)	7.4	6.9	0.25
Bifurcation (%)	**14.7**	**14.9**	**0.81**
Reference vessel diameter (mm)	2.76 ± 0.48	2.76 ± 0.47	0.95
MLD (mm)	0.87 ± 0.41	0.88 ± 0.41	0.42
% Diameter stenosis	68.6 ± 13.4	68.2 ± 13.5	0.36
Lesion length (mm)	**18.28 ± 10.76**	**18.46 ± 10.89**	**0.59**
Number of stents per patient	**1.6 ± 0.8**	**1.6 ± 0.8**	**0.33**
Stent length per patient (mm)	**32.75 ± 19.84**	**32.73 ± 20.01**	**0.99**

Radial access was performed in 40% of all cases. Angiographic (QCA) analysis performed by independent core laboratory.

DAPT Usage


3 Months DAPT (N = 1563)
12 Months DAPT (N = 1556)
Patients on DAPT (%)
99.4
99.6
99.1
99.3
5.3
98.4
5.8
96.9
30 days
3 Months
6 Months
12 Months
Time After Initial Procedure

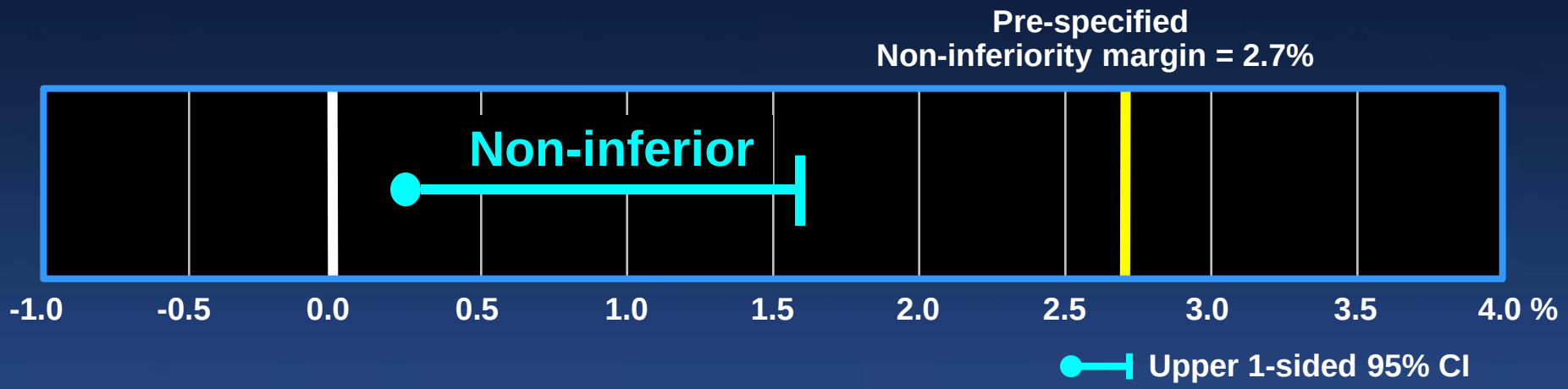
Primary Endpoint: NACCE at 1 Year
(All-Cause Death, MI, Stroke, Major Bleeding)



Month	0	1	3	6	12
No. at risk	1563	1520	1504	1468	1384
No. events	18	25	11	18	21
No. at risk	1556	1514	1497	1466	1381
No. events	16	25	11	16	22

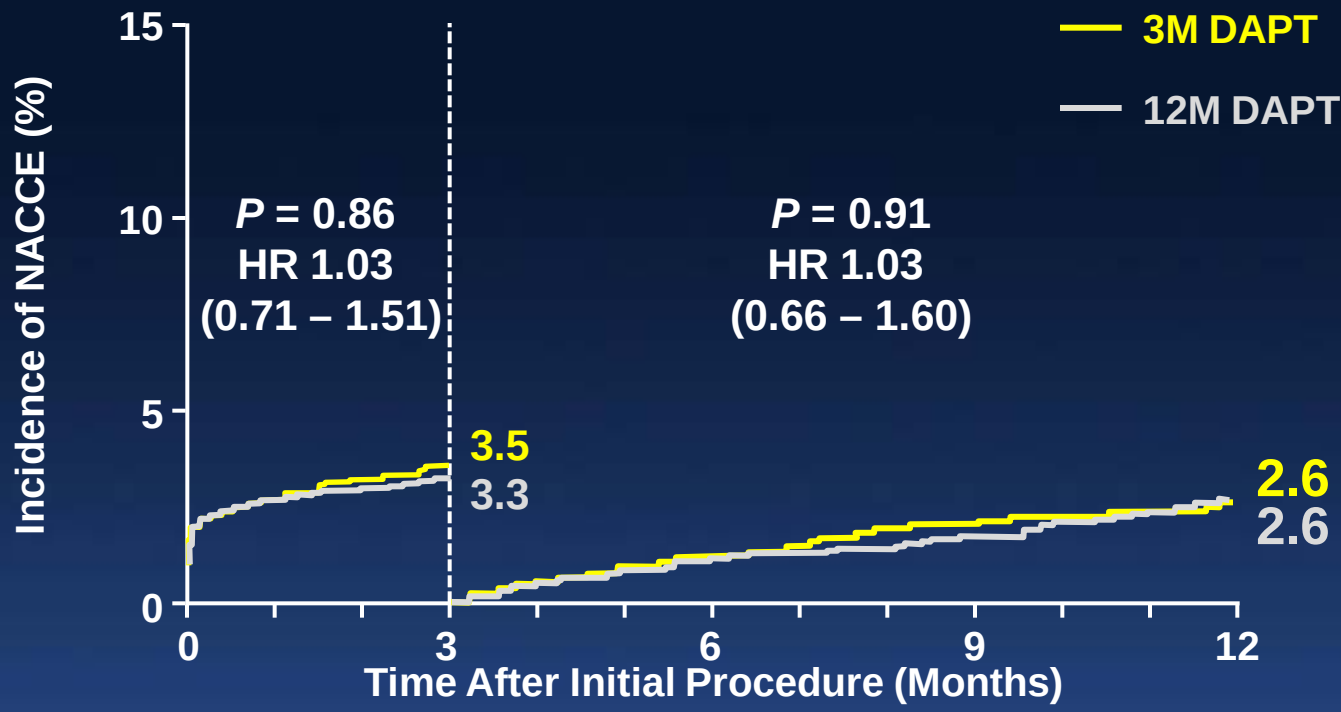
Primary Endpoint: NACCE at 1 Year
(All-Cause Death, MI, Stroke, Major Bleeding)

3M DAPT (N = 1563)	12M DAPT (N = 1556)			Non-inferiority *P*-value
6.0%	5.8%	Difference	: 0.2%	= 0.002
		Upper 1-sided 95% CI	: 1.6%	



Primary Non-Inferiority Endpoint Met

Landmark at 3M: NACCE
(All-Cause Death, MI, Stroke, Major Bleeding)



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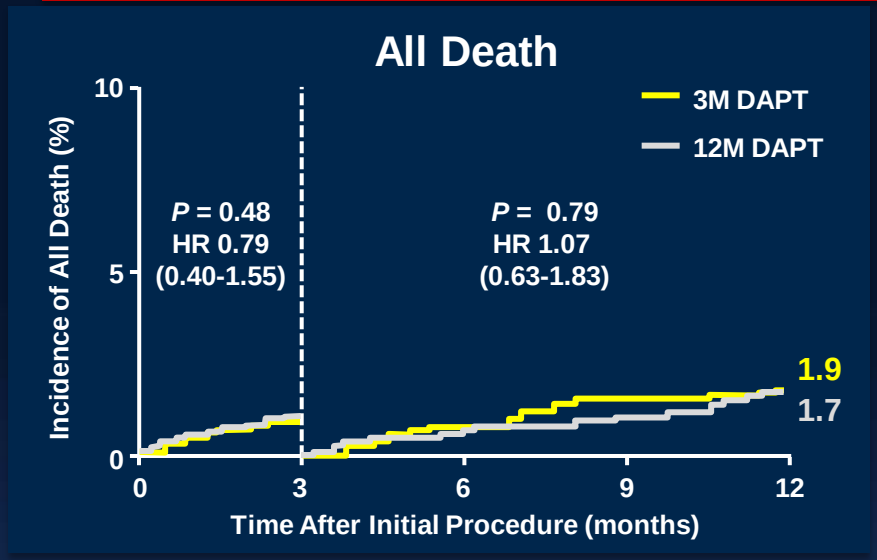
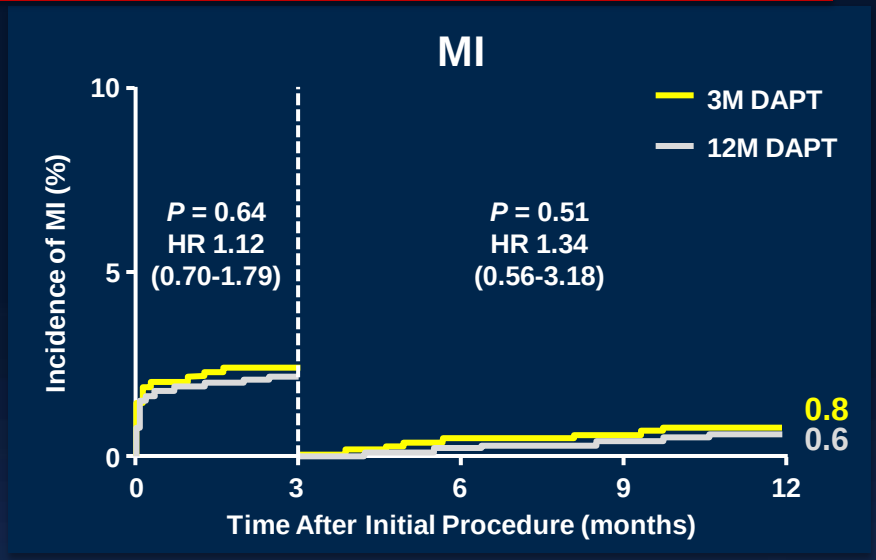
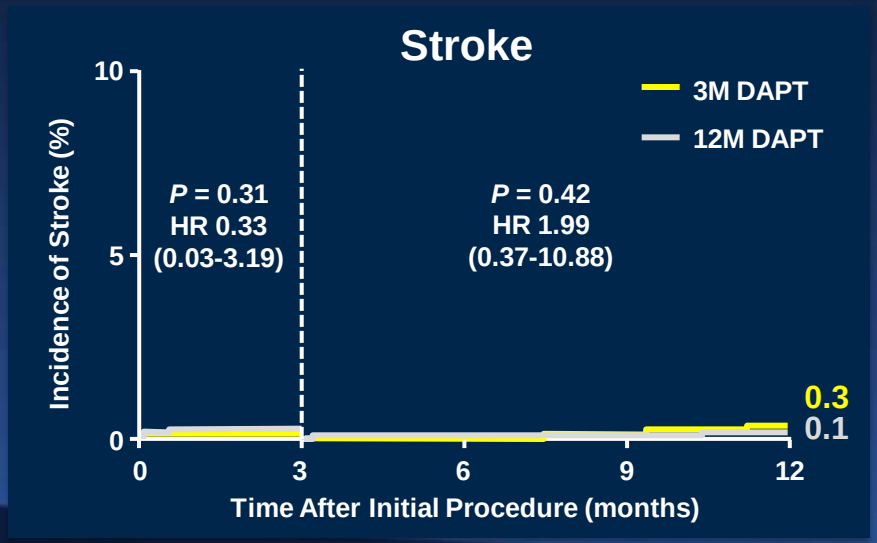
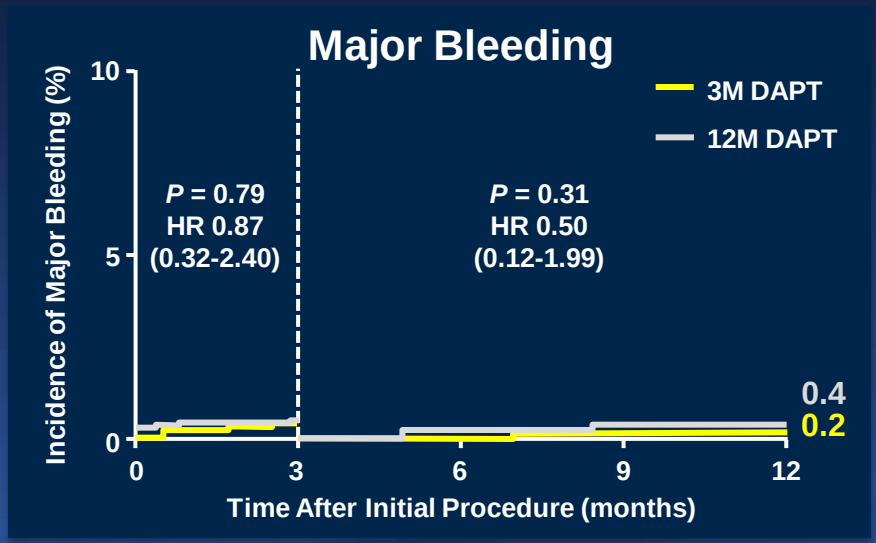
NACCE Components – Landmark



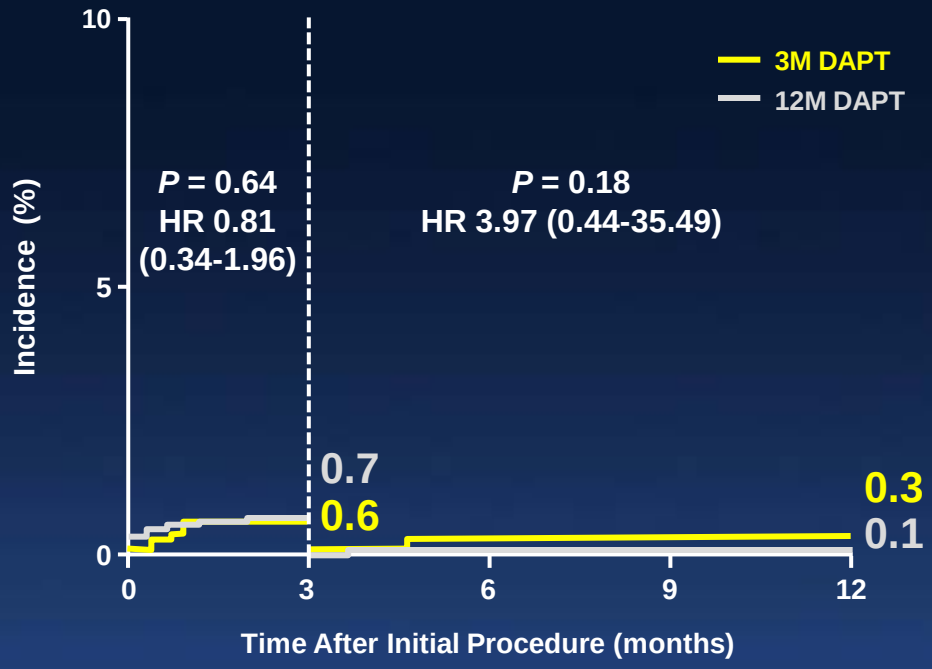






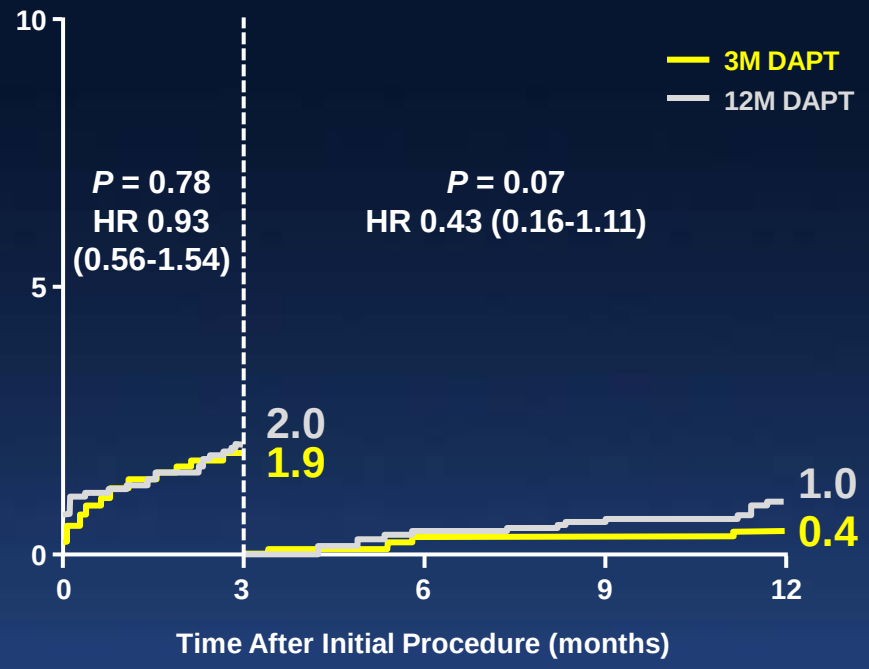
Stent Thrombosis *vs.* Bleeding

ARC Def./Prob. Stent Thrombosis



Month	0	1	3	6	12
No at risk	1563	1555	1540	1506	1505
No events	0	6	3	4	0
No at risk	1556	1541	1525	1501	1500
No events	5	3	3	1	0

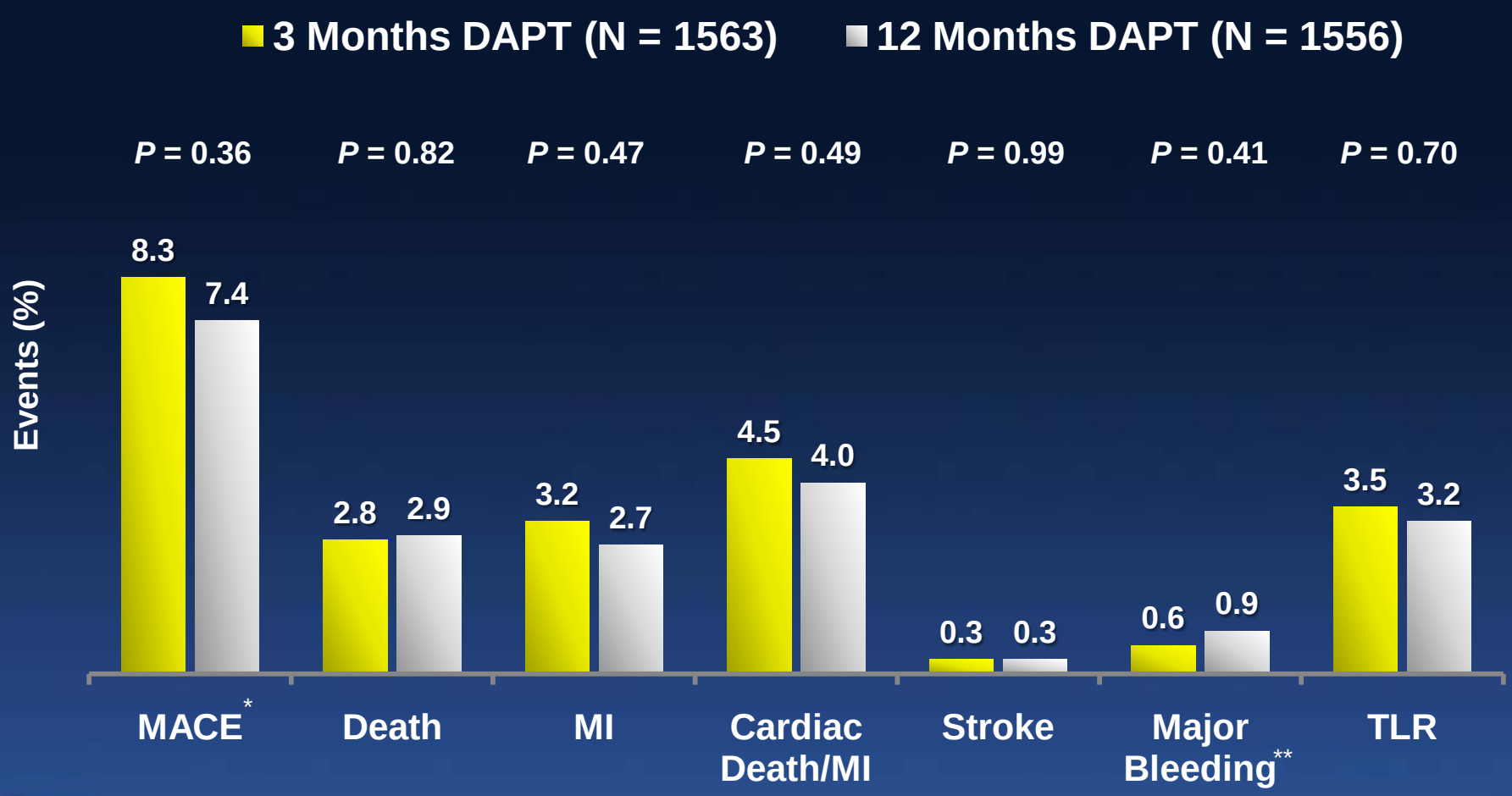
Any Bleeding*



Month	0	1	3	6	12
No at risk	1563	1538	1516	1482	1439
No events	4	15	10	4	2
No at risk	1556	1528	1501	1472	1387
No events	11	8	12	6	8

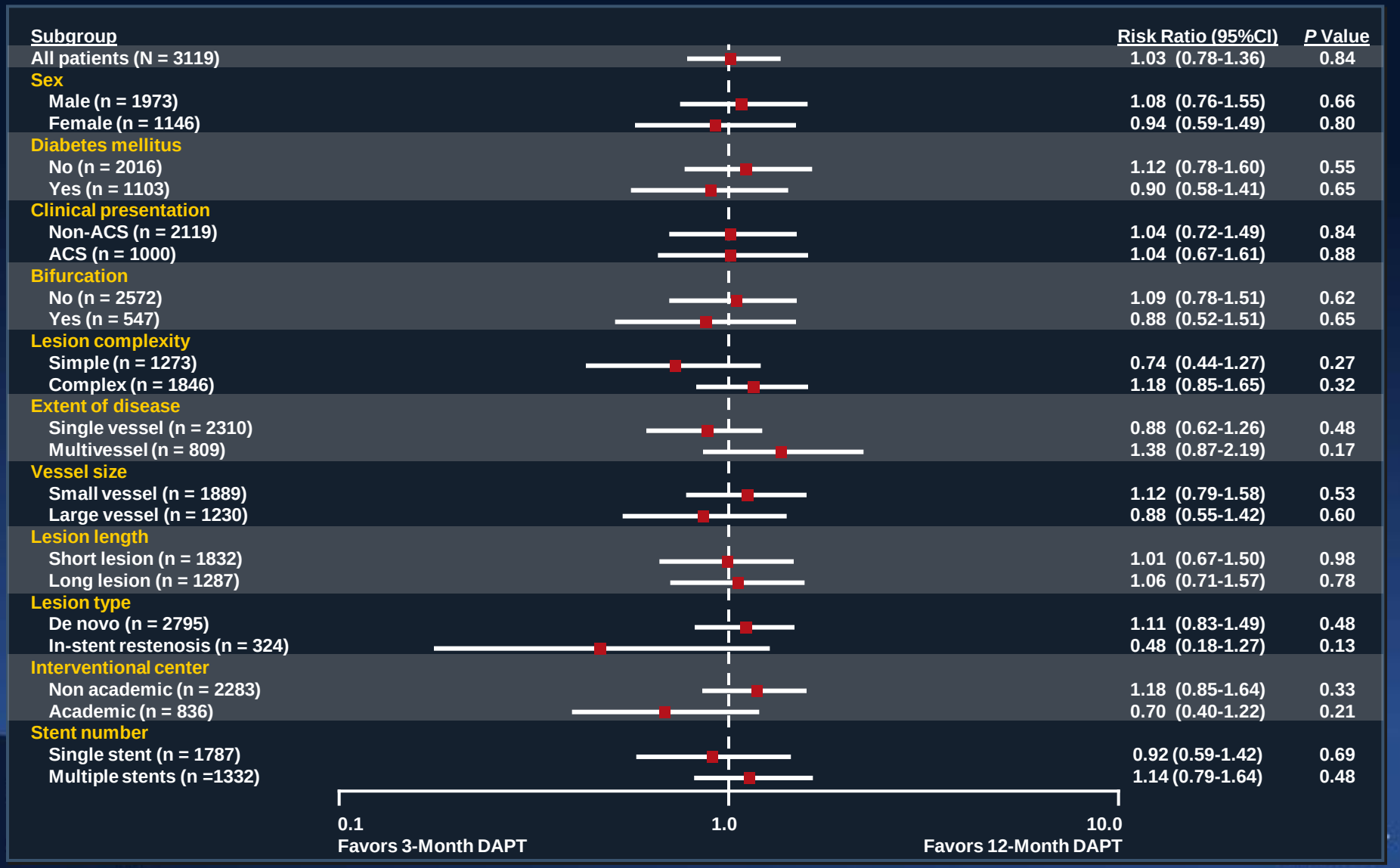
*Any bleeding according to the combined REPLACE-2 and GUSTO criteria.

Other Clinical Events at 1 Year



Event rates are expressed as Kaplan Meier estimates.
*MACE is composed of all cause Mortality, MI, Emergent CABG or TLR.
**Major bleeding according to REPLACE-2 and GUSTO criteria.

Subgroup Analysis: NACCE at 1 Year
(All-Cause Death, MI, Stroke, Major Bleeding)



Considerations

1. Study not powered to detect small differences in ischemic events after 90 days.
2. Primary endpoint (NACCE) event rate lower than expected (6% vs. 9%). However, MACE rate at 1 year was 8.4% w/ 3-mo. *vs.* 7.5% w/ 12-mo.
3. Patient population mostly comprised of stable coronary artery disease and low risk ACS.
4. NACCE: a combination of hard endpoints associated with DAPT compliance.
5. Randomization at index procedure.

Summary

- **OPTIMIZE compared 3 *vs.* 12 months DAPT in a patient population from daily clinical practice treated with a single 2nd generation DES.**
- **At 1 year, *NACCE* (Death / MI / Stroke / Major Bleeding) rate was *non-inferior* in patients receiving *3 months DAPT* compared with prolonged standard DAPT.**
  - **6.0%** w/ 3-mo. *vs.* **5.8%** w/ 12-mo. DAPT ($P_{non\text{-}inf}$=0.002)
- **Landmark analysis at 90 days demonstrated:**
  - ***Comparable rates* of NACCE, ST, and TLR/TVR.**
  - **A *trend* towards *increased* rate of any *bleeding* events with longer DAPT arm.**

Conclusions

In patients from daily clinical practice with stable coronary artery disease or low risk ACS undergoing PCI with E-ZES, *short-term DAPT* (3 months) *is non-inferior to long-term DAPT* (12 months) in terms of the occurrence of death, MI, stroke, or major bleeding.

Clinical Implications

- **Consistent with other recent studies on shorter DAPT durations, this prospective randomized trial showed that *2nd generation DES might not always require 12 months DAPT* to reduce the risk of adverse thrombotic events.**
- **These outcomes may be especially *relevant for patients who are at high risk of bleeding complications* following PCI, such as the elderly and patients with a history of hemorrhagic events, who might need to stop DAPT earlier.**

For Full Details, Please Go to

Thank you