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# PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY

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On behalf of the PRODIGY Investigators

clinicaltrials.gov Identifier: NCT00611286

# Disclosures

**The PRODIGY Trial was entirely supported by the Chair of Cardiology of the University of Ferrara**

Dr Valgimigli has received:

honoraria for lectures/advisory board and research grants from Merck, Iroko, Eli Lilly and Medtronic;

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honoraria for lectures from Cordis, CID and Terumo, Accumetrics

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# Drivers for Duration of Dual Anti-platelet therapy Post-Stenting

***Data suggest that certain patient population (e.g. high risk for thrombotic events, patients after SES or PES implantation) may benefit from prolonged DAPT beyond 1 year*.** I B

**....**3 lines below

***Recent data suggest that DAPT for 6 months may be sufficient because late and very late stent thrombosis correlate poorly with discontinuation of DAPT*** I B

**If the risk of morbidity because of bleeding outweights the <u>anticipated benefit</u> afforded by thienopyridine therapy, earlier discontinuation should be considered (I C)**

*: DUKE heart registry, JAMA 07; 159-68

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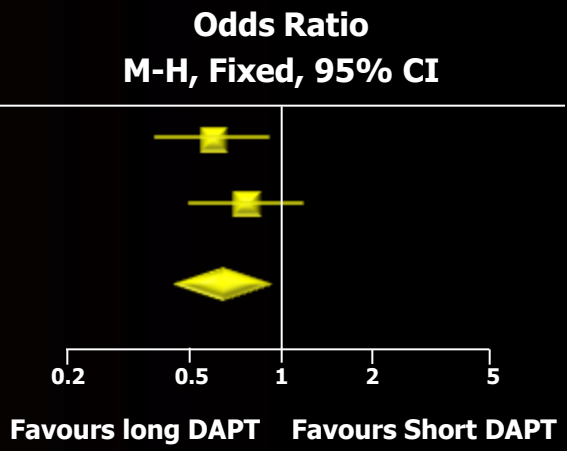
# Current Evidence for indication to the Procedure as *driver* for prolonged DAPT

| Study | LONG Events | LONG Total | SHORT Events | SHORT Total | Weight | Odds Ratio M-H, 95% CI |
|---|---|---|---|---|---|---|
| CREDO | 35 | 1053 | 55 | 1063 | 50.2% | 0.63 [0.41-0,97] |
| PCI-CURE | 42 | 1313 | 55 | 1345 | 49.8% | 0.78 [0.51-1,17] |
| **Total** | | | | | | **0.70 [0.52-0,95]** |

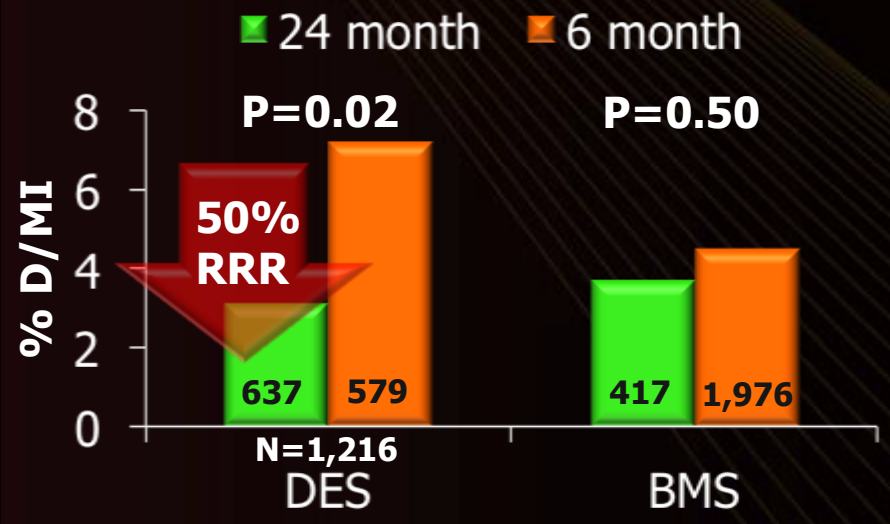
Heterogeneity: Chi2=0.46, P=0.50;I2=0%
Test for overall effect: P=0.02




## Pre-treatment effect: potential for bias in both studies

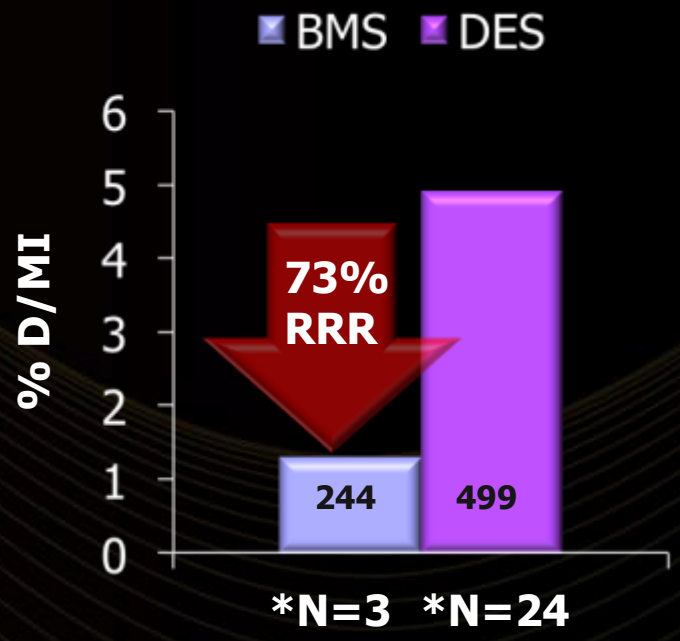
# Quoted Registries by Guidelines for prolonged DAPT after DES

**24 Month Events in Patients who Discontinued or did not Discontinue Clopidogrel at 6 Months Stratified by Stent**




Eisenstein EL et al, JAMA 2007

**18 Month Events After Clopidogrel Discontinuation at 6 Months Stratified by Stent Type***




Pfisterer M et al, J Am Coll Cardiol 2006

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# Study Methodology

**Hypothesis**

24 months duration of aspirin and clopidogrel is *superior* to a short course of up to 6 month aspirin and clopidogrel therapy

**Population**

All comer PCI pts receiving via balancing randomization 1° and 2° gen DES and BMS at equal proportions

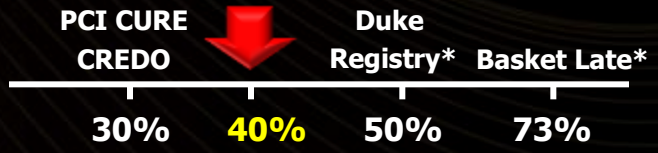
**1° Endpoint**

Death from any cause, MI or CVA

**Assumptions**

With an 8% event rate, ≥80% power, two-sided α 0.05

**Relative Risk Reduction**




≥1,700 pts needed → Fatalities, Non compliance, Loss to follow-up → ***2,000 patients***

*: for all cause death or MI

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# Selection Criteria and Endpoints

## Elegibility Criteria

### Inclusion Criteria

Any indication to PCI
(Stable, ACS, STEMI)
Intent to stent

### Exclusion Criteria

known allergy to ASA or clopidogrel
planned Major surgery within 24 months
major surgery within 15 days,
history of bleeding diathesis,
previous stroke in the last 6 months,
Concomitant oral anticoagulation

## EFFICACY

Death, Myocardial infarction, Cerebrovascular Accident and Stent Thrombosis according to ARC criteria

## SAFETY

TIMI and Bleedscore[1] → Type 5, 3 and 2 BARC[2]

*1: Serebruany VL et al. Am J Cardiol.* Jan 15 2007;99(2):288-290;
2: Mehran R et al. *Circulation.* Jun 14 2011;123(23):2736-2747

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# Study Organization and Sites

**Sponsor: University of Ferrara**

## University Hospital of Ferrara

R. Ferrari, M. Valgimigli, G. Campo
M. Monti, M . Tebaldi, C. Tumscitz,
J. Marchesini, M. Borghesi, A. Scalone
M. Minarelli, C. Cavazza, E. Cangiano
G. Fuca', F. Ferrari

## Delta Hospital, Lagosanto

GF. Percoco, Moh'd Kubbajeh, A. Frangione

## Villa Maria Cecilia, Cotignola

A. Cremonesi, F. Castriota, K. Oshoala,
F. Colombo, C. Garattoni, P. Sbarzaglia

**Clinical Event Committee**

P. Vranckx, *Chair*
S. Curello
G. Guardigli

**Data Management and Monitoring**

Medical Trial Analysis
Eustrategy Research Coordination

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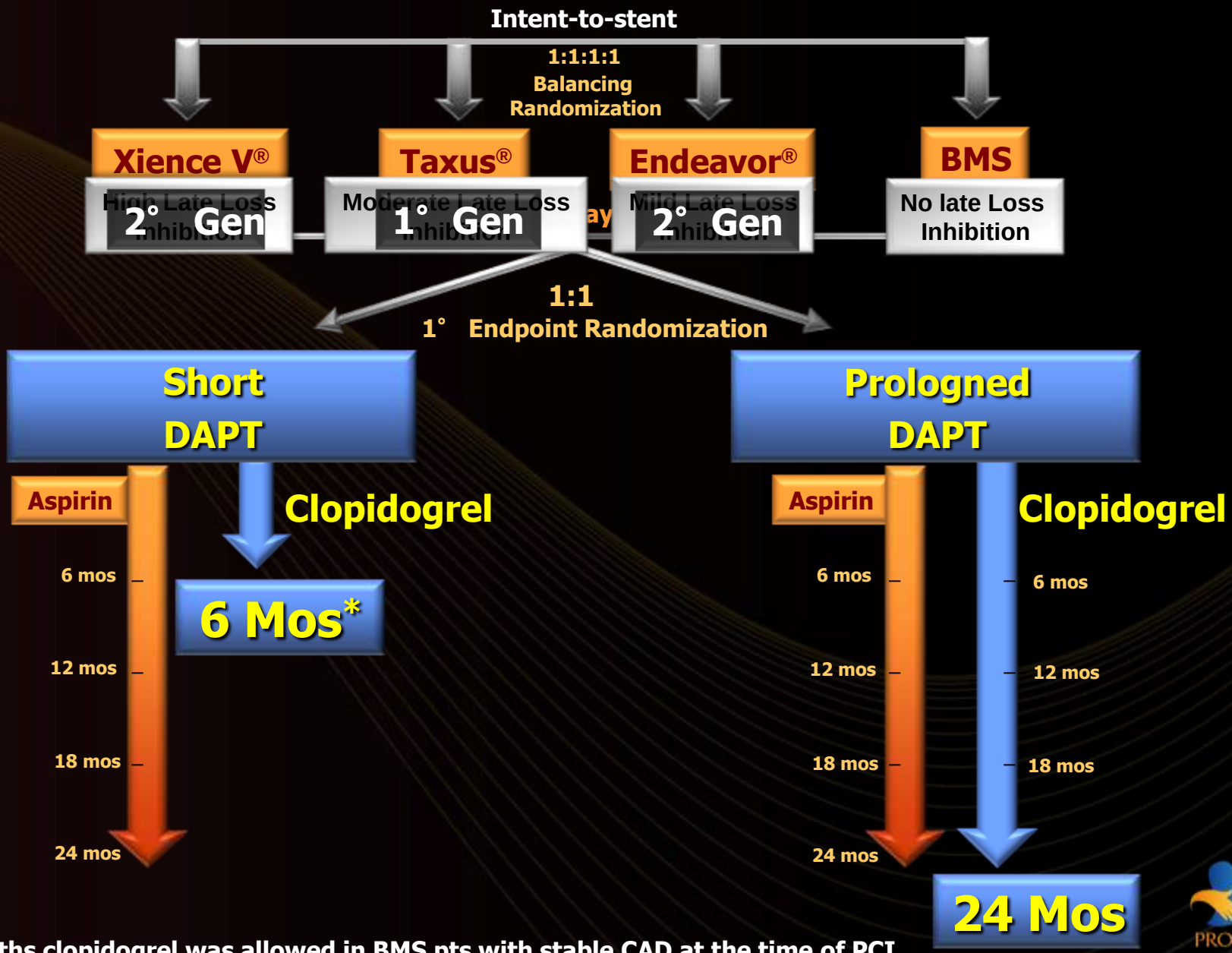
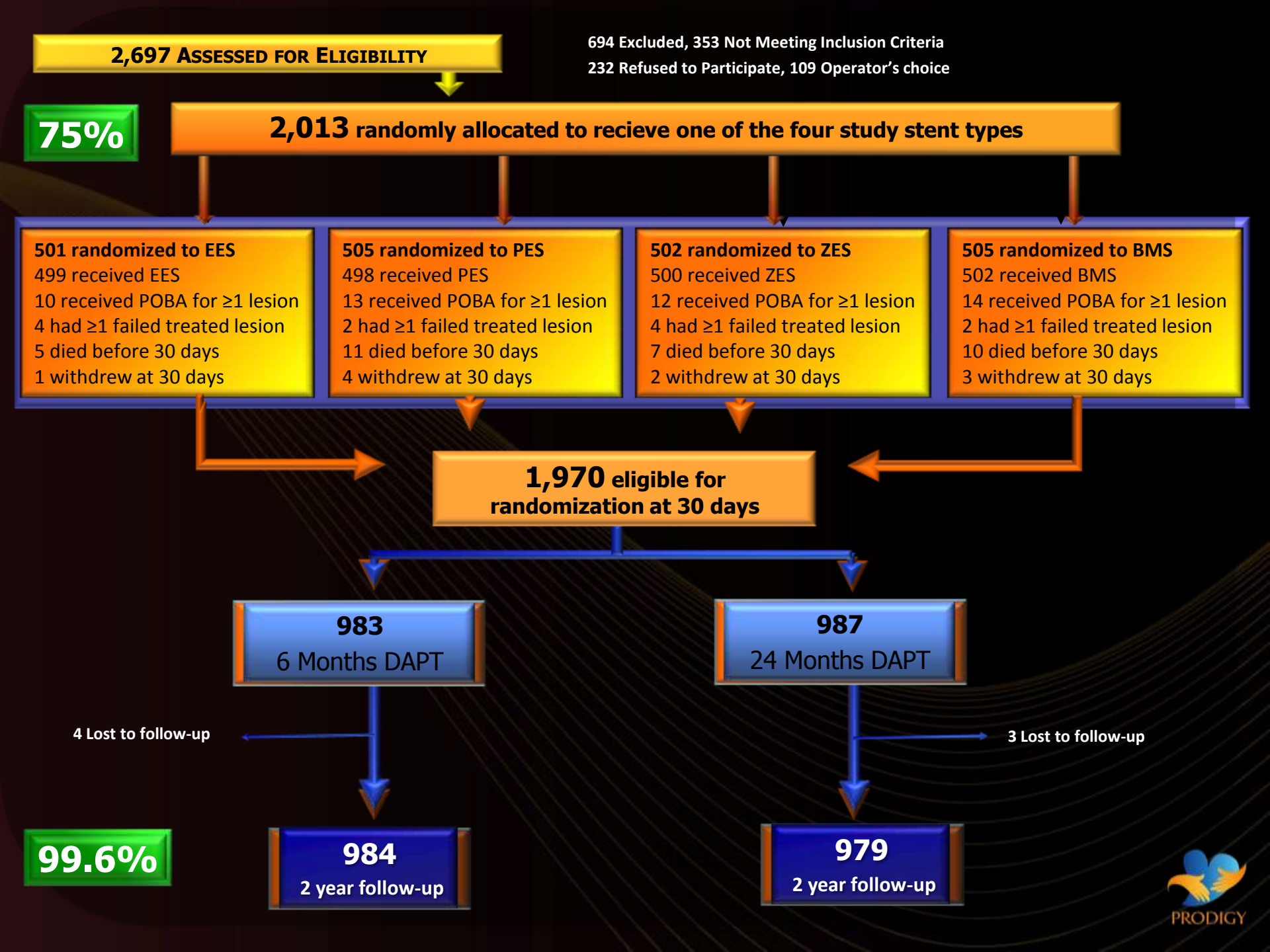
# PRODIGY Study Flow Chart




*: <6 months clopidogrel was allowed in BMS pts with stable CAD at the time of PCI


2,697 Assessed for Eligibility
694 Excluded, 353 Not Meeting Inclusion Criteria
232 Refused to Participate, 109 Operator's choice
75%
2,013 randomly allocated to recieve one of the four study stent types
501 randomized to EES
499 received EES
10 received POBA for ≥1 lesion
4 had ≥1 failed treated lesion
5 died before 30 days
1 withdrew at 30 days
505 randomized to PES
498 received PES
13 received POBA for ≥1 lesion
2 had ≥1 failed treated lesion
11 died before 30 days
4 withdrew at 30 days
502 randomized to ZES
500 received ZES
12 received POBA for ≥1 lesion
4 had ≥1 failed treated lesion
7 died before 30 days
2 withdrew at 30 days
505 randomized to BMS
502 received BMS
14 received POBA for ≥1 lesion
2 had ≥1 failed treated lesion
10 died before 30 days
3 withdrew at 30 days
1,970 eligible for randomization at 30 days
983
6 Months DAPT
987
24 Months DAPT
4 Lost to follow-up
3 Lost to follow-up
99.6%
984
2 year follow-up
979
2 year follow-up
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# Baseline Characteristics

## Duration of DAPT

| | 24 Mo | 6 Mo | P-value |
|---|---|---|---|
| **Age** (yr) | N=987 | N=983 | |
| mean±SD | 68±11 | 68±11 | 0.85 |
| Median [IQR] | 69 [61-76] | 69 [60-77] | |
| **Male Sex** (%) | 74 | 76 | 0.46 |
| **Diabetes** (%) | 25 | 24 | 0.87 |
| **CrCl** (ml/min) | 74 [57-99] | 75 [57-95] | 0.53 |
| **Prior MI** (%) | 27 | 26 | 0.67 |
| **Prior PCI** (%) | 19 | 18 | 0.65 |
| **Prior CVA** (%) | 3.7 | 4.0 | 0.81 |
| **Stable CAD** (%) | 26 | 25 | 0.75 |
| **ACS** (%) | 74 | 75 | 0.88 |
| UA (%) | 18.5 | 18.5 | 0.99 |
| NSTEMI (%) | 22.9 | 22.8 | 0.95 |
| STEMI (%) | 32.5 | 33.3 | 0.73 |
| **Multivessel CAD** (%) | 65 | 66 | 0.89 |

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# Angiographic Results

## Duration of DAPT

| | 24 Mo | 6 Mo | P-value |
|---|---|---|---|
| **Treated Lesions** | **N=1500** | **N=1546** | |
| mean±SD | **1.52±0.86** | **1.57±0.94** | 0.37 |
| Median [IQR] | **1 [1-2]** | **1 [1-2]** | |
| ≥2 treated lesions **(%)** | **37** | **38** | 0.73 |
| **LAD treated (%)** | **53** | **53** | 0.92 |
| **LMCA treated (%)** | **5.6** | **5.7** | 0.90 |
| **≥1 B2/C lesion (%)** | **65** | **68** | 0.24 |
| **ACC/AHA score(no)** | **3 [2-4]** | **3 [2-5]** | 0.19 |
| **Xience(%)** | **25** | **25** | 0.99 |
| **Taxus(%)** | **25** | **25** | 0.99 |
| **Endeavor (%)** | **25** | **25** | 0.99 |
| **BMS**(%) | **25** | **25** | 0.99 |
| **Implanted stent**(no) | **1.82±1.23** | **1.90±1.25** | 0.27 |
| **Total stent length**(mm) | **30 [20-48]** | **30 [20-48]** | 0.43 |
| Range (mm) | **8-303** | **8-250** | |

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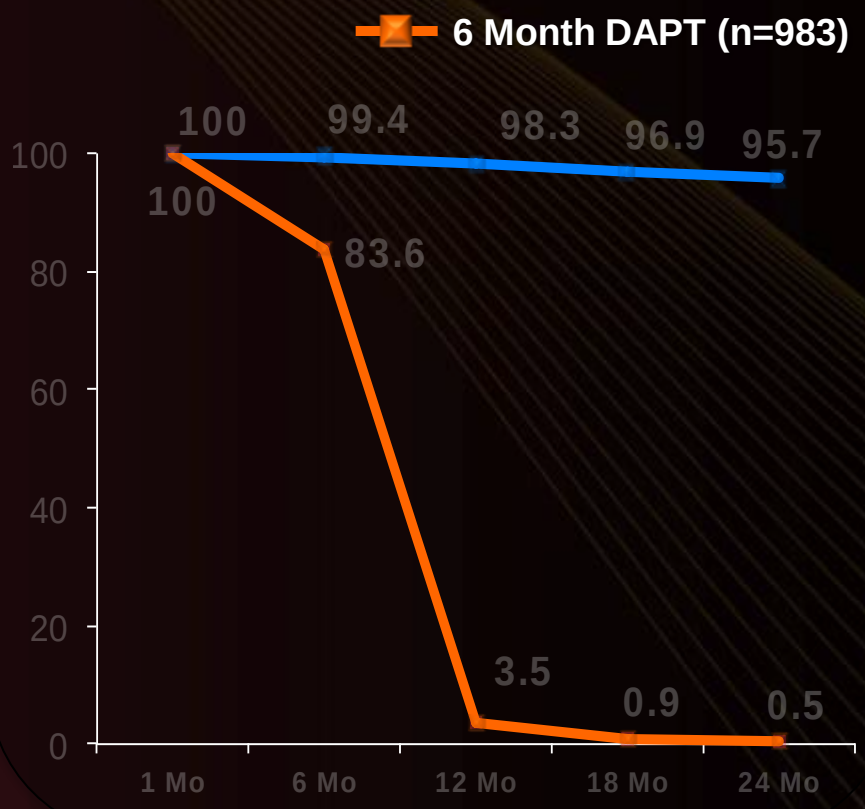
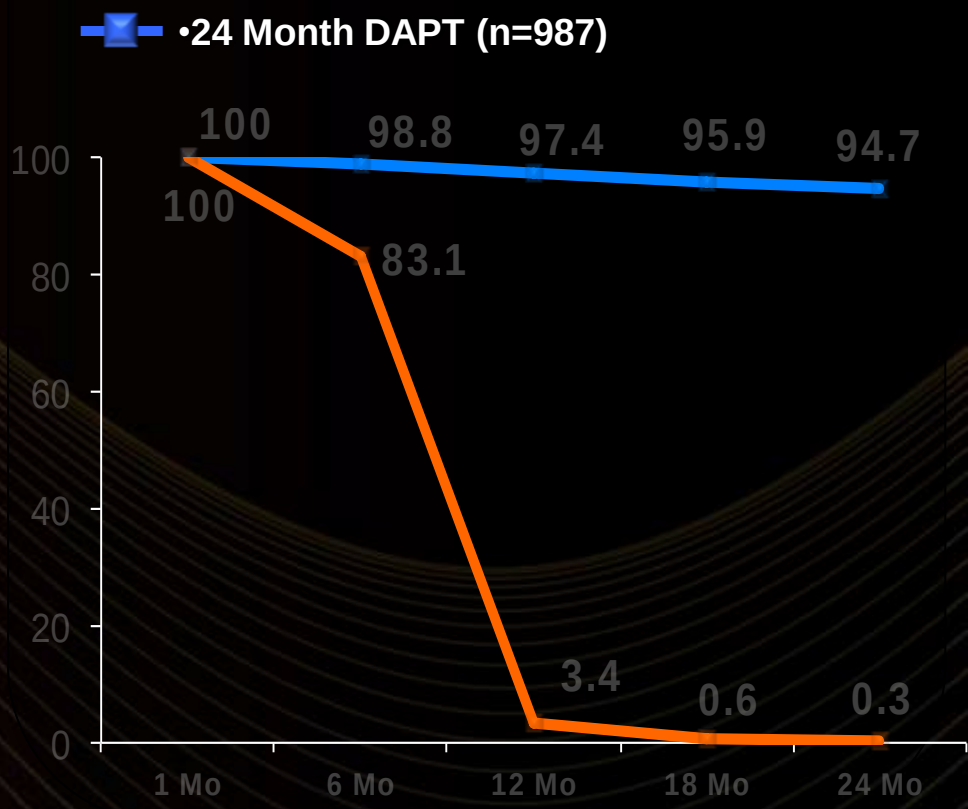
# Clopidogrel and Dual Anti-Platelet Therapy Use

## Compliance to Clopidogrel (%)




## Compliance to DAPT (%)




**P<0.001 for all time points from 6 months onwards**

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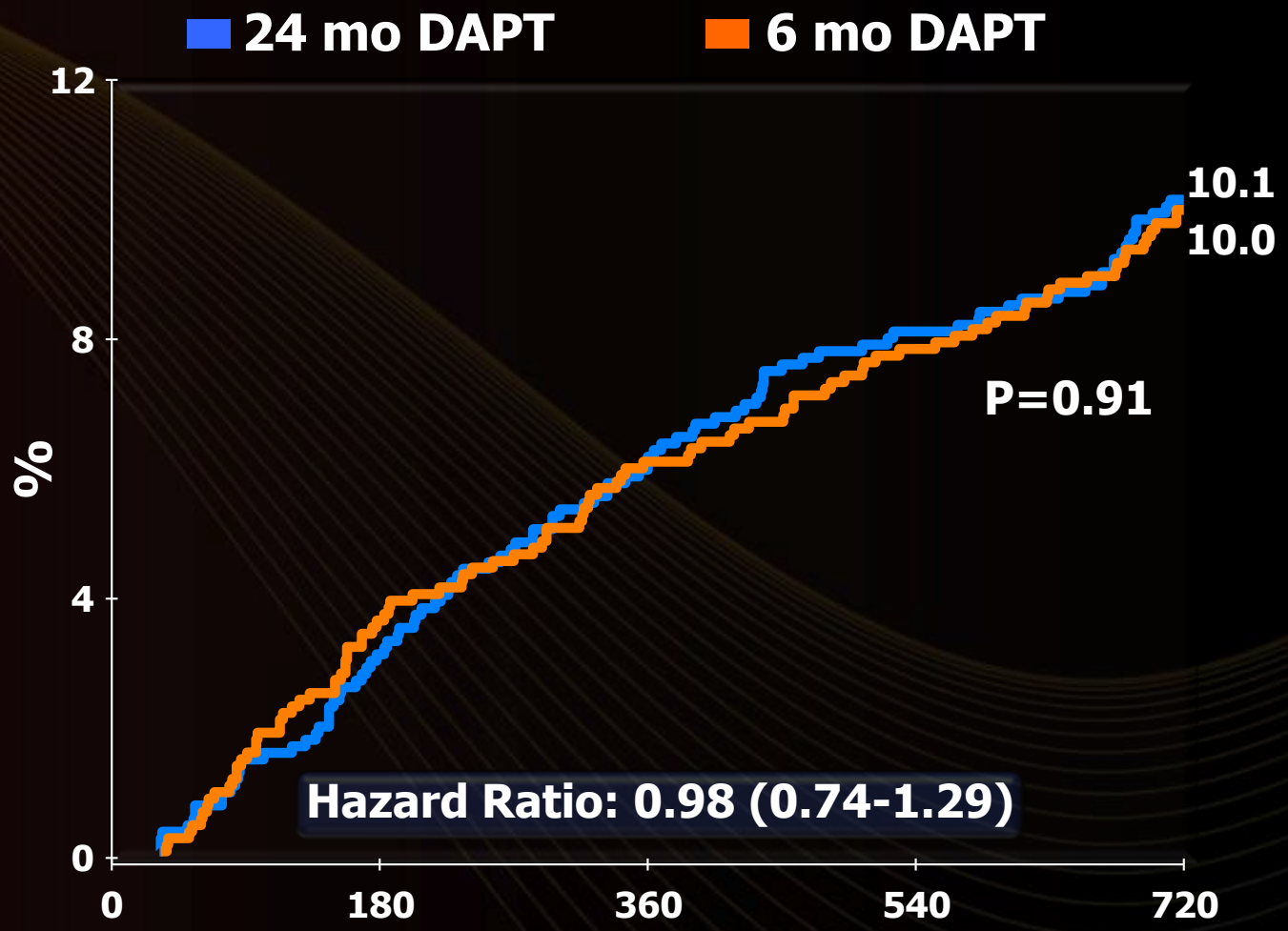
# Primary Endpoint

## Overall Death, MI or CVA

### CEC adjudicated




| No. at Risk | | | | |
|---|---|---|---|---|
| 24-Month Clopidogrel | 987 | 925 | 884 | |
| 6-Month Clopidogrel | 983 | 919 | | 881 |

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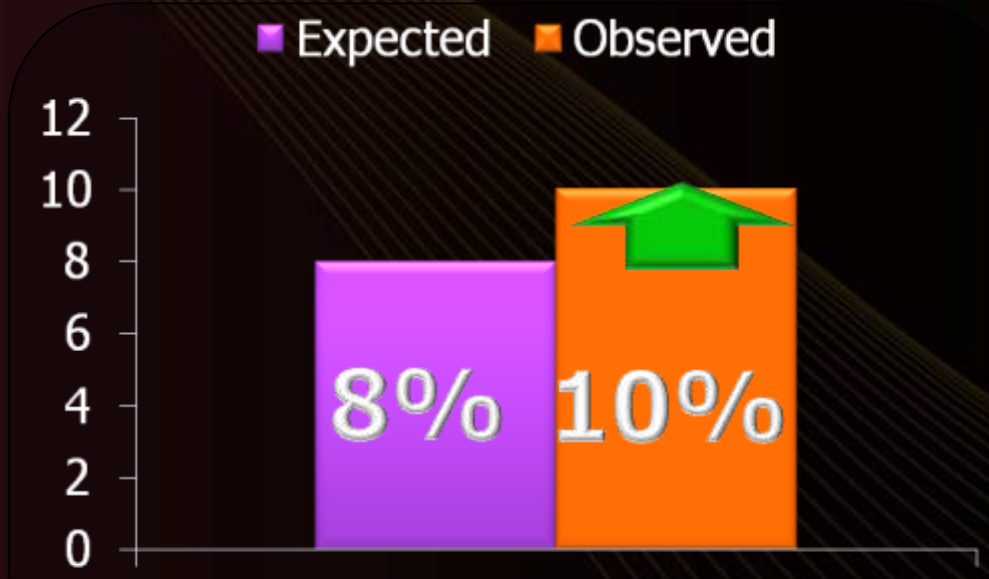
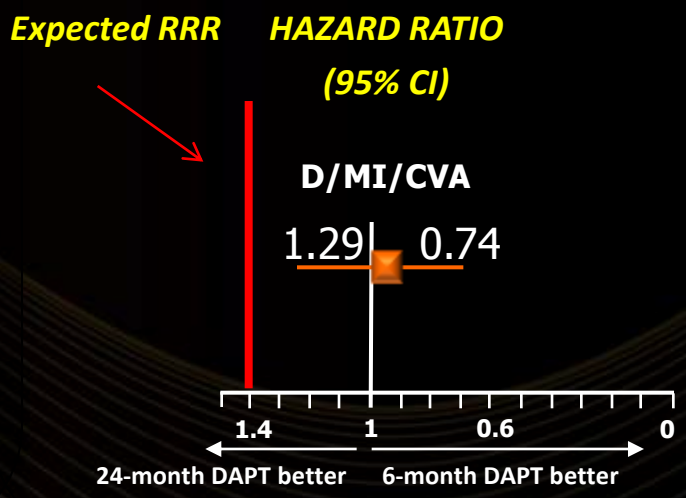
# Lack of treatment effect or lack of power to detect the anticipated treatment effect?




**Anticipated:** 850 pts per group with adherence to protocol for 80% power
**Actual:** >920 pts per group with adherence to protocol

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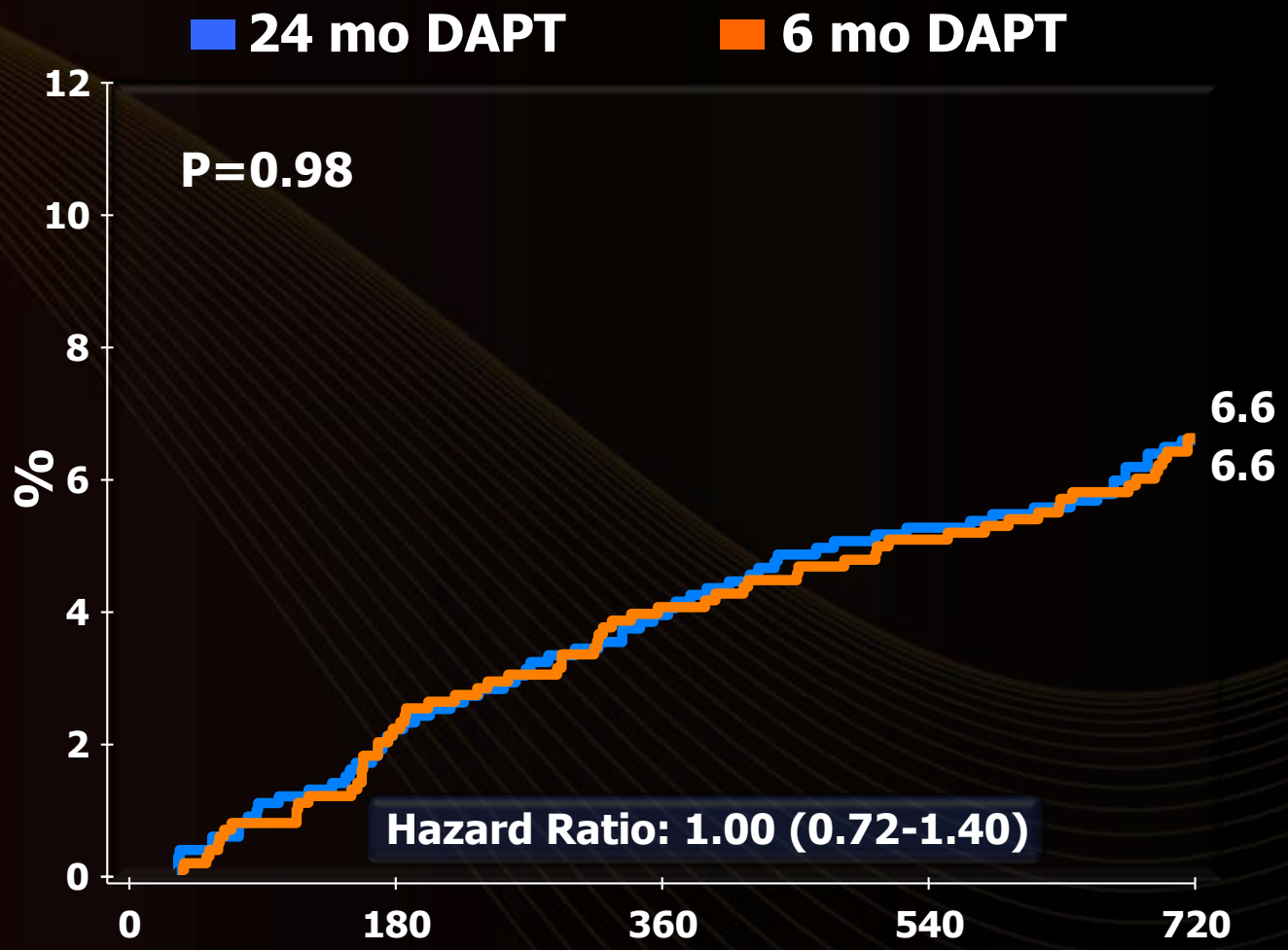
# Secondary Endpoint

## Death from any cause




| No. at Risk | | | |
|---|---|---|---|
| 24-Month Clopidogrel | 987 | 925 | 884 |
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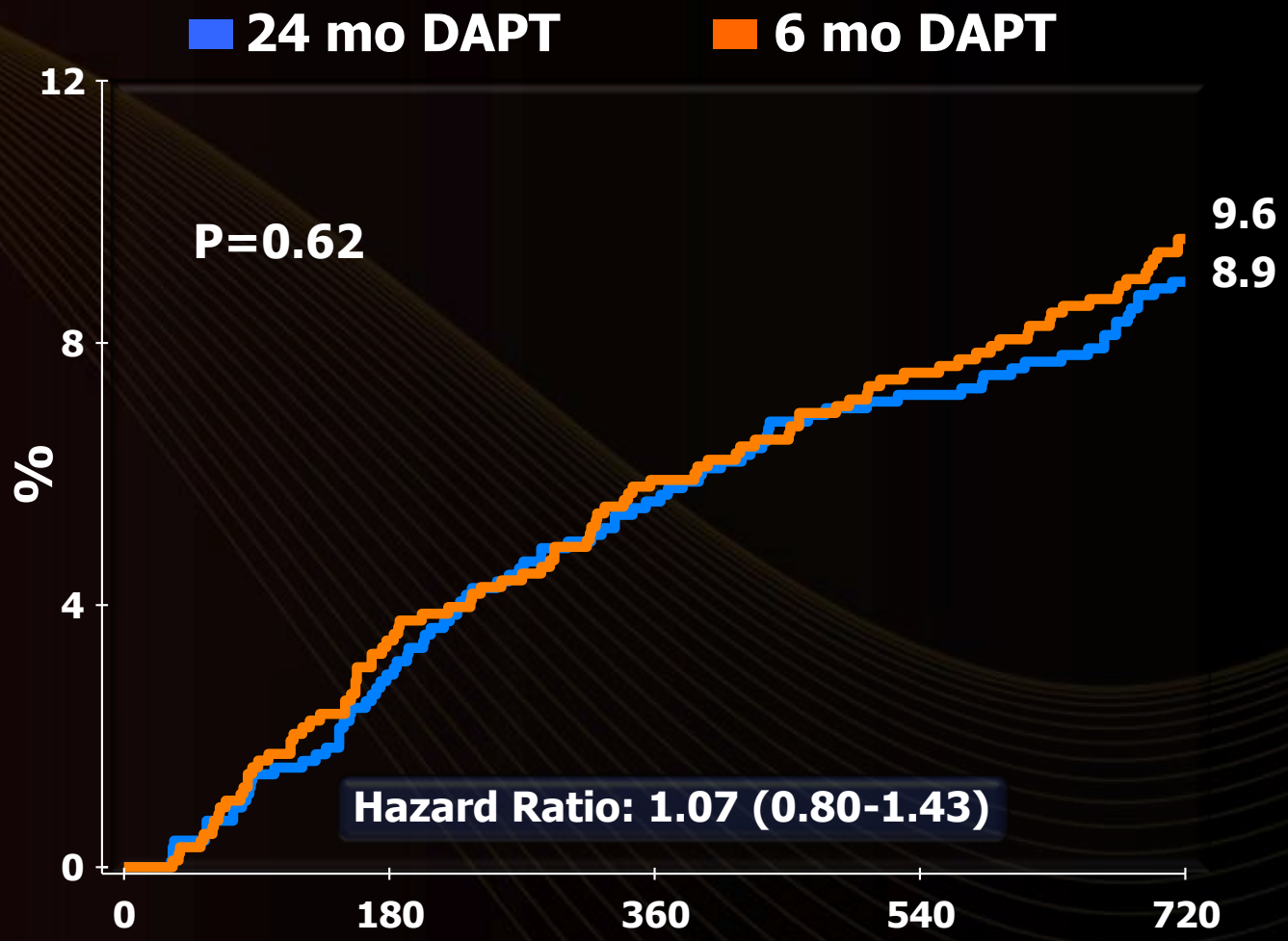
## Secondary Endpoint

# Death from any cause or MI

### CEC adjudicated




| No. at Risk | | | |
|---|---|---|---|
| 24-Month Clopidogrel | 987 | 925 | 884 |
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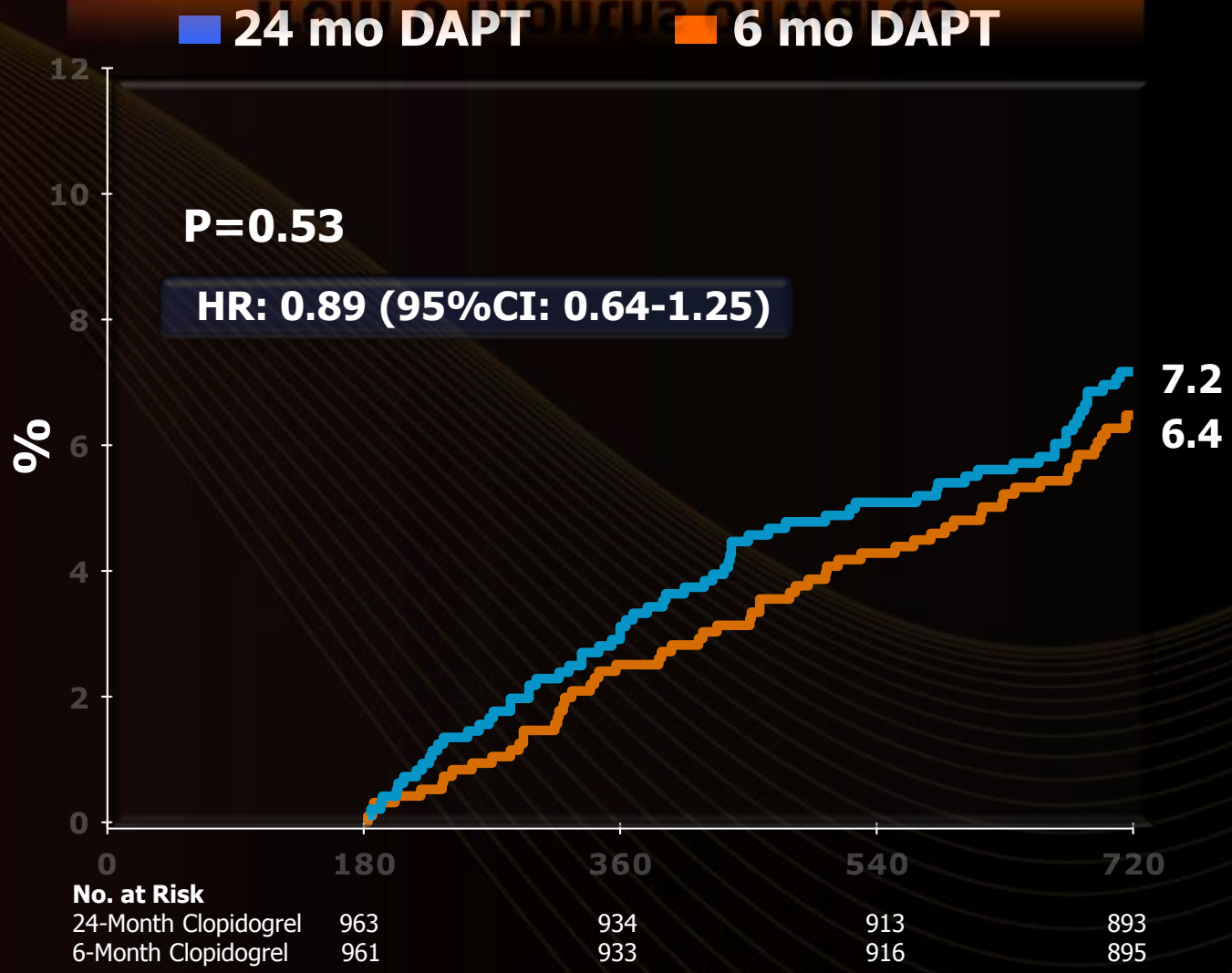
# Landmark Analysis

CEC adjudicated

## Death from any cause, MI or CVA from 6 months onwards

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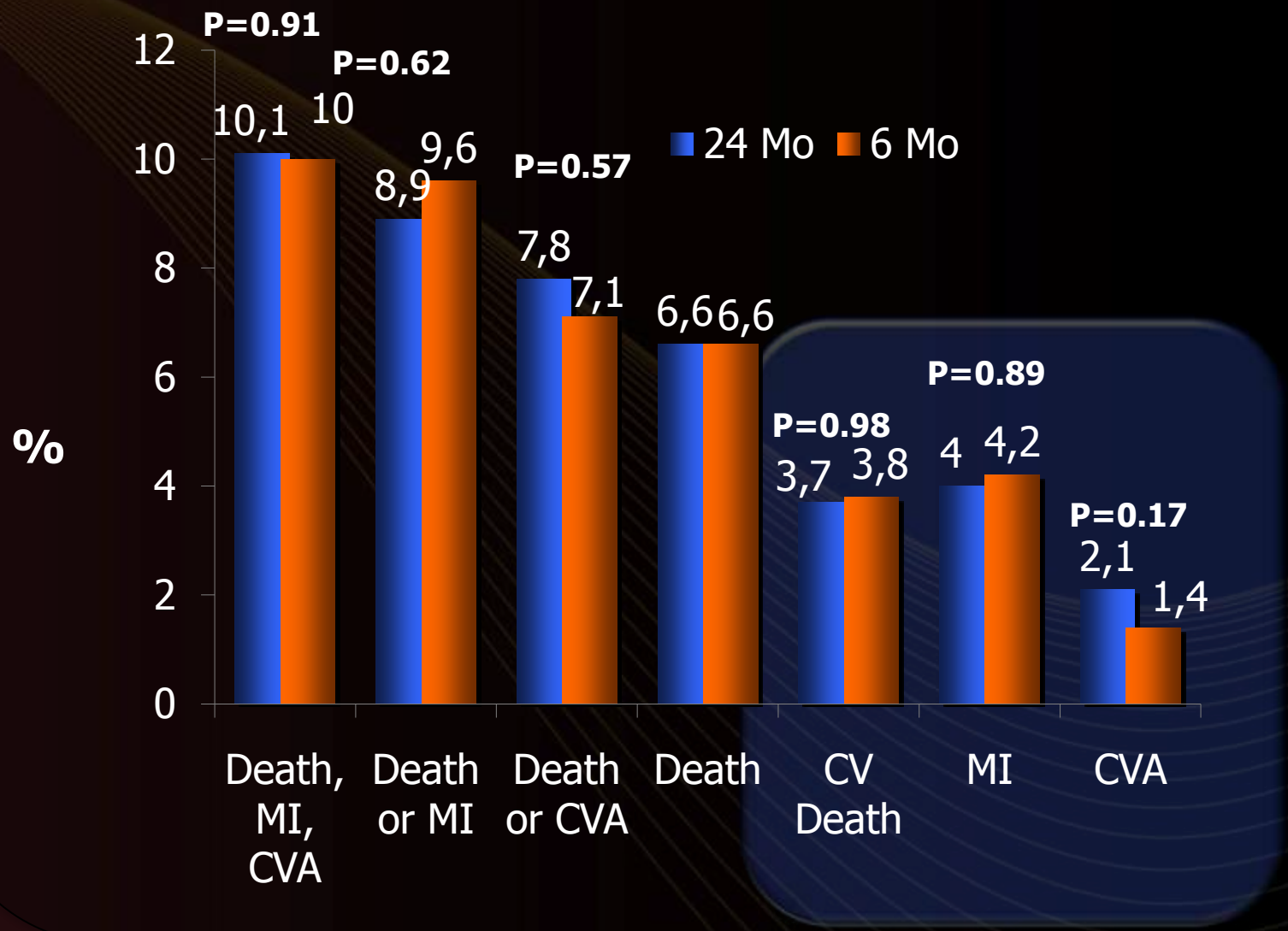
# Cumulative Ischemic Events at 24 Mos

## CEC adjudicated

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# Subgroup analysis of the Primary Endpoint

| | HAZARD RATIO (95% CI) | P-VALUES | |
|---|---|---|---|
| | | Superiority | Interaction |
| Overall | 0.98 (0.74-1.29) | 0.91 | |
| Male | 1.09 (0.77-1.55) | 0.85 | *0.91* |
| Female | 1.00 (0.60-1.68) | 0.66 | |
| ≥ 65 yr | 1.12 (0.82-1.51) | 0.48 | *0.09* |
| < 65 yr | 0.57 (0.28-1.16) | 0.12 | |
| Diabetes | 0.85 (0.53-1.38) | 0.72 | *0.47* |
| No Diabetes | 1.06 (0.76-1.50) | 0.52 | |
| Bare metal stents | 1.13 (0.68-1.86) | 0.64 | *0.53* |
| Drug-eluting Stents | 0.93 (0.67-1.30) | 0.66 | |
| Stable Coronary Disease | 0.60 (0.29-1.23) | 0.16 | *0.14* |
| Unstable Coronary Disease | 1.07 (0.79-1.45) | 0.63 | |
| Single Lesion Treatment | 0.88 (0.62-1.28) | 0.51 | *0.38* |
| Multiple Lesions Treatment | 1.14 (0.74-1.76) | 0.55 | |
| Complex Lesion(s) Treated | 1.07 (0.77-1.49) | 0.68 | *0.31* |
| Simple Lesion(s) Treated | 0.78 (0.46-1.32) | 0.35 | |
| Creatinine Clearance > 60 ml/min | 0.90 (0.58-1.38) | 0.62 | *0.38* |
| Creatinine Clearance ≤ 60 ml/min | 1.14 (0.78-1.65) | 0.50 | |

LOG HAZARD RATIO (95% CI)

10 — 1 — 0.1

24-month DAPT better

6-month DAPT better

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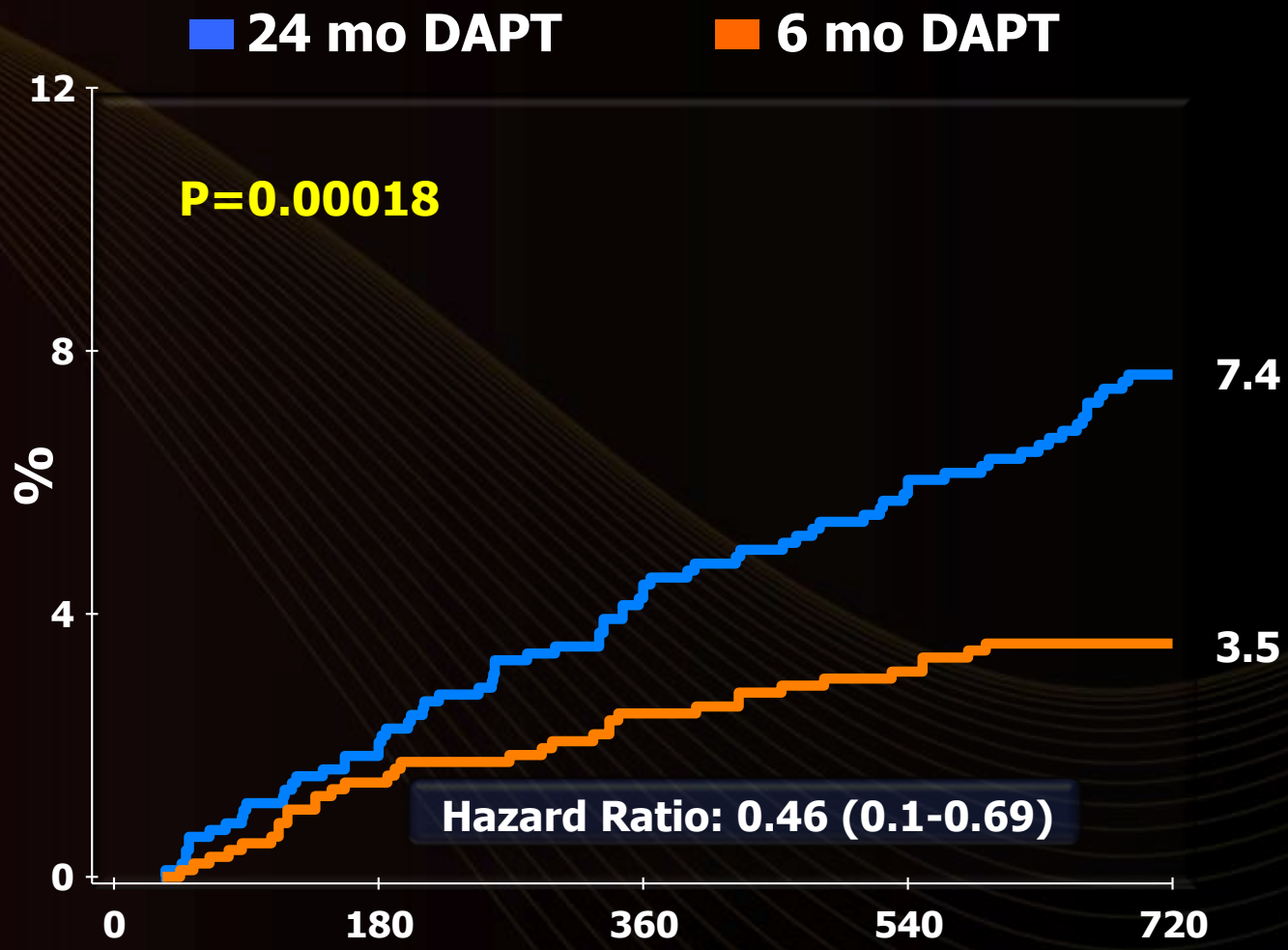
# Key Safety Endpoint

## Type II, III or V BARC bleeding

### CEC adjudicated




| No. at Risk | | | |
|---|---|---|---|
| 24-Month Clopidogrel | 987 | 925 | 884 |
| 6-Month Clopidogrel | 983 | 919 | 881 |

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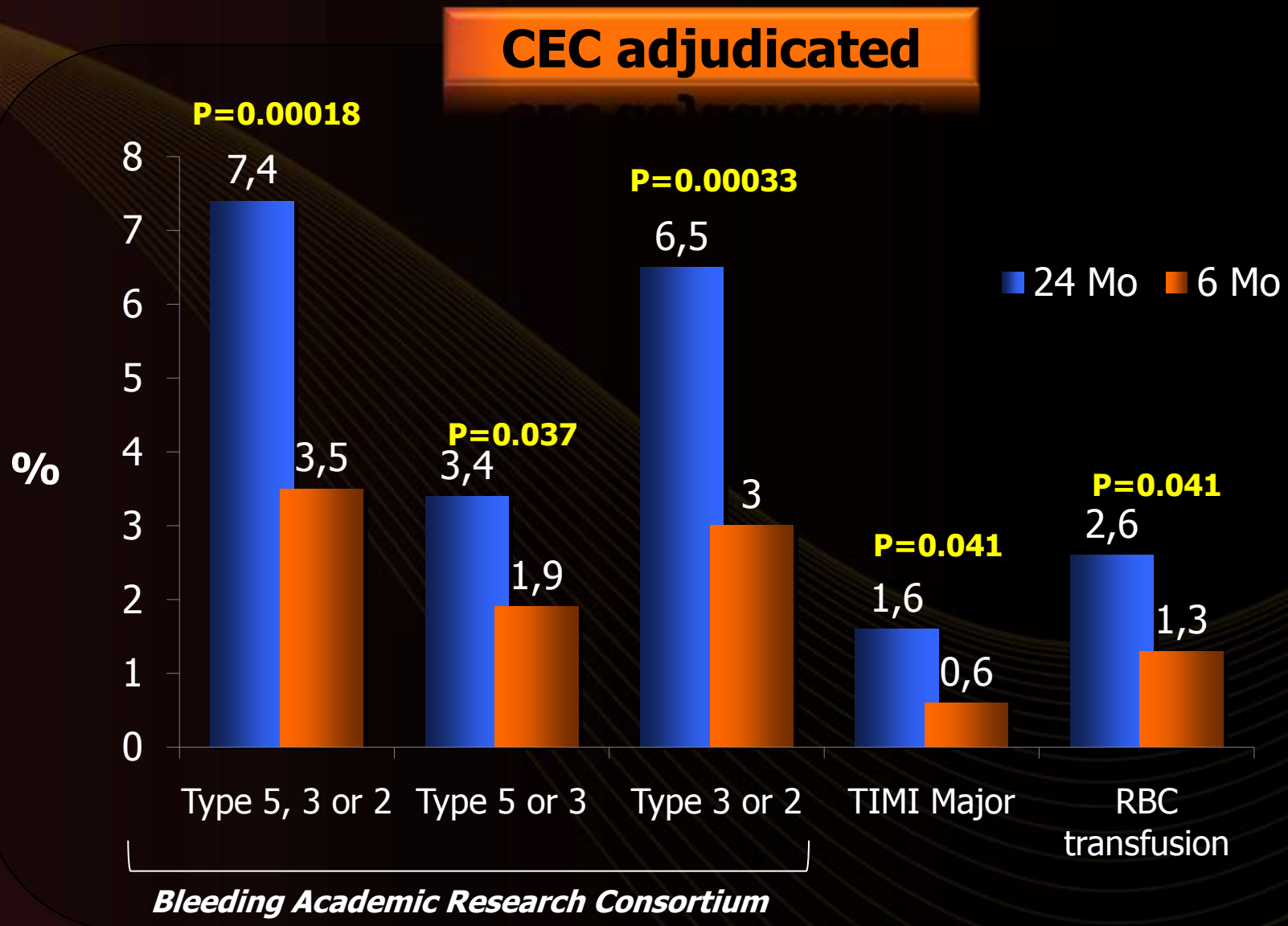
# Bleeding Events and RBC Transfusion

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# Summary

Our study failed to show that prolonging DAPT for 24 months is superior to 6 month duration of Tx in pts receiving 1 or 2 gen DES or at least 1 month after BMS

While we cannot rule out the possibility that a smaller than previously anticipated benefit may exist, the clear increase in bleeding, transfusion and net adverse clinical events, suggests that current recommendations may have overemphasized the benefit over the risk of long-term treatment with aspirin and clopidogrel