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**PROlonging Dual
antiplatelet treatment after
Gradings stent-induced
Intimal hyperplasia studY**

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On behalf of the PRODIGY
Investigators**

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;

honoraria for advisory board and lectures from The Medicines Company and Eli Lilly Co; Daiichi Sankyo, Inc., St Jude and Abbott Vascular;

honoraria for lectures from Cordis, CID and Terumo, Accumetrics

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.

....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

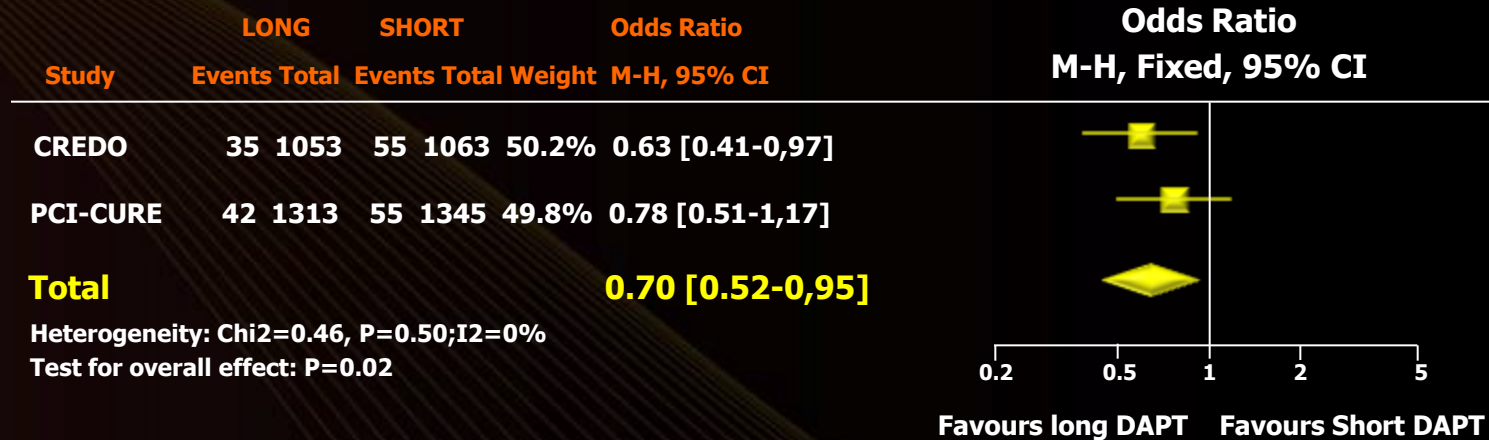


I B



If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered (I C)

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

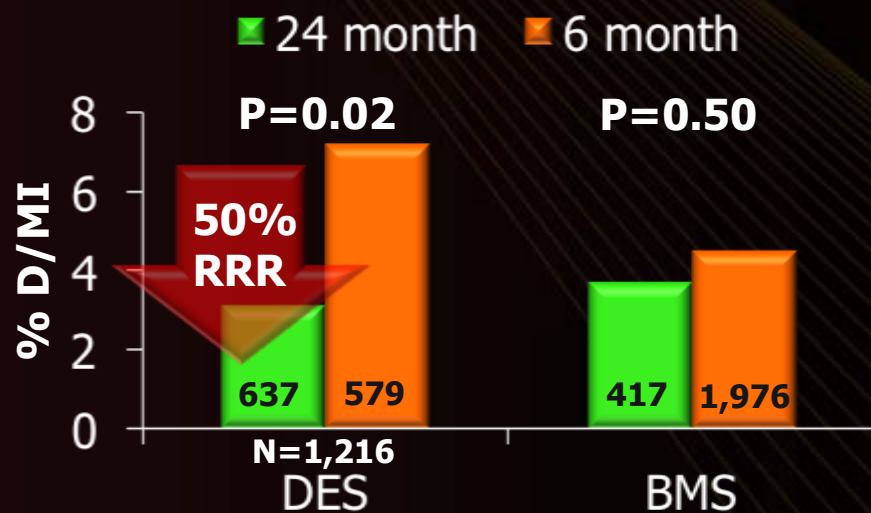


Pre-treatment effect: potential for bias in both studies



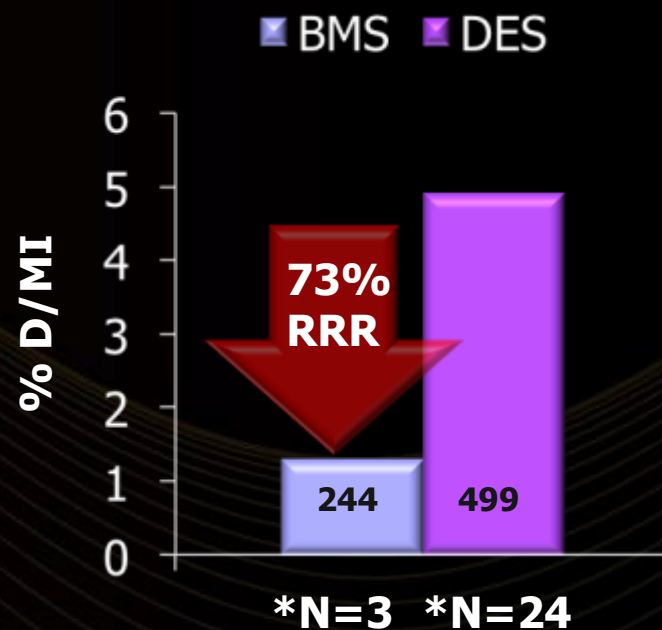
Quoted Registries by Guidelines for prolonged DAPT after DES

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

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, $\geq 80\%$ power, two-sided α 0.05

Relative Risk Reduction



$\geq 1,700$ pts needed

Fatalities, Non compliance,
Loss to follow-up

2,000 patients

*: for all cause death or MI

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 Bleedscore¹



Type 5, 3 and 2 BARC²

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

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 Kubbaheh, 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

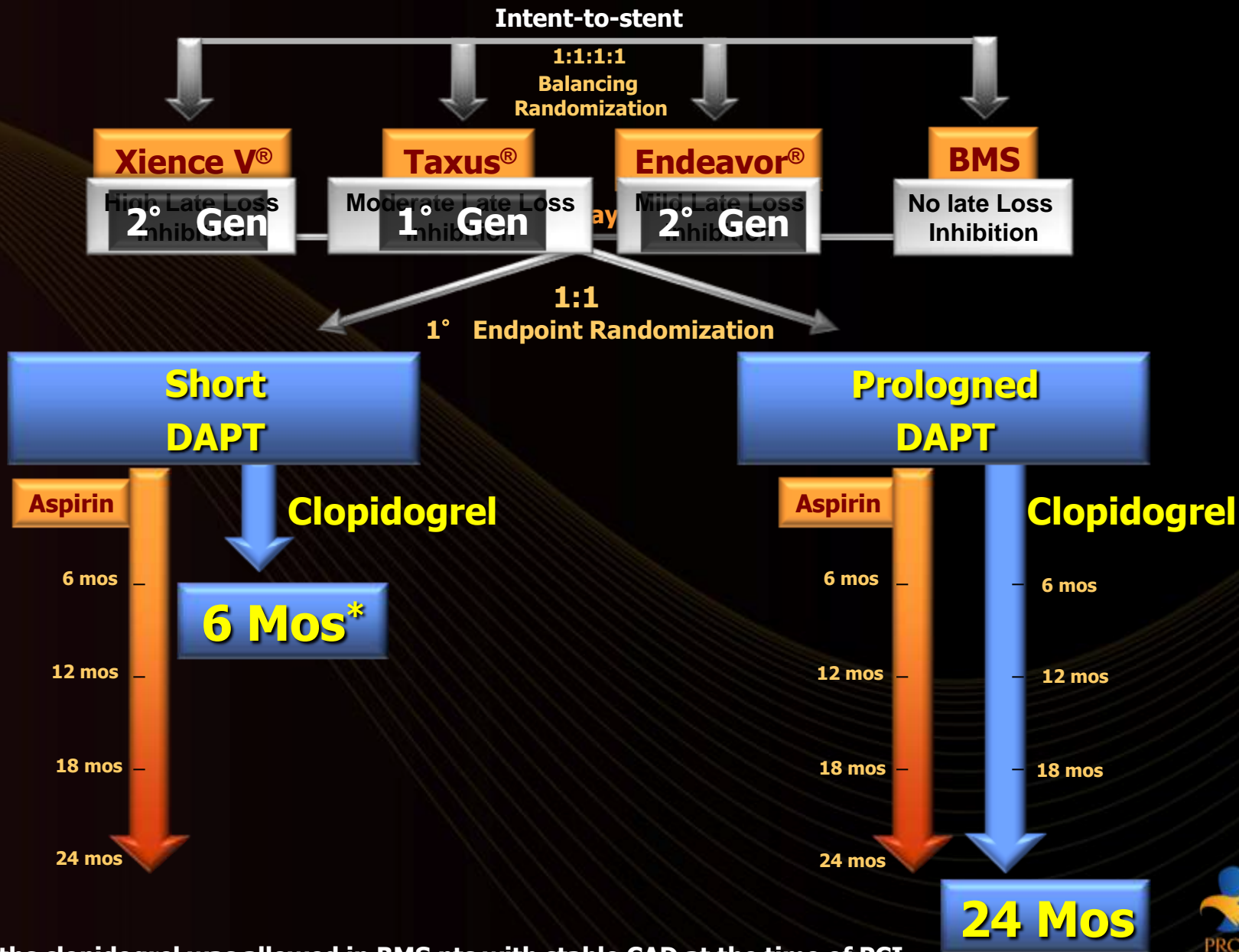


Data Management and Monitoring

Medical Trial Analysis

Eustrategy Research Coordination

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 receive 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

4 Lost to follow-up

984

2 year follow-up

987

24 Months DAPT

3 Lost to follow-up

979

2 year follow-up

99.6%

Baseline Characteristics

Duration of DAPT

	24 Mo	6 Mo	P-value
Age (yr)	N=987	N=983	
mean \pm SD	68 \pm 11	68 \pm 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

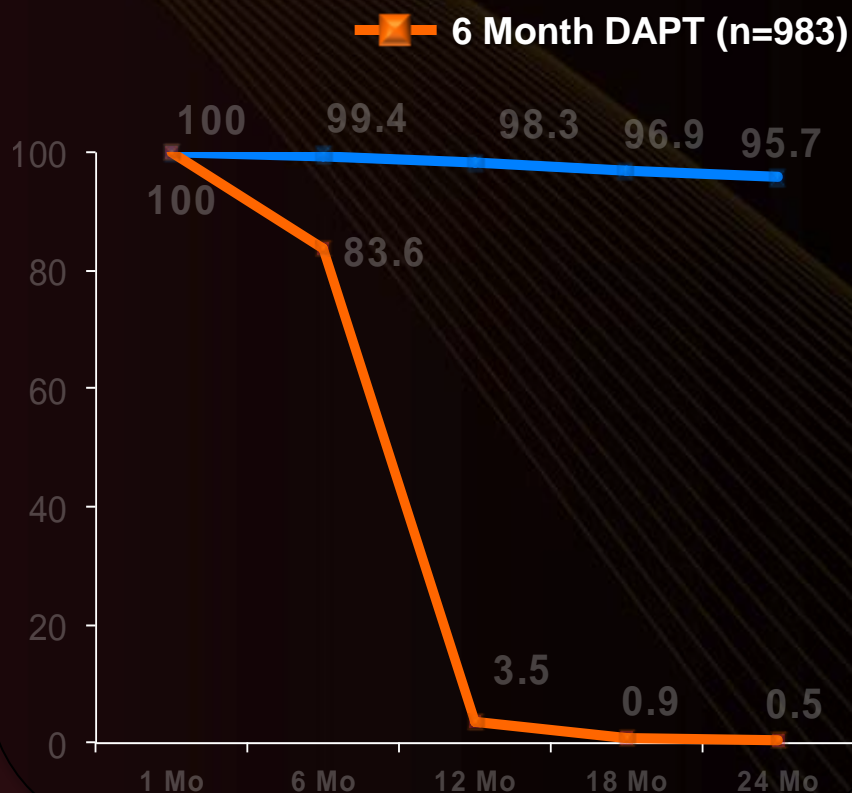
Angiographic Results

Duration of DAPT

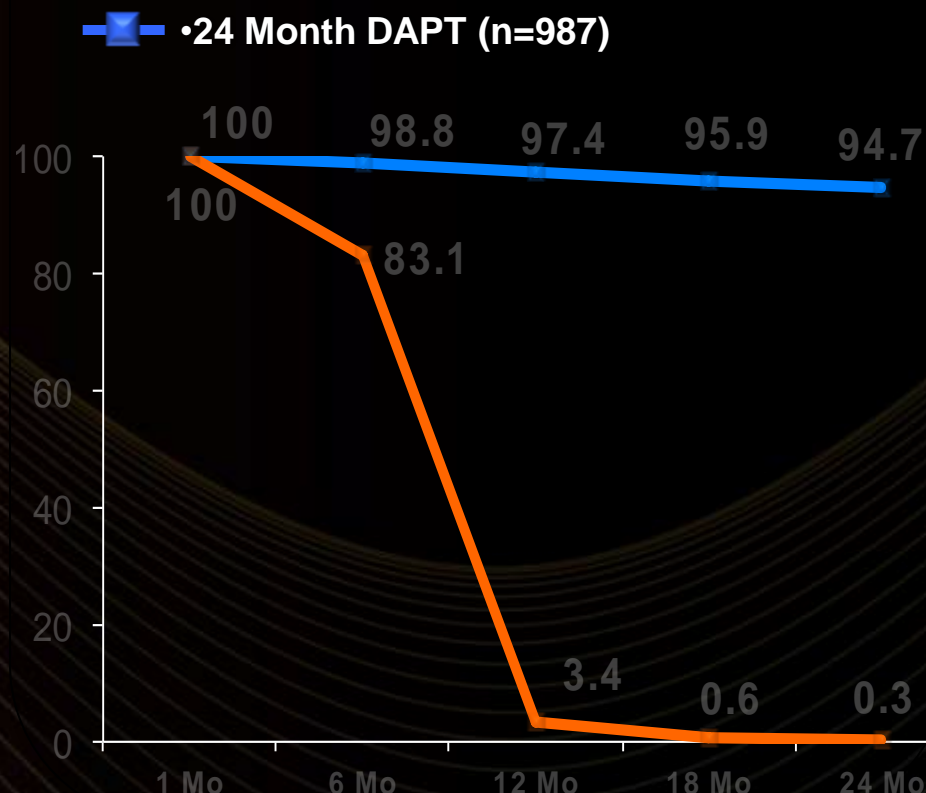
	24 Mo	6 Mo	P-value
Treated Lesions	N=1500	N=1546	
mean±SD	1.52±0.86	1.57±0.94	0.37
Median [IQR]	1 [1-2]	1 [1-2]	
≥2 treated lesions (%)	37	38	0.73
LAD treated (%)	53	53	0.92
LMCA treated (%)	5.6	5.7	0.90
≥1 B2/C lesion (%)	65	68	0.24
ACC/AHA score_(no)	3 [2-4]	3 [2-5]	0.19
Xience_(%)	25	25	0.99
Taxus_(%)	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	

Clopidogrel and Dual Anti-Platelet Therapy Use

Compliance to Clopidogrel (%)



Compliance to DAPT (%)



P<0.001 for all time points from 6 months onwards

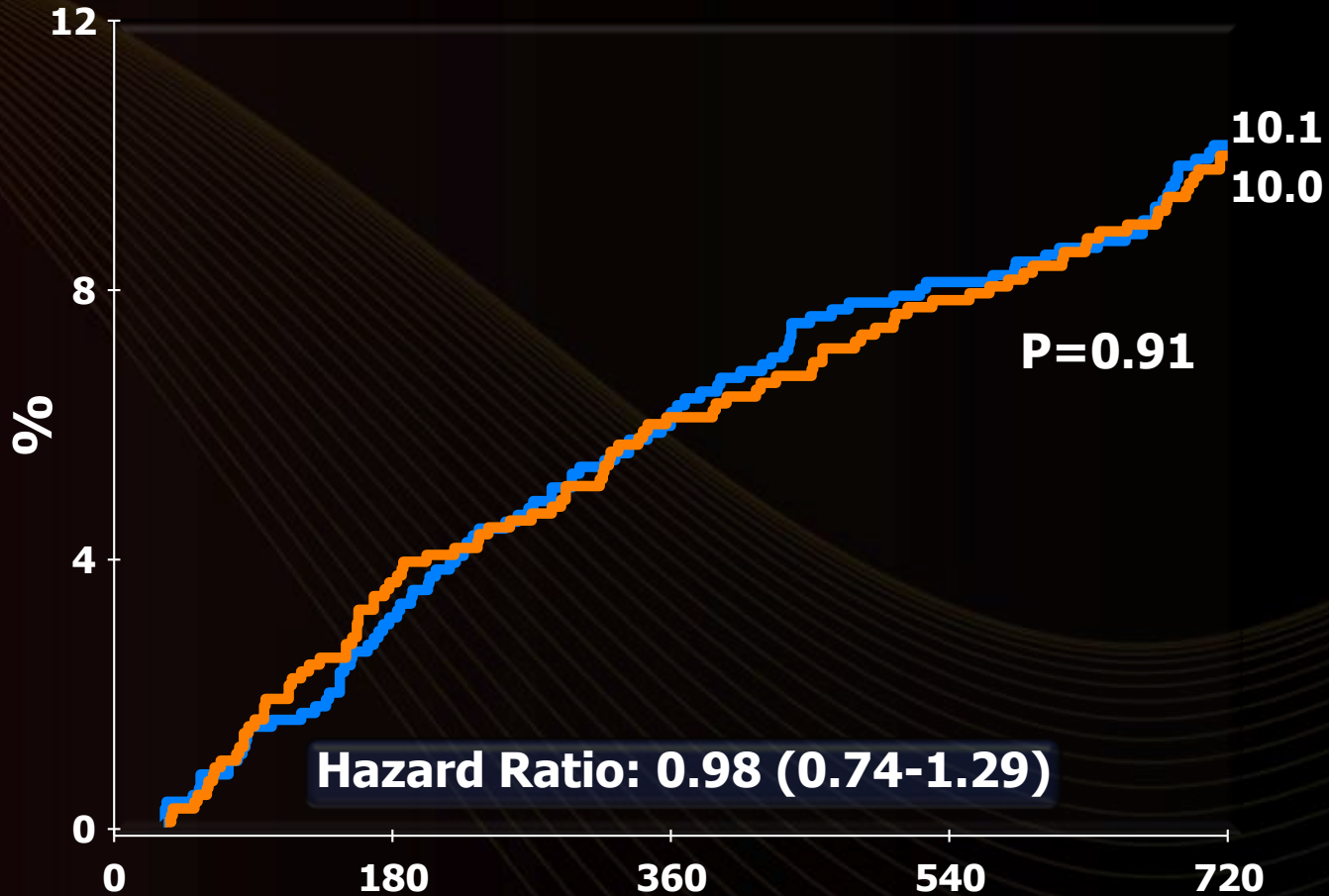
Primary Endpoint

Overall Death, MI or CVA

CEC adjudicated

■ 24 mo DAPT

■ 6 mo DAPT



No. at Risk

24-Month Clopidogrel 987
6-Month Clopidogrel 983

925

919

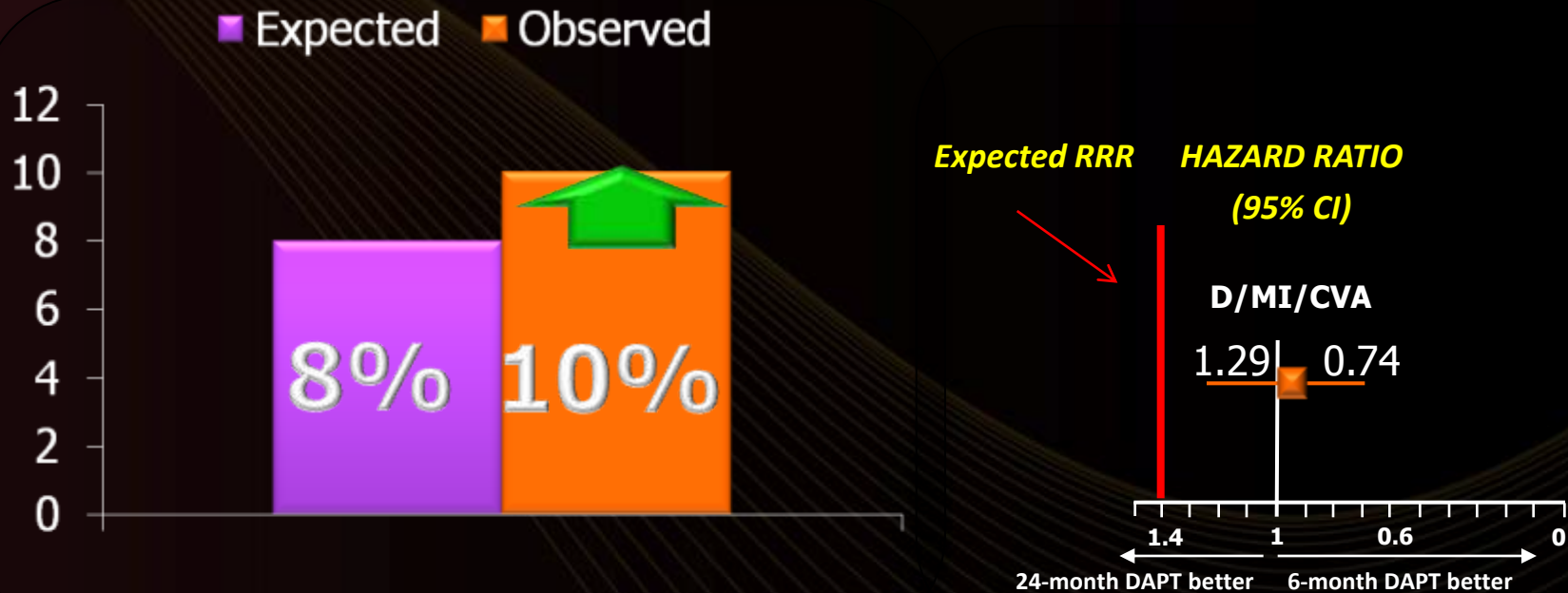
884

881



PRODIGY

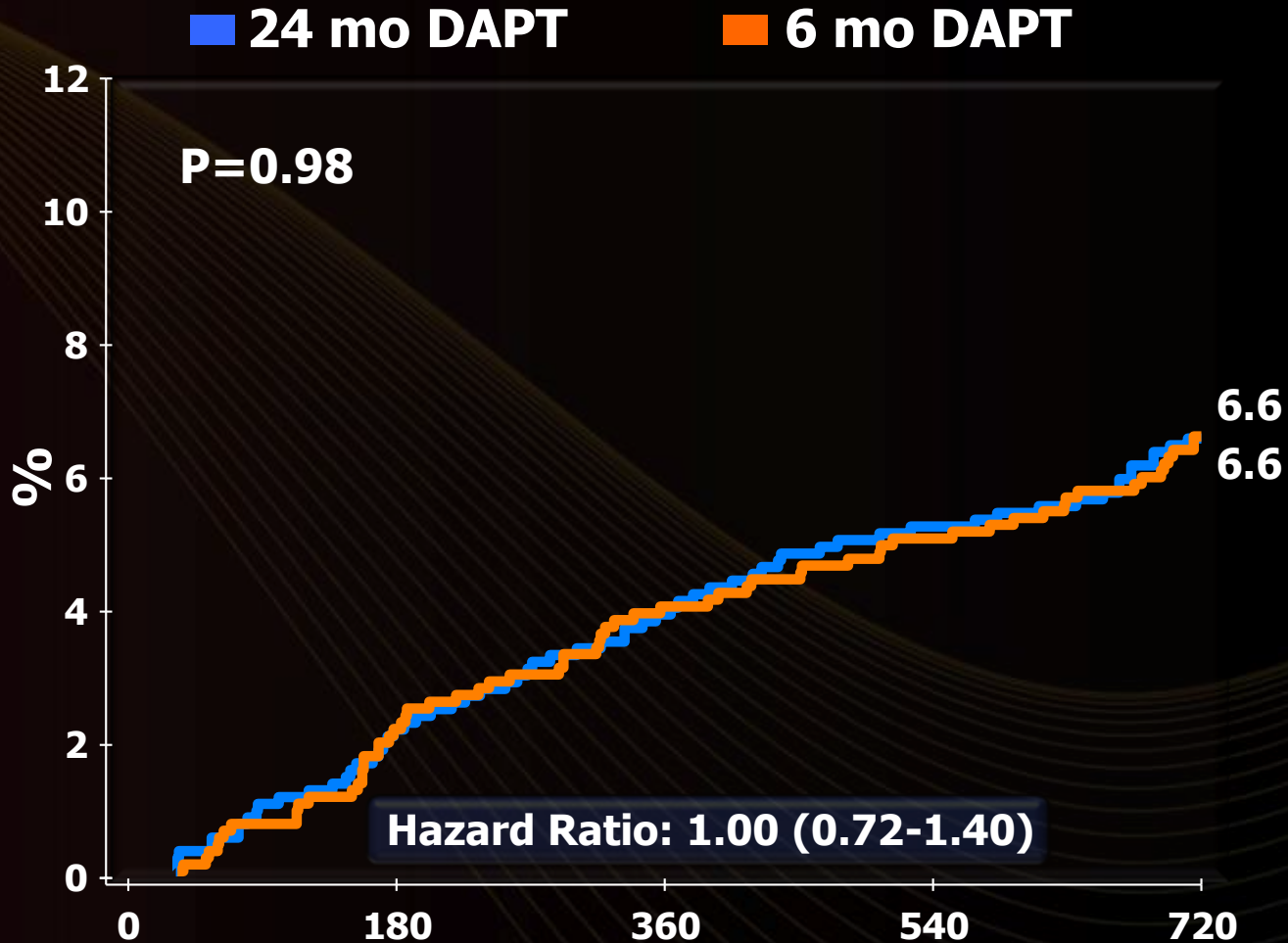
Lack of treatment effect or lack of power to detect the anticipated treatment effect?



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

Secondary Endpoint

Death from any cause



No. at Risk

24-Month Clopidogrel	987	925	884
6-Month Clopidogrel	983	919	881



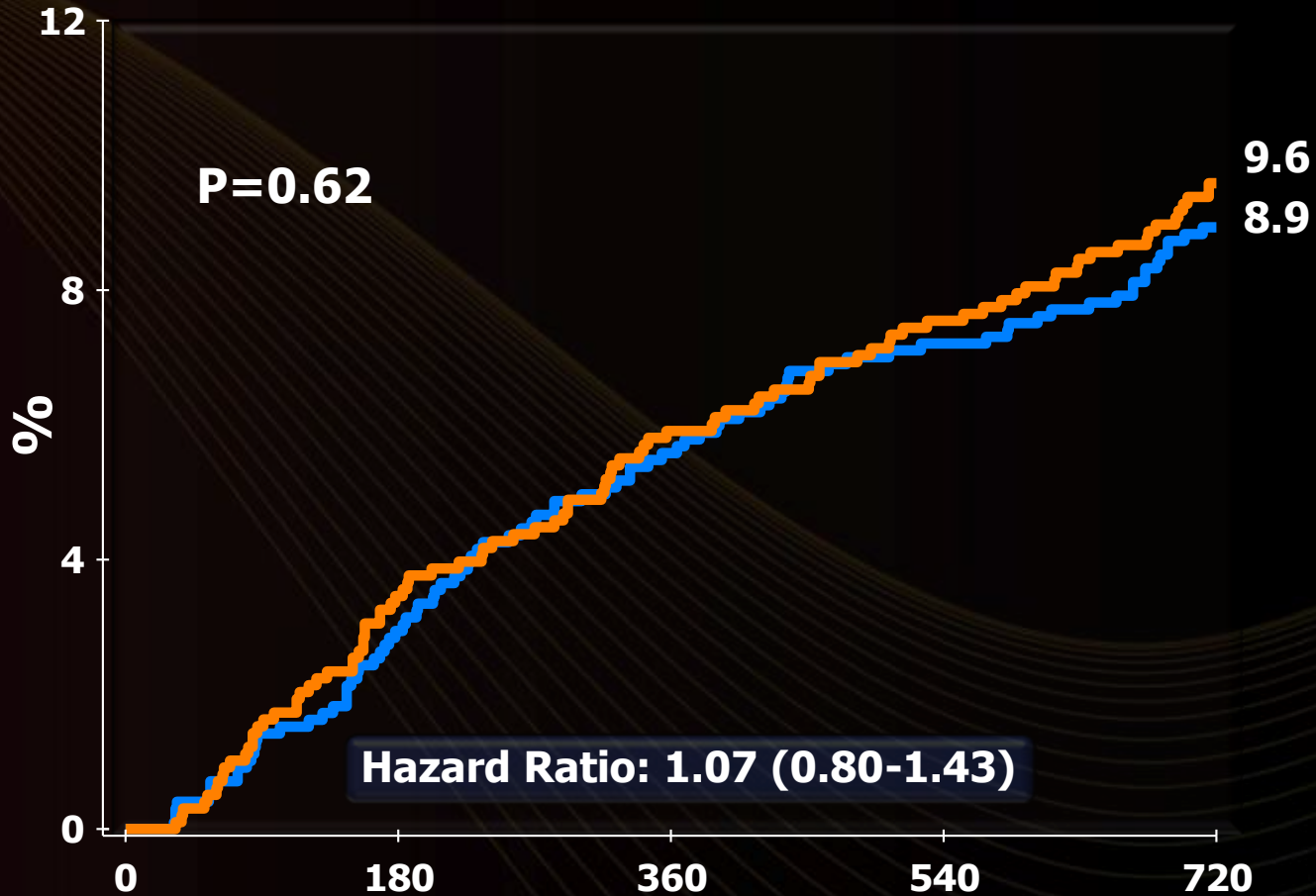
Secondary Endpoint

Death from any cause or MI

CEC adjudicated

24 mo DAPT

6 mo DAPT



No. at Risk

24-Month Clopidogrel	987
6-Month Clopidogrel	983

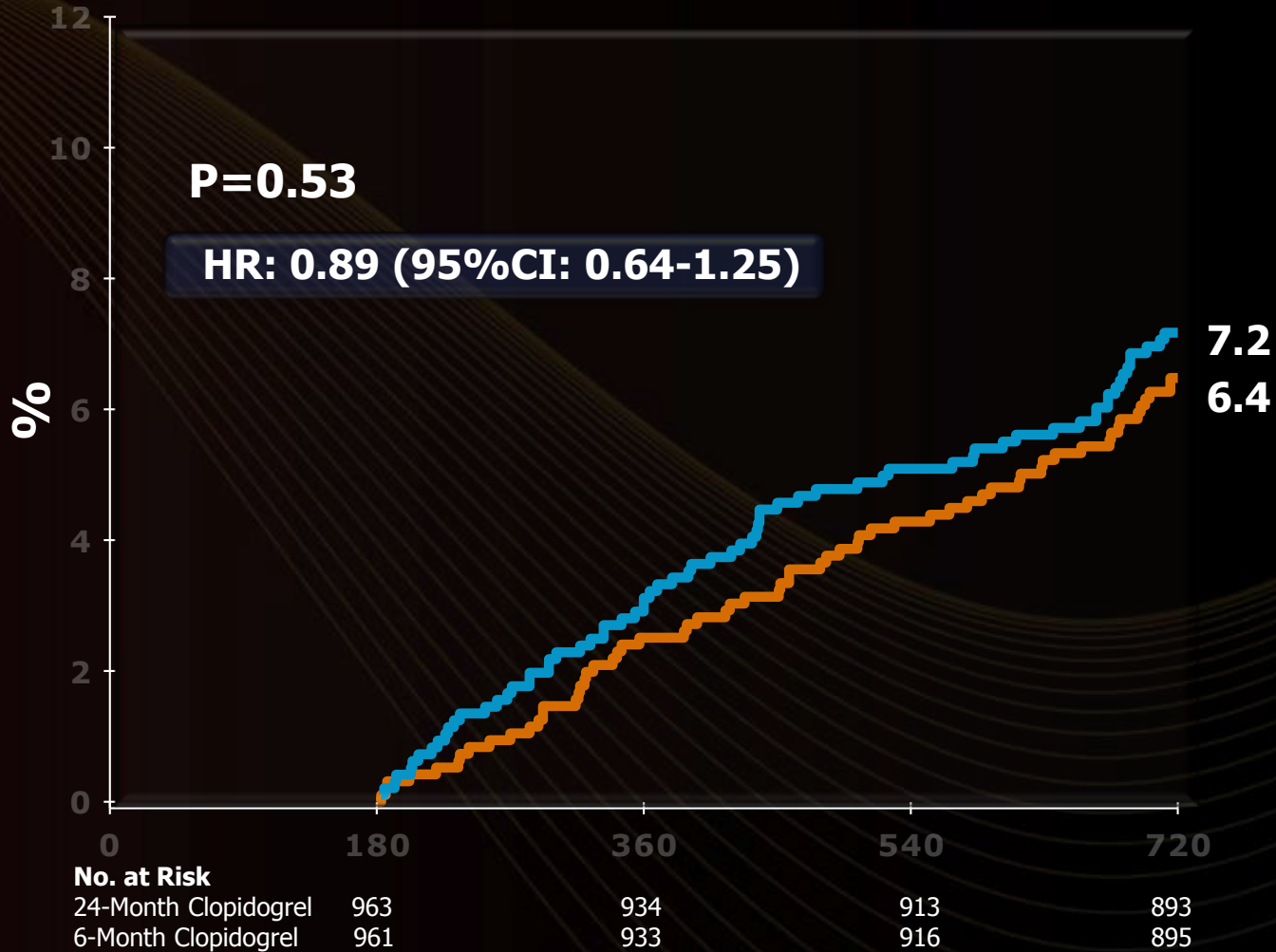
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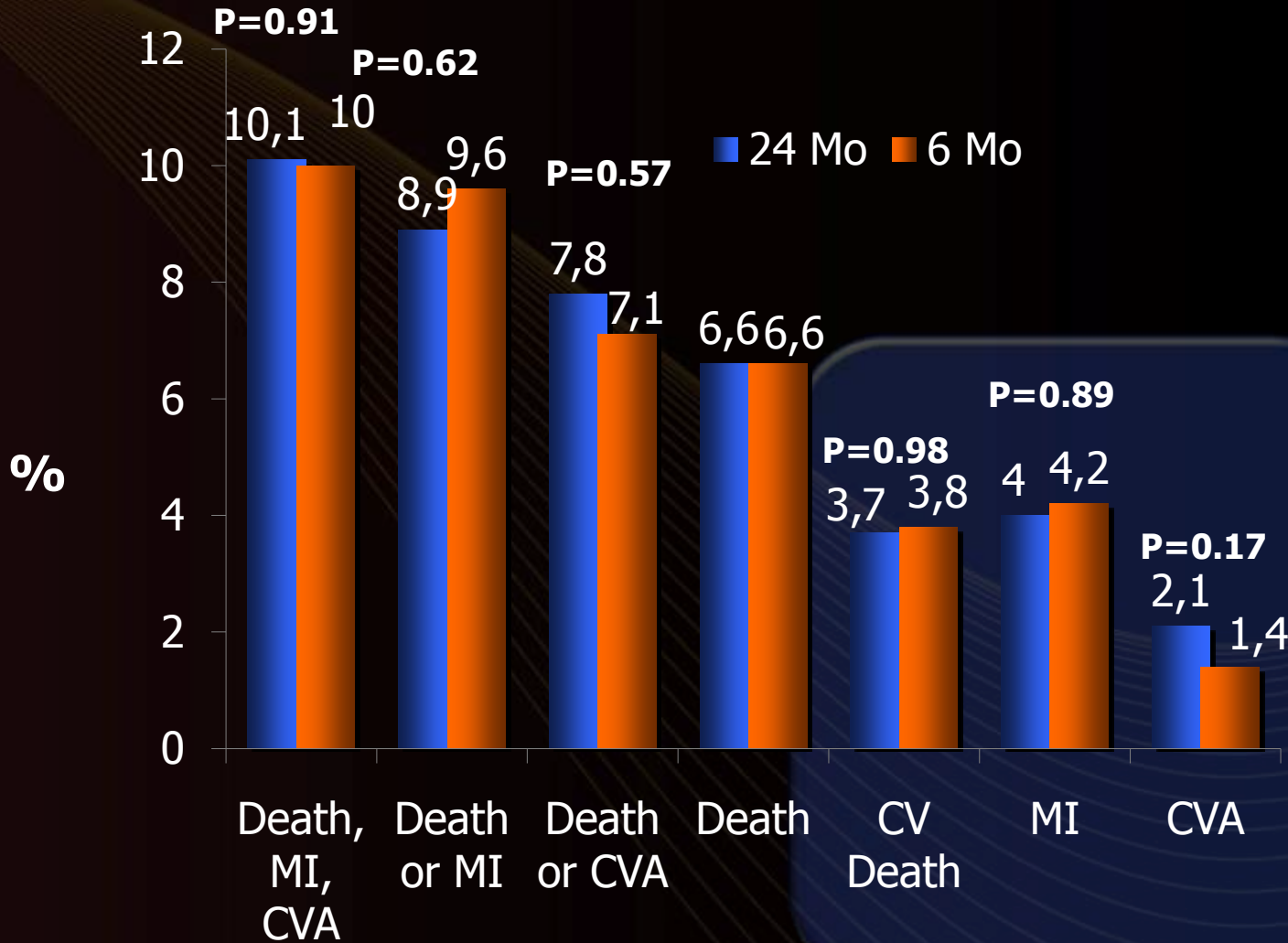
Death from any cause, MI or CVA from 6 months onwards

■ 24 mo DAPT ■ 6 mo DAPT

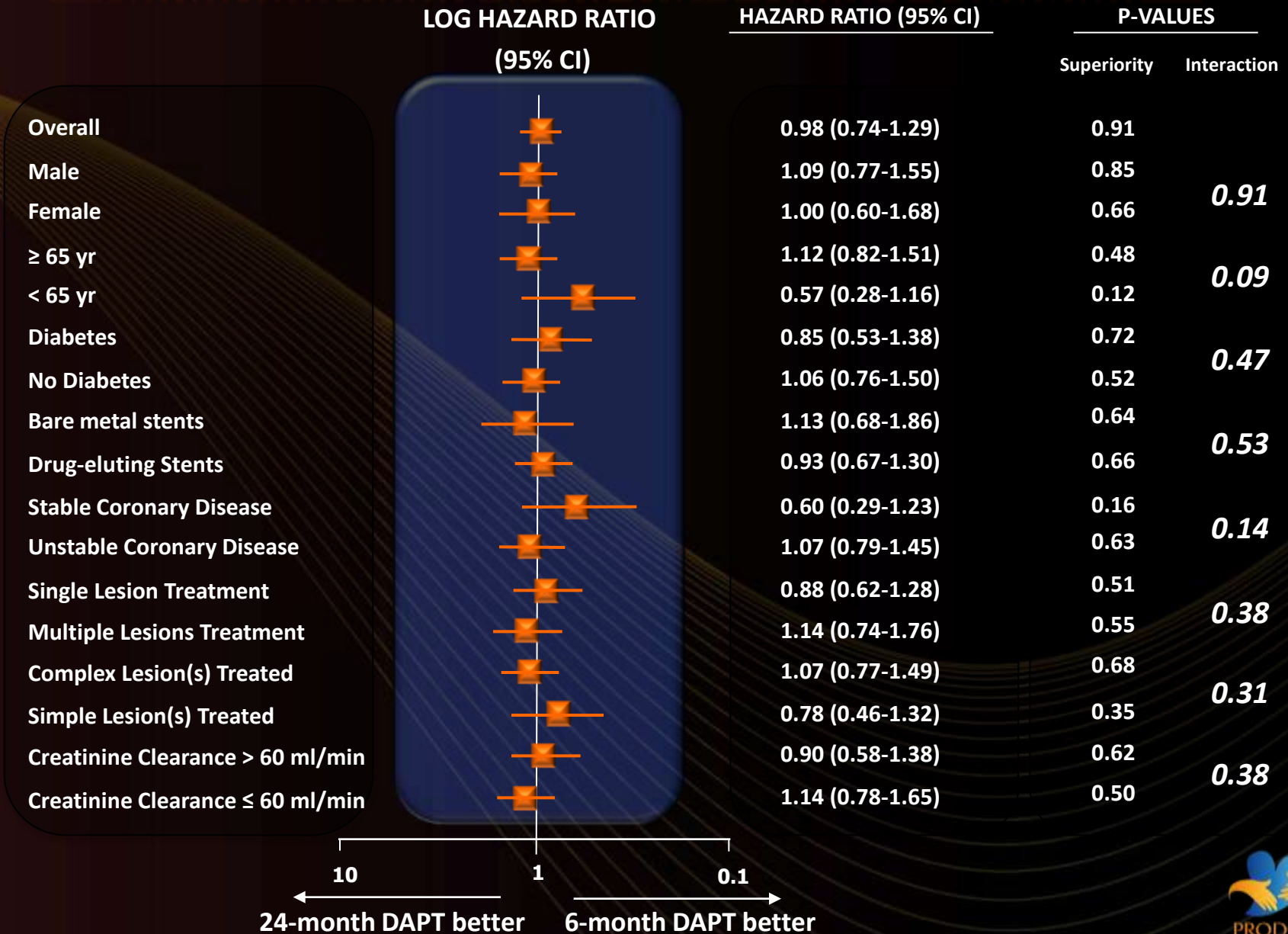


Cumulative Ischemic Events at 24 Mos

CEC adjudicated



Subgroup analysis of the Primary Endpoint



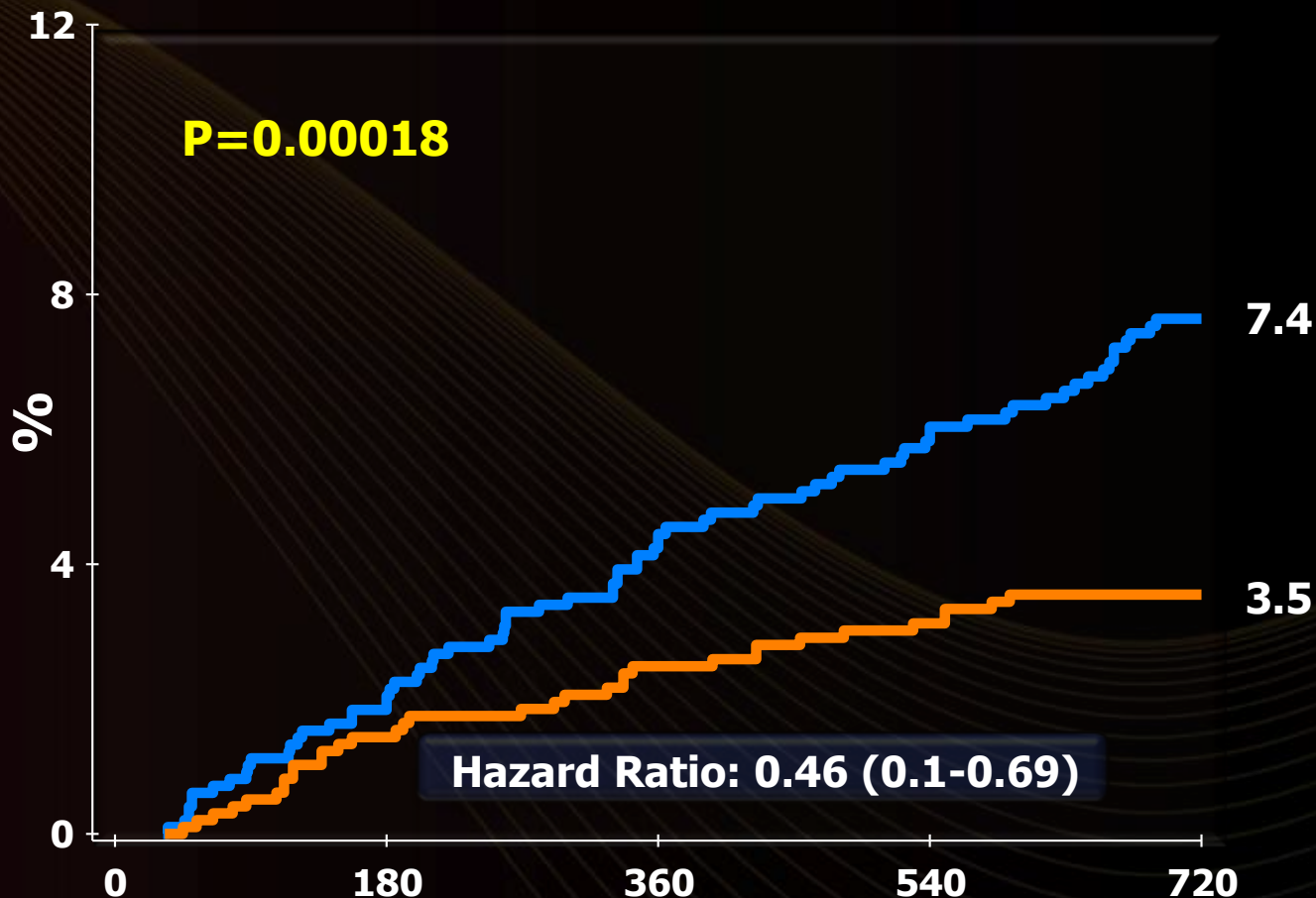
Key Safety Endpoint

Type II, III or V BARC bleeding

CEC adjudicated

■ 24 mo DAPT

■ 6 mo DAPT



No. at Risk

24-Month Clopidogrel	987
6-Month Clopidogrel	983

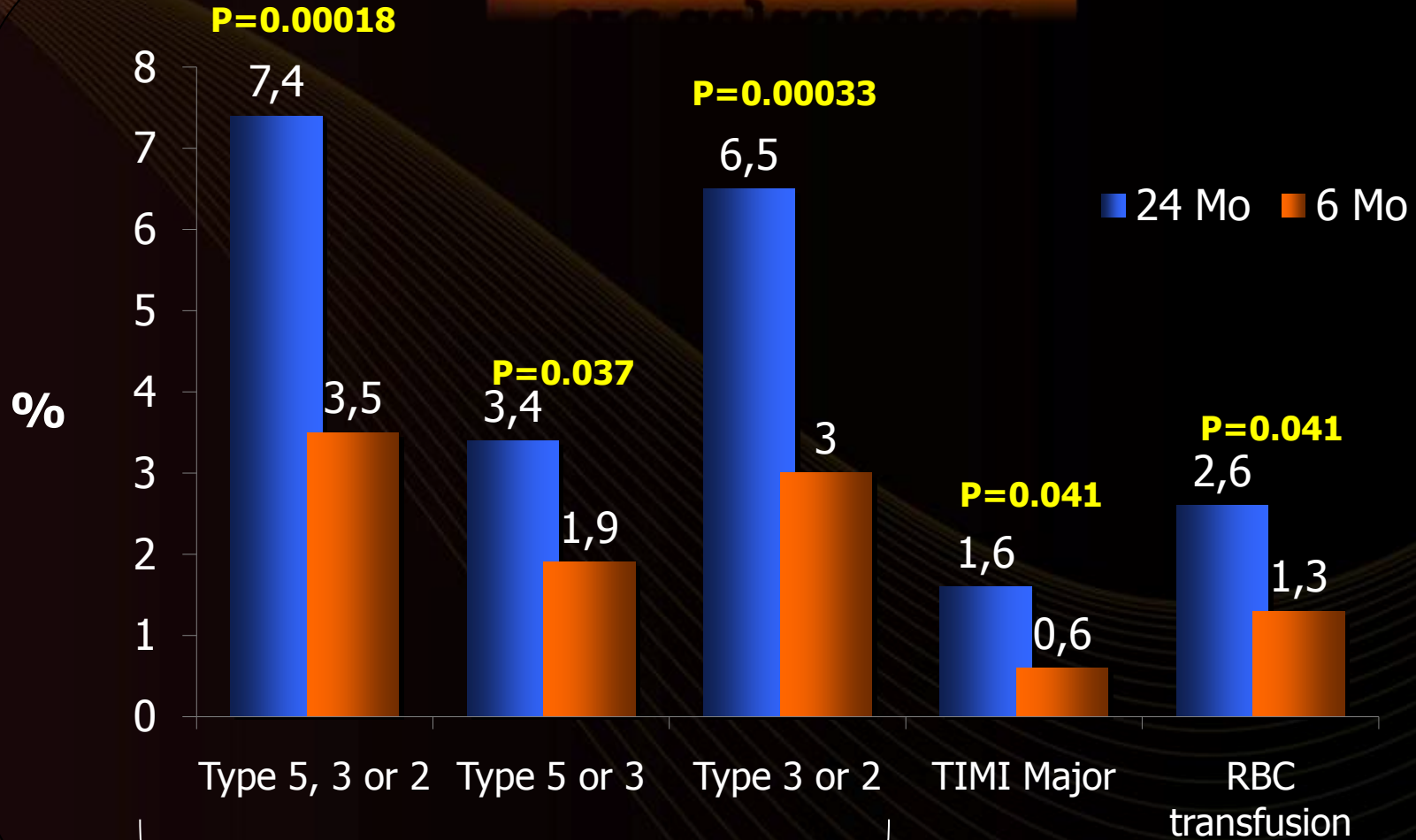
925
919

884
881



Bleeding Events and RBC Transfusion

CEC adjudicated



Bleeding Academic Research Consortium

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

