Predictors of Acute, Subacute and Late Stent Thrombosis After Acute MI Primary Angioplasty in the Horizons AMI Trial

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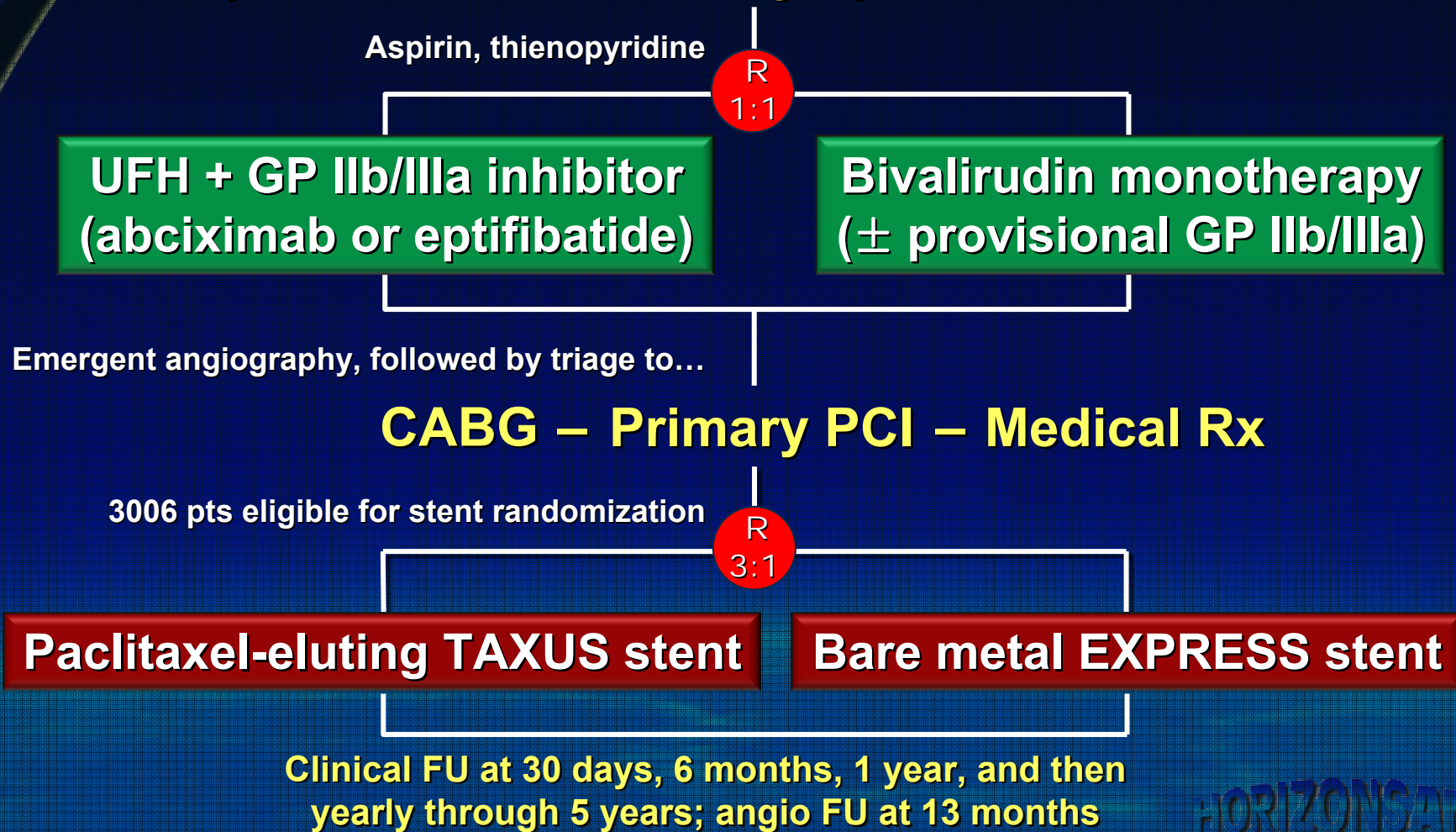# Background

- Stent thrombosis (ST) is a serious adverse event which occurs more frequently in pts with STEMI

- Since the pathophysiologic mechanisms of ST may vary, it is conventionally categorized according to its timing after stenting:
  - 0-24 hours (acute ST)
  - 1-30 days (subacute ST)
  - 1-12 months (late ST)

- We sought to determine the clinical and angiographic predictors of ST according to its timing in pts with STEMI undergoing primary PCI

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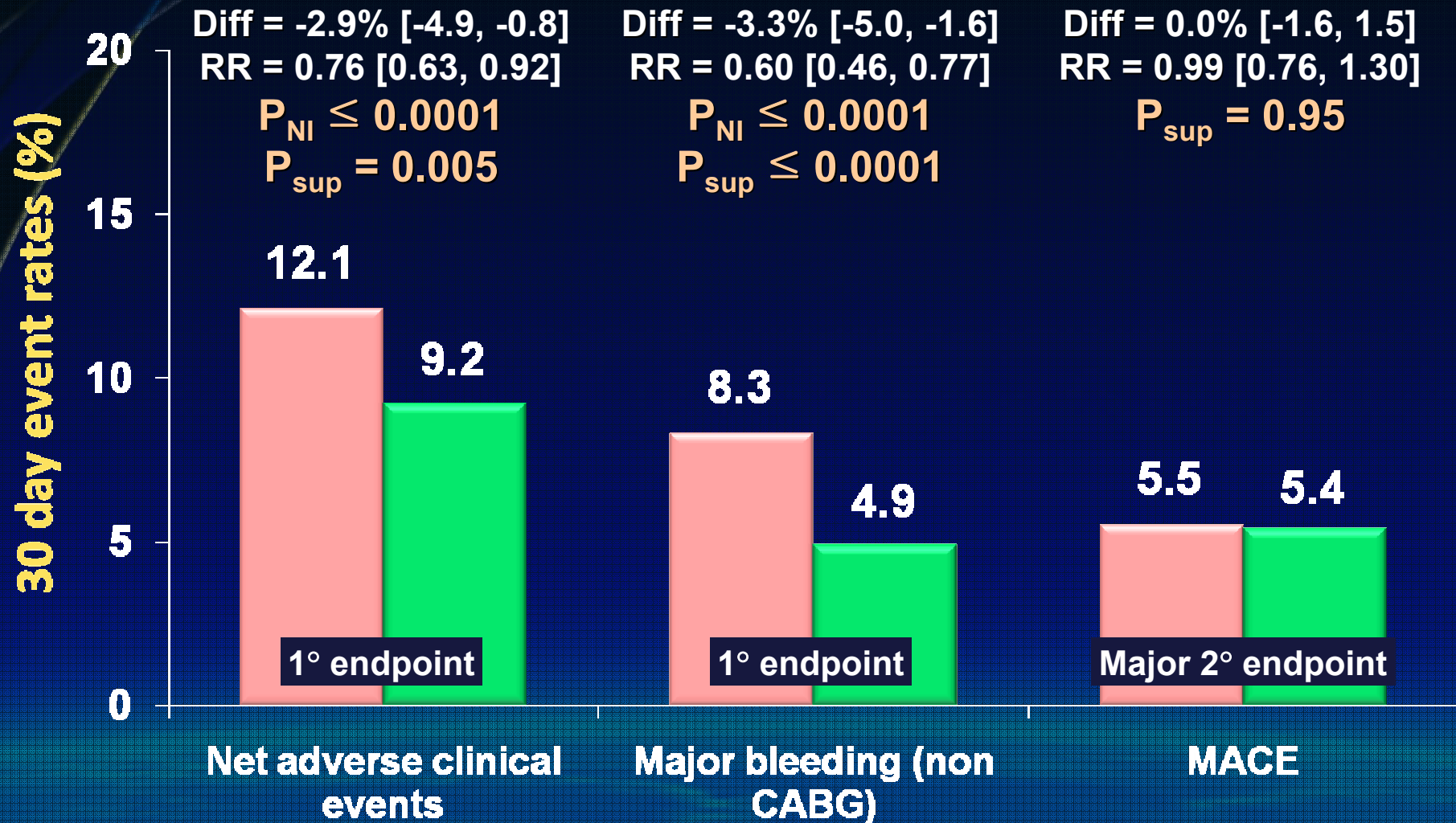**Harmonizing Outcomes with Revascularization and Stents in AMI**
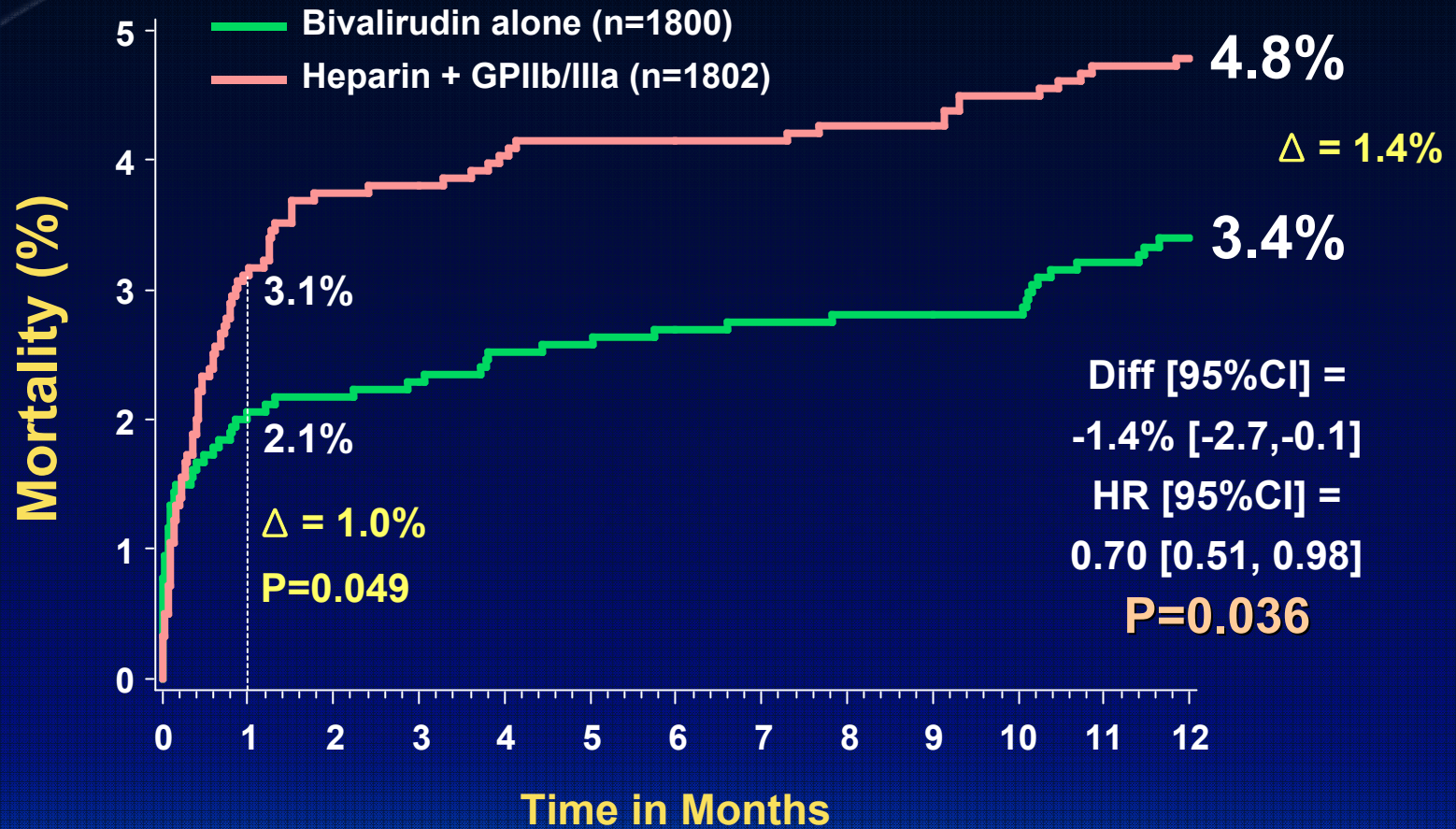
3602 pts with STEMI with symptom onset ≤12 hours

Aspirin, thienopyridine

R 1:1

| UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide) | Bivalirudin monotherapy (± provisional GP IIb/IIIa) |

Emergent angiography, followed by triage to…

CABG – Primary PCI – Medical Rx

3006 pts eligible for stent randomization

R 3:1

| Paclitaxel-eluting TAXUS stent | Bare metal EXPRESS stent |

Clinical FU at 30 days, 6 months, 1 year, and then yearly through 5 years; angio FU at 13 months

Primary Endpoints at 30 Days

Stone GW et al. *NEJM* 2008;358:2218-30

1-Year Mortality (All-Cause)

Mortality (%)

- Bivalirudin alone (n=1800)
- Heparin + GPIIb/IIIa (n=1802)

4.8%

Δ = 1.4%

3.4%

3.1%

2.1%

Δ = 1.0%

P=0.049

Diff [95%CI] =
-1.4% [-2.7,-0.1]
HR [95%CI] =
0.70 [0.51, 0.98]
P=0.036

Time in Months

Number at risk					
Bivalirudin alone	1800	1705	1684	1669	1520
Heparin+GPIIb/IIIa	1802	1679	1664	1647	1487

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Stent Thrombosis Analysis

In the current analysis we included all HORIZONS-AMI pts who received a stent, either DES (any type) or only BMS **(n=3203)**

Stent thrombosis **(n=107 [3.3%] within 1-year)** was defined as Definite or Probable by the ARC criteria, as adjudicated by an independent CEC blinded to stent and pharmacology use

Objectives

- **Stent thrombosis and timing according to:**
  - Stent type (any DES vs. onlyBMS, 94% rand)
  - Antithrombin type (UFH+GPI vs. Bival, 100% rand)
  - GPI selection (abciximab vs. eptifibatide, stratified)
  - Clopidogrel loading dose (300 vs. 600 mg, stratified)
  - Pre randomization UFH (yes vs. no, stratified)

- **Univariate and multivariable predictors of stent thrombosis (ARC Def/Prob) from 36 variables**
 - Acute, subacute, late, and 1-year

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Statistical Methods

- **Kaplan-Meier methods were used to plot landmark time-to-event curves, compared using the logrank test**

- **Cox proportional hazards used to derive the independent predictors of ST via stepwise regression (α=0.05)**

- **Potential covariates (36) for inclusion in the models:**

  - **CLINICAL (20):** Bivalirudin (randomized v. UFH+IIb/IIIa), Any DES (v. BMS only), Age, Sex (Male), US clinical center, Clopidogrel Loading Dose, Pre-Randomization Heparin, Current Smoking, History of IDDM, History of MI, History of CHF, Killip Class 2-4, History of PVD, Anemia, Baseline Platelet Count, Renal Insufficiency (Baseline CrCl<60), Anterior MI, Direct Stenting Attempted, Post Dilation balloon used, Max Balloon Pressure

  - **ANGIOGRAPHIC (16):** Baseline RVD, Total Lesion Length, Stent to Lesion Length Ratio, Number of stents, Worst angiographic view - Thrombus, Worst angiographic view - Ulceration, Aneurysm, Baseline TIMI flow 0/1, Bifurcation lesion, Moderate/Severe Calcification, Multiple Vessels Treated, Sustained ventricular tachycardia or fibrillation on admission, Final TIMI flow 0/1, Final Lesion MLD , Final Lesion DS>50%, Final Angiography with No Reflow

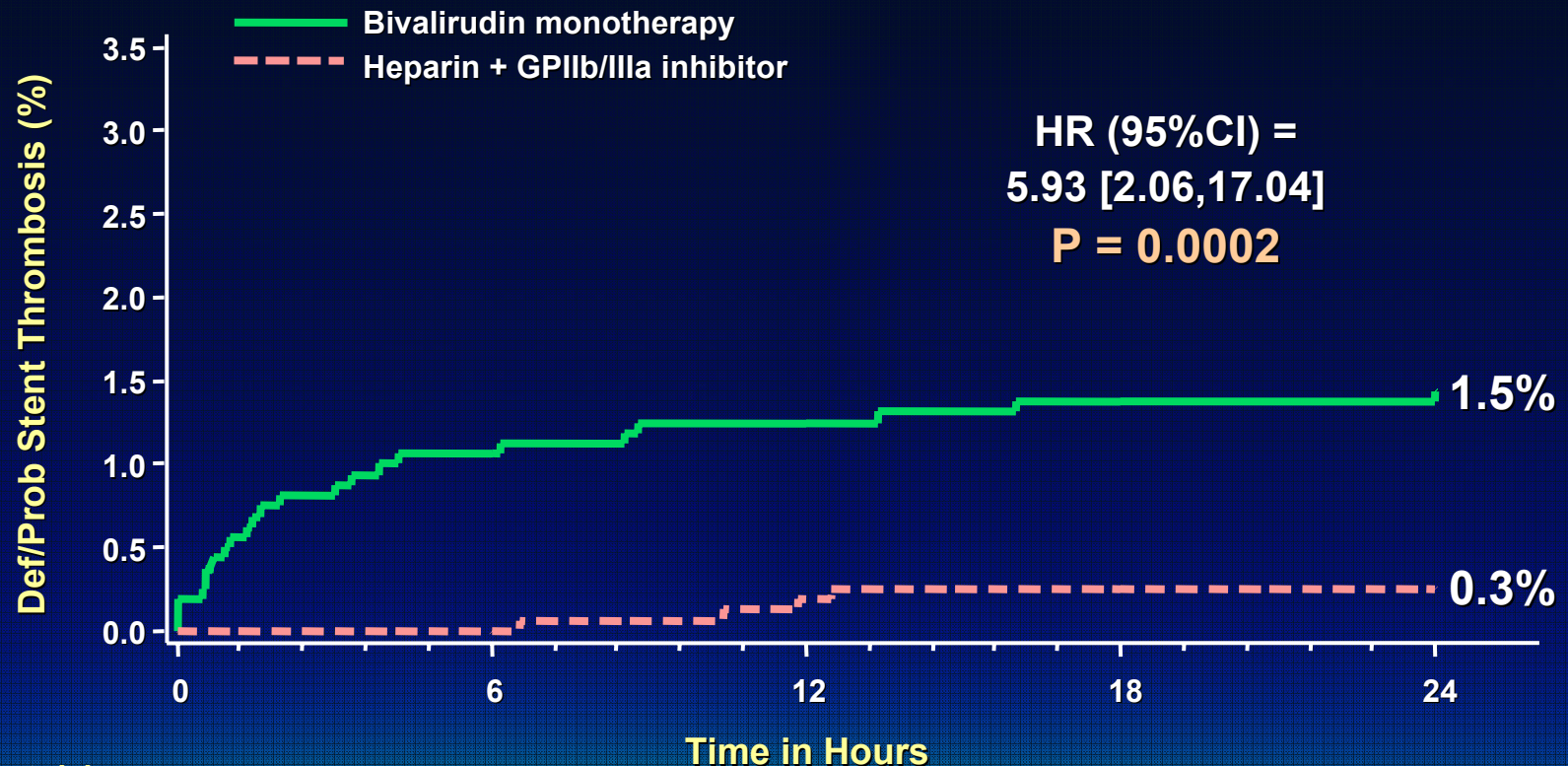HORIZONSAMI

1-Year Stent Thrombosis: Impact of Implanted Stent Type
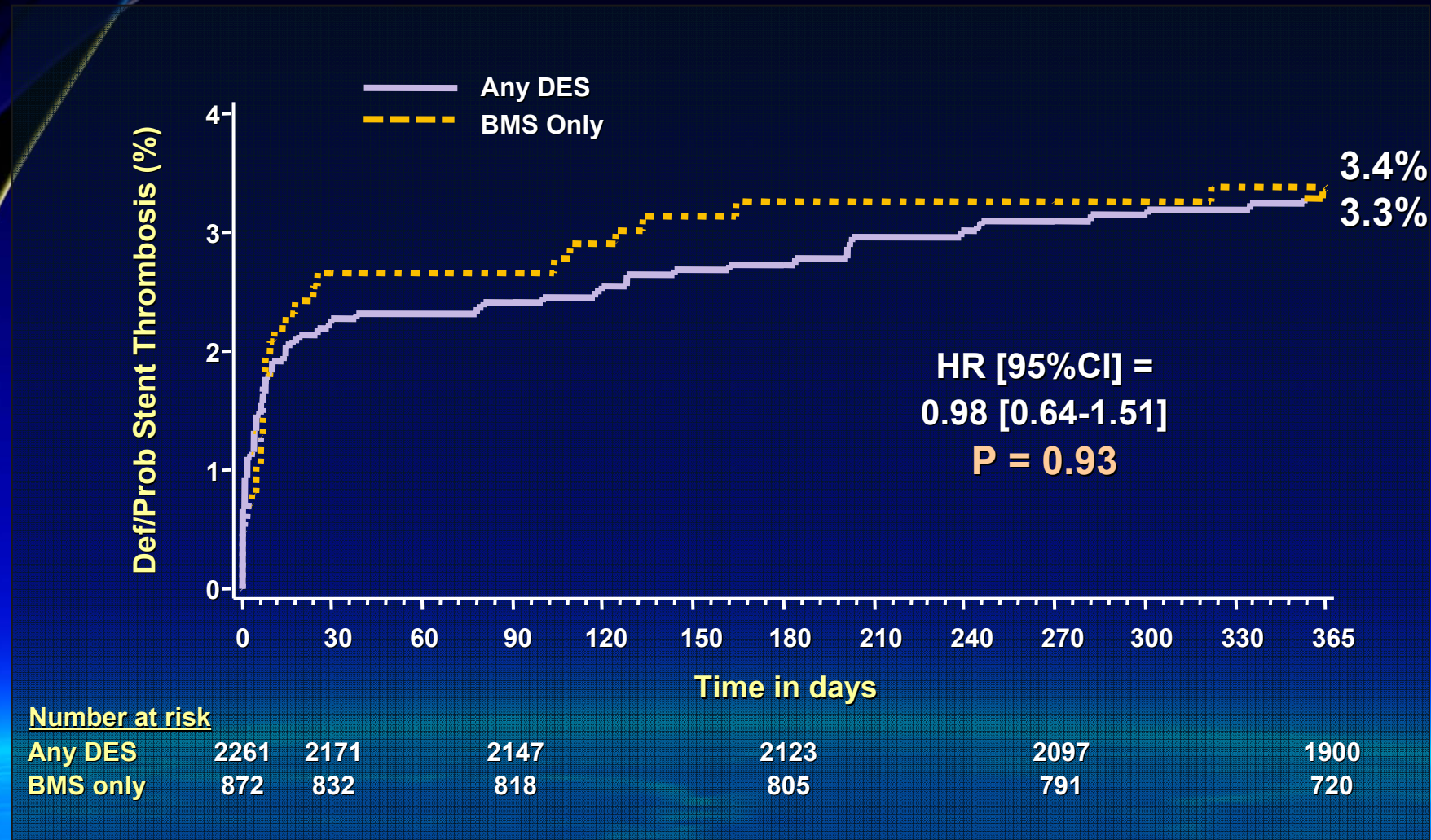
1-Year Stent Thrombosis: Impact of Antithrombin (Primary Randomization)
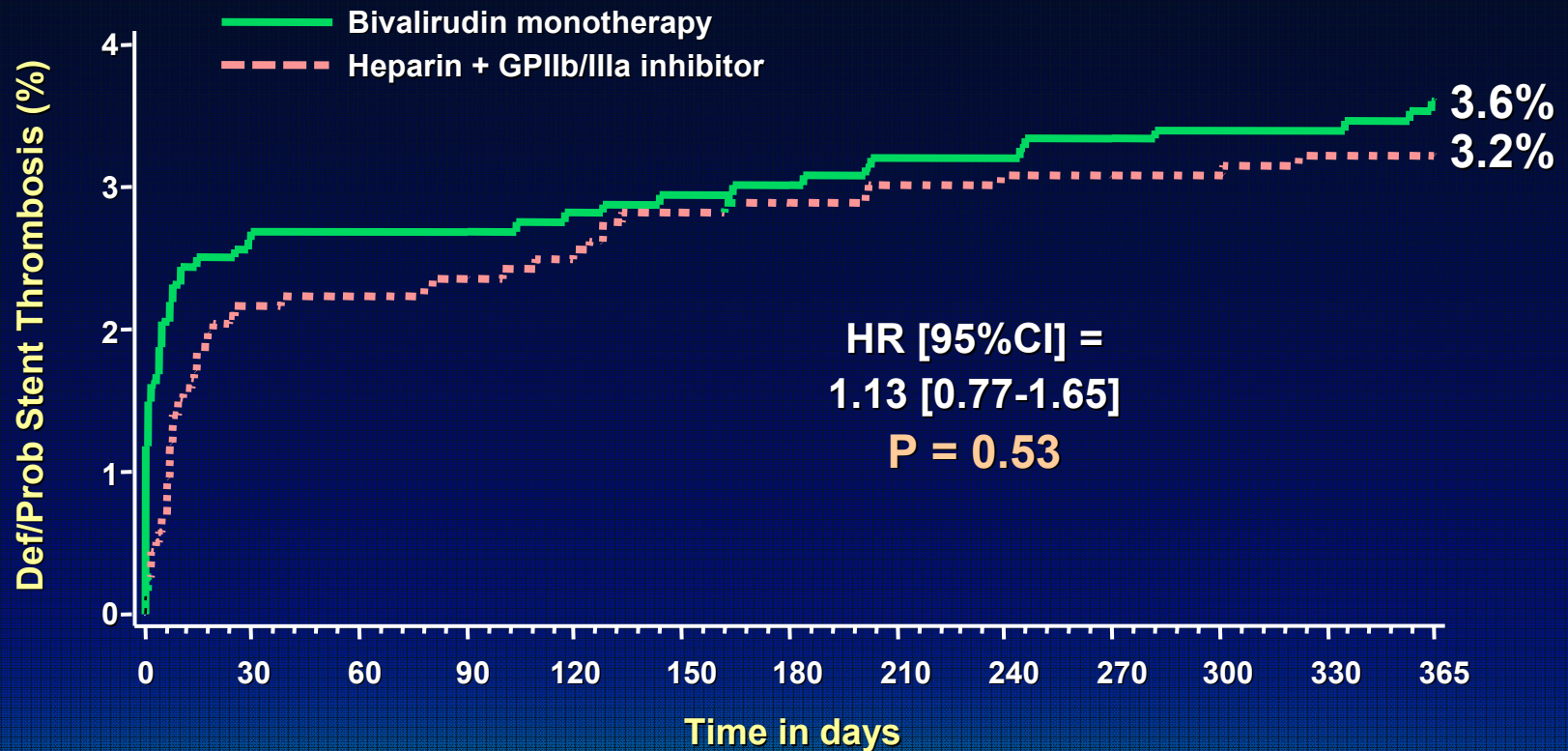
Number at risk

Bivalirudin	1611	1540	1525	1506	1485	1355
UFH+GPIIb/IIIa	1591	1518	1495	1476	1457	1315

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Acute Stent Thrombosis: Impact of Antithrombin (Primary Randomization)

Stent Thrombosis 1-Day Landmark Analysis: Impact of Antithrombin

Legend:
- Bivalirudin monotherapy (solid pink line)
- Heparin + GPIIb/IIIa inhibitor (dashed green line)

Y-axis: Def/Prob Stent Thrombosis (%), ranging from 0.0 to 3.5

X-axis: Time in Days (0, 1, 30, 90, 180, 270, 365)

HR [95%CI] = 5.93 [2.06-17.04]
P = 0.0002

1.5%
0.3%

HR [95%CI] = 1.73 [0.47-1.13]
P = 0.06

3.0%
2.2%
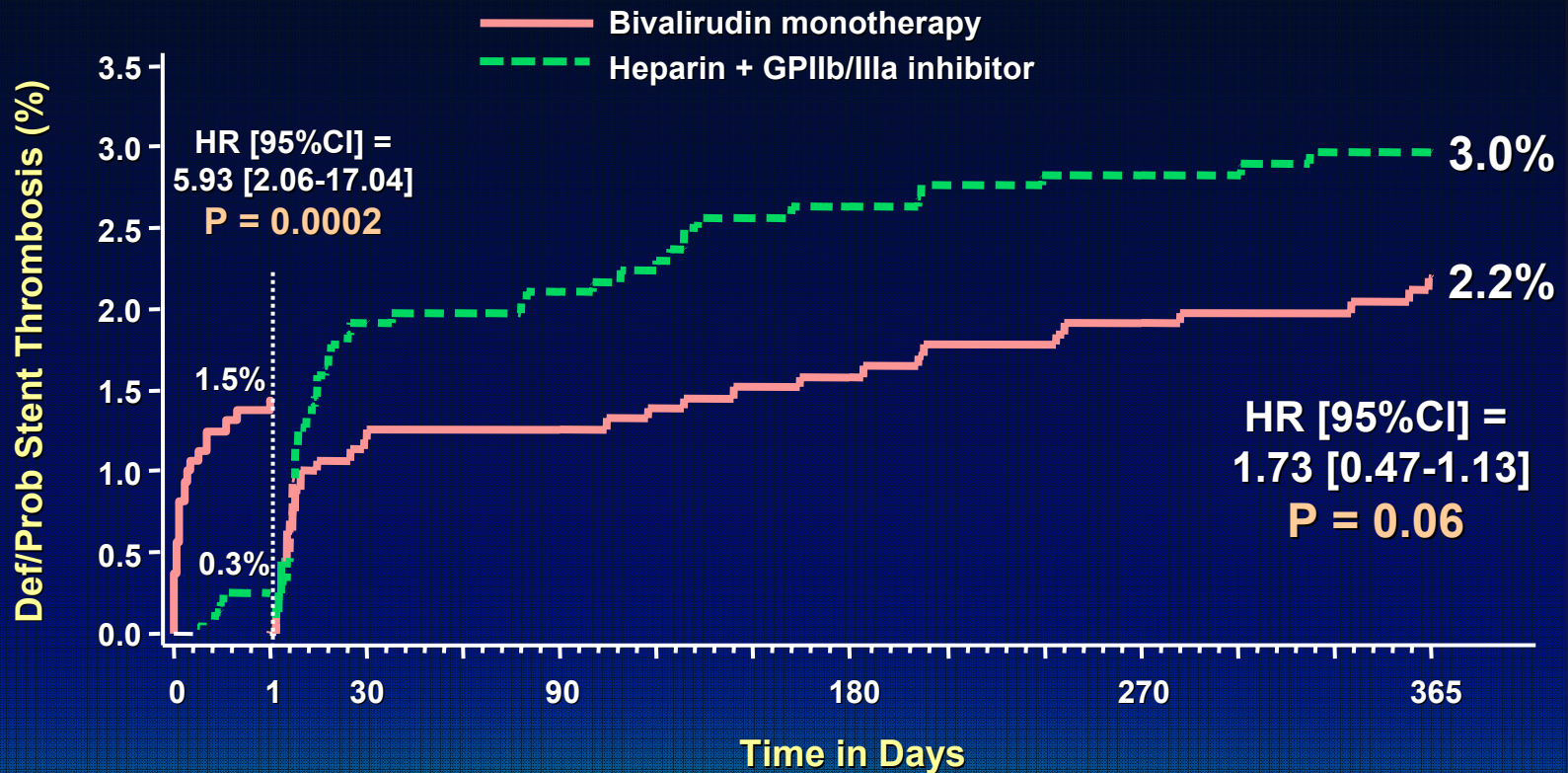
Number at risk	0	1	30	90	180	270	365
Bivalirudin	1611	1600	1562	1525	1506	1485	1355
UFH+GPIIb/IIIa	1591	1587	1521	1495	1476	1457	1315

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1-Year Stent Thrombosis: Impact of GPI in the UFH Group

Eptifibatide
Abciximab

HR [95%CI] =
0.78 [0.44-1.37]
P = 0.38

Y-axis: Def/Prob Stent Thrombosis (%)
X-axis: Time in days
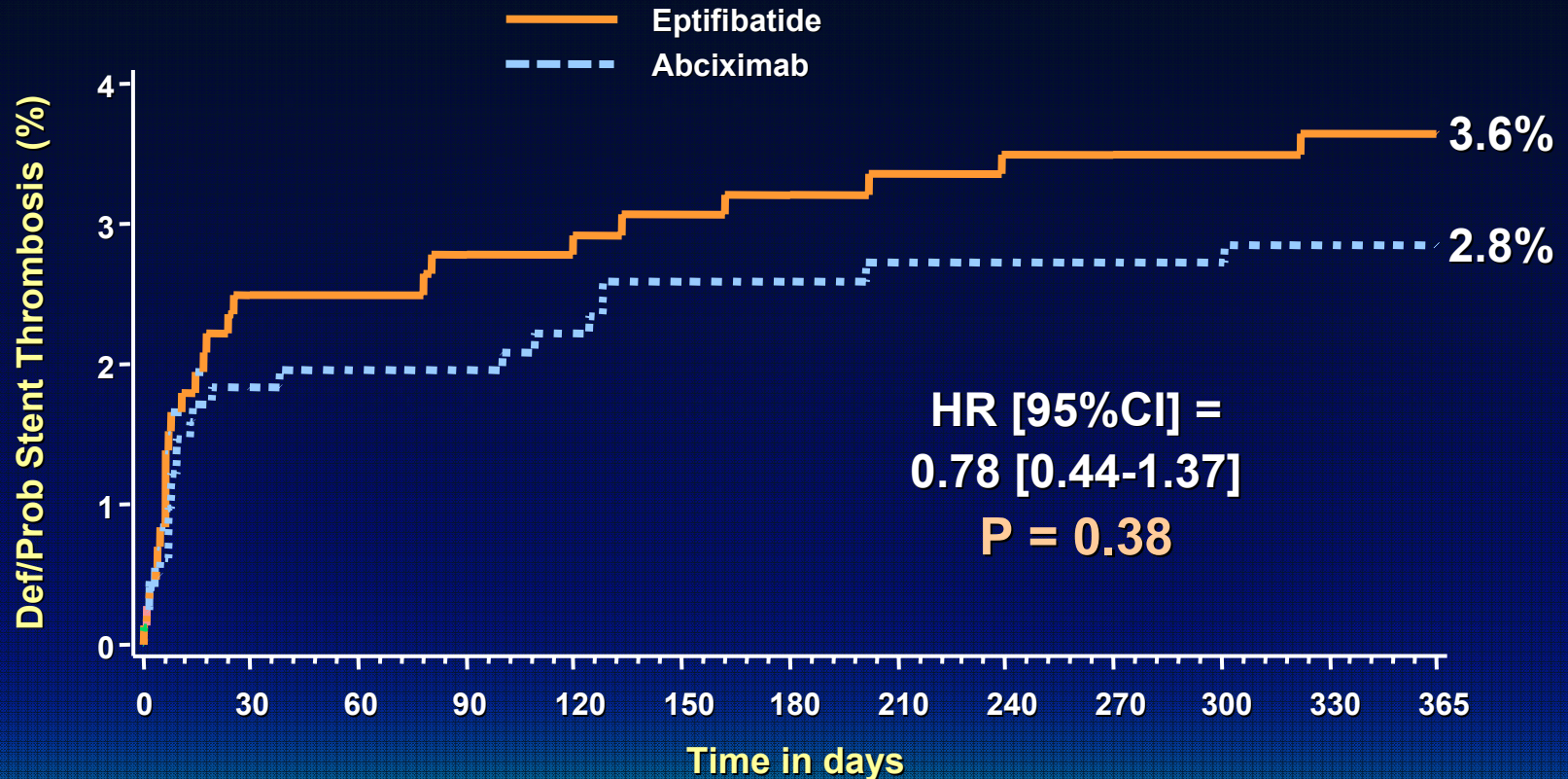
Number at risk	0	30	60	120	270	365
Eptifibatide	727	693	685	678	668	592
Abciximab	829	793	778	768	759	698

3.6%
2.8%

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Acute Stent Thrombosis: Impact of Pre-Randomization Heparin
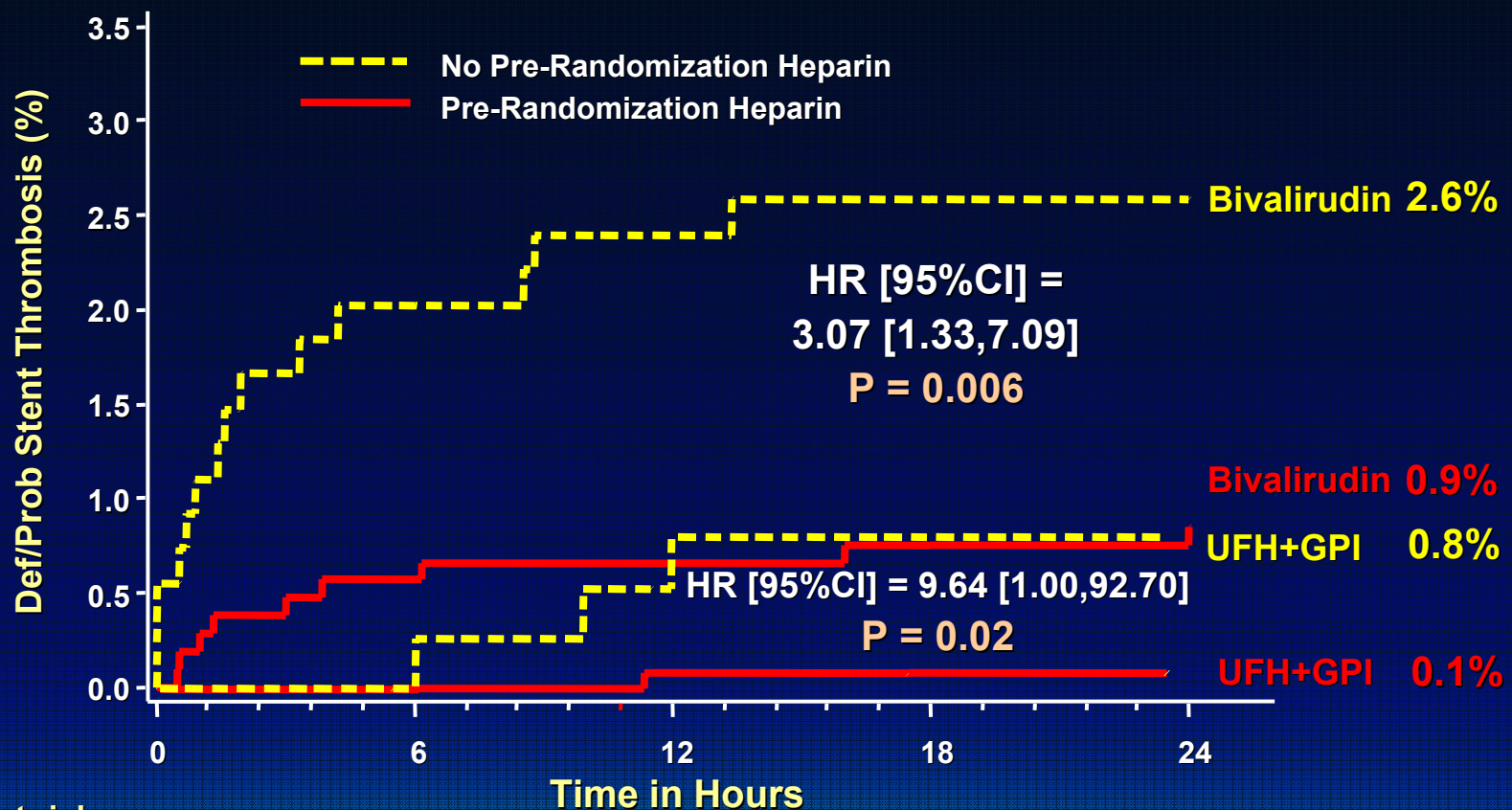
Number at risk

P-R Heparin	1066	1052	1051	1050	1049
No P-R Heparin	545	531	529	528	528
P-R Heparin	1211	1208	1207	1207	1207
No P-R Heparin	378	377	375	374	374

P_{int} antithrombin x pre-rand hep = 0.39
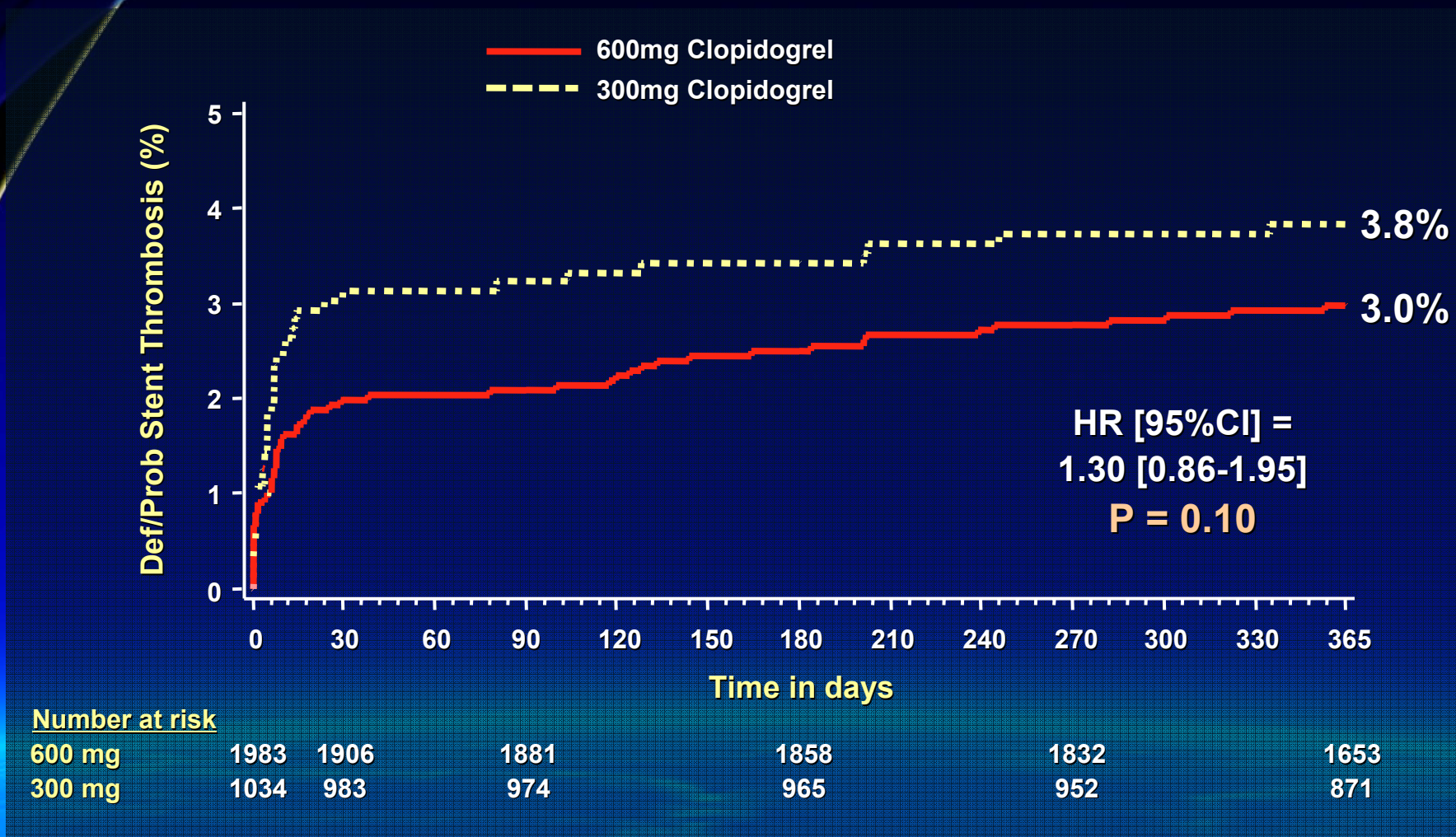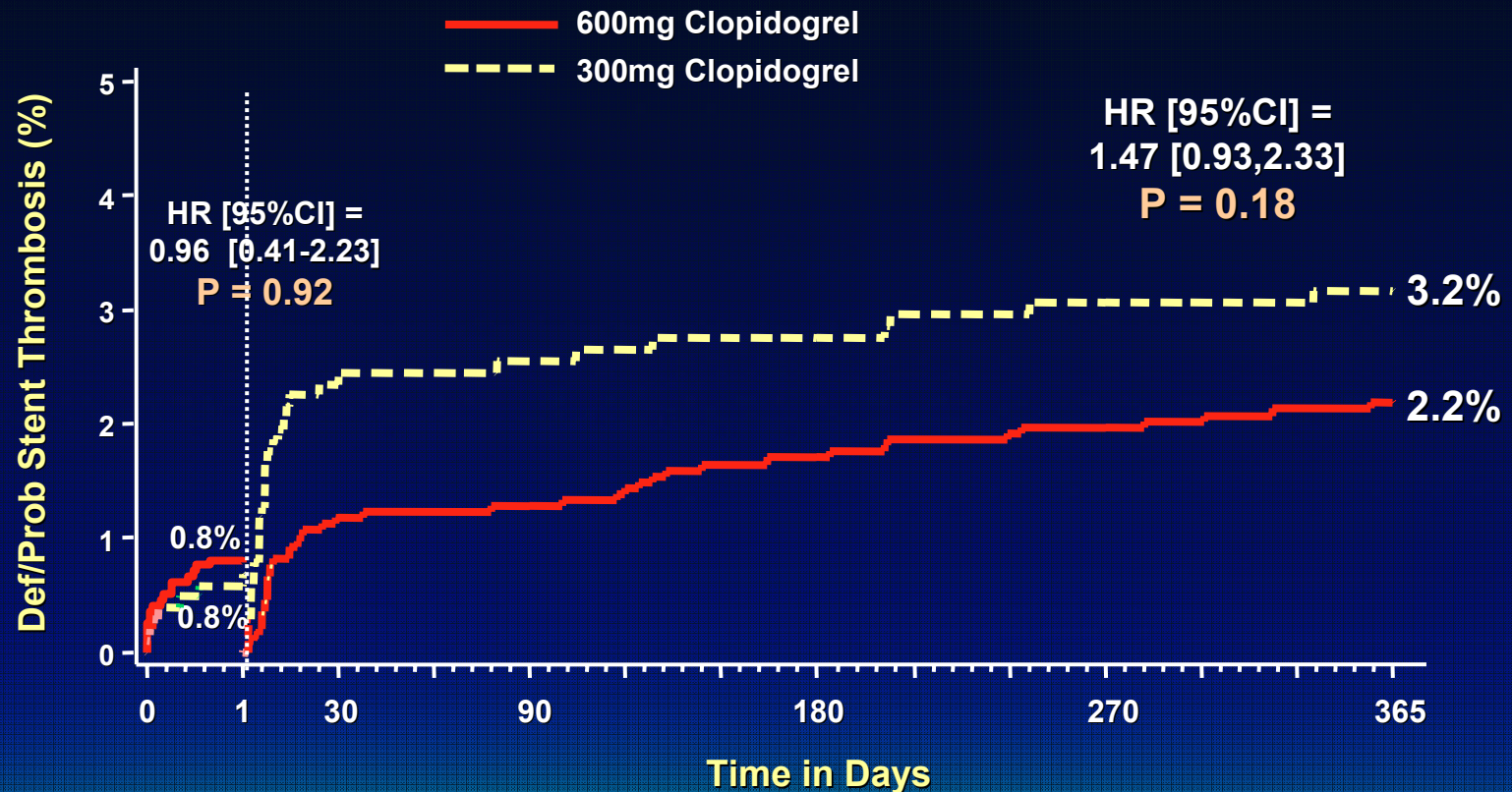
Stent Thrombosis 1-Day Landmark Analysis: Impact of Clopidogrel Loading

Stent Thrombosis 1-Day Landmark Analysis: Impact of Clopidogrel Loading (Bivalirudin)
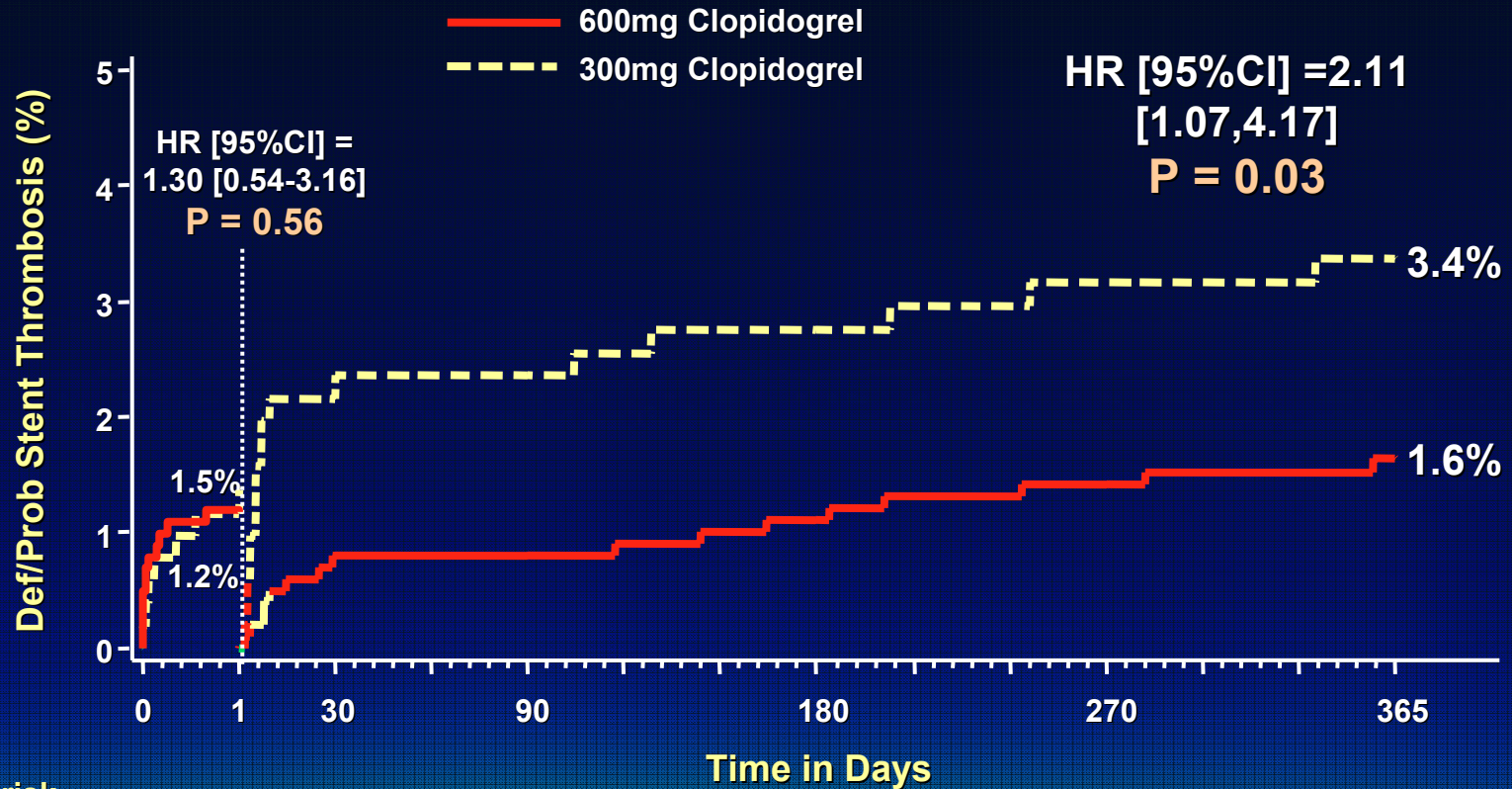
Stent Thrombosis 1-Day Landmark Analysis:
Impact of Clopidogrel Loading (UFH+GPI)

600mg Clopidogrel
300mg Clopidogrel

HR=0.21
CI=0.01-3.88
P = 0.30

2.9%
2.8%

HR=1.08
CI= [0.57,2.05]
P = 0.81

0.4%
0%

Def/Prob Stent Thrombosis (%)

Time in Days

Number at risk	0	1	30	90	180	270	365
600 mg	1035	1034	995	977	963	951	852
300 mg	559	557	537	531	528	521	482
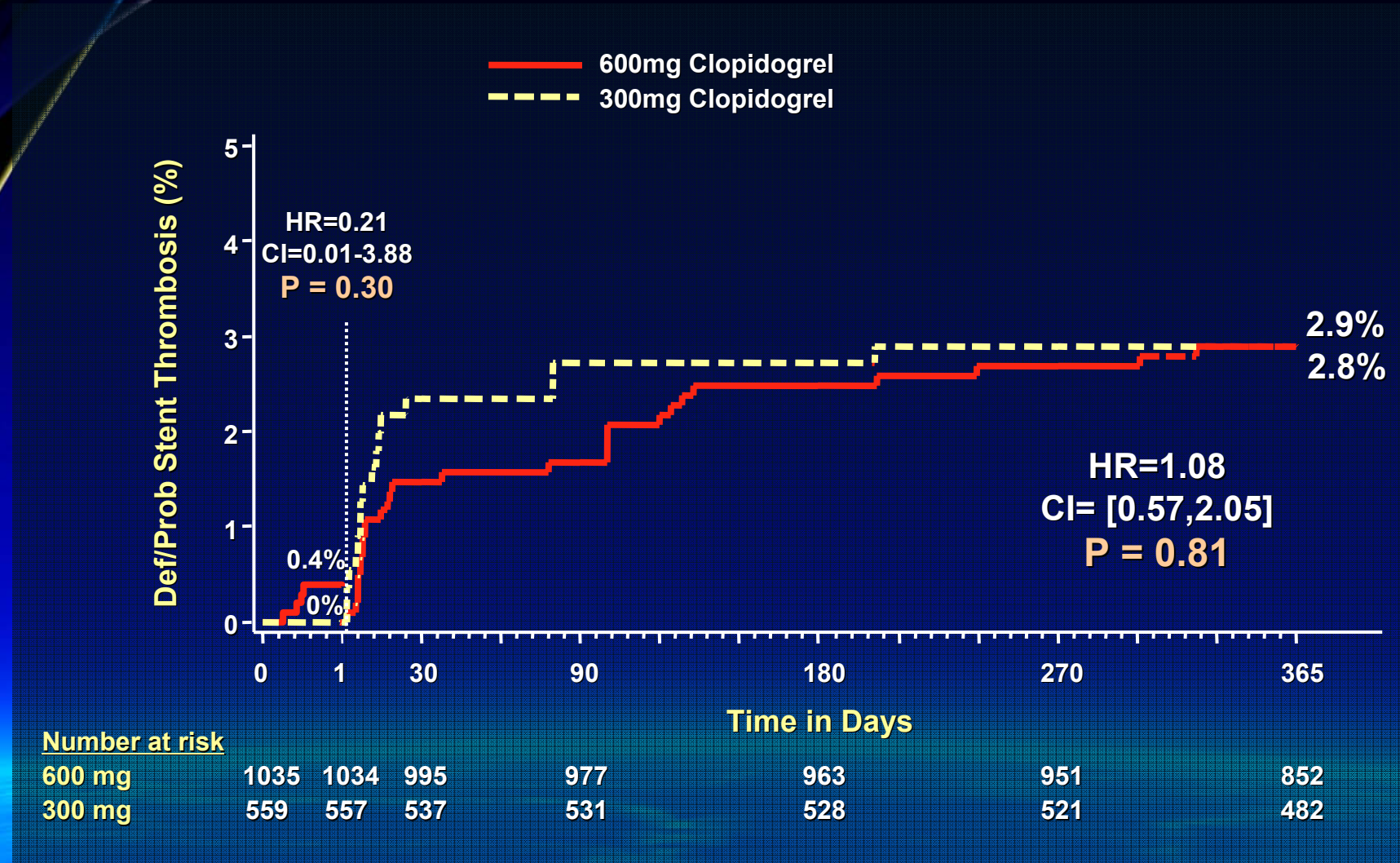
P_{int} antithrombin x clopidogrel LD = 0.16

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Angiographic Characteristics (QCA)

	ST (N=107)	No ST (N=3096)	P-Value
Target lesion vessel			
LAD	39.8%	40.2%	0.93
RCA	41.4%	43.9%	0.57
LCX	17.3%	15.0%	0.47
SVG	1.5%	0.9%	0.37
Lesion characteristics			
Eccentric	4.5%	7.0%	0.27
Bend >45 degrees	7.6%	10.0%	0.37
Thrombus	70.7%	70.4%	0.95
Thrombus area mean	31.7 [23.0,43.4]	27.4 [17.1,40.4]	0.01
Calcification: Moderate/severe	34.6%	35.1%	0.90
Ulceration	4.5%	2.3%	0.14
Aneurysm	3.8%	1.4%	0.05
Mod. ACC/AHA lesion class B2/C	87.2%	85.5%	0.58

Index PCI Procedure QCA

	ST (N=107)	No ST (N=3096)	P-Value
Baseline			
Lesion length (mm)	14.2 [10.4,20.0]	14.7 [10.2,20.3]	0.84
Baseline RVD (mm)	2.87 [2.53,3.21]	2.87 [2.53,3.22]	0.94
Pre TIMI Flow 0/1	75.7%	59.4%	0.0006
Post procedure			
Lesion MLD (mm)	2.30 [1.94,2.61]	2.34 [2.01,2.70]	0.20
Lesion DS%	20.1 [12.8,27.4]	18.4 [12.5,25.1]	0.11
Stent length	22.1 [16.5,33.1]	21.34 [16.0,28.3]	0.23
Stent overlap (mm)	3.1 [2.1,4.2]	2.8 [2.1,3.9]	0.41
Final TIMI flow 3	79.3%	88.1%	0.005

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Independent Predictors of 1-Year ST (Cox Model)

Variable	HR [95% CI]	P-value
Insulin-treated diabetes	3.42 [1.81, 6.47]	0.0002
Lesion ulceration	2.28 [0.99, 5.27]	0.05
Pre-PCI TIMI flow 0/1	2.22 [1.37, 3.61]	0.001
Current smoking	1.81 [1.20, 2.72]	0.005
Number of stents	1.31 [1.07, 1.60]	0.04
Clopidogrel loading dose 600mg	0.65 [0.44, 0.97]	0.04

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Independent Predictors of Acute ST (Cox Model)

Variable	HR [95% CI]	P-value
Pre-PCI TIMI flow 0/1	6.10 [1.43, 26.04]	0.01
Lesion ulceration	4.80 [1.41, 16.37]	0.01
Bivalirudin (v. UFH+GPI)	4.65 [1.59, 13.54]	0.005
Number of stents	1.50 [1.06, 2.12]	0.02
Pre-rand heparin	0.27 [0.12, 0.60]	0.002

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Independent Predictors of Subacute ST (Cox Model)

Variable	HR [95% CI]	P-value
Insulin-treated diabetes	4.43 [2.03, 9.65]	0.0002
History of CHF	4.16 [1.61, 10.76]	0.003
Pre-PCI TIMI flow 0/1	2.21 [1.05, 4.63]	0.04
Final TIMI flow 0/1	3.72 [1.10, 12.55]	0.03
Stent to lesion length ratio	1.44 [1.20, 1.71]	<0.0001
Clopidogrel loading dose 600 mg (vs. 300 mg)	0.49 [0.27, 0.89]	0.01

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Independent Predictors of Late ST
(Cox Model)

Variable	HR [95% CI]	P-value
Current smoking	4.05 [1.73, 9.48]	0.001
Insulin-treated diabetes	3.17 [0.95, 10.61]	0.06
History of prior MI	3.15 [1.39, 7.13]	0.006
Post stent dilation balloon used	2.75 [1.31, 5.80]	0.008

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Conclusions (1)

- **Following stent implantation in STEMI, ST occurs frequently within the first 24 hours (0.9%), between 1 and 30 days (1.6%), and between 1 month and 1 year (1.0%) – 3.3% in total by 1 year**

- **Acute, subacute and late ST appear to be related to different factors**

  - **Pharmacological therapy, vessel flow, lesion characteristics and number and length of stents are the most important predictors of acute and subacute ST events**

  - **Patient related factors including cigarette smoking and prior MI are the most important predictors of late ST events**

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Conclusions (2)

- **The type of stent implanted (DES vs. BMS) was not related to ST during any time interval up to 1-year**

- **ST within 1-year occurred with similar frequency in patients treated with UFH+GPI and bivalirudin alone**

  - **However, acute ST was more common with bivalirudin, especially within the 1st 5 hours, whereas ST tended to be less common with bivalirudin than with UFH+GPI between 24 hours and 1-year**

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Implications

- In the primary results of the HORIZONS-AMI trial, bivalirudin monotherapy resulted in less major bleeding, comparable rates of ischemia and improved survival compared to UFH+GPI at 30 days and 1-year

- The results of the present analysis suggest that optimizing adjunct pharmacology with bivalirudin during primary PCI may further improve outcomes:

    – Pre-randomization UFH attenuated the risk of acute ST

    – A 600 mg clopidogrel LD attenuated the risk of subacute ST

- Whether a prolonged bivalirudin infusion (4-6 hrs) post-PCI and/or an even more potent and rapid acting thienopyridine agent might further reduce early ST in pts with STEMI treated with bivalirudin (without increasing bleeding) warrants further study

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