Focusing on Mortality and Attributable Death Analysis in the Primary PCI STEMI Setting What Do Drug and Device Trials Teach Us?

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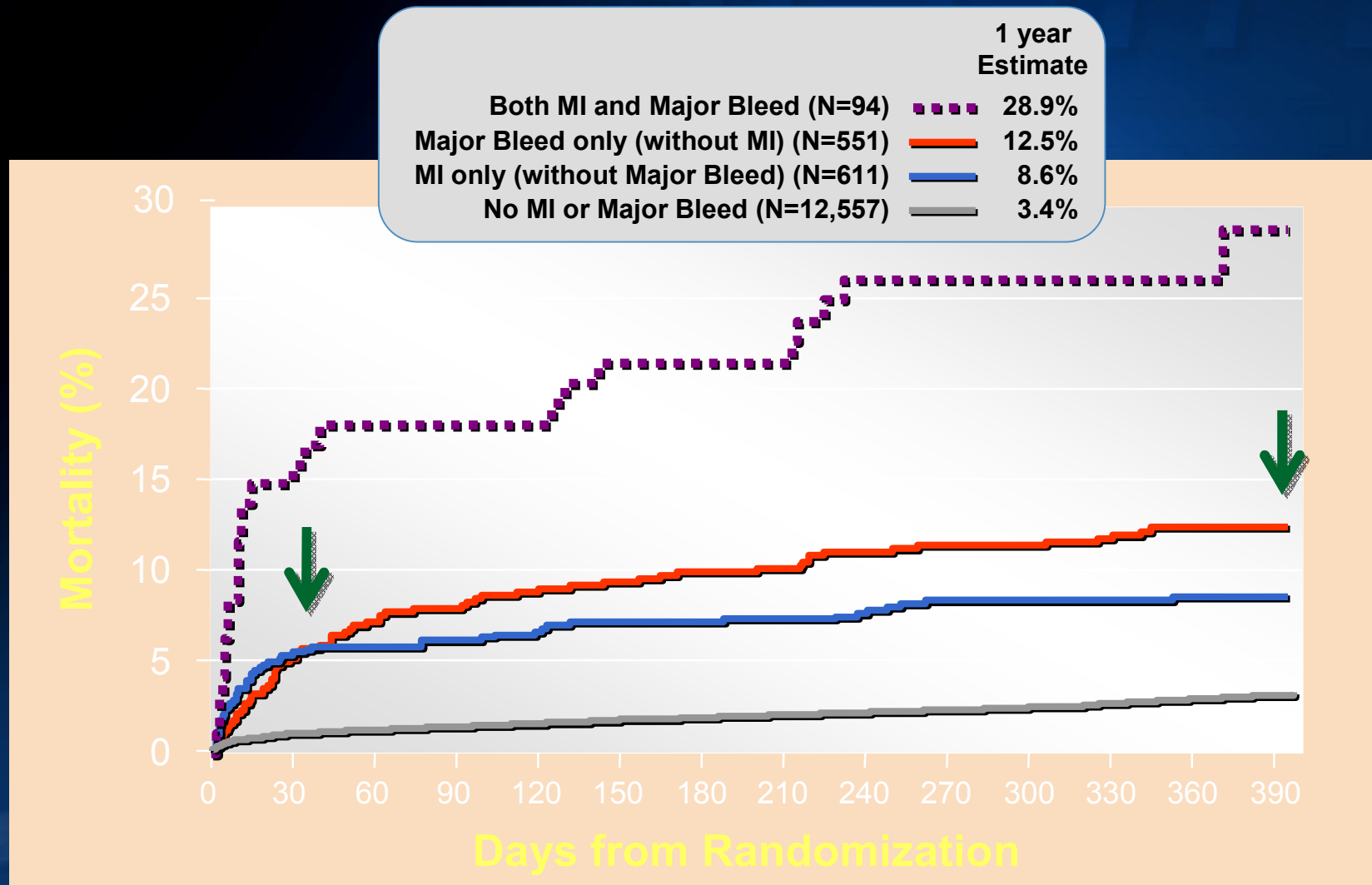CARDIOVASCULAR RESEARCH
F O U N D A T I O N

COLUMBIA UNIVERSITY
MEDICAL CENTER

Disclosures

- **Gregg W. Stone**
    - **Research support from The Medicines Company**

ACUITY: Impact of MI and Major Bleeding in the First 30 Days on Risk of Death Over 1 Year

HORIZONS: 30 Day Adverse Events

Heparin + GPIIb/IIIa inhibitor (N=1802) Bivalirudin monotherapy (N=1800)

30 day event rates (%)

Reinfarction
- Heparin + GPIIb/IIIa: 1.8
- Bivalirudin: 1.8
- P = 0.90

Major bleeding*
- Heparin + GPIIb/IIIa: 8.3
- Bivalirudin: 4.9
- P<0.001

Thrombocytopenia**
- Heparin + GPIIb/IIIa: 3.9
- Bivalirudin: 1.8
- P = 0.002
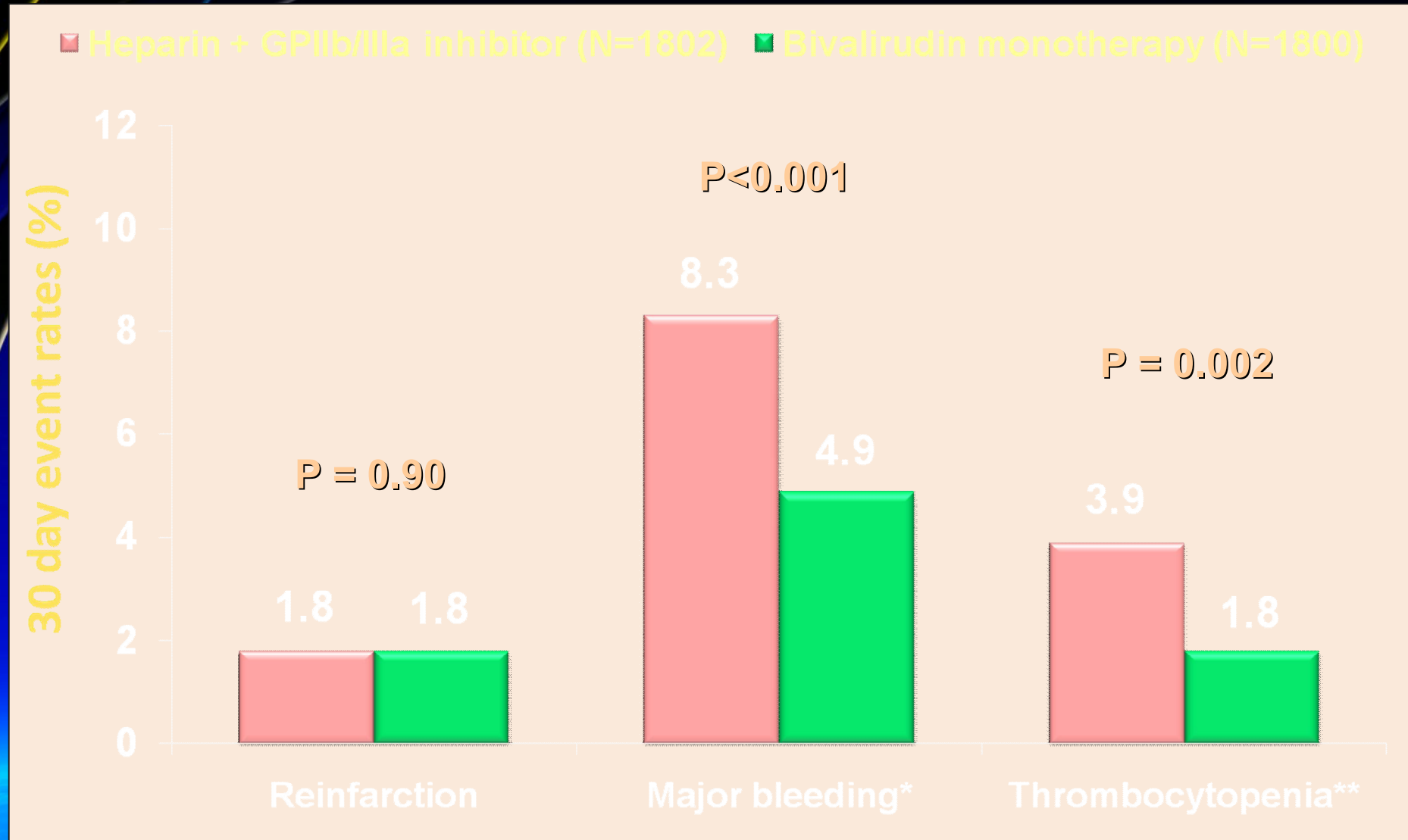
*Not related to CABG   Stone GW et al. NEJM 2008;358:2218-30
** Plat cnt <100,000 cells/mm^3

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30 Day Mortality

Heparin + GPIIb/IIIa inhibitor (n=1802)
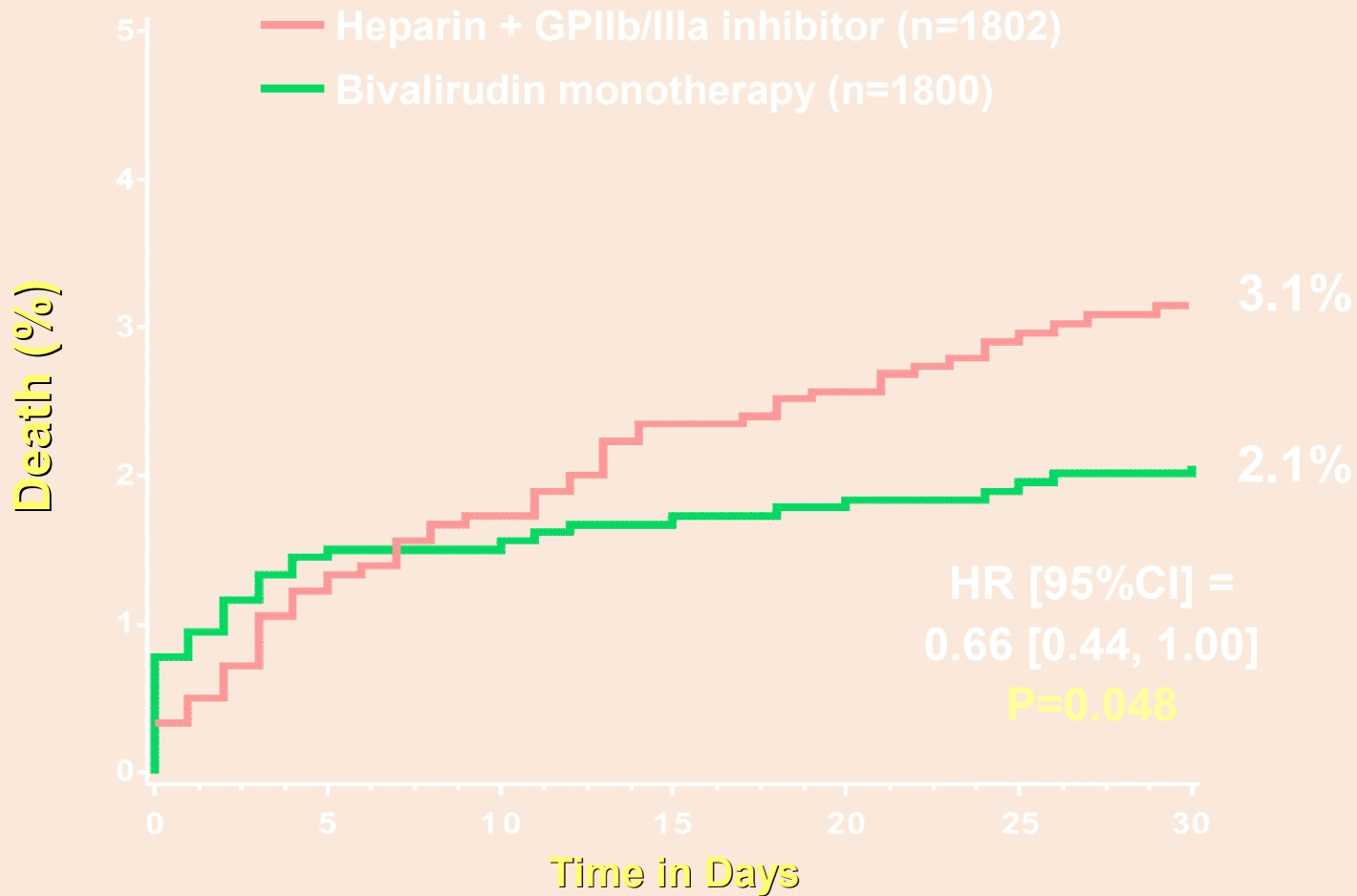Bivalirudin monotherapy (n=1800)

Death (%)

3.1%

2.1%

HR [95%CI] =
0.66 [0.44, 1.00]
P=0.048

Time in Days

Number at risk
Bivalirudin   1800   1758   1751   1746   1742   1729   1666
Heparin + GPIIb/IIIa 1802   1764   1748   1736   1728   1707   1630
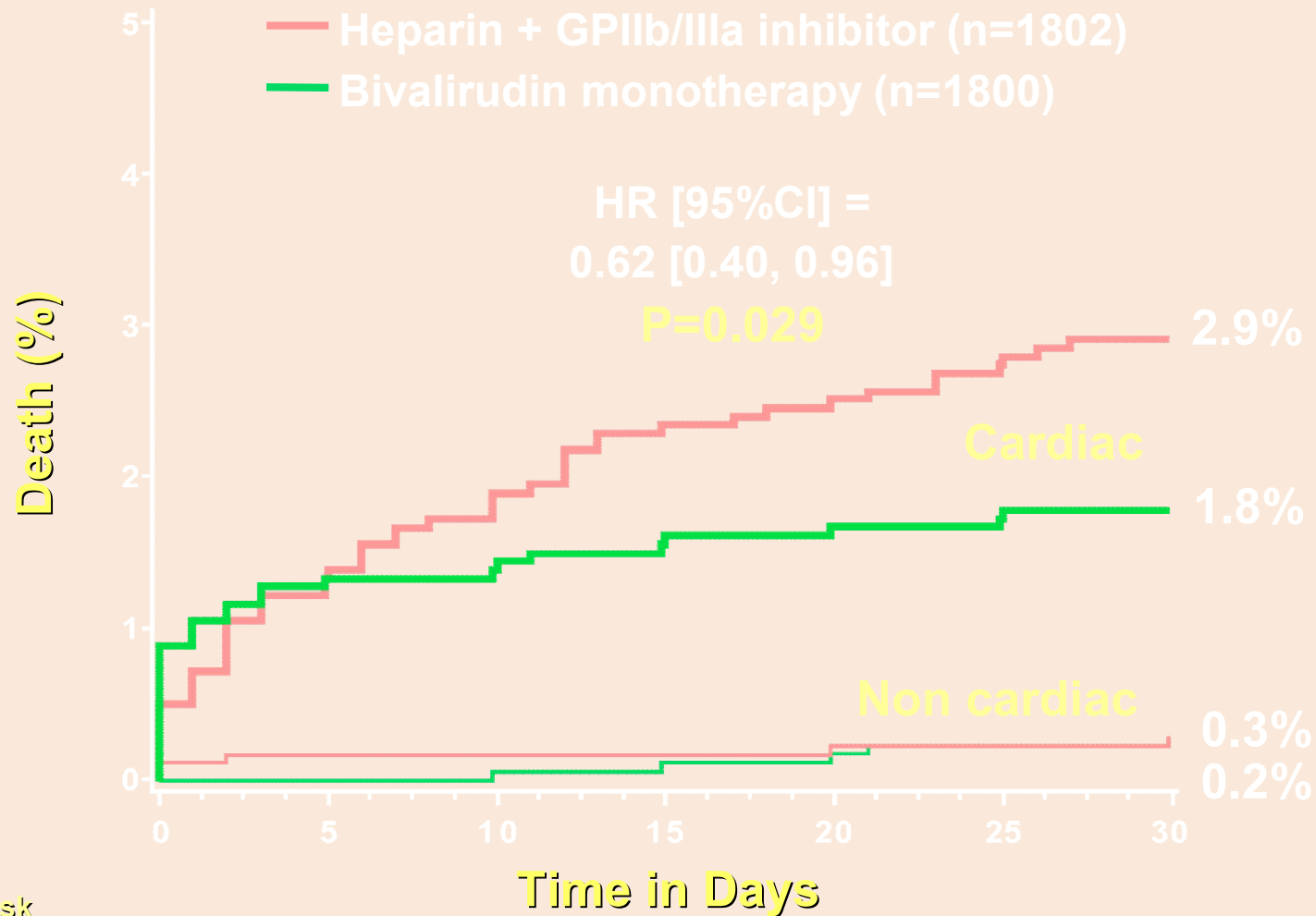
Stone GW et al. NEJM 2008;358:2218-30

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30 Day Stent Thrombosis (N=3,124)

	UFH + GP IIb/IIIa (N=1553)	Bivalirudin (N=1571)	P Value
ARC 30d definite or probable stent thrombosis*	1.9%	2.5%	0.30
- definite	1.4%	2.2%	0.09
- probable	0.5%	0.3%	0.24
- acute (≤24 hrs)	0.3%	1.3%	0.0007
- subacute (>24 hrs – 30d)	1.7%	1.2%	0.28

*Protocol definition of stent thrombosis, CEC adjudicated

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30 Day Mortality: Cardiac and Non Cardiac

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

Predictors of 30 Day Mortality
32 Candidate Baseline Variables*

Demographic: Age; sex; race; US vs. OUS; HTN, hyperlipidemia, smoking, diabetes, diabetes on insulin, MI, PCI, CABG, CAD, angina, CHF, major cardiac rhythm/rate disturbances, PVD

Medication use at home previous 5 days: aspirin, beta blocker, thienopyridines, calcium channel blocker, ACE/ARB, diuretic

Time from symptom onset to hospital ER

Physical exam: BMI; KILLIP class

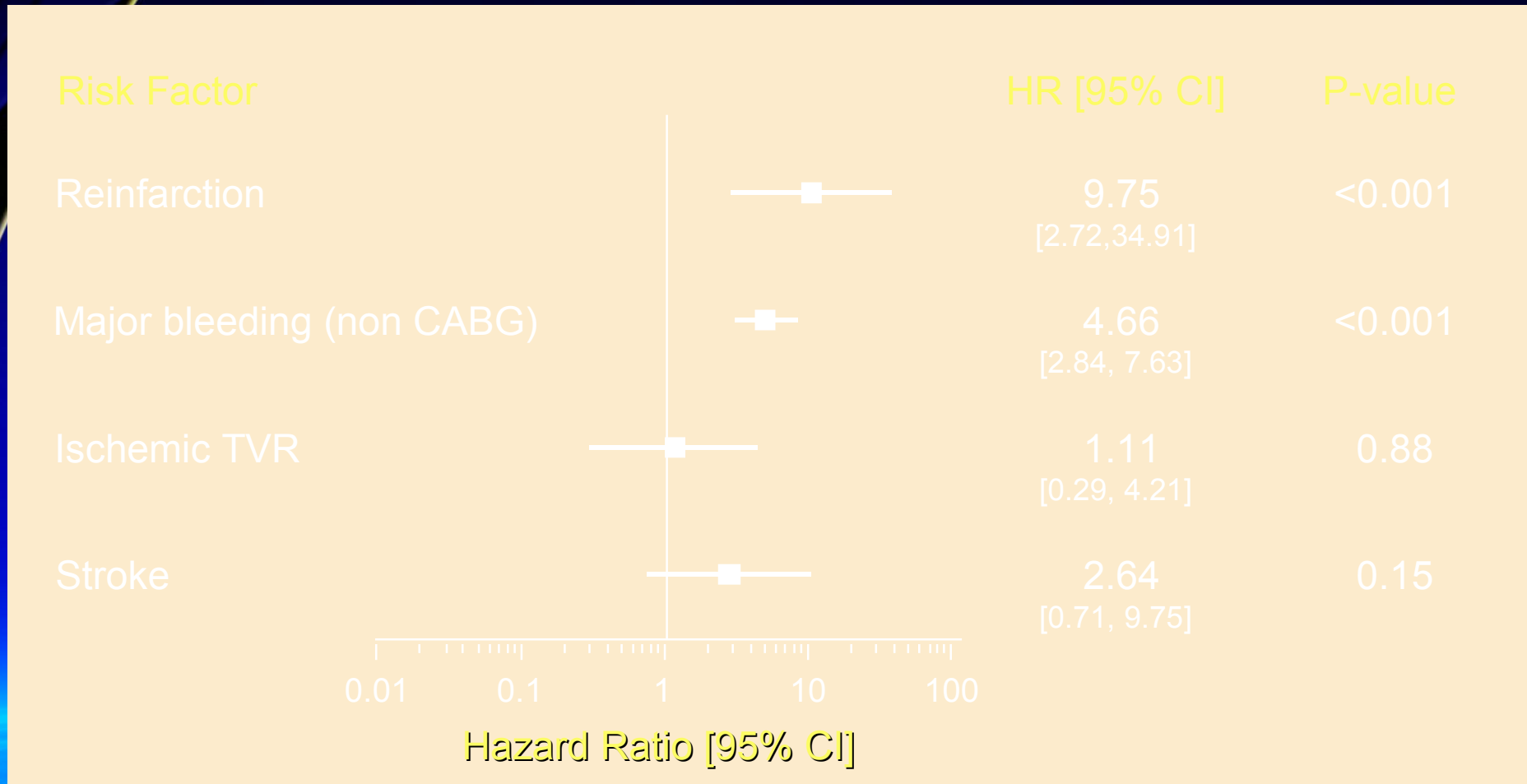**Baseline labs:** Estimated CrCl, anemia, platelet count

Medications in hospital prior to angiography: Randomized treatment (bivalirudin vs. heparin + GPI; pre-procedure heparin; clopidogrel load

* Angiographic variables not yet available;
- treatment related variables not used

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Time-updated covariate adjusted Cox model relating 30-day events to 30-day mortality
- Complete model with MACE components and major bleeding -

Risk Factor	HR [95% CI]	P-value
Reinfarction	9.75 [2.72, 34.91]	<0.001
Major bleeding (non CABG)	4.66 [2.84, 7.63]	<0.001
Ischemic TVR	1.11 [0.29, 4.21]	0.88
Stroke	2.64 [0.71, 9.75]	0.15

Hazard Ratio [95% CI]

(x-axis: 0.01 0.1 1 10 100)

C-statistic = 0.87.

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Time-updated covariate adjusted Cox model relating 30-day events to 30-day mortality
- Complete model with MACE components and major bleeding -

Risk Factor	HR [95% CI]	P-value	Attributable Deaths
Reinfarction Incidence 69 (2.2%) 10 deaths with event	9.75 [2.72, 34.91]	<0.001	9.0* [6.3, 9.7]
Major bleeding (Non CABG) Incidence 238 (6.8%) 26 deaths with event	4.66 [2.84, 7.63]	<0.001	20.4** [16.8, 22.6]

0.01   0.1   1   10   100

Hazard Ratio [95% CI]

*9.7% of 93 total deaths
**21.9% of 93 total deaths

C-statistic = 0.87. Attributable deaths = N deaths among pts with the time updated event (attribute) X (adj. HR – 1)/adj. HR

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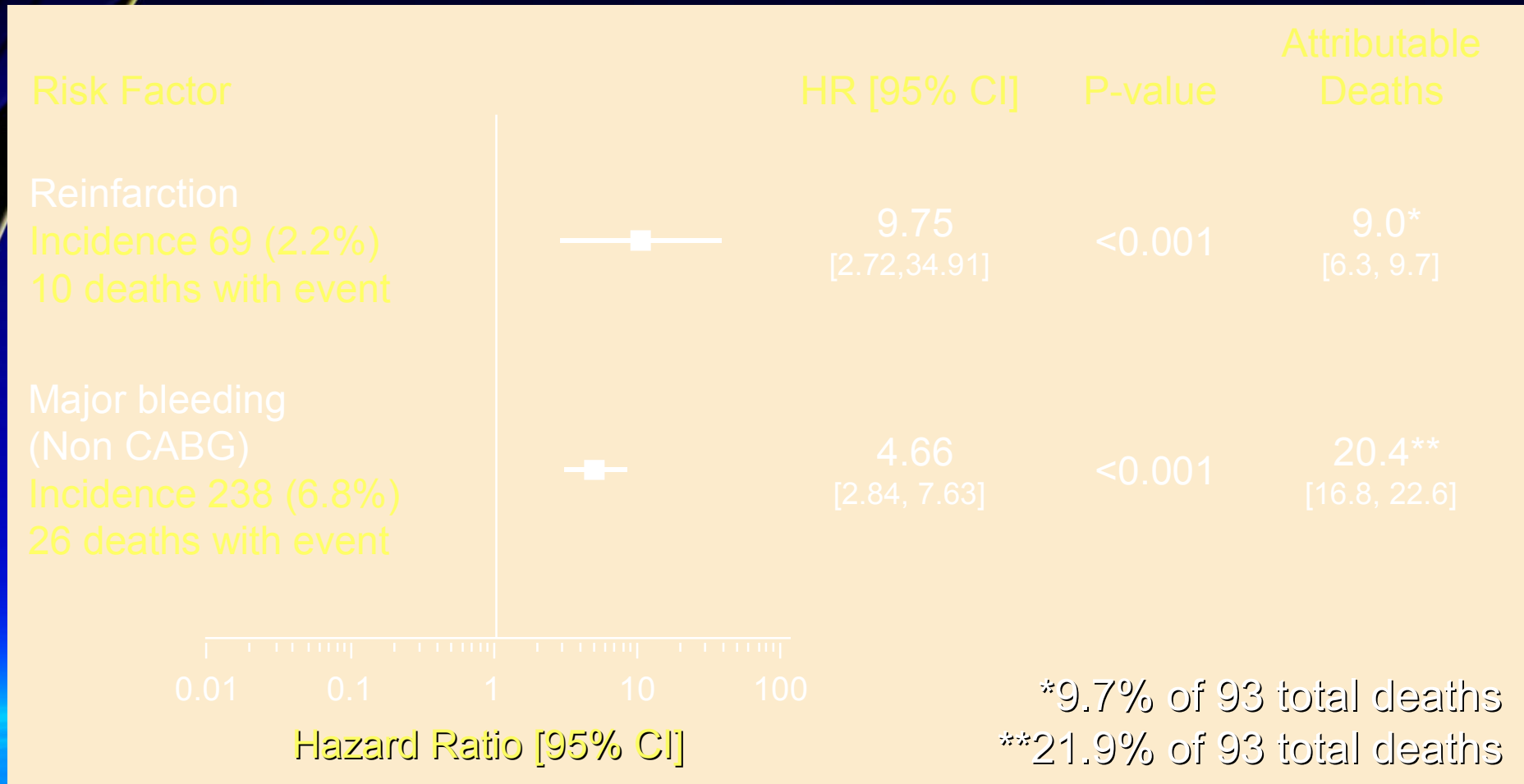
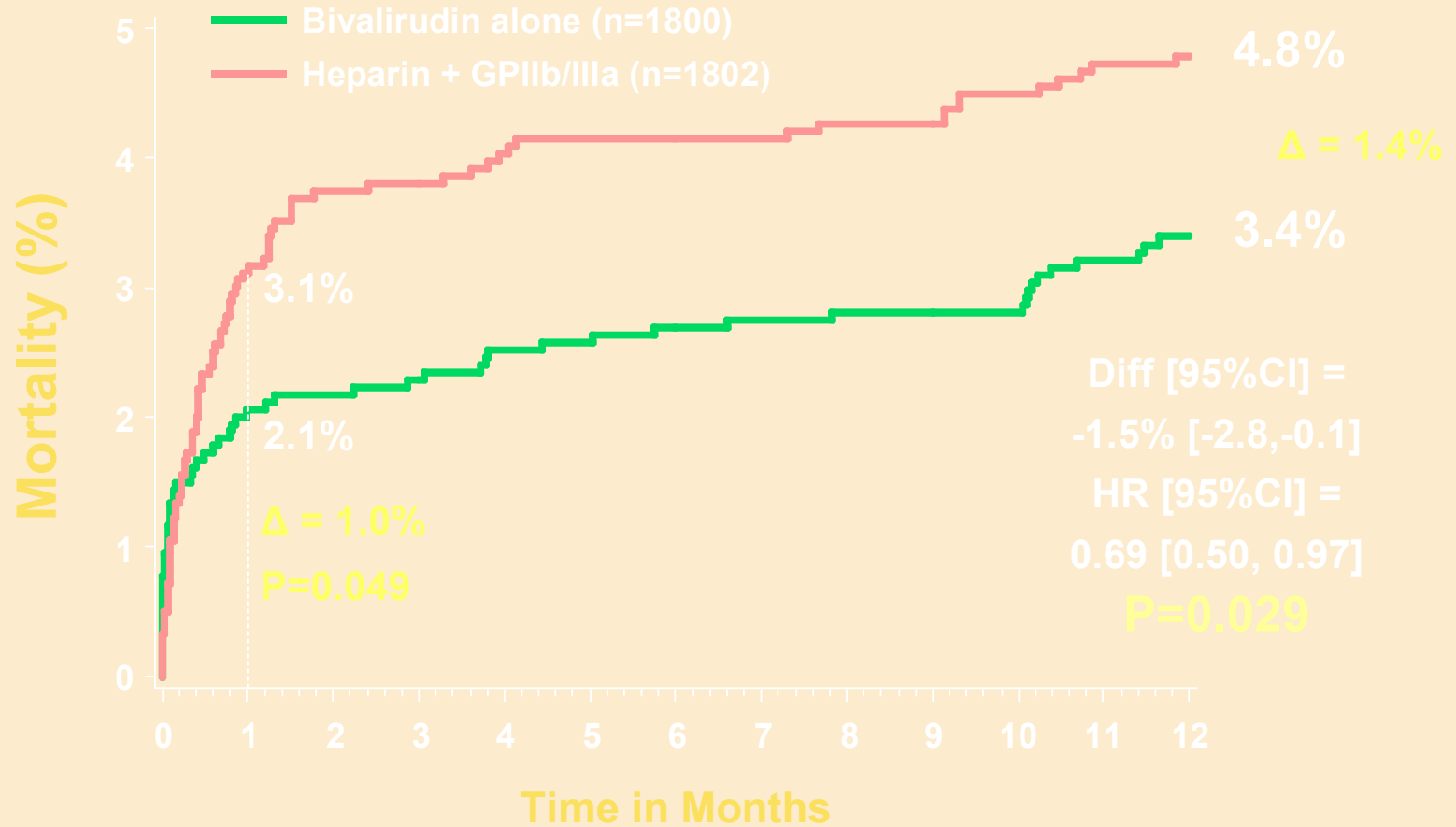# Time-updated covariate adjusted Cox model relating 30-day events to 30-day mortality

- Complete model in 3,124 pts with successfully implanted stents -
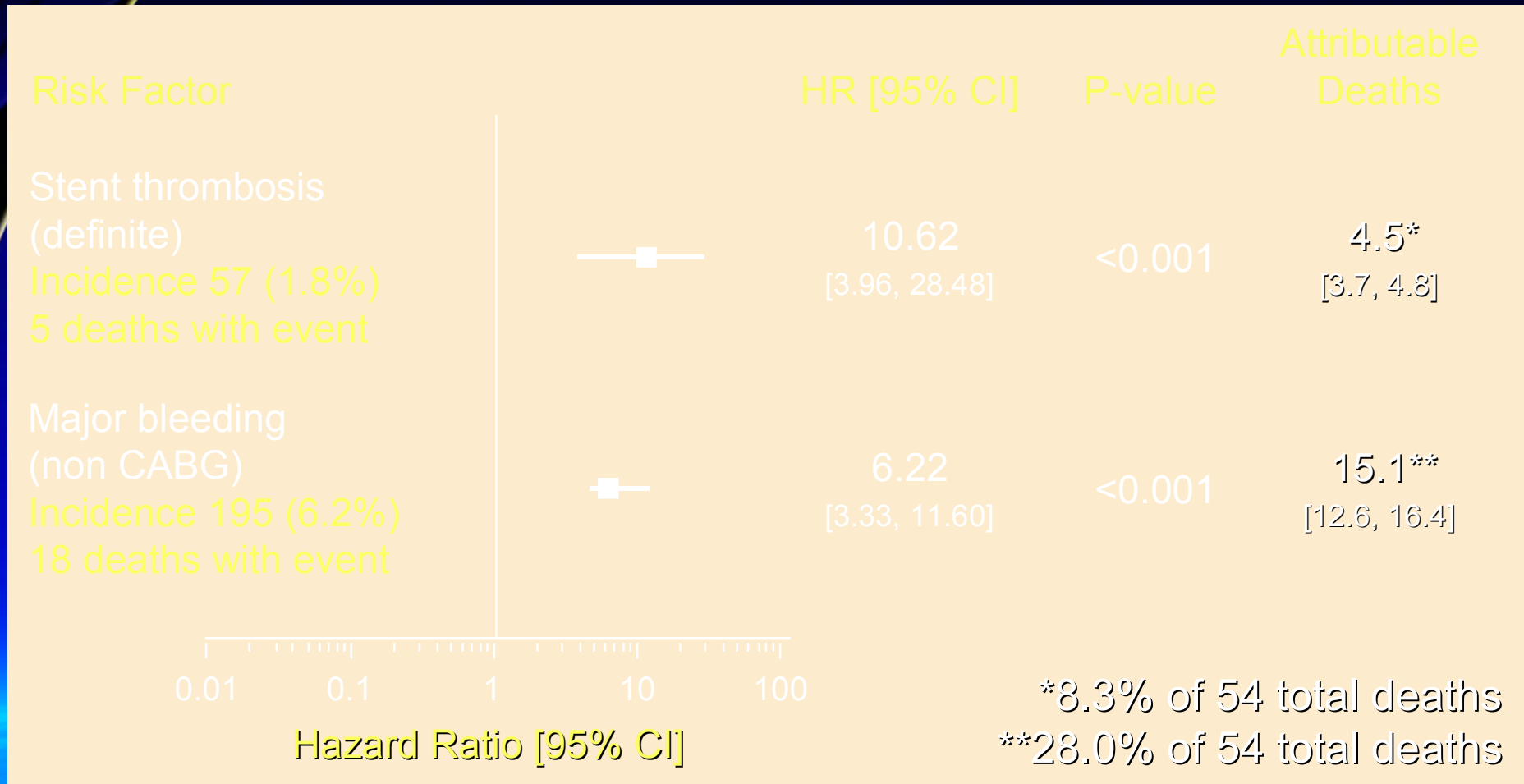
Risk Factor	HR [95% CI]	P-value	Attributable Deaths
Stent thrombosis (definite) Incidence 57 (1.8%) 5 deaths with event	10.62 [3.96, 28.48]	<0.001	4.5* [3.7, 4.8]
Major bleeding (non CABG) Incidence 195 (6.2%) 18 deaths with event	6.22 [3.33, 11.60]	<0.001	15.1** [12.6, 16.4]

0.01   0.1   1   10   100

Hazard Ratio [95% CI]

*8.3% of 54 total deaths
**28.0% of 54 total deaths

C-statistic = 0.87. Attributable deaths = N deaths among pts with the time updated event (attribute) X (adj. HR – 1)/adj. HR

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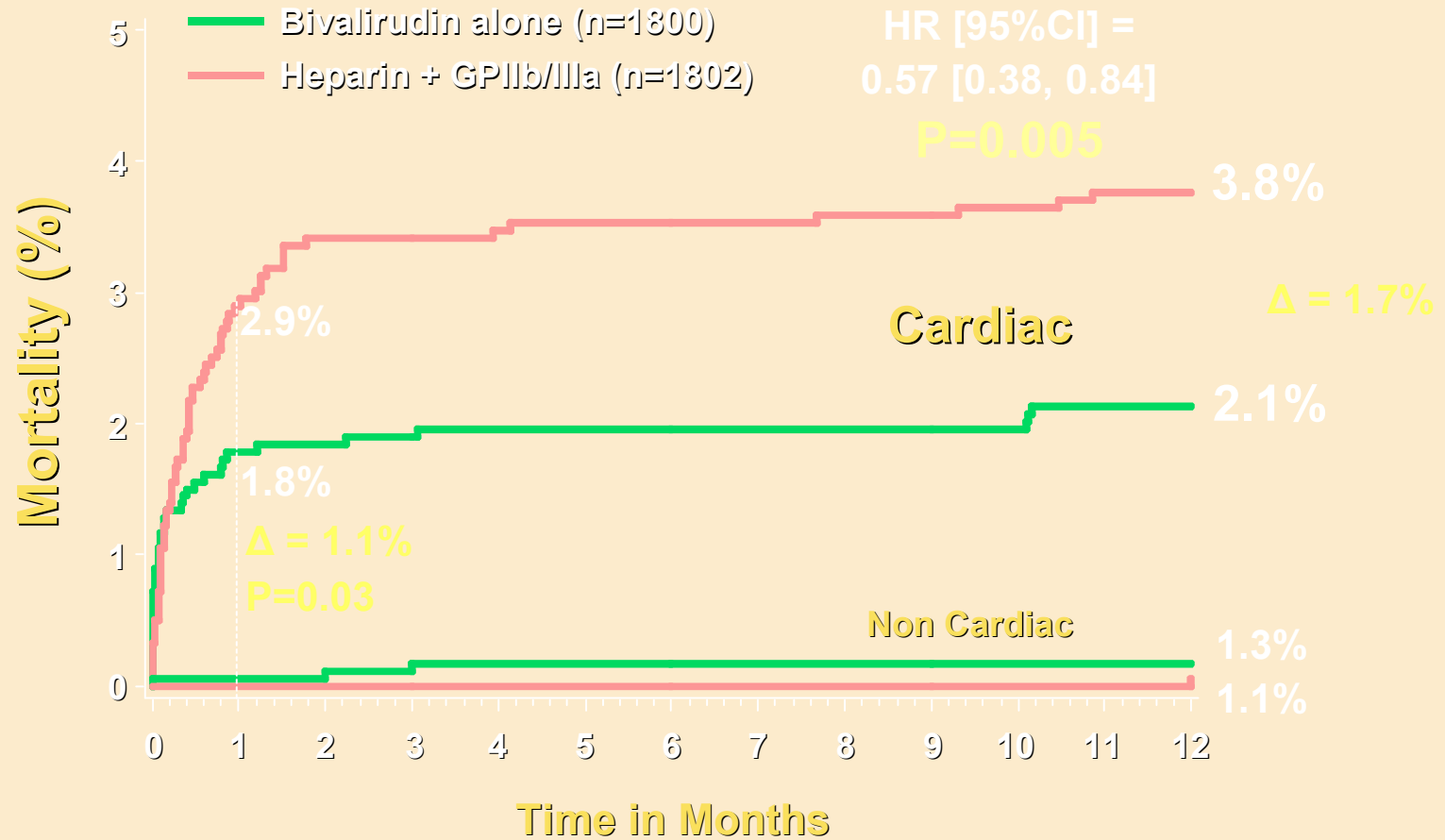# 1-Year All-Cause Mortality

1-Year MACE Components*

	UFH + GPI (N=1802)	Bivalirudin (N=1800)	HR [95%CI]	P Value
Death	4.8%	3.4%	0.69 [0.50,0.97]	**0.029**
- Cardiac	3.8%	2.1%	0.57 [0.38,0.84]	**0.005**
- Non cardiac	1.1%	1.3%	1.14 [0.62,2.11]	0.67
Reinfarction	4.4%	3.6%	0.81 [0.58,1.14]	0.22
- Q-wave	2.1%	2.2%	1.06 [0.67,1.67]	0.81
- Non Q-wave	2.7%	1.4%	0.53 [0.32,0.86]	**0.01**
Death or reinfarction	8.5%	6.6%	0.77 [0.61,0.98]	**0.04**
Ischemic TVR	5.9%	7.2%	1.23 [0.94,1.60]	0.12
- Ischemic TLR	4.5%	6.0%	1.34 [1.00,1.80]	0.051
- Ischemic remote TVR	2.0%	2.3%	1.13 [0.71,1.79]	0.60
Stroke	1.2%	1.1%	1.00 [0.54,1.85]	0.99

*All Kaplan-Meier estimates, CEC adjudicated

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Adverse Events Between 30 Days and 1-Year

	UFH + GPI (N=1802)	Bivalirudin (N=1800)	P Value
Death	1.8%	1.4%	0.31
- Cardiac	0.9%	0.4%	**0.046**
- Non cardiac	0.9%	1.0%	0.75
Reinfarction	2.8%	1.7%	**0.04**
Death or reinfarction	4.4%	3.0%	**0.02**
Ischemic TVR	4.3%	4.7%	0.57
Stroke	0.5%	0.4%	0.77
MACE	7.3%	6.8%	0.52
Major bleeding (non CABG)	0.7%	0.8%	0.71
NACE	7.8%	7.3%	0.52

*Kaplan-Meier estimates, landmark analysis, CEC adjudicated

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1-Year Stent Thrombosis (ARC Definite/Probable)

Stent Thrombosis (%) vs Time in Months

- Bivalirudin alone (n=1611)
- Heparin + GPIIb/IIIa (n=1591)

Δ = 0.3%

3.5%
3.2%

2.7%

2.2%

Δ = 0.5%
P=0.31

HR [95%CI] =
1.11 [0.76, 1.63]
P=0.59
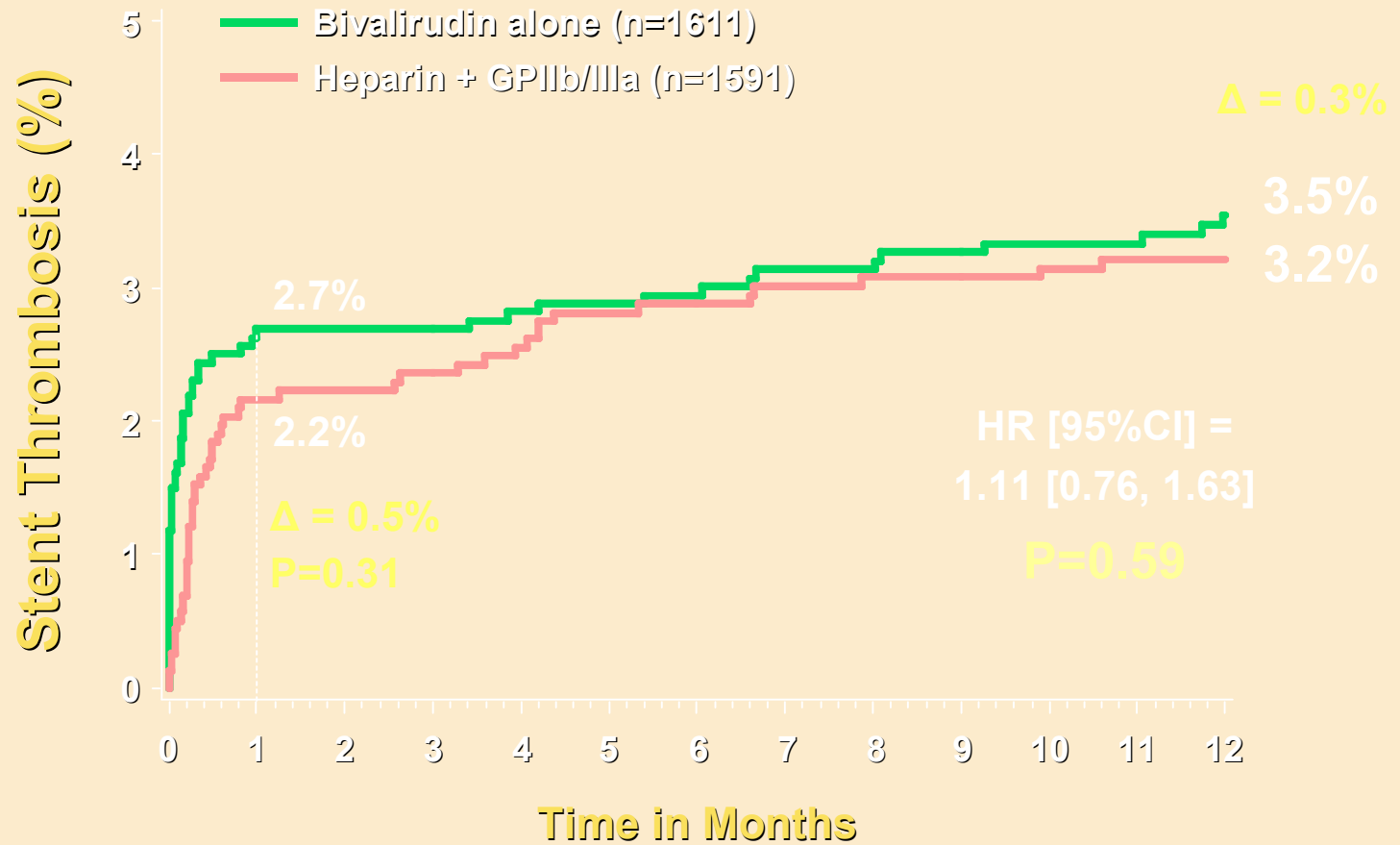
Number at risk

Bivalirudin alone	1611	1525	1504	1486	1356
Heparin+GPIIb/IIIa	1591	1495	1475	1457	1315

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Conclusions

– In this large scale, prospective, randomized trial of pts with STEMI undergoing a primary PCI management strategy, bivalirudin monotherapy compared to UFH plus the routine use of GP IIb/IIIa inhibitors resulted in:

– **Significant 31% and 43% reductions in the 1-year rates of all-cause and cardiac mortality (absolute 1.4% and 1.7% reductions)**, with non significantly different rates of reinfarction, stent thrombosis, stroke and TVR at 1-year

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Clinical Implications

– HORIZONS has demonstrated that the prevention of hemorrhagic complications after primary PCI in STEMI results in improved early and late survival

– Optimal drug selection and technique to minimize bleeding are essential to enhance outcomes for pts undergoing interventional therapies

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