Individual Patient Data Pooled Analysis of Randomized Trials of Bivalirudin Versus Heparin in Acute Myocardial Infarction

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On behalf of

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Disclosures

Speaker honoraria from Cook; Consultant to Valfix, TherOx, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, Abiomed, Ancora, Vectorious, Cardiomech; Equity/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix

Relevant disclosures

None

Background

- Individual RCTs of periprocedural anticoagulation with bivalirudin versus heparin during PCI in AMI have reported conflicting results
- Study-level meta-analyses lack granularity to adjust for confounders, explore heterogeneity, or identify subgroups that may particularly benefit or be harmed

Objective

- We therefore performed an individual patient data pooled analysis of all the major RCTs comparing bivalirudin versus heparin to determine the optimal anticoagulant to be used during PCI in patients with AMI

Methods

- A systematic review identified all RCTs in which ≥1000 pts with AMI (STEMI or biomarker + NSTEMI) undergoing PCI were assigned to bivalirudin without routine GPI (± post-PCI bivalirudin infusion) vs. heparin (UFH or LMWH, ± routine GPI)
- The PI from each trial sent de-identified raw data to be pooled into a database at the Cardiovascular Research Foundation in NY
- Data accuracy was validated against all published reports with discrepancies addressed by consulting with the trialists; consensus-based definitions were created to resolve differing antithrombotic, procedural, and outcome definitions; a pre-specified statistical analysis plan was published before data unblinding*
- The study was performed according to the PRISMA-IPD statement, was registered at PROSPERO and required 3.5 years to complete

*Bikdeli B et al. Thromb Haemost. 2020;120:348-62

Methods

- The primary analysis population was pts in whom PCI was attempted as first treatment (modified ITT)
- The primary effectiveness outcome was mortality at 30 days
- The primary safety outcome was serious bleeding at 30 days
  - Defined as TIMI major or minor (if available); BARC type 3 or 5 otherwise

*Bikdeli B et al. Thromb Haemost. 2020;120:348-62

Methods

- Outcomes are reported from Cox models adjusted for age, sex, weight, recent smoker, diabetes mellitus, hypertension, previous MI, presentation (STEMI vs. NSTEMI), access site, serum creatinine, pre-Rx with heparin, pre-Rx with a P2Y12 inhibitor (clopidogrel/ticlopidine vs. prasugrel/ticagrelor vs. none) and study as a random effect
- Heterogeneity was assessed and identified in pts with STEMI vs. NSTEMI; outcomes in these two groups are reported separately
- Models were further adjusted for:
  - Randomized planned vs. unplanned GPI use in the heparin arm
  - Randomized planned vs. unplanned post-PCI bivalirudin infusion (and its dose)

*Bikdeli B et al. Thromb Haemost. 2020;120:348-62

Study Screening

738 citations were identified from PubMed search

→

29 RCTs of bivalirudin vs. heparin were considered for inclusion

→

8 RCTs selected for the pooled analysis (N=38,565 pts at 832 sites)

- ACUITY
- BRIGHT
- EUROMAX
- HEAT-PPCI
- HORIZONS-AMI
- ISAR-REACT 4
- MATRIX
- VALIDATE-SWEDEHEART

↓

21 RCTs were excluded

- <1000 pts (n=18)
- >1000 pts total, but <1000 MI pts (n=3)

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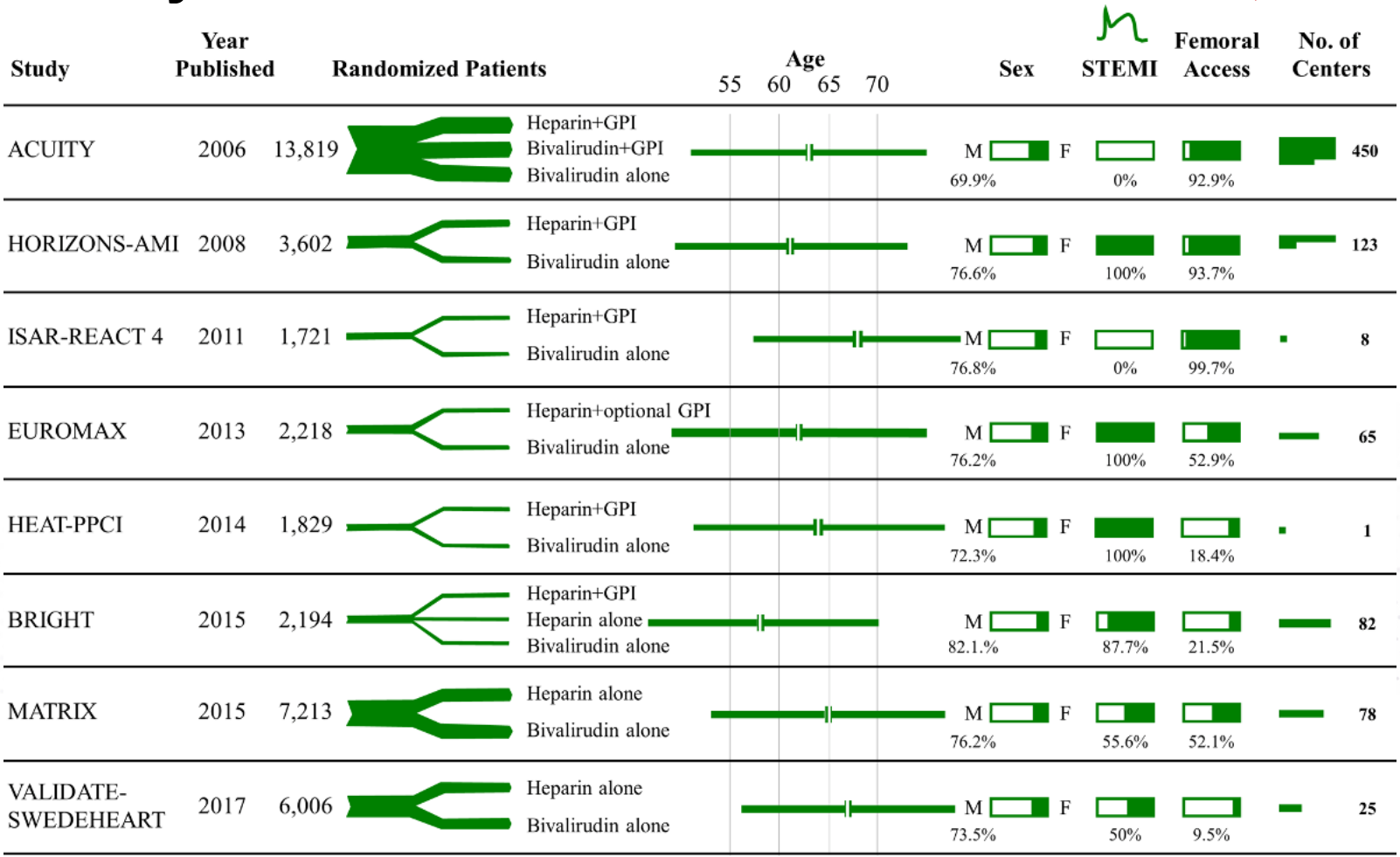
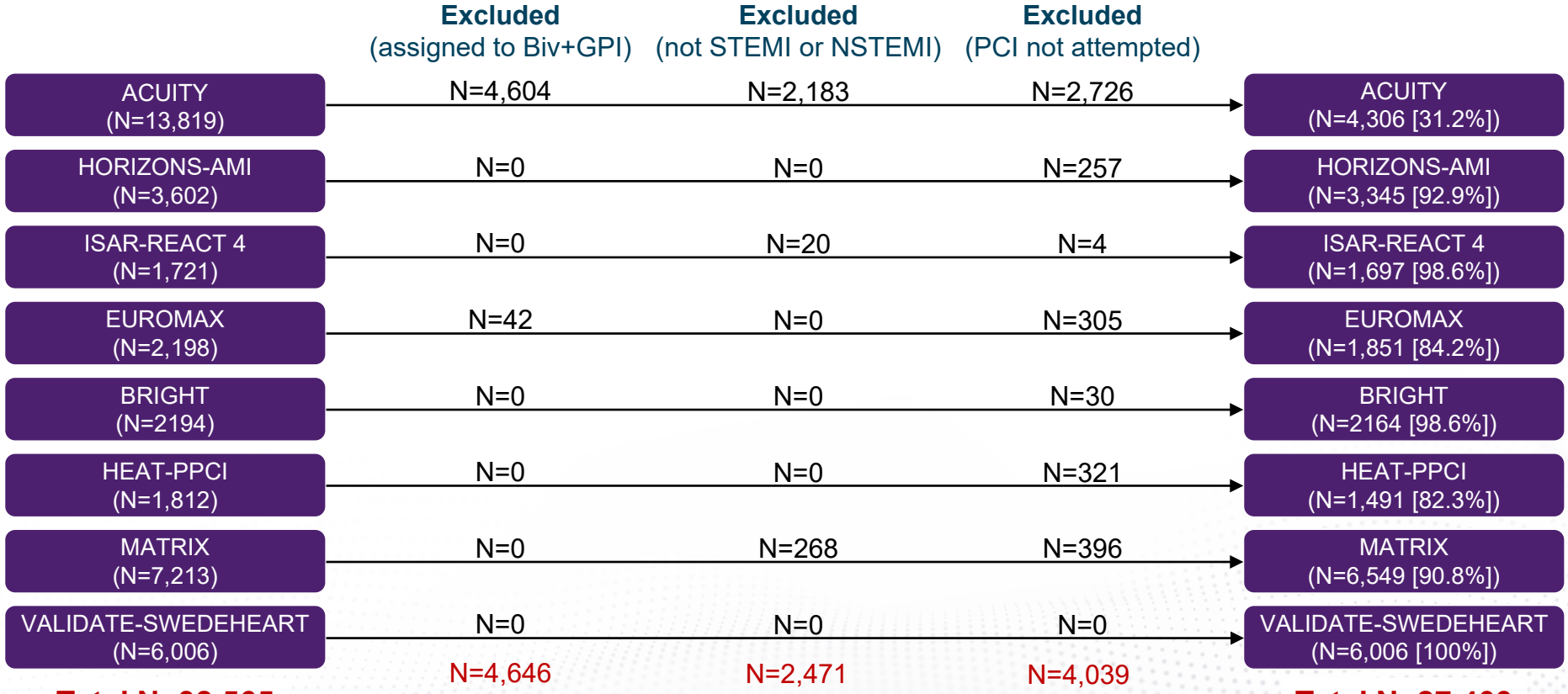
No studies excluded

*Bikdeli B et al. Thromb Haemost. 2020;120:348-62

Study Characteristics of the 8 Trials: N=38,565



mITT Patient Population Selection: N=27,409



Baseline Characteristics

	Bivalirudin (n=13,346)	Heparin (n=14,063)
Age (yrs, median [Q1, Q3])	64.0 [55.0, 73.0]	64.0 [55.0, 73.0]
Sex, female	24.2% (3227/13,342)	23.9% (3365/14,059)
Region		
Europe	81.4% (10860/13,346)	77.6% (10910/14,063)
North America	11.6% (1554/13,346)	10.8% (1521/14,063)
- United States	11.1% (1481/13,346)	10.3% (1443/14,063)
- Canada	0.5% (73/13,346)	0.6% (78/14,063)
Asia (China)	5.4% (723/13,346)	10.2% (1441/14,063)
Australia or New Zealand	0.8% (110/13,346)	0.7% (95/14,063)
South America (Argentina)	0.7% (99/13,346)	0.7% (96/14,063)

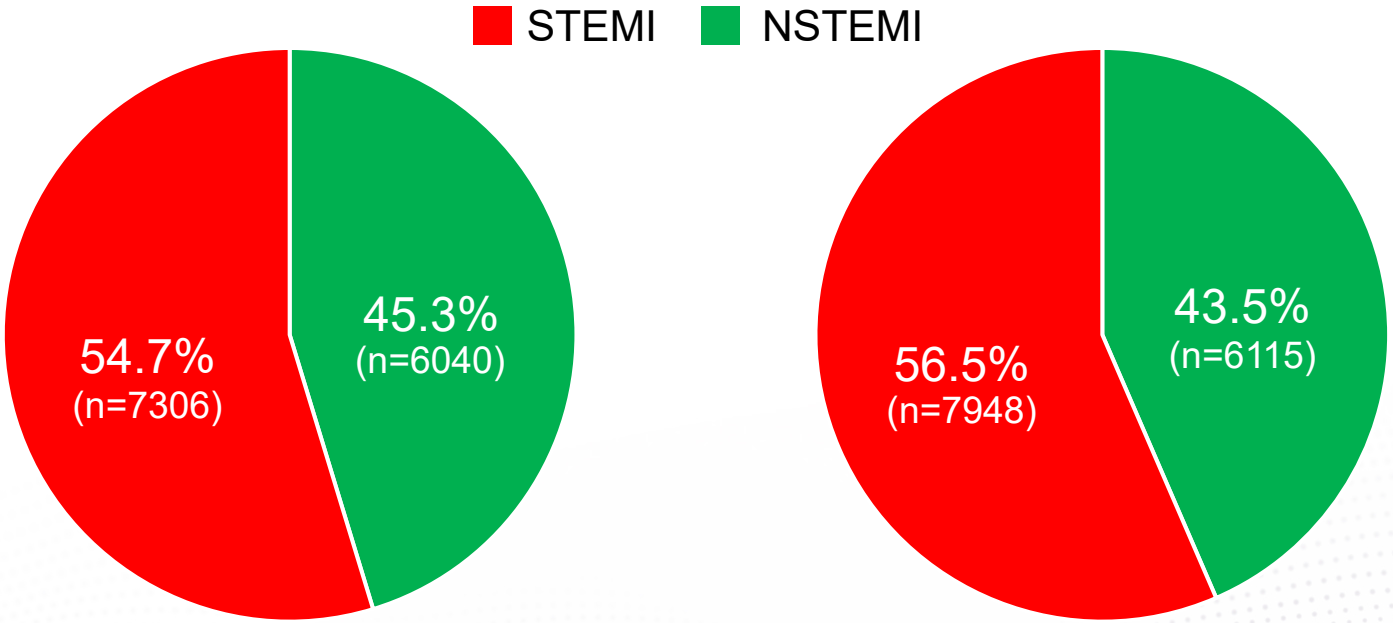
P=NS for all

Baseline Characteristics

	Bivalirudin (n=13,346)	Heparin (n=14,063)
Diabetes mellitus	19.7% (2619/13,310)	20.2% (2828/14,018)
Recent smoker	36.6% (4809/13,131)	37.6% (5191/13,821)
Hypertension	56.4% (7509/13,309)	56.2% (7871/14,014)
Hyperlipidemia	42.9% (5658/13,201)	42.6% (5927/13,921)
Previous MI	15.5% (2061/13,261)	15.2% (2115/13,954)
Previous PCI	16.8% (2232/13,318)	15.8% (2212/14,034)
Previous CABG	5.7% (765/13,332)	5.1% (717/14,050)
Previous stroke	5.3% (477/9076)	5.2% (512/9762)
Peripheral vascular disease	5.8% (330/5659)	5.2% (329/6371)
COPD	5.0% (199/3989)	4.4% (209/4724)
Body mass index (kg/m^2)	27.0 [25.0, 30.0]	27.0 [24.0, 30.0]

P=NS for all

Clinical Presentation



Bivalirudin (n=13,346)

Heparin (n=14,063)

P=NS for all

Baseline Laboratory Findings

	Bivalirudin (n=13,346)	Heparin (n=14,063)
Hemoglobin (g/dL)	14.3 [13.1, 15.3]	14.2 [13.1, 15.2]
Hematocrit (%)	42.0 [39.0, 45.0]	42.0 [39.0, 45.0]
White blood cell count (cells/mL)	9.5 [7.5, 12.0]	9.4 [7.6, 12.0]
Platelet count (x10^9/L)	226.0 [188.0, 270.0]	225.0 [189.0, 269.0]
Creatinine clearance (mL/min)*	85.3 [65.7, 108.5]	85.6 [65.9, 108.6]
C-reactive protein (mg/dL)	5.00 [1.90, 15.00]	5.00 [1.81, 14.00]

*Cockcroft-Gault; P=NS for all except hgb (P=0.02)

Pharmacology Administration I

	Bivalirudin (n=13,346)	Heparin (n=14,063)
Randomized to bivalirudin		
No post-PCI infusion	41.0% (5471/13,329)	-
Post-PCI infusion	59.0% (7858/13,329)	-
- Low-dose (≤0.30 mg/kg/hr)	21.3% (1656/7781)	-
- Intermediate dose (>0.30 to <1.65 mg/kg/hr)	3.9% (300/7781)	-
- High-dose (≥1.65 mg/kg/hr)	74.9% (5825/7781)	-
- Duration (mins, median [Q1, Q3])	120 [47, 299]	-
Randomized to heparin		
Planned GPI use	-	47.8% (6719/14,063)
No planned GPI use	100% (13,346/13,346)	52.2% (7344/14,063)
- GPI administered (bailout)*	5.5% (728/13,254)	5.5% (402/7324)
All patients		
Heparin prior to cath lab**	16.7% (2223/13,329)	34.3% (4825/14,047)

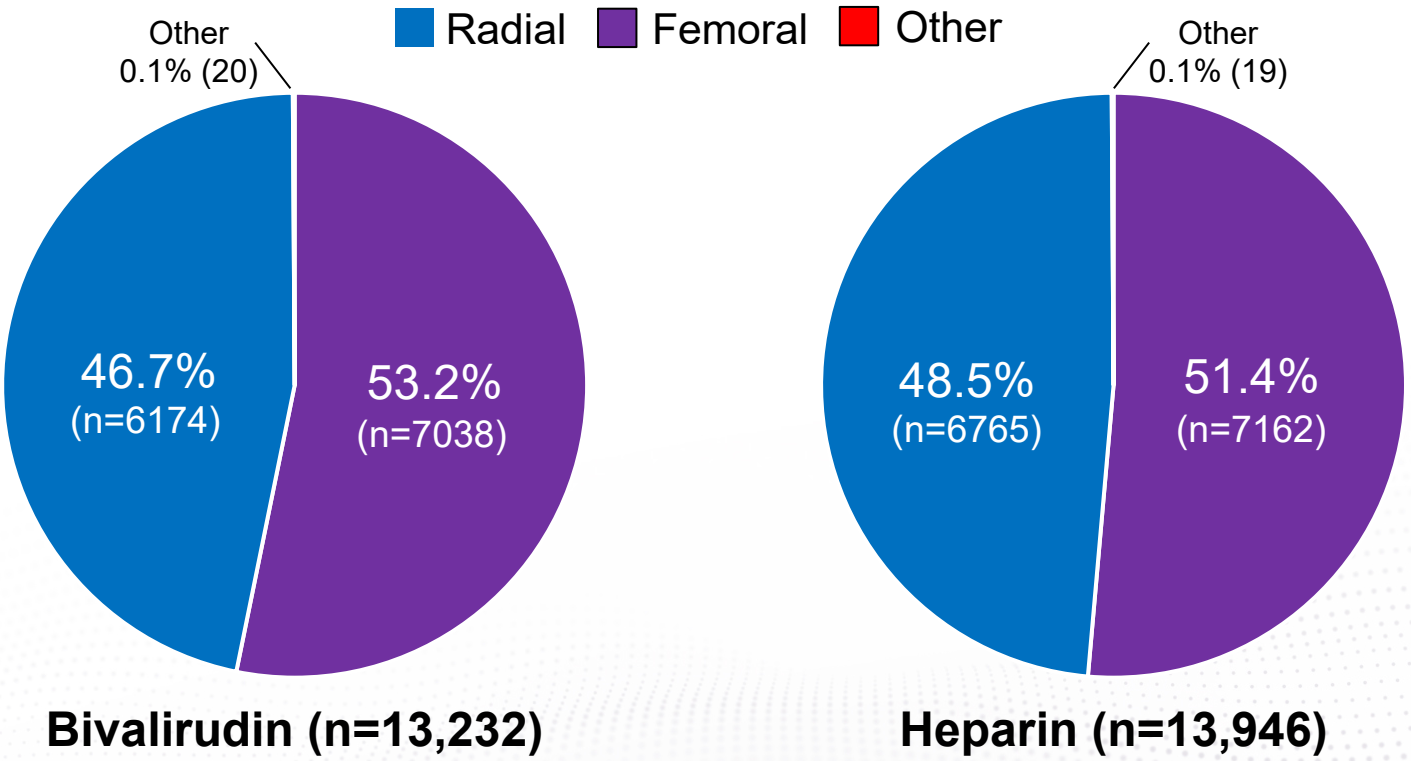
*P=NS; **P<0.0001

Pharmacology Administration II

	Bivalirudin (n=13,346)	Heparin (n=14,063)
Aspirin		
Home (pre-admission)	32.1% (3712/11,575)	29.7% (3639/12,264)
Pre-procedure	94.9% (12,644/13,317)	95.1% (13,338/14,028)
Discharge	96.7% (12,666/13,095)	96.5% (13,292/13,776)
- Dose (mg, median [Q1, Q3])	75 [75, 200]	75 [75, 200]
P2Y12 inhibitor		
Home (pre-admission)	8.3% (689/8308)	8.1% (725/8981)
Pre-procedure	83.3% (11,091/13,322)	83.9% (11,777/14,033)
- Clopidogrel or ticlopidine	49.8% (6634/13,319)	51.6% (7243/14,032)
- Prasugrel or ticagrelor	34.1% (4545/13,320)	32.9% (4617/14,032)
Discharge	95.9% (12,564/13,098)	96.0% (13,225/13,781)
- Clopidogrel or ticlopidine	54.1% (6600/12,208)	56.8% (7299/12,853)
- Prasugrel or ticagrelor	41.8% (5109/12,208)	39.2% (5041/12,853)

P=NS for all except baseline aspirin (P=0.006)

Access Site



Bivalirudin (n=13,232)

Heparin (n=13,946)

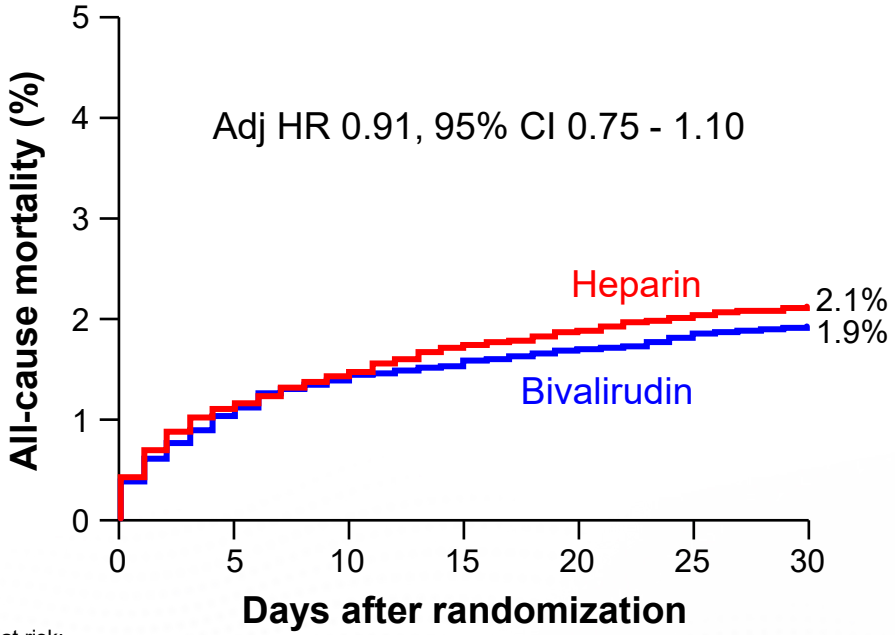
P=NS for all

PCI Procedure

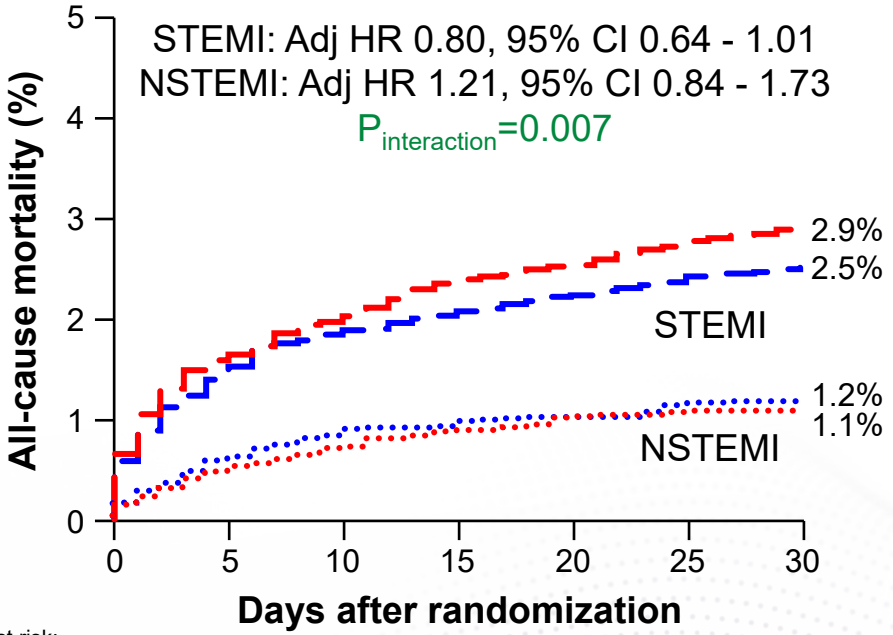
	Bivalirudin (n=13,346)	Heparin (n=14,063)
Vessels treated		
Number (mean ± SD)	1.1 ± 0.4	1.1 ± 0.4
>1 vessel treated	13.5% (1781/13,152)	12.8% (1776/13,869)
- Left main	2.5% (328/13,091)	2.3% (316/13,795)
- LAD	47.9% (6270/13,091)	47.9% (6614/13,794)
- LCX	27.2% (3560/13,091)	26.7% (3689/13,795)
- RCA	37.3% (4878/13,091)	36.9% (5095/13,795)
- Bypass graft	1.5% (194/13,091)	1.3% (186/13,796)
Lesions treated		
Number (mean ± SD)	1.3 ± 0.6	1.3 ± 0.7
>1 lesion treated	23.0% (2141/9314)	22.8% (2264/9947)
Stent implantation		
BMS only	25.1% (2430/9696)	23.3% (2407/10,316)
DES only	70.8% (6868/9696)	72.7% (7503/10,316)
BMS and DES	4.1% (398/9696)	3.9% (406/10,316)
Number of stents (mean ± SD)	1.3 ± 0.9	1.3 ± 0.9

P=NS for all

30-Day All-cause Mortality



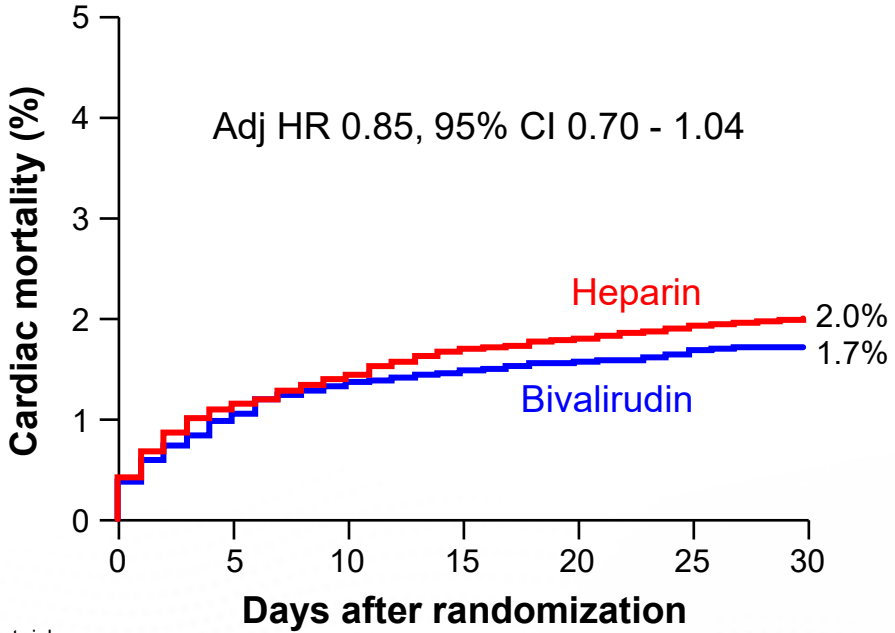
N at risk:				
Bivalirudin	13,346	13,141	13,098	13,002
Heparin	14,063	13,835	13,768	13,659



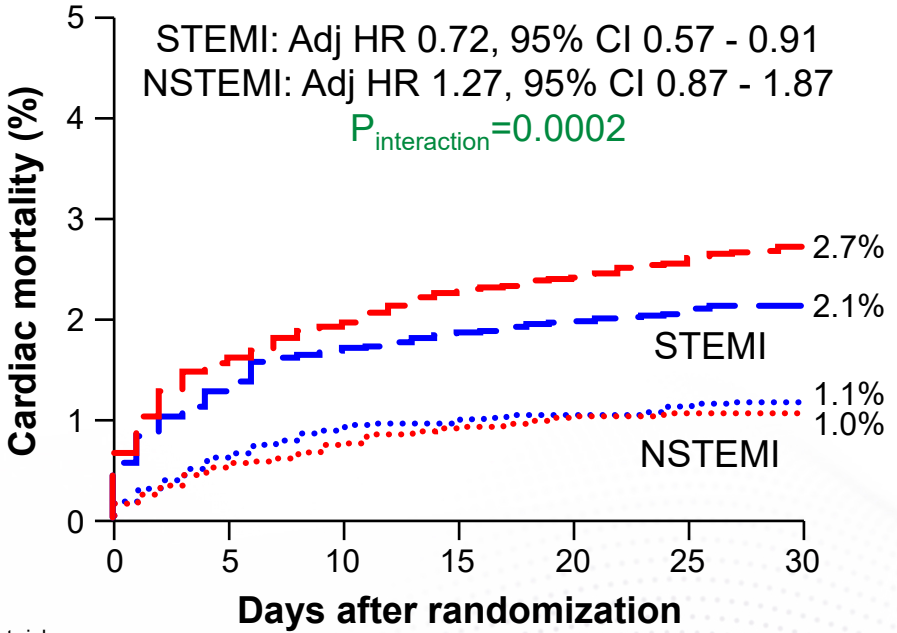
N at risk:				
STEMI - B	7,306	7,164	7,133	7,056
STEMI - H	7,948	7,775	7,728	7,631
NSTEMI - B	6,040	5,977	5,965	5,946
NSTEMI - H	6,115	6,060	6,040	6,028

30-day follow-up
Bivalirudin 13,316/13,346 (99.8%)
Heparin 14,025/14,063 (99.7%)

30-Day Cardiac Mortality



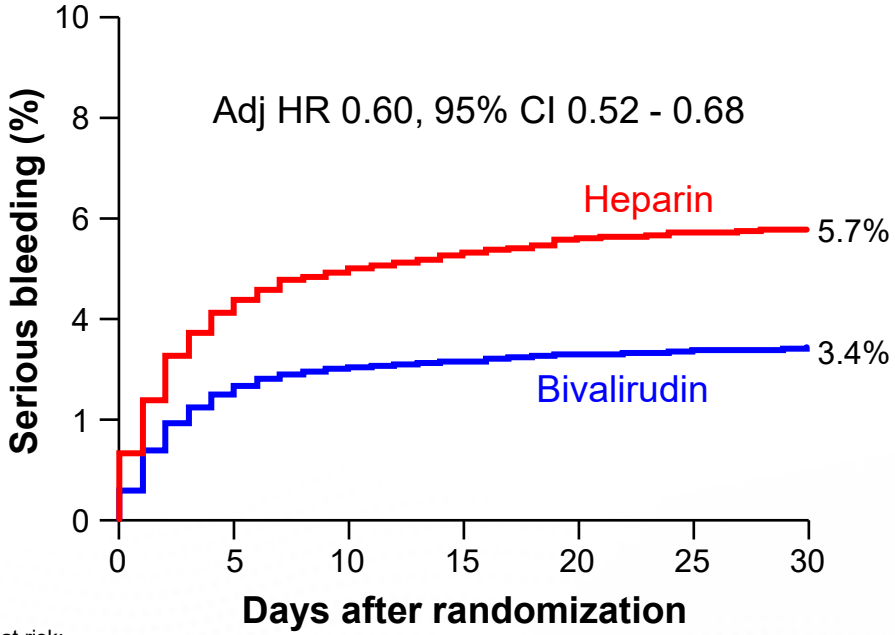
N at risk:				
Bivalirudin	13,346	13,122	13,075	12,979
Heparin	14,063	13,818	13,747	13,637



N at risk:				
STEMI - B	7,306	7,153	7,122	7,045
STEMI - H	7,948	7,768	7,718	7,621
NSTEMI - B	6,040	5,969	5,953	5,934
NSTEMI - H	6,115	6,050	6,029	6,016

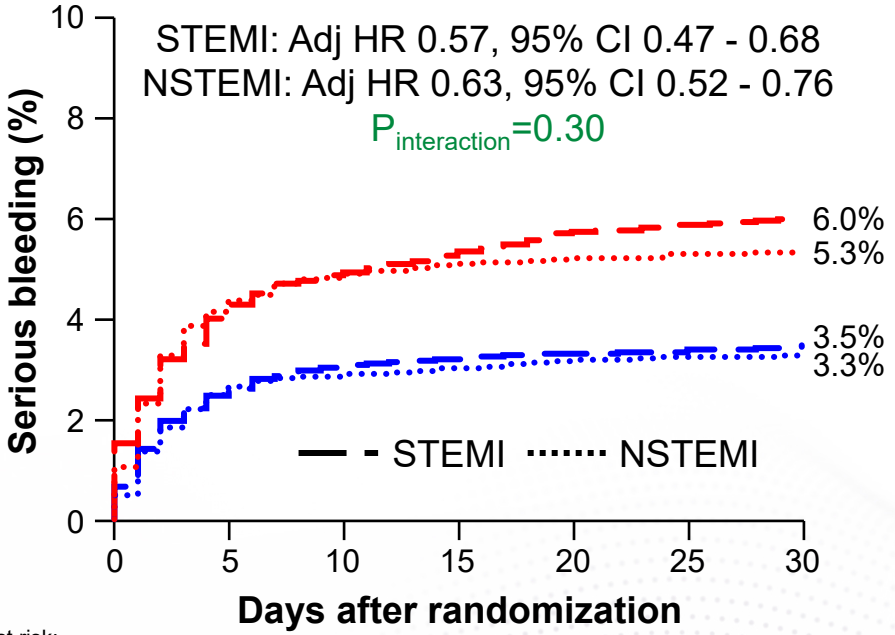
30-day follow-up
Bivalirudin 13,316/13,346 (99.8%)
Heparin 14,025/14,063 (99.7%)

30-Day Serious Bleeding



N at risk:

Bivalirudin	13,346	12,743	12,657	11,740
Heparin	14,063	13,162	13,013	12,074



N at risk:

STEMI - B	7,306	6,942	6,889	5,995
STEMI - H	7,948	7,397	7,284	6,366
NSTEMI - B	6,040	5,967	5,950	5,931
NSTEMI - H	6,115	6,046	6,025	6,012

30-day follow-up
Bivalirudin 13,316/13,346 (99.8%)
Heparin 14,025/14,063 (99.7%)

30-Day Outcomes: STEMI (n=15,254)

	Bivalirudin (n=7306)	Heparin (n=7948)	Adj HR (95% CI)
All-cause death	2.5% (179)	2.9% (228)	0.80 (0.64, 1.01)
- Cardiac death	2.1% (156)	2.7% (216)	0.72 (0.57, 0.91)
MI (reinfarction)	2.4% (171)	1.7% (135)	1.29 (1.02, 1.64)
Stent thrombosis	1.7% (126)	1.2% (93)	1.45 (1.05, 1.91)
Stroke	0.6% (40)	0.8% (61)	0.76 (0.49, 1.18)
Clinically-driven TVR	2.4% (171)	2.0% (160)	1.16 (0.92, 1.47)
MACCE	6.0% (440)	6.2% (488)	0.98 (0.85, 1.13)
Serious bleeding	3.5% (251)	6.0% (472)	0.57 (0.47, 0.68)
- Access site-related	0.7% (48)	1.3% (101)	0.45 (0.31, 0.67)
- Non-access site-related	2.8% (203)	4.7% (371)	0.61 (0.50, 0.75)
NACE	8.7% (634)	11.2% (886)	0.78 (0.70, 0.88)

MACCE = all-cause death, MI, stroke, or CD-TVR
NACE = MACCE or serious bleeding

30-Day Outcomes: NSTEMI (n=12,155)

	Bivalirudin (n=6040)	Heparin (n=6115)	Adj HR (95% CI)
All-cause death	1.2% (75)	1.1% (68)	1.21 (0.84, 1.73)
- Cardiac death	1.1% (68)	1.0% (60)	1.27 (0.87, 1.87)
MI (reinfarction)	8.0% (480)	7.9% (482)	0.98 (0.86, 1.12)
Stent thrombosis	0.9% (52)	0.9% (53)	0.91 (0.59, 1.41)
Stroke	0.5% (29)	0.4% (22)	1.41 (0.77, 2.59)
Clinically-driven TVR	1.7% (100)	1.6% (97)	0.95 (0.70, 1.30)
MACCE	10.2% (617)	9.9% (602)	1.02 (0.91, 1.15)
Serious bleeding	3.3% (198)	5.3% (325)	0.63 (0.52, 0.76)
- Access site-related	0.8% (51)	1.9% (113)	0.50 (0.35, 0.73)
- Non-access site-related	2.4% (147)	3.5% (212)	0.70 (0.56, 0.88)
NACE	12.8% (773)	14.1% (863)	0.91 (0.82, 1.01)

MACCE = all-cause death, MI, stroke, or CD-TVR
NACE = MACCE or serious bleeding

30-Day Outcomes
Models Accounting for Post-PCI Bivalirudin Infusion

All-cause Death

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin, all (± planned GPI use)	1.00 (0.75, 1.33)	1.20 (0.78, 1.84)
Bivalirudin + post-PCI infusion	Heparin, all (± planned GPI use)	0.67 (0.50, 0.89)	1.22 (0.79, 1.88)

Cardiac Death

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin, all (± planned GPI use)	0.89 (0.66, 1.20)	1.31 (0.83, 2.06)
Bivalirudin + post-PCI infusion	Heparin, all (± planned GPI use)	0.60 (0.44, 0.81)	1.23 (0.77, 1.96)

30-Day Outcomes
Models Accounting for Post-PCI Bivalirudin Infusion

All-cause Death

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin, all (± planned GPI use)	1.00 (0.75, 1.33)	1.20 (0.78, 1.84)
Bivalirudin + post-PCI infusion	Heparin, all (± planned GPI use)	0.67 (0.50, 0.89)	1.22 (0.79, 1.88)
- High-dose post-PCI infusion	Heparin, all (± planned GPI use)	0.70 (0.51, 0.96)	1.25 (0.76, 2.04)
- Low-dose post-PCI infusion	Heparin, all (± planned GPI use)	0.49 (0.26, 0.94)	1.24 (0.63, 2.43)

Cardiac Death

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin, all (± planned GPI use)	0.89 (0.66, 1.20)	1.31 (0.83, 2.06)
Bivalirudin + post-PCI infusion	Heparin, all (± planned GPI use)	0.60 (0.44, 0.81)	1.23 (0.77, 1.96)
- High-dose post-PCI infusion	Heparin, all (± planned GPI use)	0.63 (0.45, 0.88)	1.42 (0.85, 2.38)
- Low-dose post-PCI infusion	Heparin, all (± planned GPI use)	0.41 (0.20, 0.85)	1.00 (0.45, 2.25)

30-Day Outcomes: Models Accounting for Post-PCI Bivalirudin Infusion and Planned GPI Use with Heparin

All-cause Death

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin + planned GPI use	0.88 (0.62, 1.25)	1.48 (0.86, 2.56)
Bivalirudin + no post-PCI infusion	Heparin + no planned GPI use	1.07 (0.79, 1.46)	1.00 (0.61, 1.64)

Cardiac Death

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin + planned GPI use	0.79 (0.55, 1.16)	1.55 (0.87, 2.77)
Bivalirudin + no post-PCI infusion	Heparin + no planned GPI use	0.94 (0.68, 1.31)	1.11 (0.65, 1.91)

30-Day Outcomes: Models Accounting for Post-PCI Bivalirudin Infusion and Planned GPI Use with Heparin

All-cause Death

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin + planned GPI use	0.88 (0.62, 1.25)	1.48 (0.86, 2.56)
Bivalirudin + no post-PCI infusion	Heparin + no planned GPI use	1.07 (0.79, 1.46)	1.00 (0.61, 1.64)
Bivalirudin + post-PCI infusion	Heparin + planned GPI use	0.59 (0.42, 0.83)	1.51 (0.87, 2.62)
Bivalirudin + post-PCI infusion	Heparin + no planned GPI use	0.72 (0.53, 1.00)	1.02 (0.62, 1.68)

Cardiac Death

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin + planned GPI use	0.79 (0.55, 1.16)	1.55 (0.87, 2.77)
Bivalirudin + no post-PCI infusion	Heparin + no planned GPI use	0.94 (0.68, 1.31)	1.11 (0.65, 1.91)
Bivalirudin + post-PCI infusion	Heparin + planned GPI use	0.54 (0.38, 0.78)	1.50 (0.83, 2.72)
Bivalirudin + post-PCI infusion	Heparin + no planned GPI use	0.64 (0.46, 0.90)	1.08 (0.62, 1.86)

30-Day Outcomes: Models Accounting for Post-PCI Bivalirudin Infusion and Planned GPI Use with Heparin

Serious Bleeding

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin, all (± planned GPI use)	0.68 (0.51, 0.89)	0.60 (0.47, 0.77)
Bivalirudin + post-PCI infusion	Heparin, all (± planned GPI use)	0.53 (0.43, 0.65)	0.66 (0.51, 0.85)

30-Day Outcomes: Models Accounting for Post-PCI Bivalirudin Infusion and Planned GPI Use with Heparin

Serious Bleeding

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin, all (± planned GPI use)	0.68 (0.51, 0.89)	0.60 (0.47, 0.77)
Bivalirudin + post-PCI infusion	Heparin, all (± planned GPI use)	0.53 (0.43, 0.65)	0.66 (0.51, 0.85)
Bivalirudin, all (± post-PCI infusion)	Heparin + planned GPI use	0.47 (0.38, 0.58)	0.60 (0.49, 0.75)
Bivalirudin, all (± post-PCI infusion)	Heparin + no planned GPI use	0.72 (0.57, 0.90)	0.73 (0.49, 1.08)

30-Day Outcomes: Models Accounting for Post-PCI Bivalirudin Infusion Dose and Planned GPI Use with Heparin

MI (Reinfarction)

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin + planned GPI use	1.34 (0.91, 1.98)	1.04 (0.85, 1.26)
Bivalirudin + no post-PCI infusion	Heparin + no planned GPI use	1.30 (0.92, 1.84)	0.96 (0.78, 1.19)
Bivalirudin + LD post-PCI infusion	Heparin + planned GPI use	2.01 (1.29, 3.16)	1.10 (0.83, 1.47)
Bivalirudin + LD post-PCI infusion	Heparin + no planned GPI use	1.96 (1.29, 2.96)	1.02 (0.79, 1.30)
Bivalirudin + HD post-PCI infusion	Heparin + planned GPI use	1.02 (0.68, 1.53)	0.91 (0.71, 1.17)
Bivalirudin + HD post-PCI infusion	Heparin + no planned GPI use	0.99 (0.67, 1.45)	0.84 (0.64, 1.11)

Stent Thrombosis

Bivalirudin regimen	Heparin regimen	Adj HR (95% CI) STEMI	Adj HR (95% CI) NSTEMI
Bivalirudin + no post-PCI infusion	Heparin + planned GPI use	1.43 (0.91, 2.25)	0.96 (0.51, 1.81)
Bivalirudin + no post-PCI infusion	Heparin + no planned GPI use	1.84 (1.16, 2.93)	0.59 (0.26, 1.35)
Bivalirudin + LD post-PCI infusion	Heparin + planned GPI use	2.49 (1.42, 4.35)	1.72 (0.69, 4.29)
Bivalirudin + LD post-PCI infusion	Heparin + no planned GPI use	3.21 (1.81, 5.69)	1.06 (0.44, 2.59)
Bivalirudin + HD post-PCI infusion	Heparin + planned GPI use	0.88 (0.55, 1.41)	0.95 (0.47, 1.92)
Bivalirudin + HD post-PCI infusion	Heparin + no planned GPI use	1.14 (0.68, 1.90)	0.59 (0.24, 1.46)

Conclusions

- In pts with STEMI undergoing primary PCI, bivalirudin use was associated with reductions in the 30-day rates of mortality, serious bleeding and NACE despite increased rates of MI and stent thrombosis compared with heparin
  - The mortality benefit of bivalirudin in STEMI was pronounced in pts treated with a post-PCI bivalirudin infusion (low-dose or high-dose); a high-dose infusion mitigated the MI and stent thrombosis risk
- In pts with NSTEMI undergoing PCI, bivalirudin use was associated with a reduction in the 30-day rate of serious bleeding but similar rates of mortality, MI, and stent thrombosis compared with heparin