Bivalirudin versus Heparin and Heparin plus Tirofiban in Patients with AMI Undergoing PCI

Thirty-Day and One-Year Outcomes of the

BRIGHT Trial

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On behalf of the BRIGHT investigators

Presenter Disclosure Information

- The BRIGHT trial was supported by a research grant from Salubris Pharmaceutical Co. Ltd (Shenzhen, China)
- Supported by nonprofit grants from National Key R&D project for 12th five year plan (2011BAI11B07, 2012ZX093016-002)
- No personal conflicts of interest

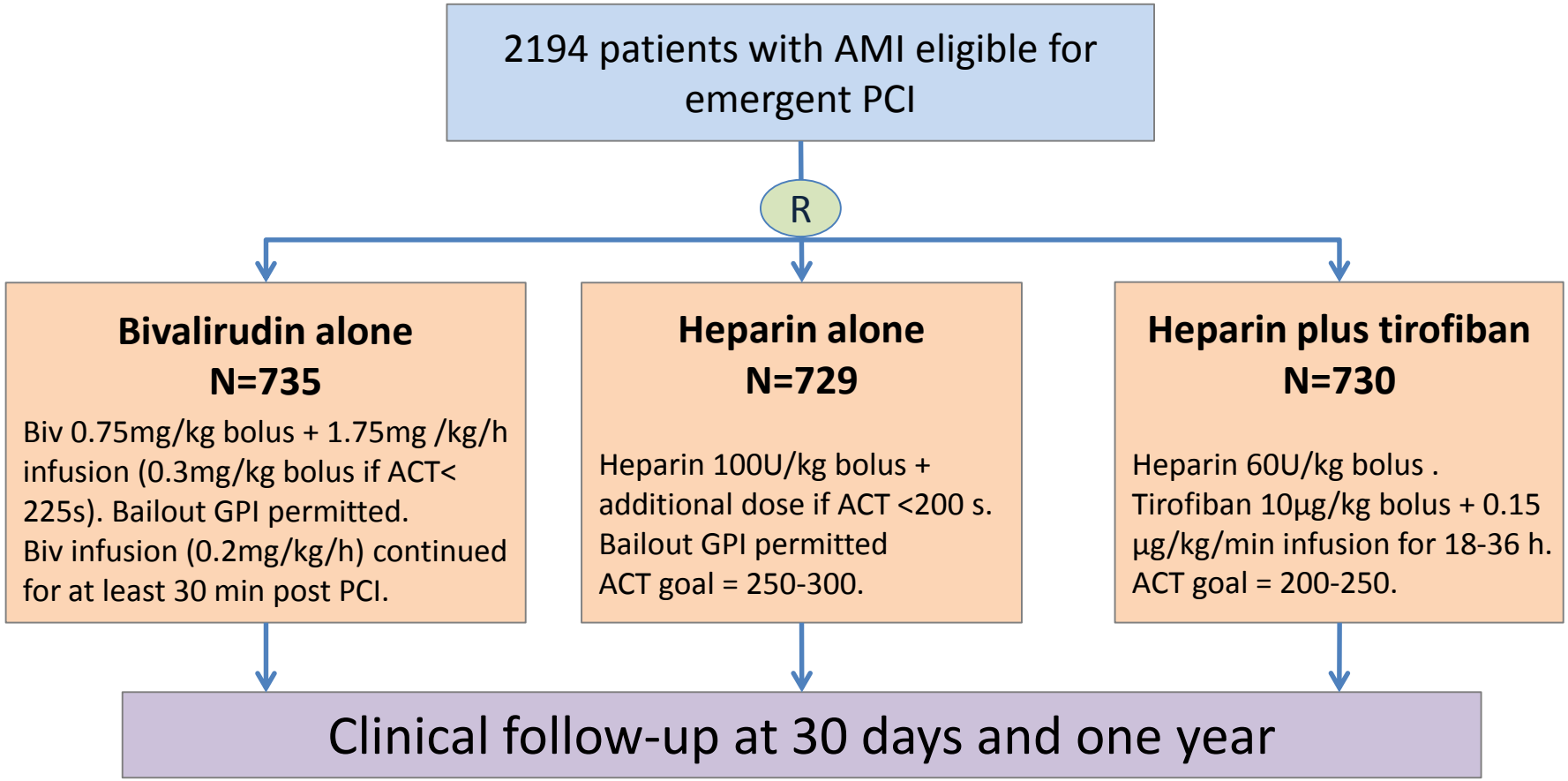
Background

- The HORIZONS-AMI and EUROMAX trials showed that bivalirudin is superior to heparin plus GPI in reducing net adverse clinical events (NACE) in patients with AMI undergoing primary PCI, at the cost of an increased rate of acute stent thrombosis[1,2]
- The outcome of bivalirudin compared to heparin alone with GPI reserved for bailout use in primary PCI is controversial,[2,3] and has not been studied in a dedicated large, multicenter, randomized trial

1. Stone GW, et al. N Engl J Med 2008;358:2218-30.
2. Steg PG, et al. N Engl J Med 2013;369:2207-17.
3. Shahzad A, et al. Lancet 2014;S0140-6736:60924-7.

Trial Design

(clinicaltrials.gov number: NCT01696110)



Inclusion and Exclusion Criteria

Inclusion criteria

- 18 to 80 years old
- STEMI within 12 h of symptom onset, or within 12-24 h if ongoing chest pain, continuous ST elevation or new LBBB
- NSTEMI within 72 h of symptom onset
- Planned emergency PCI
- Written informed consent before catheterization

Key exclusion criteria

- Thrombolysis within 72 hours
- Cardiogenic shock
- Any anticoagulant agents used within 48 h before randomization
- Active bleeding or bleeding diathesis
- Hemoglobin <100 g/L or platelet count <100 $\times$ 10^9/L
- Creatinine clearance <30 mL/min
- Known allergy to the study drugs or devices (including heparin induced thrombocytopenia)

Study Endpoints

Primary endpoint

- NACE at 30 days

A composite of death from any cause, reinfarction, ischemia-driven target vessel revascularization (TVR), stroke or any bleeding

Secondary endpoints

- NACE at 1 year

- MACCE at 30 days and 1 year

A composite of death from any cause, reinfarction, ischemia-driven target vessel revascularization (TVR) or stroke

- Any bleeding (BARC definition) at 30 days and 1 year

Safety endpoints

- Stent thrombosis (ARC definite or probable) at 30 days and 1 year

- Thrombocytopenia at 30 days

Defined as a nadir platelet count $<100 \times 10^9$/L or drop >50% from baseline

Patient Enrollment

- 82 sites in China
- 2,194 patients randomized
- Aug 22, 2012 - Jun 25, 2013

Top 20 Centers

No.	Center	Cases
1	Shenyang Northern Hosp.	324
2	Beijing Luhe Hosp.	162
3	1st Hosp of Jilin Univ.	60
4	No.463 Hosp of PLA	60
5	General Hosp of PLA (1)	57
6	Wuhan Asican Heart Hosp.	50
7	Nanjing First Hosp.	50
8	Tianjin CAPF Hosp.	50
9	3rd Hosp of Jilin Univ.	50
10	No.210 Hosp of PLA	45

No.	Center	Cases
11	Wuhan General Hosp of PLA	40
12	2nd Hosp of Jilin Univ.	40
13	Tianjin Chest Hosp.	39
14	Shanxi Cardiovascular Hosp.	35
15	Beijing CAPF General Hosp.	30
16	Anhui Provincial Hosp.	30
17	Shenzhou Hosp. of SMC	30
18	Yingkou Centeral Hosp.	30
19	1 st Hosp. of Lanzhou Univ.	30
20	Shijiazhuang Peace Hosp.	30

Study Organization

Principal investigator: Yaling Han, MD

Steering Committee: Yaling Han, MD.
Jiyan Chen, MD.
Quanmin Jing, MD.

Contract research organization: Excellent MedSci Co.

Clinical events committee: Xiangqian Qi, MD.
Chaozhong Liu, MD.
Jinqing Yuan, MD.

Baseline Characteristics

Characteristics	Bivalirudin (N = 735)	Heparin (N = 729)	Heparin + Tirofiban (N = 730)
Age, yrs	57.3±11.6	58.1±11.7	58.2±11.8
Male (%)	608 (82.7)	595 (81.6)	599 (82.1)
Weight, kg	71.7±11.3	71.4±11.5	70.7±11.0
Diabetes (%)	168 (22.9)	137 (18.8)	160 (21.9)
Hypertension (%)	301 (41.0)	312 (42.8)	311 (42.6)
Previous MI (%)	32 (4.4)	33 (4.5)	33 (4.5)
Previous PCI (%)	37 (5.0)	35 (4.8)	37 (5.1)
Previous stroke (%)	63 (8.6)	63 (8.6)	53 (7.3)
Type of acute MI			
STEMI (%)	655 (89.1)	641 (87.9)	629 (86.2)
NSTEMI (%)	80 (10.9)	88 (12.1)	101 (13.8)
Killip class II - IV (%)	100 (13.6)	107 (14.7)	107 (14.7)
Anemia (%)	43/693 (6.2)	29/654 (4.2)	38/688 (5.5)
CrCl ≤60 ml/min (%)	66/688 (9.6)	73/681 (10.7)	82/674 (12.2)
Symptoms to hosp, hrs (STEMI)	6.9±3.9	6.9 ± 3.8	6.9± 4.1

Procedural Characteristics

Characteristic	Bivalirudin (N = 735)	Heparin (N = 729)	Heparin + Tirofiban (N = 730)
Arterial access (%)			
Transfemoral	159 (21.6)	153 (21.0)	159 (21.8)
Transradial	576 (78.4)	576 (79.0)	571 (78.2)
Multivessel disease (%)	473 (64.4)	467 (64.1)	490 (67.1)
LAD infarct vessel	391 (53.2)	394 (54.0)	385 (52.7)
Thrombectomy (%)	187/723 (25.9)	182 (25.3)	194/722 (26.9)
Door to device time, min (STEMI)	66.1±29.5	68.6±28.6	69.8±27.8
Revascularization strategy (%)			
Non-intervention	6 (0.8)	4 (0.5)	4 (0.5)
CABG	6 (0.8)	6 (0.8)	4 (0.5)
Balloon angioplasty	15 (2.0)	18 (2.5)	13 (1.8)
Stent implantation	708 (96.3)	701 (96.2)	709 (97.1)
Drug-eluting	703/708 (99.3)	696/701 (99.3)	706/709 (99.6)
Bare metal	5/708 (0.7)	5/701 (0.7)	3/709 (0.4)
Reference vessel diameter, mm	3.15±0.71	3.16±0.68	3.13±0.68
Total stent length, mm	28.5±12.1	28.5±11.5	28.2±10.5

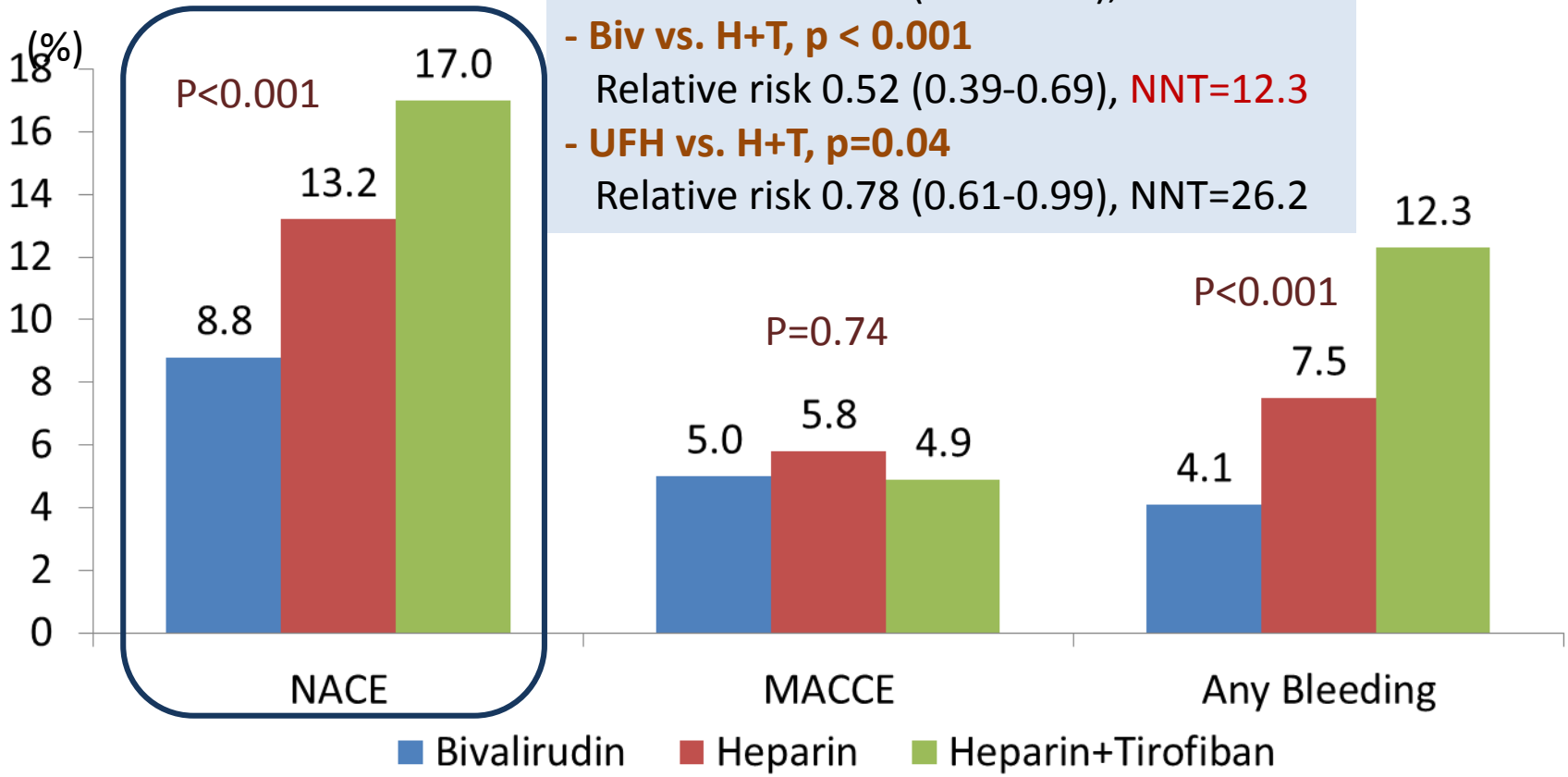
Antithrombotic Treatment

Characteristic	Bivalirudin (N = 735)	Heparin (N = 729)	Heparin + Tirofiban (N = 730)
Aspirin (%)	735 (100)	729 (100)	727 (99.6)
Clopidogrel (%)	735 (100)	729 (100)	729 (99.9)
Clopidogrel loading (%)			
600 mg	497 (67.6)	481 (66.0)	497 (68.1)
300 mg	215 (29.3)	218 (29.9)	206 (28.2)
No loading	23 (3.1)	30 (4.1)	27 (3.7)
Study medications			
Bivalirudin (%)	735 (100)	2 (0.3)	1 (0.1)
Duration post-PCI (mins)	234±117	-	-
Unfractionated heparin (%)	2 (0.3)	729 (100)	730 (100)
Tirofiban (%)	32 (4.4)	41 (5.6)	730 (100)
Activated clotting time*, s	298.4±90.3#	262.7±70.0	261.4±77.4

*By Medtronic Hemotec ACT machine; # P <0.001 compared with other two groups

Primary and Principal Secondary Endpoint Events at 30 Days

- **Biv vs. UFH, p=0.009**
  Relative risk 0.67 (0.50-0.90), NNT=23.1
- **Biv vs. H+T, p < 0.001**
  Relative risk 0.52 (0.39-0.69), NNT=12.3
- **UFH vs. H+T, p=0.04**
  Relative risk 0.78 (0.61-0.99), NNT=26.2

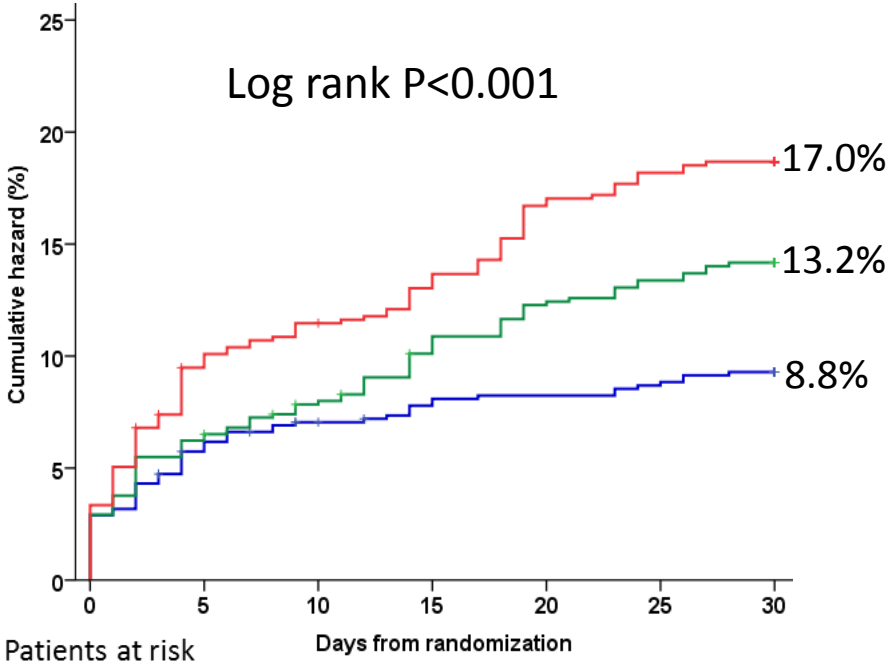


Biv=bivalirudin; UFH=Heparin; H+T=heparin + tirofiban

Time-to-Event Curves

Bivalirudin — Heparin — Heparin + Tirofiban

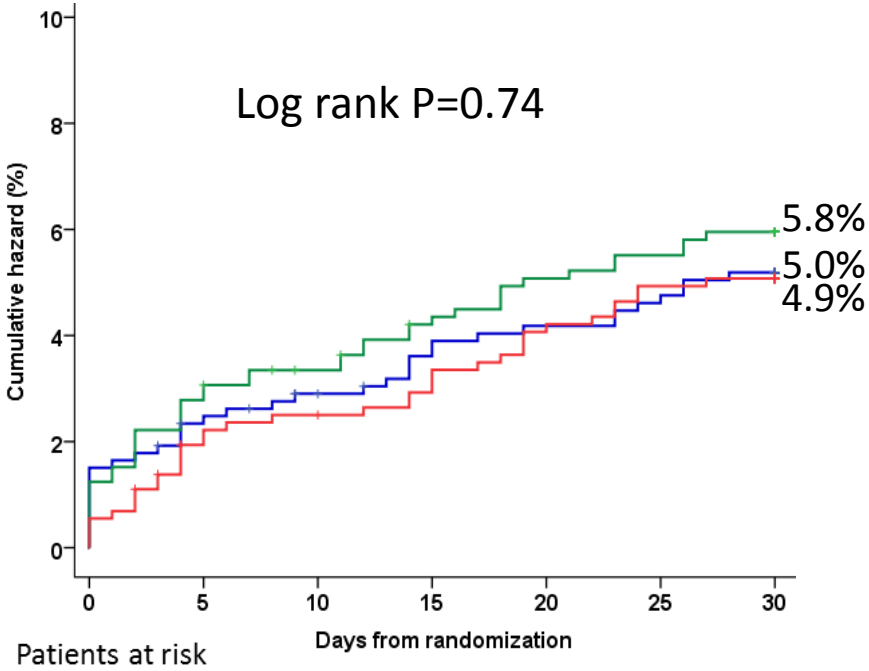
NACE at 30 days



Patients at risk

Biv	735	692	680	673	670	667	663
UFH	729	685	671	654	640	633	628
H+T	730	661	648	637	614	605	602

MACCE at 30 days

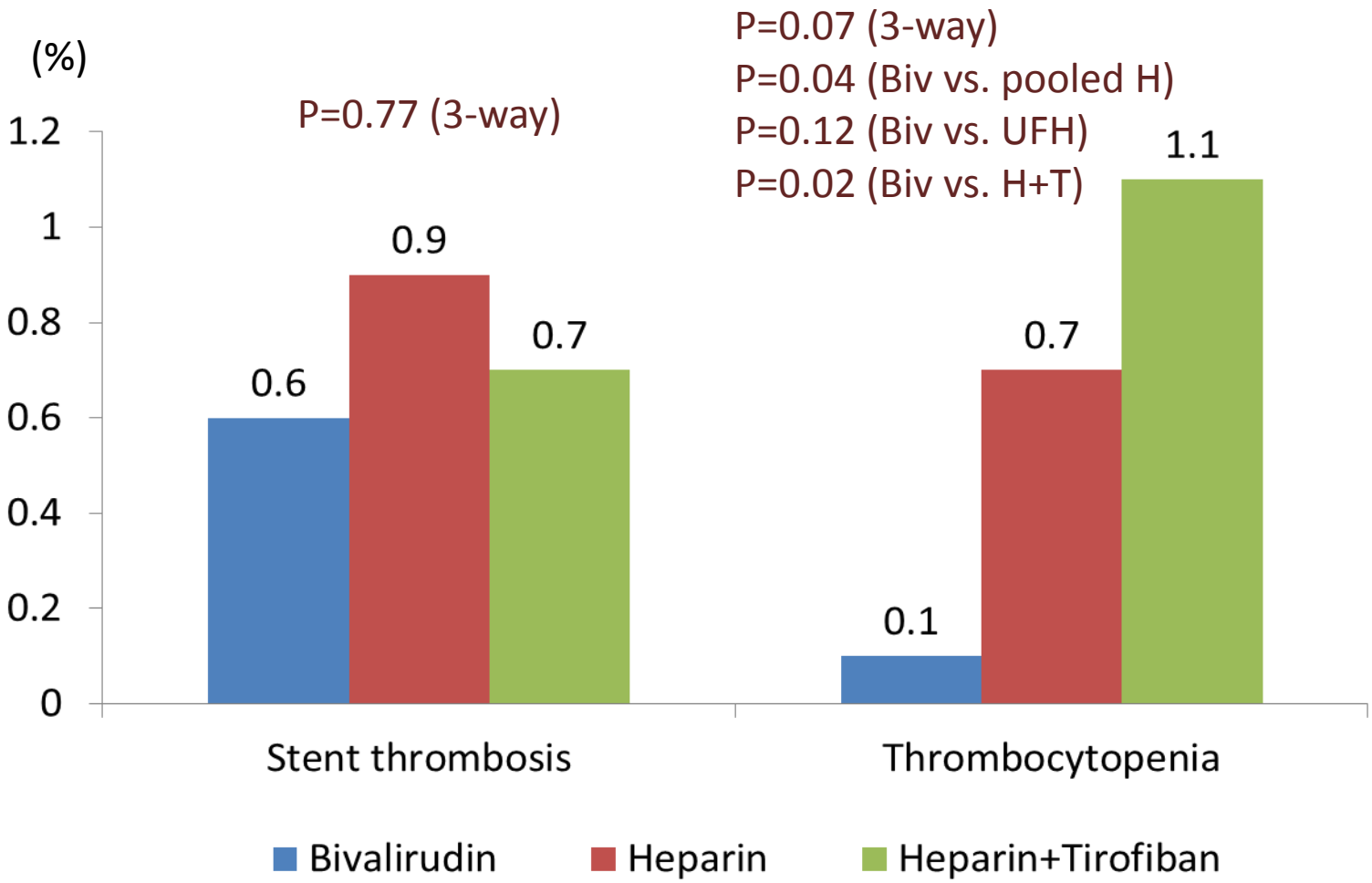


Patients at risk

Biv	735	716	709	702	698	695	691
UFH	729	709	702	694	688	685	682
H+T	730	713	709	705	697	691	690

Biv=bivalirudin; UFH=Heparin; H+T=heparin + tirofiban

Safety Endpoints at 30 days



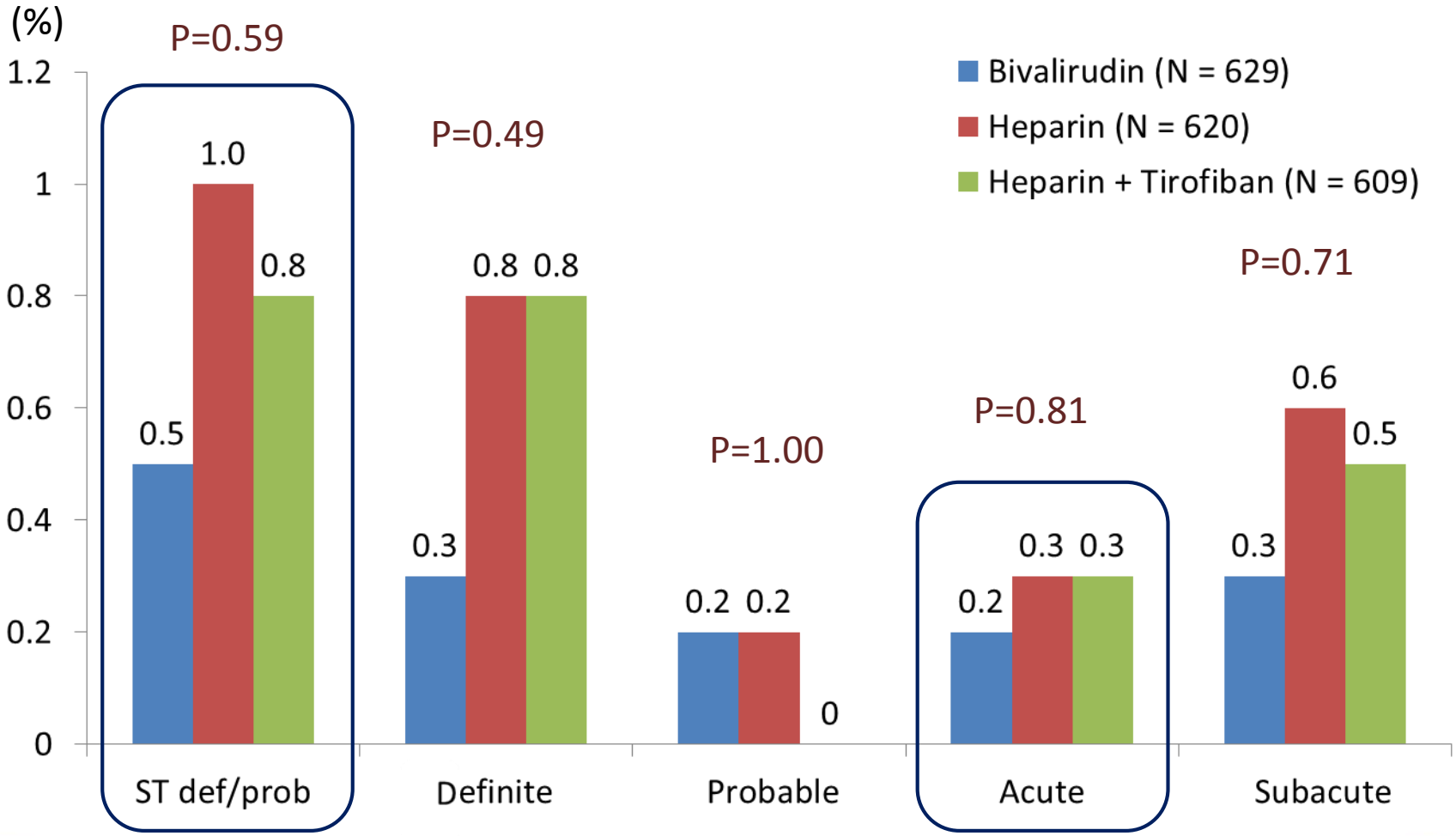
Biv=bivalirudin; UFH=Heparin; H+T=heparin + tirofiban

Ischemic Events at 30 Days

Event	Bivalirudin (N = 735)	Heparin (N = 729)	Heparin + Tirofiban (N = 730)	P value
NACE (%)	65 (8.8)	96 (13.2)	124 (17.0)	<0.001
MACCE (%)	37 (5.0)	42 (5.8)	36 (4.9)	0.74
Death (%)	13 (1.8)	13 (1.8)	15 (2.1)	0.90
Cardiac (%)	12 (1.7)	13 (1.8)	15 (2.1)	0.81
Non-cardiac (%)	1 (0.1)	0 (0)	0 (0)	0.37
Reinfarction (%)	7 (1.0)	9 (1.2)	6 (0.8)	0.72
Ischemia driven TVR (%)	12 (1.6)	13 (1.8)	9 (1.2)	0.68
Stroke (%)	5 (0.7)	7 (1.0)	6 (0.8)	0.84
Stent thrombosis, def/prob *(%)	4 (0.6)	6 (0.9)	5 (0.7)	0.77
Definite (%)	3 (0.4)	5 (0.7)	4 (0.6)	0.72
Probable (%)	1 (0.1)	1 (0.1)	1 (0.1)	1.00
Acute (<24 hrs) (%)	2 (0.3)	2 (0.3)	2 (0.3)	1.00
Subacute (1-30 days) (%)	2 (0.3)	4 (0.6)	3 (0.4)	0.66

*patients who received stent implantation

Stent Thrombosis at 30 Days – STEMI only

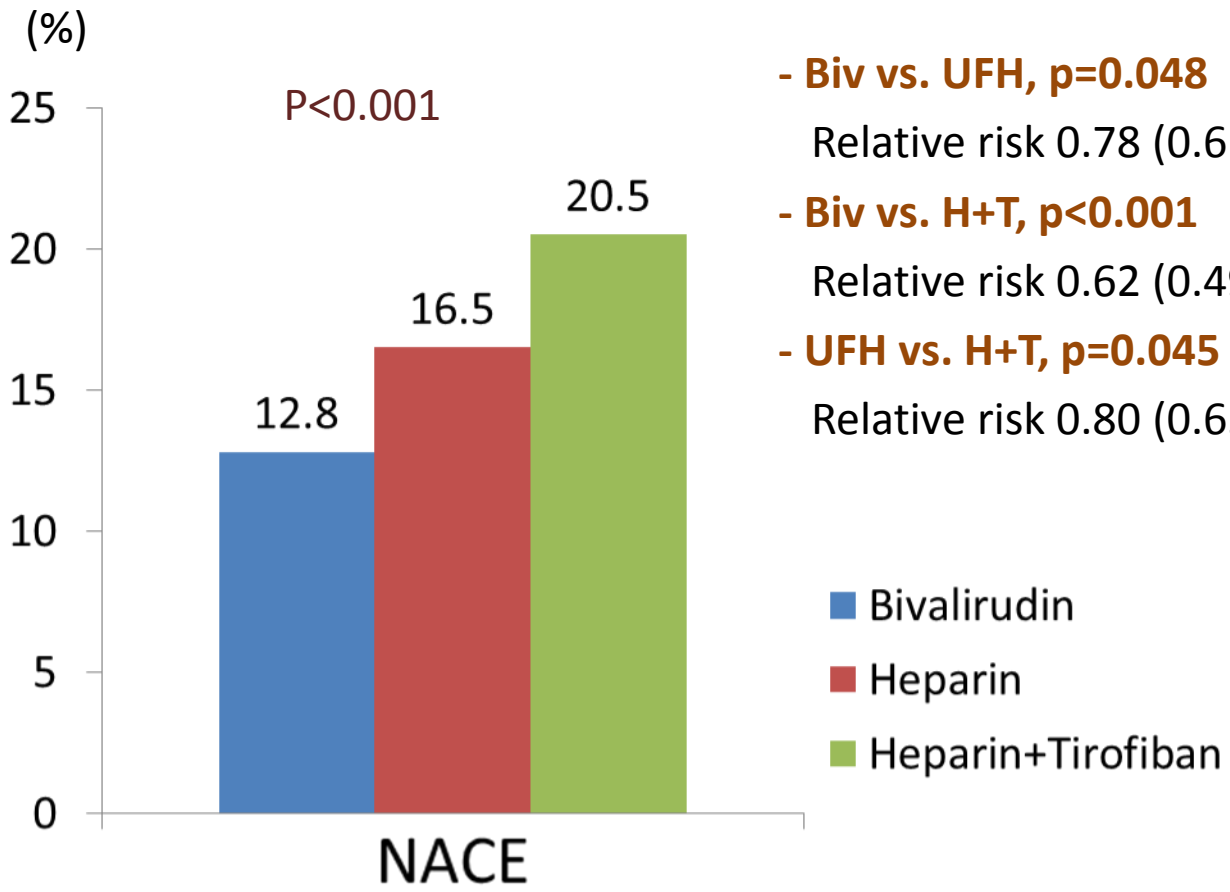


Bleeding Events at 30 Days

Event	Bivalirudin (N = 735)	Heparin (N = 729)	Heparin + Tirofiban (N = 730)	P value (3-way)	P value (B vs H)	P value (B vs H+T)
Any bleeding	30 (4.1)	55 (7.5)	90 (12.3)	<0.001	0.005	<0.001
BARC 1 (%)	21 (2.9)	29 (4.0)	53 (7.3)	<0.001		
BARC 2 (%)	5 (0.7)	15 (2.1)	22 (3.0)	0.005		
BARC 3a (%)	4 (0.5)	7 (1.0)	6 (0.8)	0.59		
BARC 3b (%)	0 (0)	4 (0.5)	8 (1.1)	0.013		
BARC 5 (%)	0 (0)	0 (0)	1 (0.1)	0.67		
BARC 2-5 (%)	9 (1.2)	26 (3.6)	37 (5.1)	<0.001	0.003	<0.001
Major (BARC 3-5) (%)	4 (0.5)	11 (1.5)	15 (2.1)	0.04	0.07	0.01

B=bivalirudin; H=Heparin; H+T= heparin + tirofiban

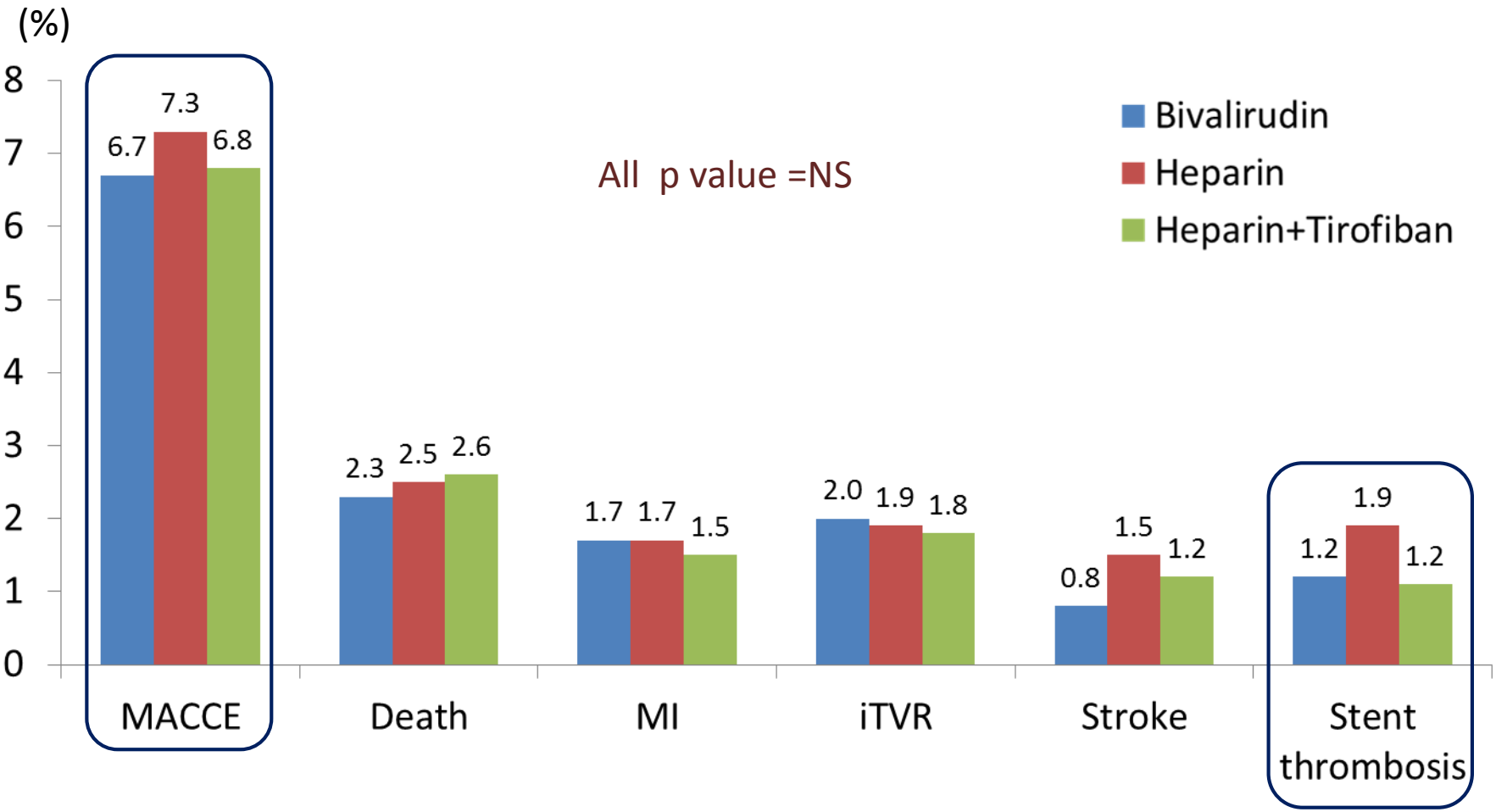
Primary Endpoint Events at 1 Year



- **Biv vs. UFH, p=0.048**
  Relative risk 0.78 (0.61-1.00), **NNT=27.2**
- **Biv vs. H+T, p<0.001**
  Relative risk 0.62 (0.49-0.79), **NNT=12.9**
- **UFH vs. H+T, p=0.045**
  Relative risk 0.80 (0.65-0.99), NNT=24.5

Biv=bivalirudin; UFH=Heparin; H+T=heparin + tirofiban

Major Ischemic Events at 1 Year

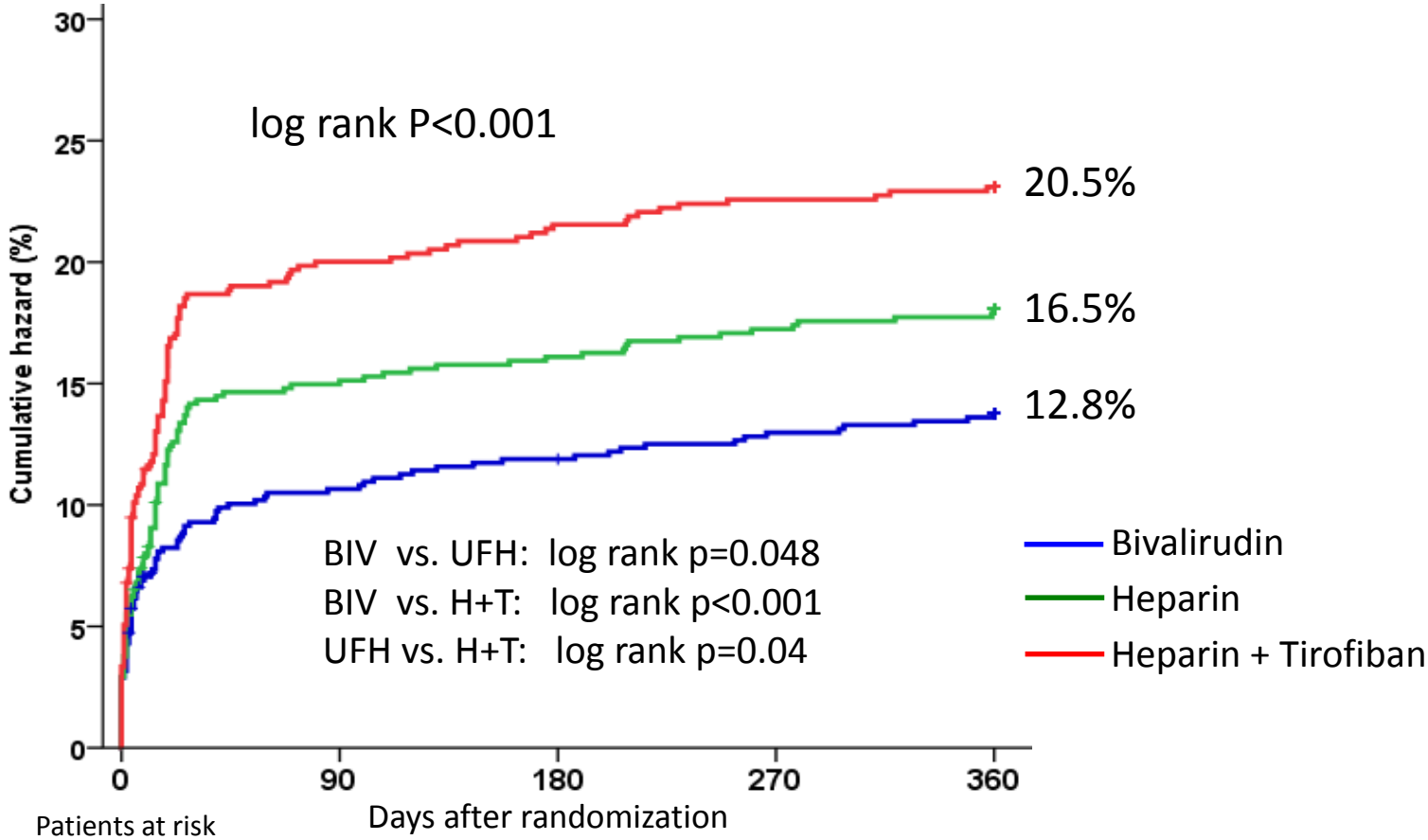


Bleeding Events at 1 Year

Event	Bivalirudin (N = 735)	Heparin (N = 729)	Heparin + Tirofiban (N = 730)	P value (3-way)	P value (B vs H)	P value (B vs H+T)
Any bleeding	46 (6.3)	72 (9.9)	104 (14.2)	<0.001	0.01	<0.001
BARC 1 (%)	35 (4.8)	44 (6.0)	64 (8.8)	0.007		
BARC 2 (%)	7 (1.0)	17 (2.3)	23 (3.2)	0.01		
BARC 3a (%)	4 (0.5)	7 (1.0)	8 (1.1)	0.51		
BARC 3b (%)	0 (0)	4 (0.5)	8 (1.1)	0.01		
BARC 5 (%)	0 (0)	0 (0)	1 (0.1)	0.67		
BARC 2-5 (%)	11 (1.2)	28 (3.6)	40 (5.1)	<0.001	0.006	<0.001
Major (BARC 3-5) (%)	4 (0.5)	11 (1.5)	17 (2.1)	0.02	0.07	0.004

B=bivalirudin; H=Heparin; H+T= heparin + tirofiban

Time-to-Event Curves: NACE at 1 Year

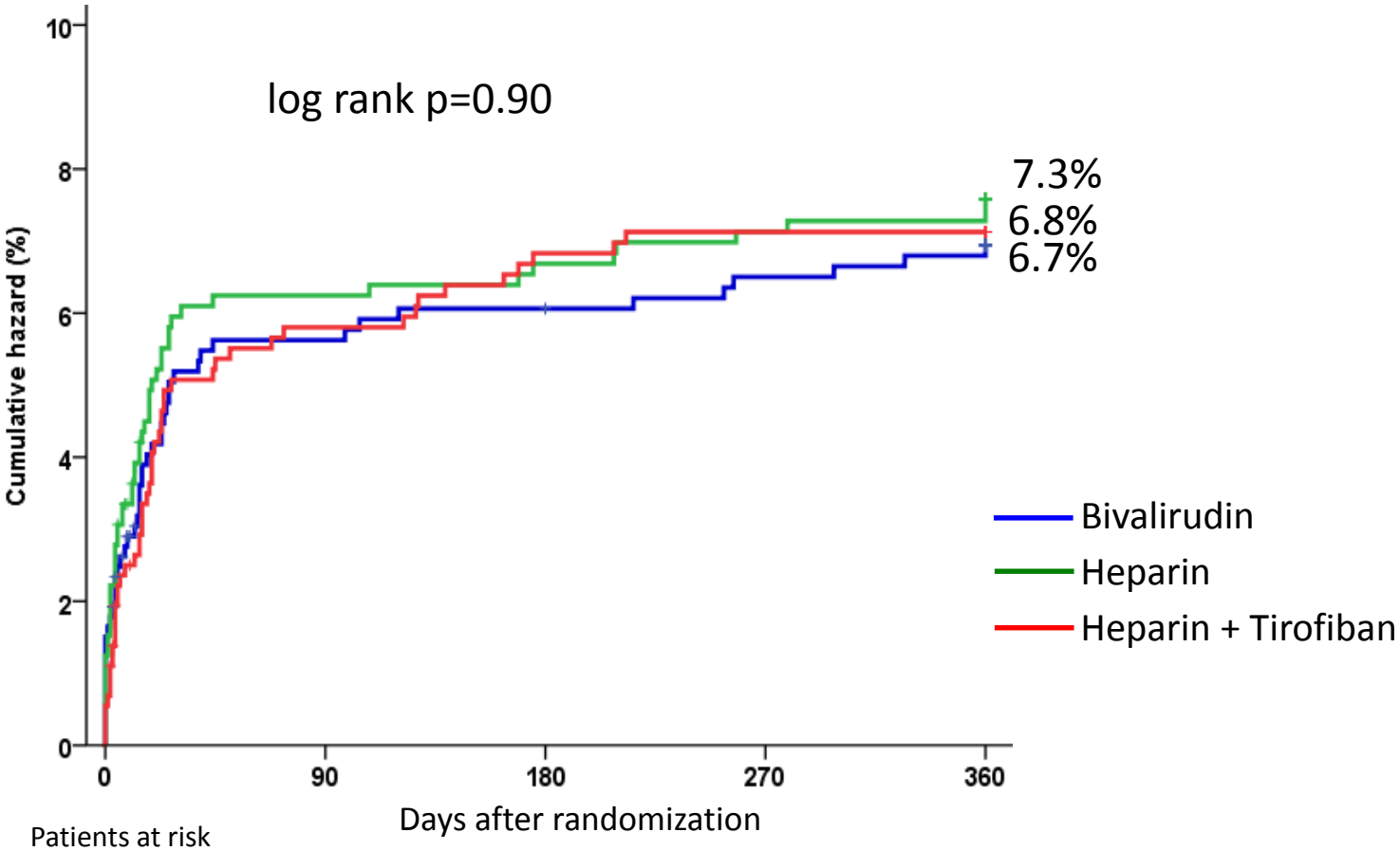


Patients at risk

Biv	735	654	646	638	634
UFH	729	623	616	609	605
H+T	730	594	585	579	576

Biv=bivalirudin; UFH=Heparin; H+T=heparin + tirofiban

Time-to-Event Curves: MACCE at 1 Year

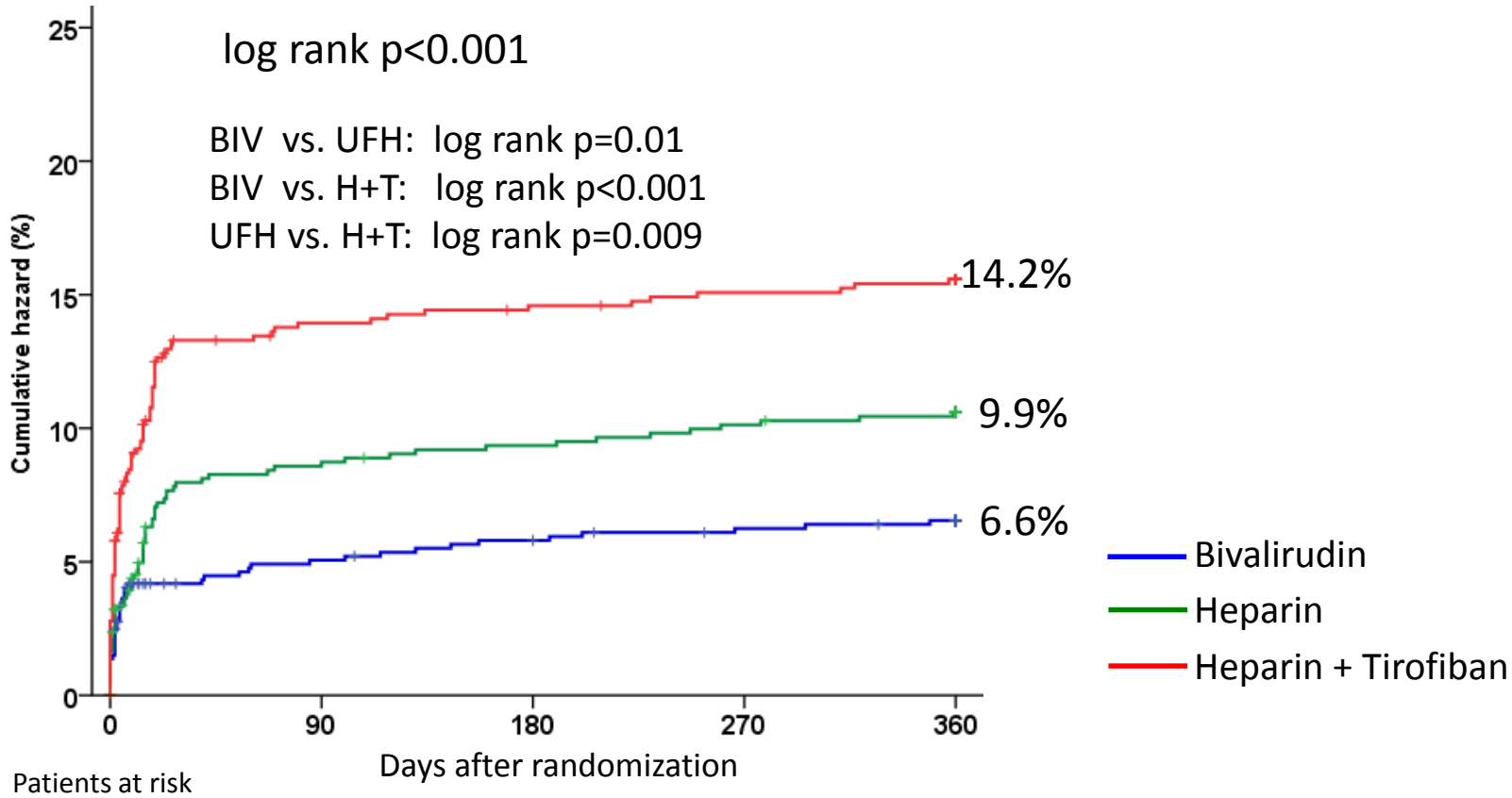


Patients at risk

Biv	735	688	685	681	679
UFH	729	680	677	674	673
H+T	730	685	678	676	676

Biv=bivalirudin; UFH=Heparin; H+T=heparin + tirofiban

Time-to-Event Curves: Any Bleeding at 1 Year



Patients at risk

Biv	735	680	674	668	665
UFH	729	652	646	641	637
H+T	730	616	611	607	604

Biv=bivalirudin; UFH=Heparin; H+T=heparin + tirofiban

Limitations

- Open-label trial
  - Endpoints adjudicated by a committee blinded to randomization
- Study population comprised of 87.7% STEMI and 12.3% NSTEMI patients; underpowered for evaluation of NSTEMI subgroup
- Chinese domestic bivalirudin was used (Salubris Corp.)
  - Shown to have equivalent MW and potency to The Medicines Company's bivalirudin, with similar half-life (31 minutes)
- Prasugrel and ticagrelor were not used because they were not available in China during study enrollment

Conclusions

- In the present large-scale, randomized trial of patients with AMI undergoing PCI, bivalirudin alone was superior to both heparin monotherapy and heparin plus tirofiban in reducing the primary composite endpoint of death, reinfarction, ischemia-driven TVR, stroke or bleeding at 30 days and 1 year
- Bivalirudin reduced major and minor bleeding and thrombocytopenia, with similar rates of adverse ischemic events compared to both heparin and heparin plus tirofiban
- With the use of a routine post-PCI bivalirudin infusion, the rates of acute, subacute and late stent thrombosis were similar with bivalirudin, heparin, and heparin + GPI

Thank you for you attention!

On behalf of the BRIGHT investigators