BRIGHT-4

Bivalirudin with a Post-PCI High-Dose Infusion vs. Heparin Monotherapy During Primary PCI in STEMI

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Disclosure Statement of Financial Interest

Specific to this topic: None

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Bivalirudin vs. Heparin Anticoagulation During Primary PCI in STEMI

- Six completed randomized trials have reported conflicting results[1-6]
- Substantial heterogeneity was present in the prior trial designs, in particular:
  - Routine vs. selective use of GPIIb/IIIa inhibitors (GPI) with heparin
  - Use, dose and duration of a post-PCI bivalirudin infusion
  - Radial vs. femoral vascular access
- *Post hoc* analyses suggest that **bivalirudin with a 2-4-hour post-PCI high-dose infusion** and **heparin monotherapy** are the two regimens likely to minimize both ischemic and hemorrhagic complications in STEMI patients undergoing primary PCI with radial access
- These two regimens have not been compared in an adequately powered randomized trial

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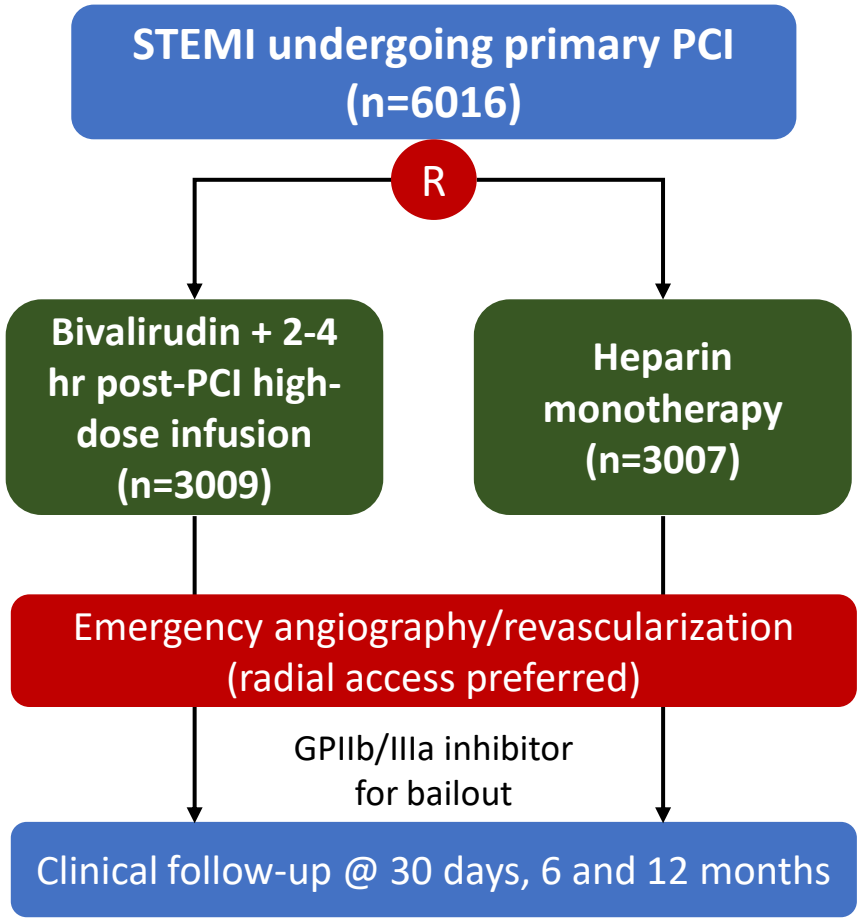
1. N Engl J Med 2008; 358(21): 2218-30. (*HORIZONS-AMI*)
2. N Engl J Med 2013; 369(23): 2207-17. (*EUROMAX*)
3. Lancet 2014; 384(9957): 1849-58. (*HEAT PPCI*)
4. JAMA 2015; 313(13): 1336-46. (*BRIGHT*)
5. N Engl J Med 2015; 373(11): 997-1009. (*MATRIX*)
6. N Engl J Med 2017; 377(12): 1132-42. (*VALIDATE-SWEDEHEART*)

Clinicaltrials.gov identifier: NCT03822975

Trial Design

***B**ivali**R**udin with prolonged full-dose **I**nfusion durin**G** primary PCI versus **H**eparin **T**rial (**BRIGHT**)-4*

Multicenter, randomized, investigator-sponsored, open-label trial



Patients

Inclusion criteria:

- Any age
- STEMI within 48h* undergoing primary PCI
- Written informed consent provided

Major exclusion criteria:

- Thrombolytic therapy
- Anticoagulant or GPI use before randomization
- Mechanical complications of MI

Study treatment

Bivalirudin:

0.75 mg/kg bolus; 1.75 mg/kg/hr during the PCI procedure and for 2-4 hours afterwards; additional bolus given if ACT <225 s

Heparin:

70 U/kg bolus; additional bolus given if ACT <225 s

Both arms:

GPI permitted only for procedural thrombotic complications

Li Y,….Han Y, Stone GW. Lancet. 2022;400:1847-57

*Eur Heart J. 2018;39(2):119-177.

Baseline and Procedural Characteristics

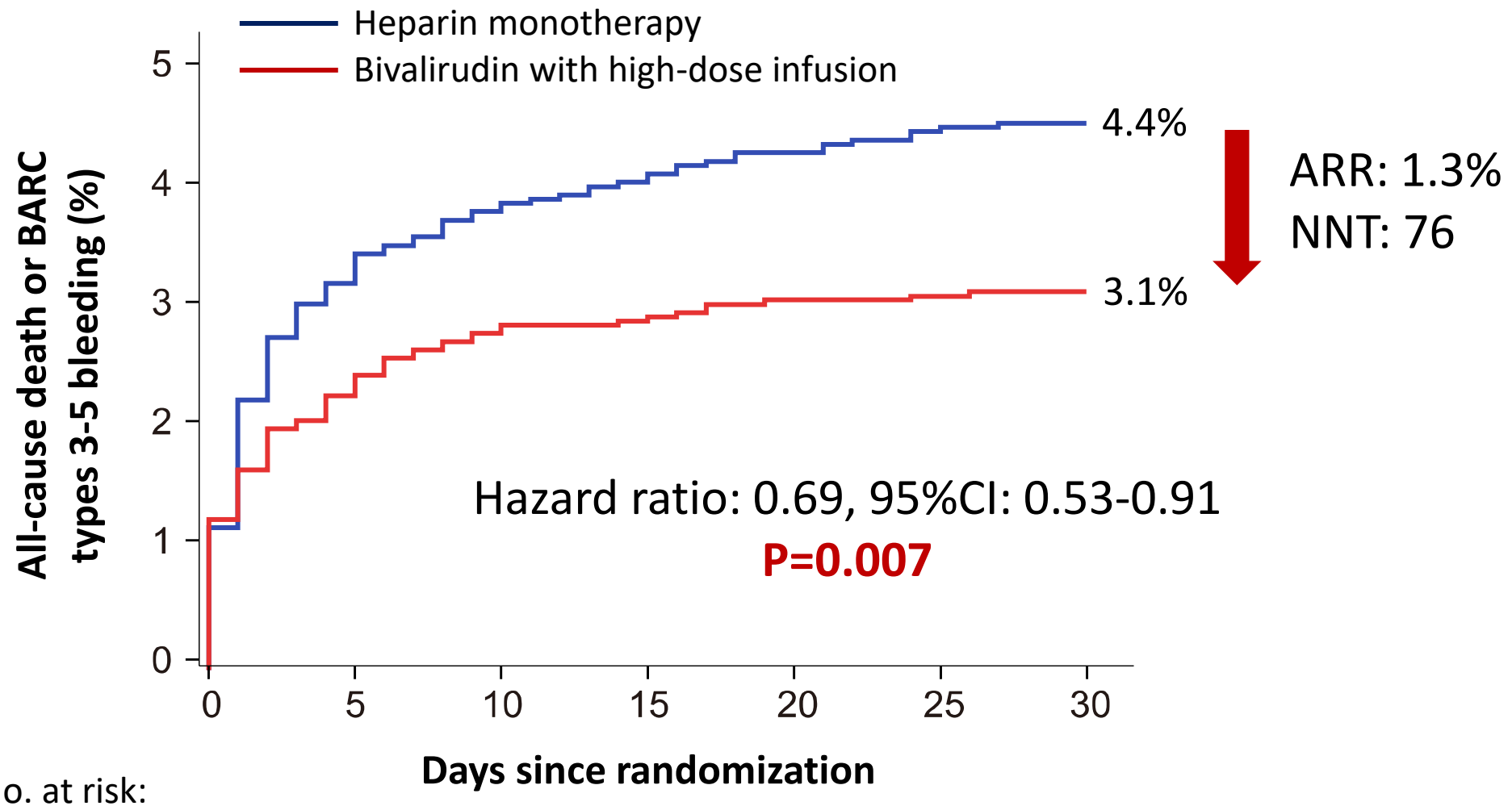
Characteristic	Heparin (N=3007)	Bivalirudin (N=3009)
Age, years	60.6 ± 12.2	60.5 ± 12.1
Male	78.9%	78.1%
Diabetes mellitus	23.2%	22.2%
Hypertension	50.5%	52.0%
BMI (kg/m^2)	25.0 ± 3.8	24.8 ± 3.6
Prior MI	6.6%	6.2%
Prior PCI	6.2%	6.2%
Prior stroke	11.4%	11.7%
Killip class III-IV	10.7%	10.2%
Sx-door time, hr	3.3 (1.7-6.7)	3.3 (1.7-6.4)
>12 hours	12.2%	11.0%

Characteristic	Heparin (N=3007)	Bivalirudin (N=3009)
P2Y12 inhibitor		
Clopidogrel	34.4%	33.7%
Ticagrelor	65.6%	66.3%
Transradial access	92.6%	93.6%
Revascularization	98.4%	98.1%
PCI	98.1%	97.8%
CABG	0.4%	0.4%
Door-wire time, hr	1.1 (0.9-1.7)	1.1 (0.9-1.6)
Thrombus aspiration	17.9%	18.1%
TIMI 0/1 pre (site read)	83.4%	82.0%
TIMI 3 post (site read)	97.5%	98.5%

Study Drug Treatments

	Heparin (N=3007)	Bivalirudin (N=3009)	P value
Heparin	98.7%	0.8%	-
Total dose, IU	5570 (4800-6775)	-	-
Bivalirudin	1.3%	99.2%	-
Post-PCI infusion administered	-	2953/2953 (100.0%)	-
Post-PCI infusion duration, hr	-	3.0 (2.2-4.0)	-
Additional bolus of study medications	35.1%	3.5%	**<0.0001**
Peak activated clotting time, sec	267 (238-317)	321 (278-365)	**<0.0001**
GPI for procedural complications	13.7%	11.5%	**0.01**

Primary Endpoint: All-cause death or BARC types 3-5 bleeding



No. at risk:

Heparin	3007	2913	2896	2889	2882	2877	2875
Bivalirudin	3009	2942	2927	2924	2919	2918	2917

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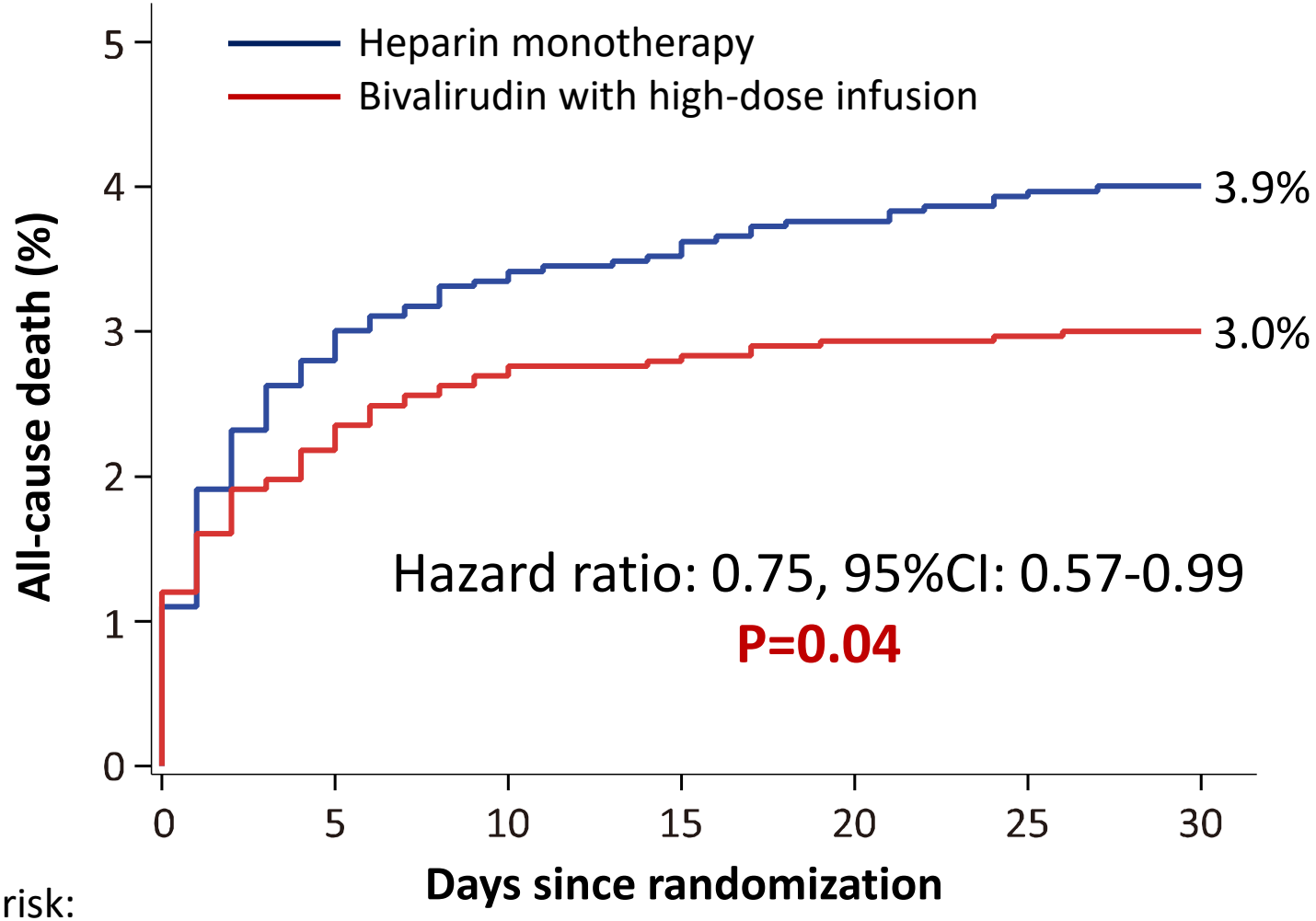
All-cause Death



No. at risk:

Heparin	3007	2924	2908	2903	2896	2891	2889
Bivalirudin	3009	2944	2929	2926	2922	2921	2920

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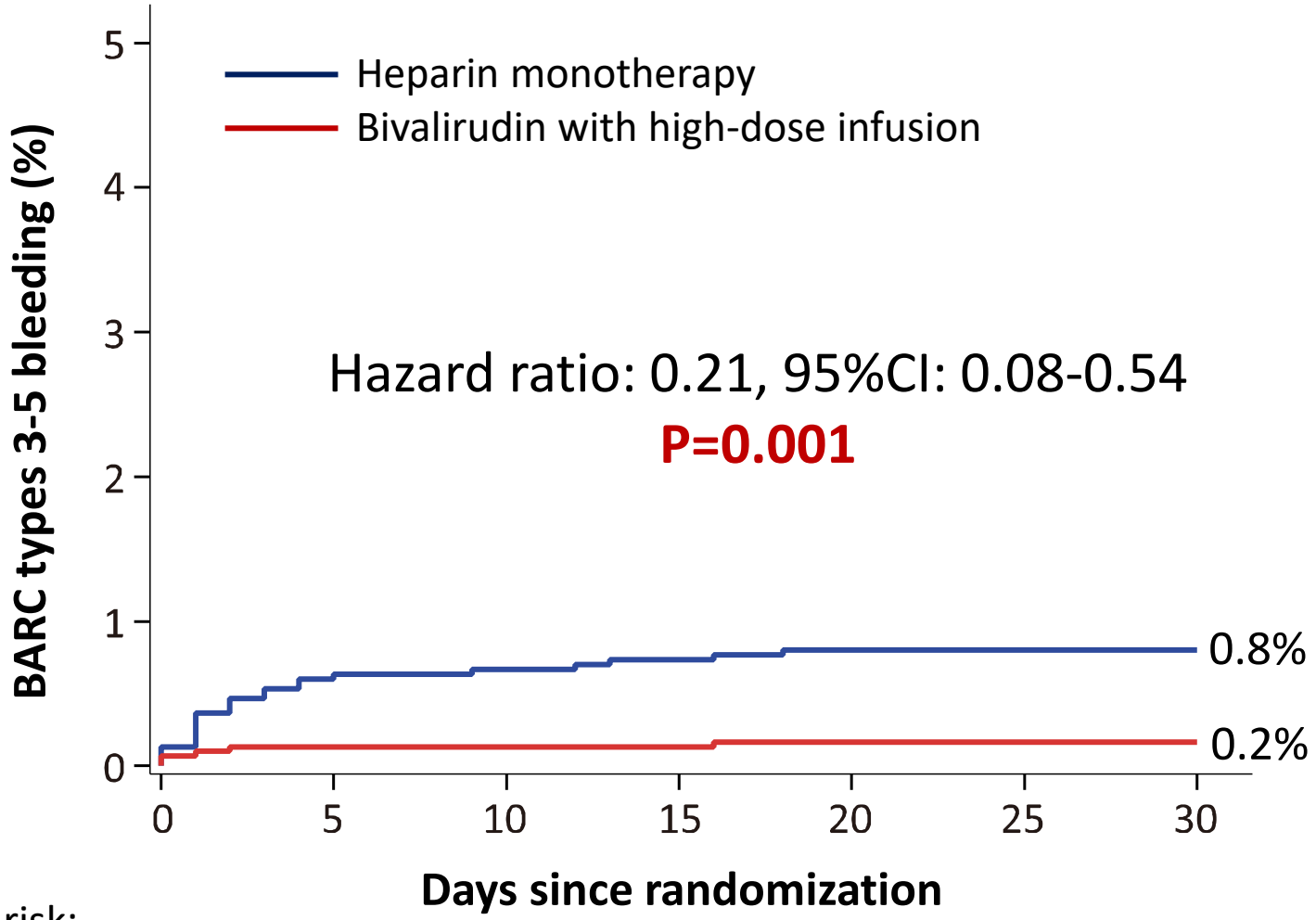
BARC 3-5 Bleeding



No. at risk:

Heparin	3007	2989	2987	2985	2983	2983	2983
Bivalirudin	3009	3005	3005	3005	3004	3004	3004

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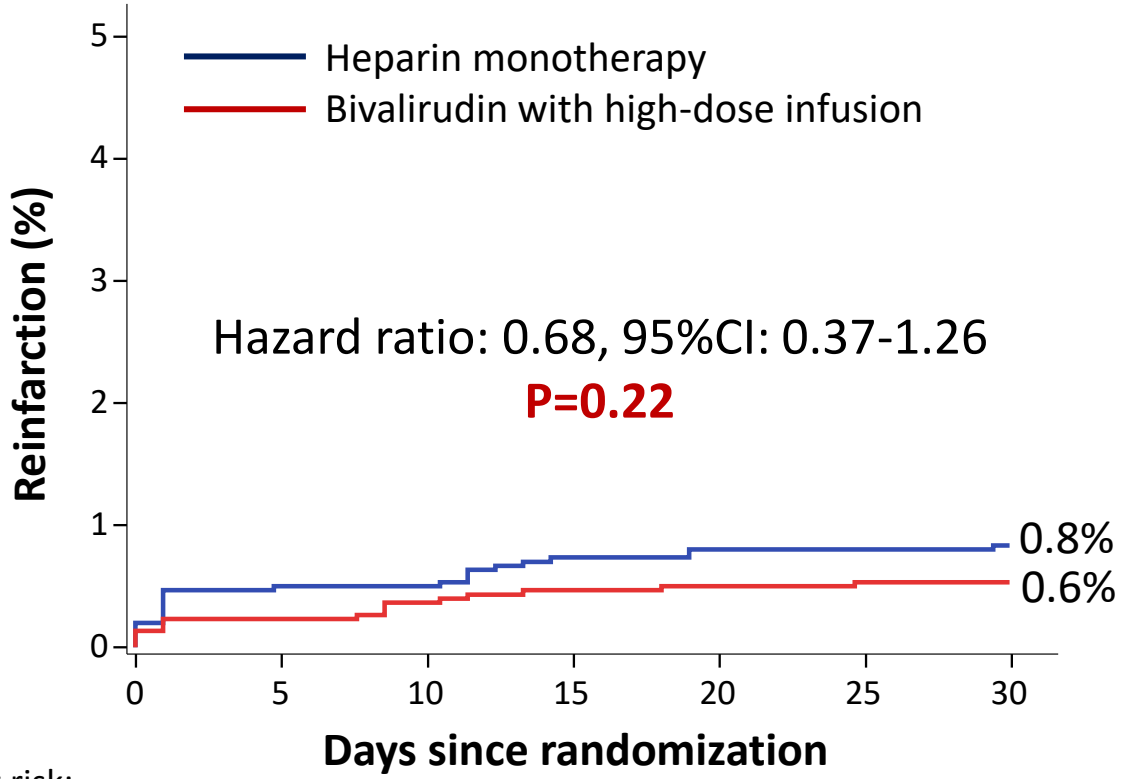
Patients with BARC 3-5 Bleeding

BARC types 3-5 bleeding	Heparin (n=24)	Bivalirudin (n=5)
Access site-related	1 (4.2%)	0 (0.0%)
Non-access site-related	23 (95.8%)	5 (100.0%)
Gastrointestinal	17 (70.8%)	4 (80.0%)
Intracranial	3 (12.5%)	1 (20.0%)
Other	3 (12.5%)	0 (0.0%)
Blood transfusion	14 (58.3%)	2 (40.0%)
Mean volume, units	2.3 ± 0.7	1.8 ± 0.4
Surgery to treat bleeding	0 (0.0%)	0 (0.0%)
Endoscopic procedure for bleeding	4/17 (23.5%)	1/4 (25.0%)
DAPT discontinuation* after bleeding†	21 (87.5%)	4 (80.0%)
Stent thrombosis after bleeding†	0 (0.0%)	0 (0.0%)
Death after bleeding†	10 (41.7%)	2 (40.0%)

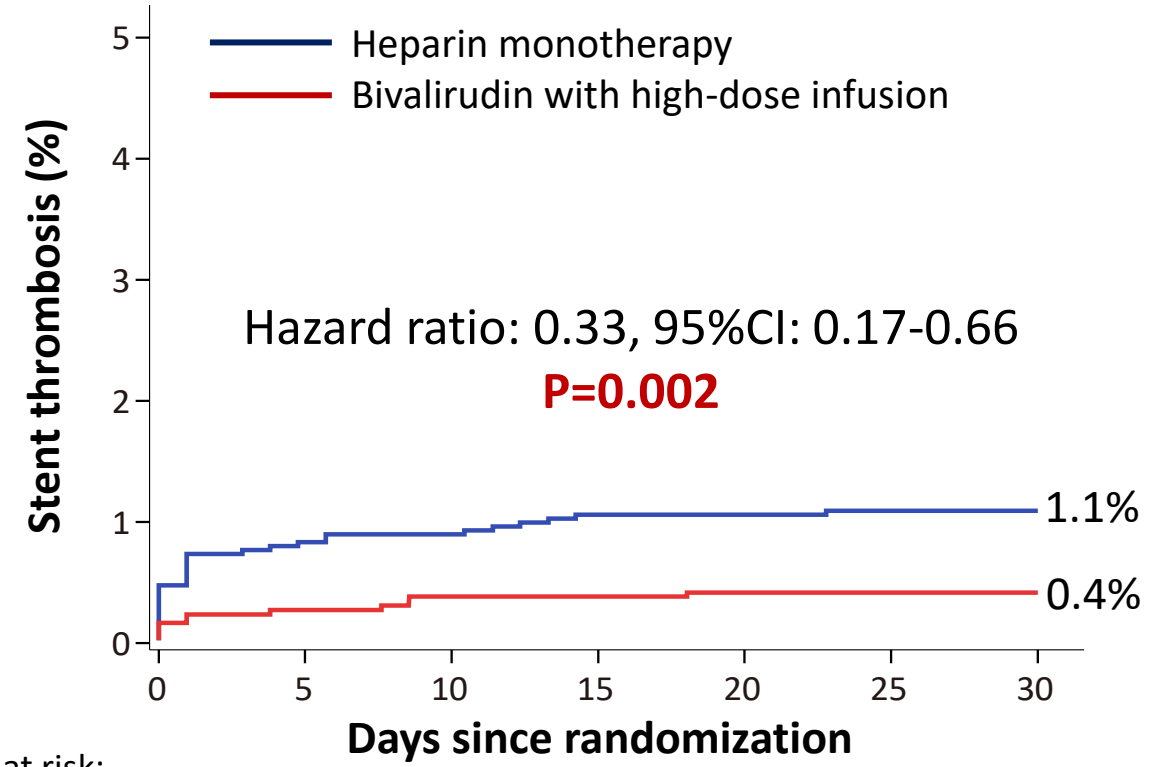
*Discontinuation of either aspirin or a P2Y12 inhibitor or both. †Within the 30-day follow-up period.

Reinfarction and Stent Thrombosis



No. at risk:

Heparin	3007	2993	2992	2986	2985	2983	2982
Bivalirudin	3009	3002	2998	2995	2994	2994	2992



No. at risk:

Heparin	3007	2983	2980	2976	2975	2974	2974
Bivalirudin	3009	3002	2999	2999	2998	2998	2998

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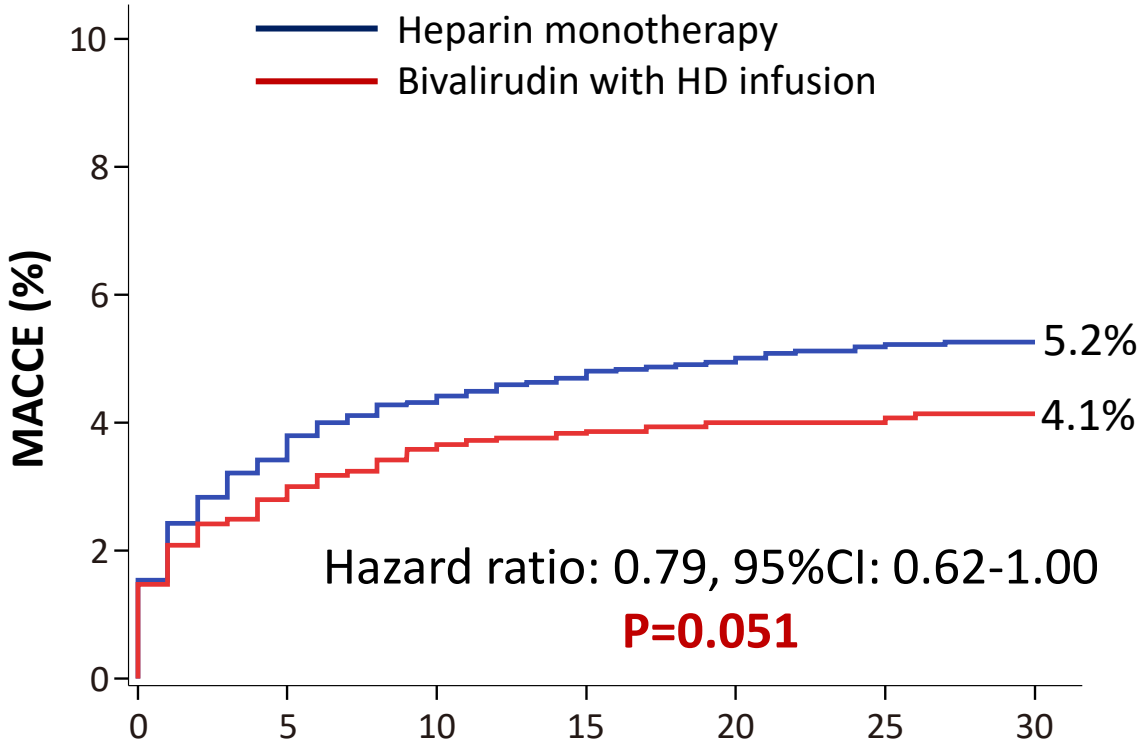
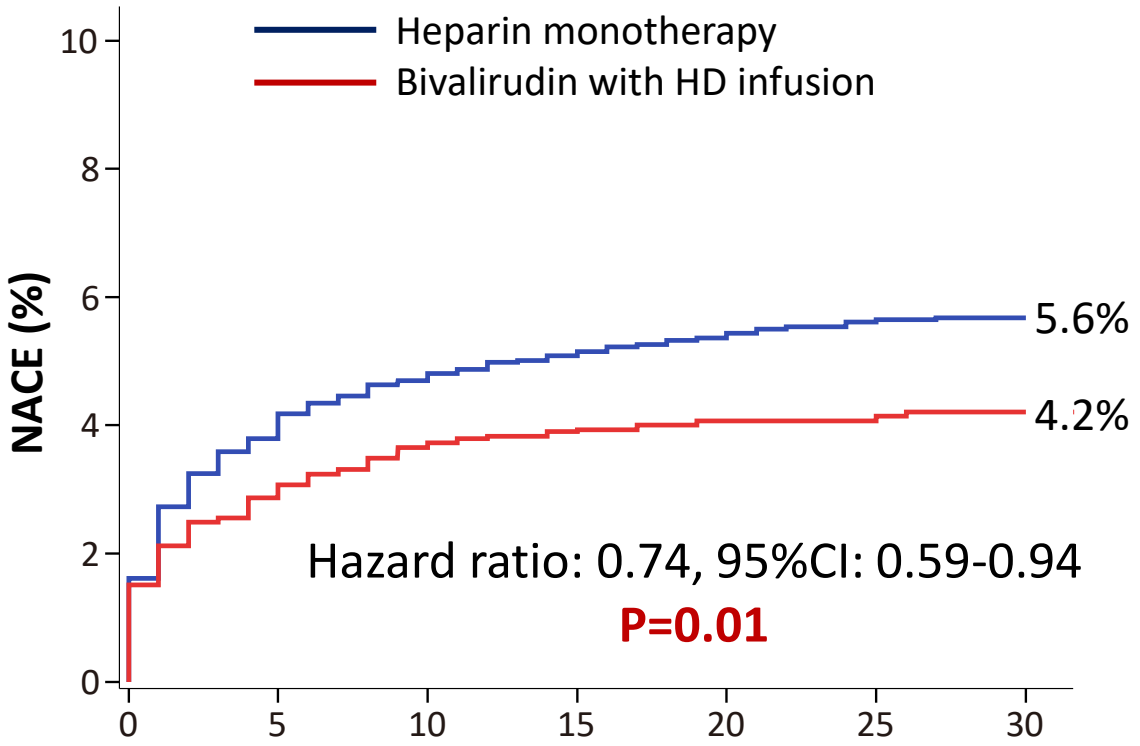
MACCE and NACE



No. at risk

Heparin	3007	2906	2880	2869	2862	2855	2853
Bivalirudin	3009	2926	2903	2896	2891	2891	2887



No. at risk

Heparin	3007	2895	2869	2858	2850	2843	2841
Bivalirudin	3009	2924	2901	2894	2889	2889	2885

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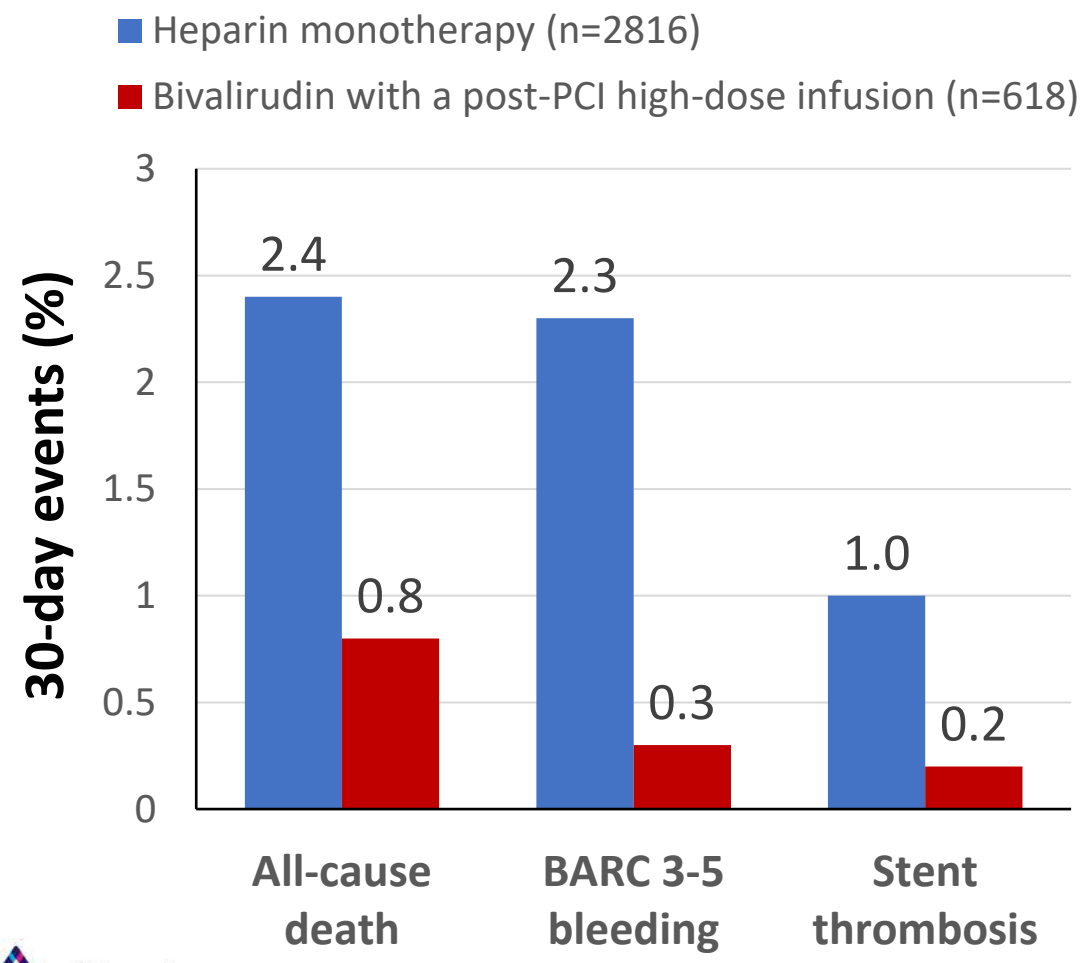
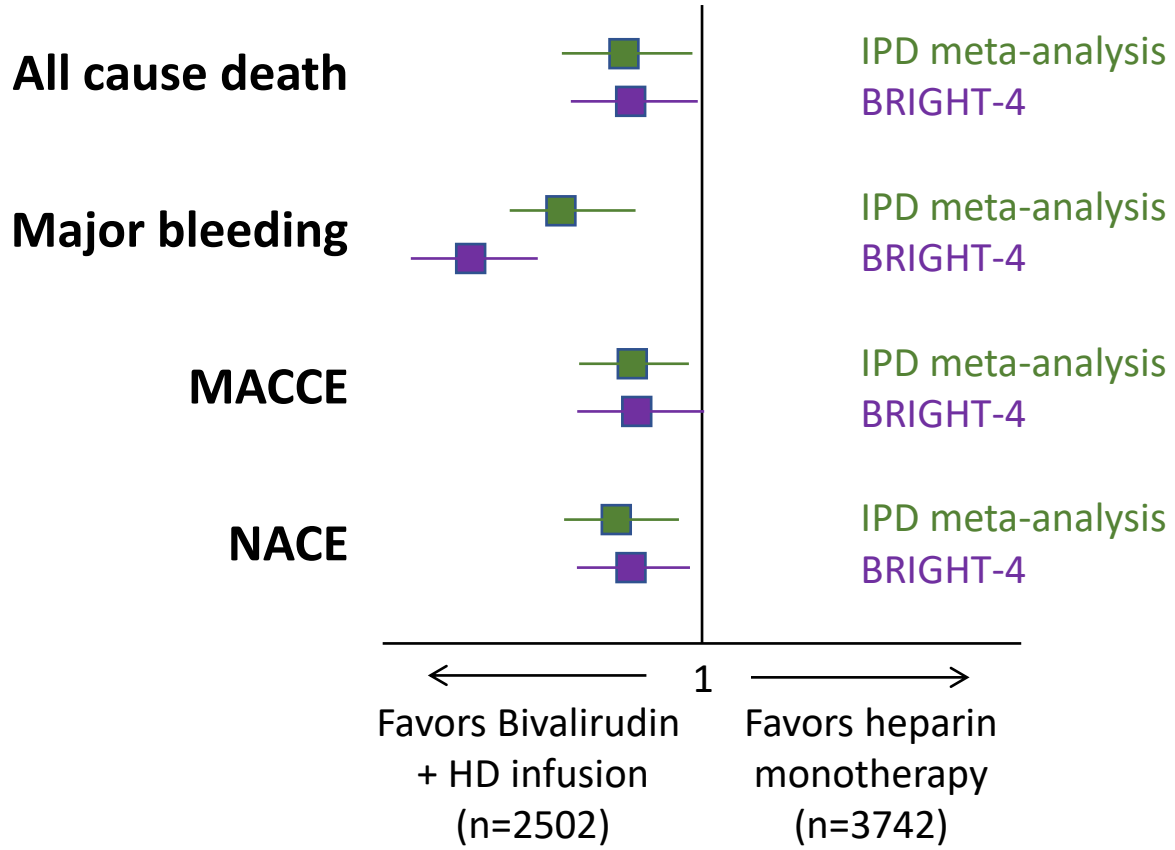
Generalizability

MATRIX Trial in Europe



Valgimigli M et al. N Engl J Med. 2015;373:997-1009

Individual patient data meta-analysis of the 6 prior RCTs of bivalirudin in STEMI



Stone GW….Bikdeli B. Submitted
Li Y,…Stone GW. Lancet. 2022

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Practical Issues

- Is it too costly?
  - NO! Bivalirudin is now generic, ~$150-200 more expensive than heparin in most countries for a bolus + infusion
- Is it difficult to use?
  - NO! Tell the cath lab nurse to “start the bival” rather than administering heparin
  - Continue the same cath lab infusion for 3 hours post-PCI
  - Start to deflate the radial hemostasis band 1 hour after infusion d/c

Bivalirudin anticoagulation during STEMI will prevent ~25% of all deaths within 30 days!*

*Steg PG. AHA 2022

Conclusions and Clinical Implications

- In BRIGHT-4, among pts with STEMI undergoing primary PCI with radial artery access, bivalirudin with a median 3-hour post-PCI high-dose infusion reduced the 30-day rates of all-cause mortality, BARC types 3-5 major bleeding, stent thrombosis and NACE compared with heparin monotherapy
- Bivalirudin is generic (and thus highly cost-effective), and easy to use
- **Bivalirudin with a median 2-4-hour post-PCI high-dose infusion should be considered standard of care for anticoagulation during primary PCI for STEMI**

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