



Results of the EUROMAX trial

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- A complete list is available in Steg PG et al. Design and methods of the EUROMAX trial.

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Ph. Gabriel Steg – Disclosures

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- **Stockholding:** Aterovax

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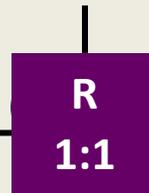
Bivalirudin for PPCI in STEMI

- The HORIZONS AMI trial established the role of bivalirudin in PPCI, with a reduction in mortality and in bleeding sustained up to 3 years compared to UFH + GPI
- However, there are new questions:
 - What is the role of bivalirudin in the ambulance for patients triaged to primary PCI (from the pre-hospital setting or from non-PCI-capable hospitals) ?
 - Is it possible to reduce the risk of acute stent thrombosis by using a prolonged infusion of bivalirudin at the end of PCI ?
 - What is the impact of contemporary practice (e.g. novel P2Y₁₂ inhibitors, increased use of radial arterial access, no systematic use of GPIs) on efficacy and safety of bivalirudin ?

EUROMAX Trial Design

2218 patients with STEMI with symptom onset >20 min and ≤12h
Randomized in ambulance or non-PCI hospital
Intent for primary PCI

*Aspirin + P2Y₁₂ inhibitor
(any) as soon as possible*



UFH/LMWH ± GPI
Per standard practice

Bivalirudin
(0.75 mg/kg bolus, 1.75 mg/kg/h infusion)
+ prolonged optional infusion
(PCI dose or 0.25 mg/kg/h)
(provisional GPI only)

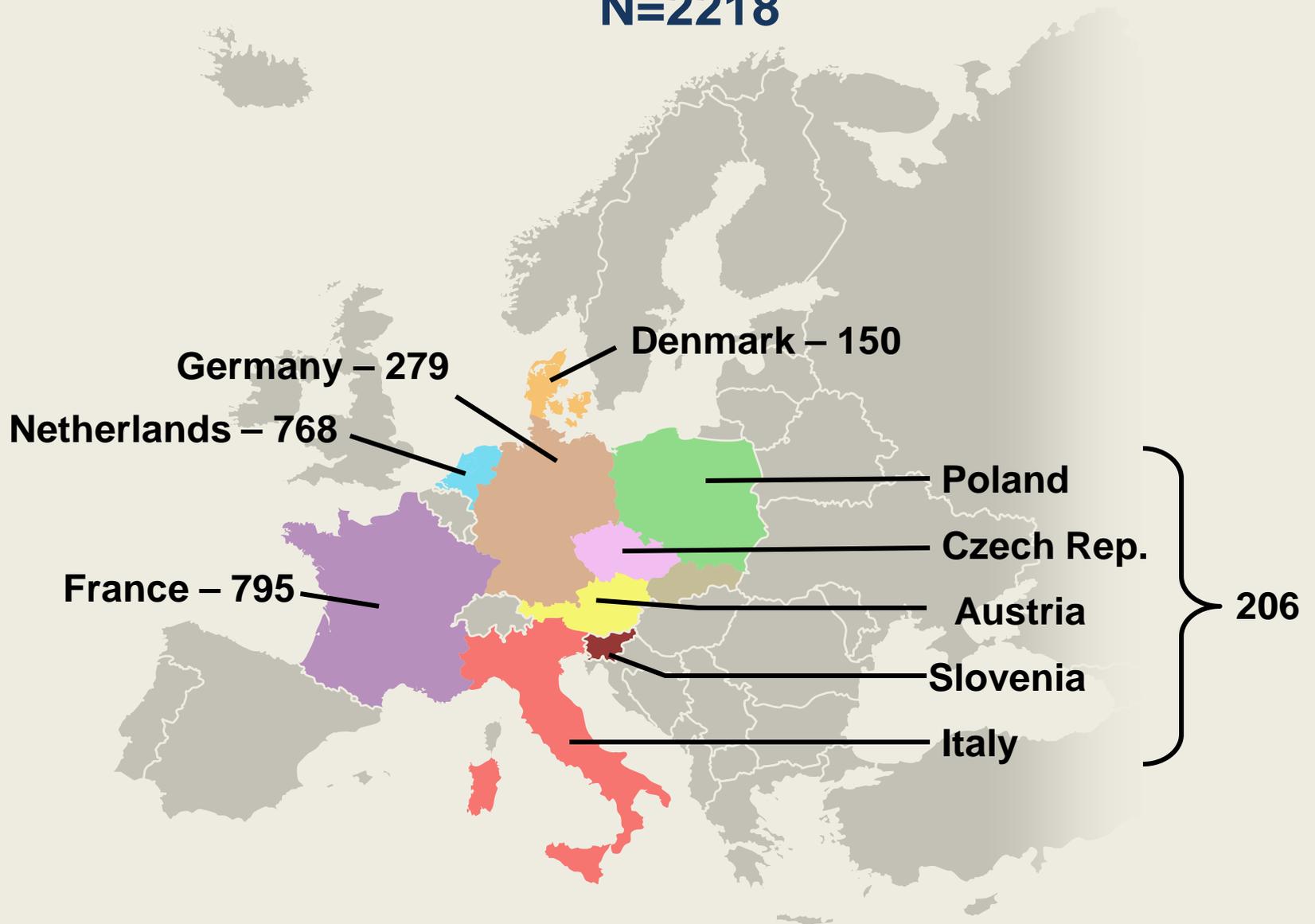
Primary endpoint: 30-day death or non-CABG related major bleeding

Key Secondary endpoint: Death, Re-infarction or non-CABG major bleeding at 30 days

Clinical FU at 30 days and 1 year

EUROMAX - A European Trial

N=2218



Baseline Characteristics

	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)
Age — median (IQR), yr	61 (52, 71)	62 (52, 72)
Age >65 yr — no. (%)	394 (36.2)	434 (39.1)
Female sex — no. (%)	275 (25.3)	248 (22.4)
Diabetes — no. (%)	127 (11.7)	169 (15.3)*
Hypertension — no. (%)	459 (42.2)	504 (45.5)
Hyperlipidemia‡ — no. (%)	398 (36.6)	417 (37.6)
Current smoker — no. (%)	453 (41.6)	472 (42.6)
Prior myocardial infarction — no. (%)	80 (7.4)	113 (10.2)*
Prior PCI — no. (%)	97 (8.9)	108 (9.7)
Prior CABG — no. (%)	18 (1.7)	29 (2.6)
Killip class II, III, or IV — no. (%)	77 (7.7)	69 (6.9)
Anemia — no. (%)	129 (13.1)	148 (15.0)
Creatinine clearance — no. (%)		
≤60 mL/min	147 (14.7)	165 (16.5)
>60 mL/min	854 (85.3)	833 (83.5)

* P < 0.05 between groups

Procedures, Medications

	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)
Randomized in ambulance no. (%)	1030 (94.6)	1045 (94.2)
Randomized in non-PCI-capable hospital— no. (%)	59 (5.4)	64 (5.8)
Aspirin use — no. (%)	1088 (100)	1107 (99.8)
P2Y ₁₂ inhibitor loading dose — no. (%)		
Yes	1048/1066 (98.3)	1058/1083 (97.7)
Clopidogrel	524/1048 (50.0)	545/1058 (51.5)
Ticlopidine	0 (0.0)	2 (0.2)
Prasugrel	323/1048 (30.8)	306/1058 (28.9)
Ticagrelor	201/1048 (19.2)	205/1058 (19.4)
P2Y ₁₂ loading before angiography — no. (%)	913/1011 (90.3)	923/1010 (91.4)
Maintenance dose - yes	957/1065 (89.9)	969/1082 (89.6)
Clopidogrel	377/957 (39.4)	407/969 (42.0)
Ticlopidine	2/957 (0.2)	5/969 (0.5)
Prasugrel	321/957 (33.5)	298/969 (30.8)
Ticagrelor	257/957 (26.9)	259/969 (26.7)

Procedures, Medications, con't

	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)
Initial anticoagulation — no. (%)		
Bivalirudin	1074 (98.6)	29 (2.6)
Unfractionated heparin	24 (2.2)	997 (89.9)
Enoxaparin	0	94 (8.5)
Time from initiating anticoagulation to angiography — median (IQR), min	50.0 (37–67)	50.0 (37–65)
Glycoprotein IIb/IIIa inhibitor use — no. (%)	125/1088 (11.5)	766/1109 (69.1)*
Routine	42/1088 (3.9)‡	649/1109 (58.5)*
Bailout §	83/1046 (7.9)	117/460 (25.4)*
Femoral access — no. (%)	558/1069 (52.2)	582/1084 (53.7)
Radial access — no. (%)	510/1069 (47.7)	502/1084 (46.3)

* P < 0.05 between groups

‡ Deviations from the protocol

§ Data given for those eligible for bailout (i.e. who did not receive routine GPI).

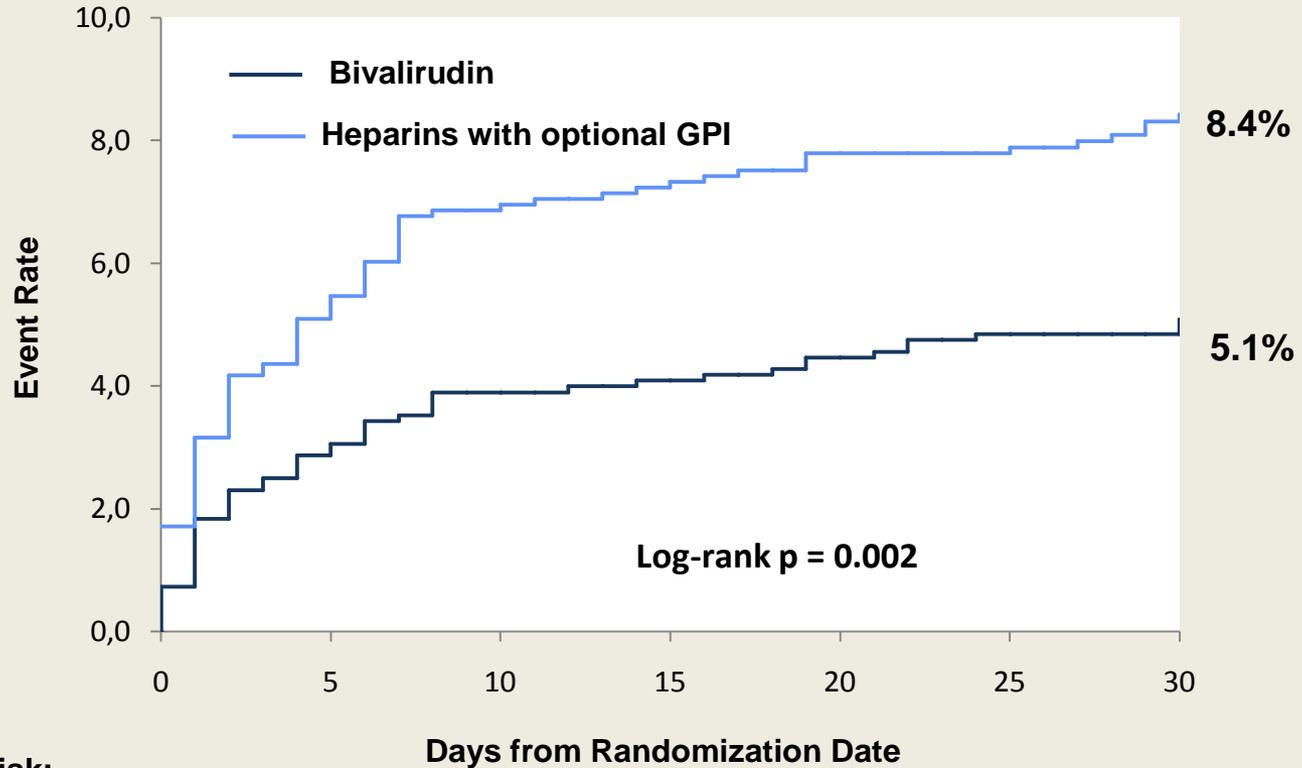
Procedural Characteristics

	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)
Single vessel disease — no. (%)	591/1069 (55.3)	556/1083 (51.3)
Infarct artery treated with primary PCI — no. (%)		
Left main coronary artery	6/943 (0.6)	13/946 (1.4)
Left anterior descending artery	425/943 (45.1)	423/946 (44.7)
Left circumflex coronary artery	115/943 (12.2)	132/946 (14.0)
Right coronary artery	417/943 (44.2)	412/946 (43.6)
Bypass graft (venous or arterial)	4/943 (0.4)	10/946 (1.1)
Balloon angioplasty only — no. (%)	48/943 (5.1)	42/946 (4.4)
Stents implanted — no. (%)	868/943 (92.0)	865/946 (91.4)
Drug-eluting stent	538/943 (57.1)	529/946 (55.9)
Thrombectomy — no. (%)	304/943 (32.2)	298/946 (31.5)
Pre-PCI TIMI flow — no. (%)		
0/1	593/931 (63.7)	563/932 (60.4)
2	143/931(15.4)	158/932 (17.0)
3	195/931 (20.9)	211/932 (22.6)
Post-PCI TIMI flow — no. (%)		
0/1	18/930 (1.9)	16/932 (1.7)
2	29/930 (3.1)	31/932 (3.3)
3	883/930 (94.9)	885/932 (95.0)
CABG during hospitalization	21/1089 (1.9)	29/1109 (2.6)

Medications at Discharge (ITT)

Variable — no. (%)	Bivalirudin (N=1089)	Heparins + optional GPI (N=1109)
ACE inhibitor or ARB	718 (65.9)	709 (63.9)
Aspirin	1000 (91.8)	1012 (91.3)
Beta-blocker	944 (86.7)	957 (86.3)
P2Y ₁₂ inhibitor	938 (86.1)	941 (84.9)
Statin	968 (88.9)	997 (89.9)

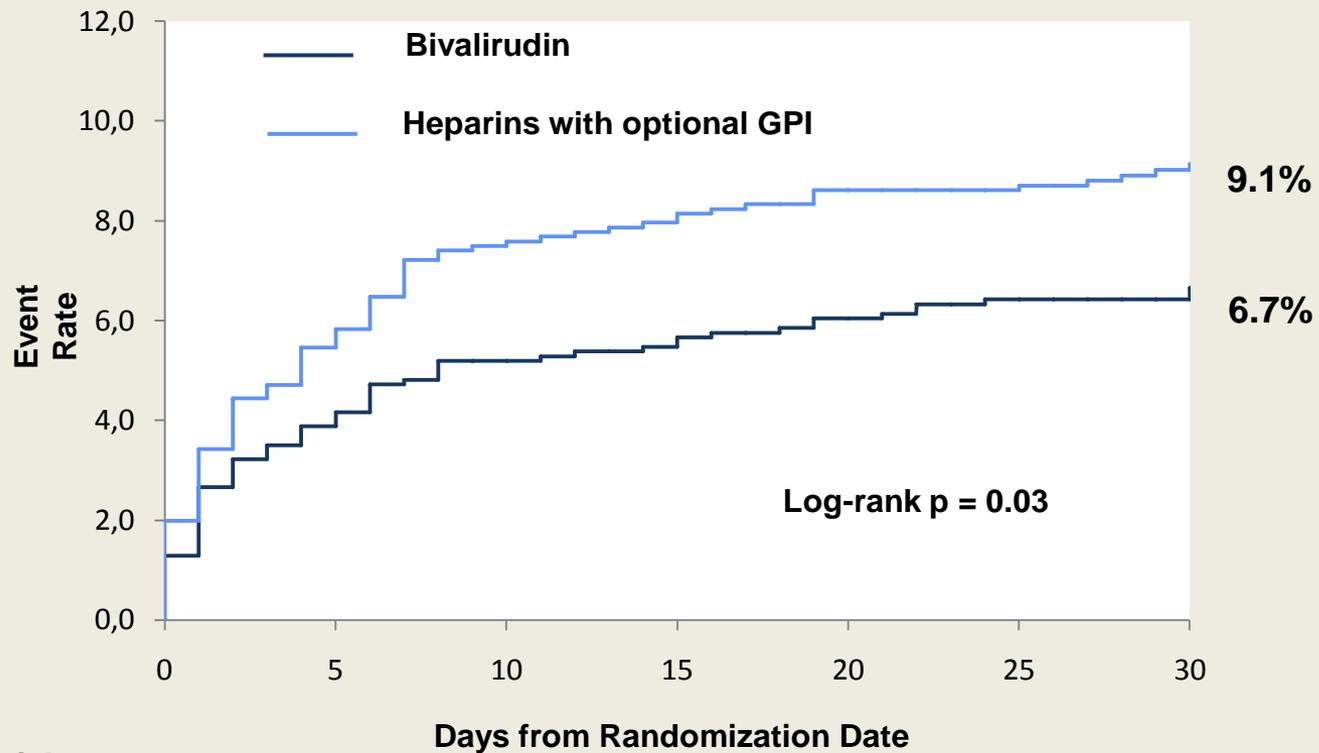
Primary Endpoint: Death or Major Bleed, 30 day



Patients at risk:

	0	5	10	15	20	25	30
Bivalirudin	1089	1038	1024	1020	1007	988	791
Heparins with optional GPI	1109	1024	1003	998	984	958	765

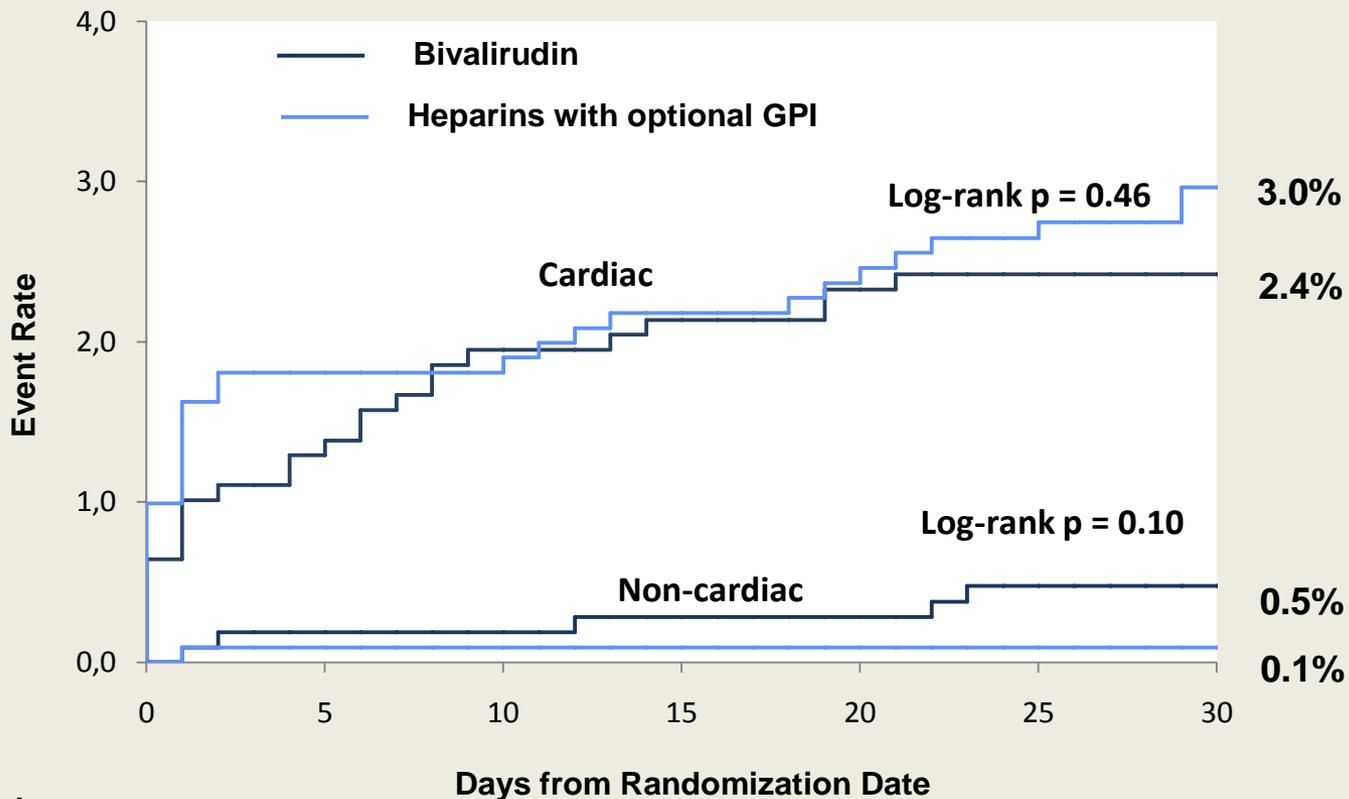
Principal Secondary Endpoint: Death/Reinfarction/Major Bleed, 30 day



Patients at risk:

Bivalirudin	1089	1027	1010	1005	990	971	779
Heparins with optional GPI	1109	1020	996	990	975	949	760

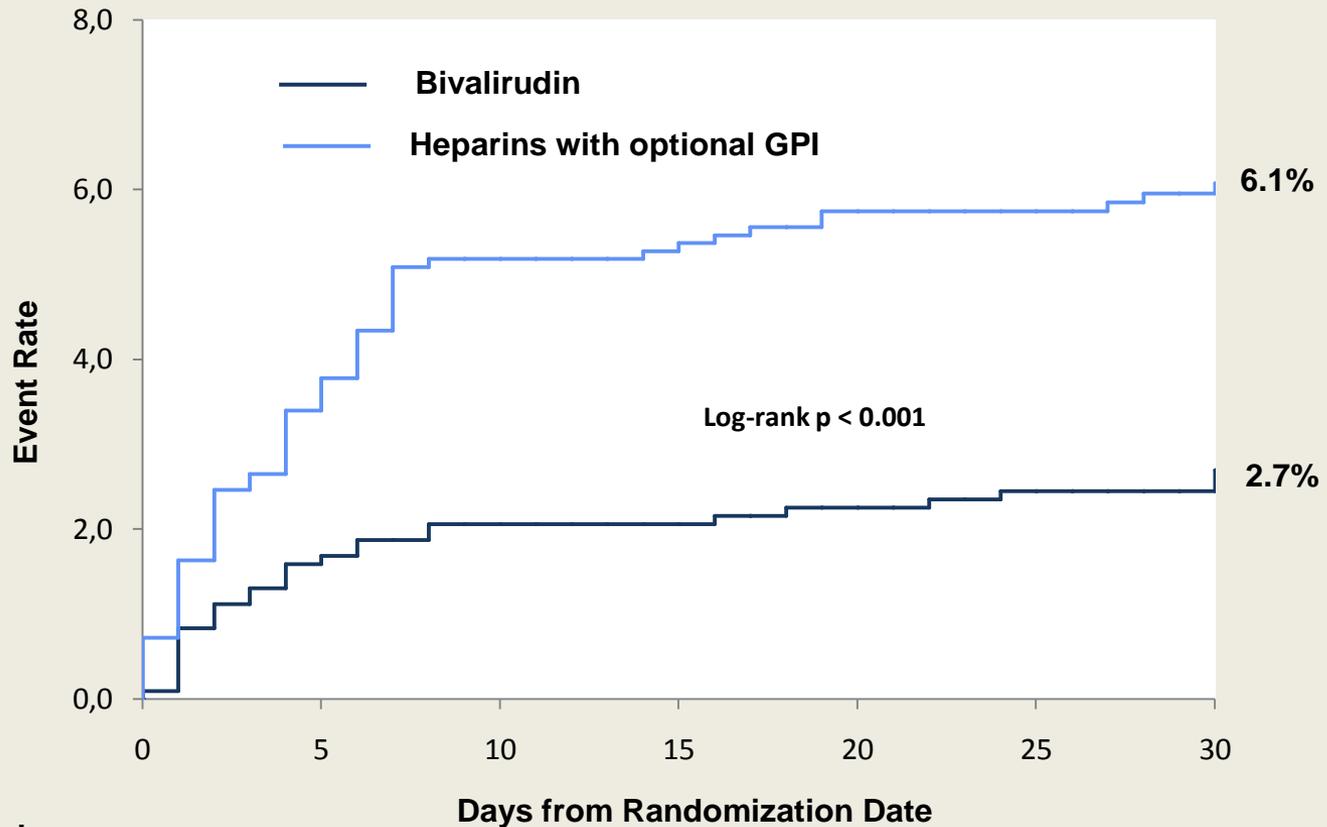
Cardiac and Non-Cardiac Death, 30-day



Patients at risk:

Bivalirudin	1089	1057	1048	1044	1039	1036	1034
Heparins with optional GPI	1109	1062	1061	1056	1050	1043	1037

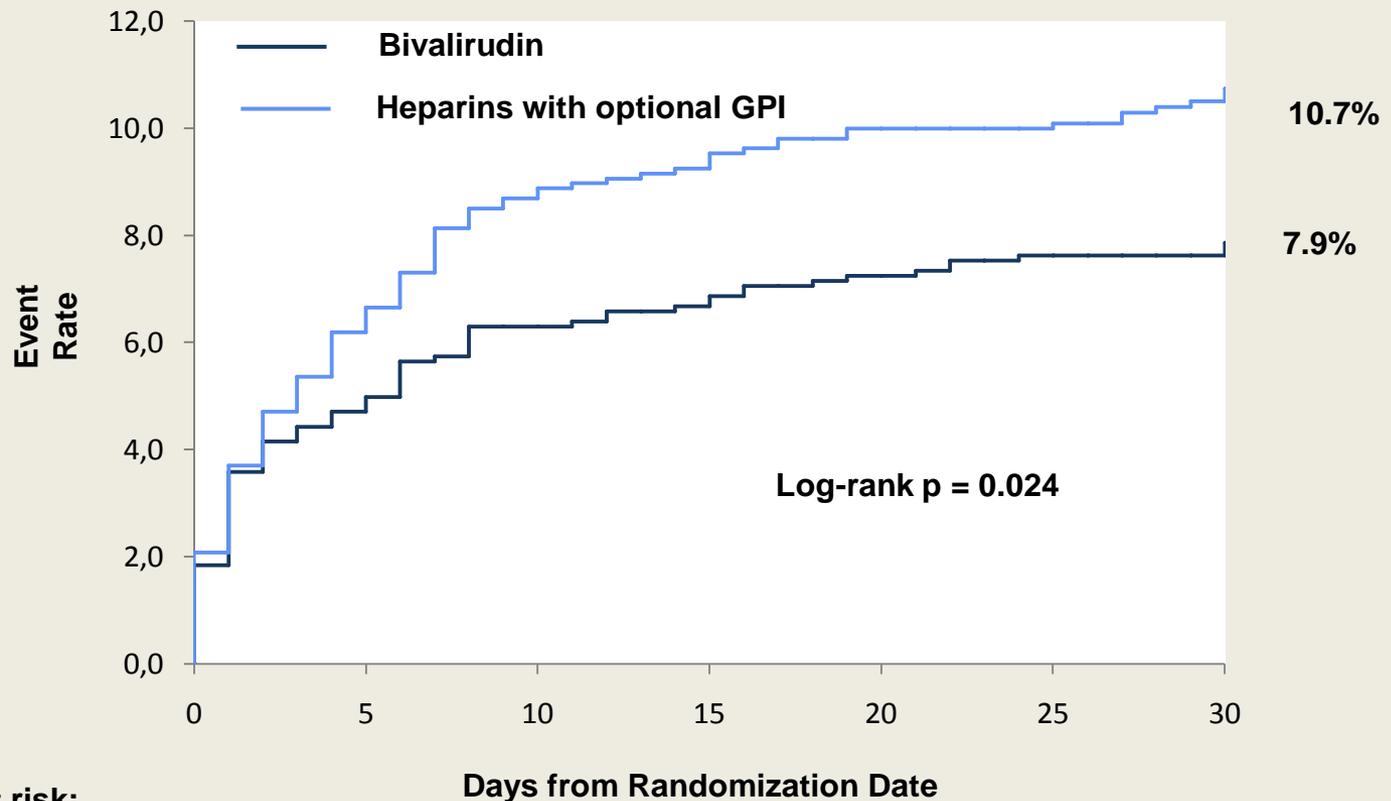
Non-CABG-related major bleed, 30 day



Patients at risk:

Bivalirudin	1089	1040	1025	1022	1010	991	794
Heparins with optional GPI	1109	1030	1009	1005	990	964	773

NACE: Death, Reinfarction, IDR, Stroke, Major Bleed, 30 day



Patients at risk:

Bivalirudin	1089	1018	998	992	977	959	769
Heparins with optional GPI	1109	1012	983	976	960	934	746

Clinical Outcomes, 30 days

	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)	Relative risk [95% CI]	P Value
Death or major bleeding (non-CABG) (primary outcome)	55 (5.1)	94 (8.5)	0.60 (0.43–0.82)	0.001
Death, reinfarction, or major bleeding (non-CABG) (key secondary outcome)	72 (6.6)	102 (9.2)	0.72 (0.54–0.96)	0.02
Death	32 (2.9)	34 (3.1)	0.96 (0.60–1.54)	0.86
Cardiac causes	27 (2.5)	33 (3.0)	0.83 (0.50–1.38)	0.48
Noncardiac causes	5 (0.5)	1 (0.1)	5.09 (0.60–43.51)	0.12
Major bleeding (non-CABG)	28 (2.6)	67 (6.0)	0.43 (0.28–0.66)	<0.001
Major adverse cardiovascular events*	65 (6.0)	61 (5.5)	1.09 (0.77–1.52)	0.64
Net adverse clinical events *	85 (7.8)	118 (10.6)	0.73 (0.56–0.96)	0.02

*Patients may have experienced more than one event.

MACE denotes death, reinfarction, ischemia-driven revascularization or stroke;

NACE denotes (death, reinfarction, ischemia-driven revascularization, stroke, or non-CABG major bleeding)

Bleeding rates, 30 days

	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)	Relative risk [95% CI]	P Value
Major bleeding (non-CABG)	28 (2.6)	67 (6.0)	0.43 (0.28–0.66)	<0.001
Major or minor bleeding (non-CABG)	85 (7.8)	149 (13.4)	0.58 (0.45–0.75)	<0.001
TIMI major bleeding (non-CABG)	14 (1.3)	23 (2.1)	0.62 (0.32–1.20)	0.15
TIMI major/minor bleeding (non-CABG)	85 (7.8)	146 (13.2)	0.59 (0.46–0.76)	<0.001
GUSTO severe/life-threatening bleeding (non-CABG)	6 (0.6)	10 (0.9)	0.61 (0.22–1.68)	0.33
GUSTO severe/life-threatening or moderate bleeding (non-CABG)	14 (1.3)	26 (2.3)	0.55 (0.29–1.04)	0.06
GUSTO any bleeding (non-CABG)	85 (7.8)	148 (13.3)	0.58 (0.45–0.75)	<0.001
Blood transfusion	23 (2.1)	43 (3.9)	0.54 (0.33–0.90)	0.02

- Patients may have experienced more than one event.

Outcomes, 30 days, con't

	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)	Relative risk [95% CI]	P Value
Reinfarction	19 (1.7)	10 (0.9)	1.93 (0.90–4.14)	0.08
Q-wave	3 (0.3)	2 (0.2)	1.53 (0.26–9.12)	0.68
Non-Q-wave	16 (1.5)	8 (0.7)	2.04 (0.88–4.74)	0.09
Stent thrombosis (ARC definition)	17 (1.6)	6 (0.5)	2.89 (1.14–7.29)	0.02
Definite	17 (1.6)	6 (0.5)	2.89 (1.14–7.29)	0.02
Probable	0 (0)	0 (0)	–	n/a
Acute (≤24 hours)	12 (1.1)	2 (0.2)	6.11 (1.37–27.24)	0.007
Subacute (>24 hours to 30 days)	5 (0.5)	4 (0.4)	1.27 (0.34–4.73)	0.75
Ischemia-driven revascularization	24 (2.2)	17 (1.5)	1.44 (0.78–2.66)	0.25
Reinfarction, ischemia-driven revascularization or stent thrombosis	29 (2.7)	21 (1.9)	1.41 (0.81–2.45)	0.23
Any stroke	6 (0.6)	11 (1.0)	0.56 (0.21–1.50)	0.24
Ischemic	6 (0.6)	9 (0.8)	0.68 (0.24–1.9)	0.46
Hemorrhagic	0	2 (0.2)	Not applicable	0.50
Acquired thrombocytopenia	7 (0.7)	14 (1.4)	0.50 (0.20–1.24)	0.13

n/a: not applicable.





Limitations of the study

- The study was open-label, for logistical reasons.
- In order to reduce sample size, the primary endpoint was changed (while still entirely blinded to results) from an original composite of death/reinfarction/major bleeding to death/major bleeding, retaining the original composite as key secondary endpoint.
- The trial was not powered to examine 30-day mortality.
- Although the trial allowed use of UFH or enoxaparin in the control arm, too few patients received the latter to reliably test the consistency of the benefit of bivalirudin across heparins.

Conclusions

- Prehospital initiation of bivalirudin, as compared with heparin with optional use of glycoprotein IIb/IIIa inhibitors, reduced the primary composite and the key secondary outcomes in patients with STEMI who were being transported for primary PCI.
- These benefits, which were consistent across subgroups, stemmed from substantial reductions in major bleeding.
- However, the risk of acute stent thrombosis was higher in the bivalirudin group.
- These results were achieved on a background of contemporary care, with a high rate of radial access, use of novel P2Y12 inhibitors, and optional GPI use in the control arm.
- They inform pre-hospital management of STEMI and support a role for bivalirudin in this setting.

Study Committees

Executive Committee	Ph.G. Steg (Chair) , J. Adgey, P. Clemmensen, P. Goldstein, M. Hamon, A. van 't Hof, L. Nibbe, U. Zeymer
International Steering Committee	C.W. Hamm (Chair) ; J. Hill, Tom Quinn (UK); P. Clemmensen, J. Steinmetz (Denmark); P. Coste, F. Lapostolle (France); C. Cavallini, G. Gordini; F.W.A. Verheugt, J. ten Berg (Netherlands); U. Zeymer, L. Nibbe (Germany); M. Hirschl, K. Huber (Austria); A. Cequier (Spain); D. Dudek (Poland); P. Widimský (Czech Republic); V. Kanic (Slovenia)
Data Monitoring Committee	N. Danchin (Chair) , I. Ford, A. Maggioni, R. Mehran, G. Montalescot
Independent statistician (interim analysis)	C.R. Mehta
Independent statistical group	T.C. Clayton, S.J. Pocock
Clinical Events Committee	K. Thygesen , J. Peder Bagger

For full details (including the protocol, statistical analysis plan and supplementary data appendix), go to www.nejm.org

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ORIGINAL ARTICLE

Bivalirudin Started during Emergency Transport for Primary PCI

Philippe Gabriel Steg, M.D., Arnoud van 't Hof, M.D., Ph.D., Christian W. Hamm, M.D., Peter Clemmensen, M.D., Ph.D., Frédéric Lapostolle, M.D., Ph.D., Pierre Coste, M.D., Jurrien Ten Berg, M.D., Ph.D., Pierre Van Grunsven, M.D., Gerrit Jan Eggink, M.D., Lutz Nibbe, M.D., Uwe Zeymer, M.D., Marco Campo dell' Orto, M.D., Holger Nef, M.D., Jacob Steinmetz, M.D., Ph.D., Louis Soulat, M.D., Kurt Huber, M.D., Efthymios N. Deliargyris, M.D., Debra Bernstein, Ph.D., Diana Schuette, Ph.D., Jayne Prats, Ph.D., Tim Clayton, M.Sc., Stuart Pocock, Ph.D., Martial Hamon, M.D., and Patrick Goldstein, M.D., for the EUROMAX Investigators*

Steg PG, van't Hof A, Hamm CW et al. *N Engl J Med* 2013

Backup slides

Patient Disposition

2218 Patients with presumed STEMI and symptom onset ≤ 12 hours underwent randomization

1102 assigned to bivalirudin after initial consent*
1089/1102 (98.8%) provided written final informed consent

1069/1089 (98.2%) underwent emergent angiography

Principal management strategy:

949/1069 (88.8%) Primary PCI

17/1069 (1.6%) CABG

103/1069 (9.6%) Medical Management

8 withdrew consent
7 were lost to follow-up

1074/1089 (98.6%) completed 30 days in the study

1089 were included in the intention-to-treat analysis

1116 assigned to standard of care after initial consent*
1109/1116 (99.4%) provided written final informed consent

1084/1109 (97.7%) underwent emergent angiography

Principal management strategy:

947/1084 (87.4%) Primary PCI

25/1084 (2.3%) CABG

112/1084 (10.3%) Medical Management

8 withdrew consent
15 were lost to follow-up

1086/1109 (97.9%) completed 30 days in the study

1109 were included in the intention-to-treat analysis

Components of Major Bleeding Up to 30 Days, ITT

Component	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)	Relative risk [95% CI]	P Value
Intracranial	0/1089 (0.0)	2/1109 (0.2)	N/A	0.50
Retroperitoneal	2/1089 (0.2)	0/1109 (0.0)	N/A	0.25
Intraocular	0/1089 (0.0)	0/1109 (0.0)	N/A	N/A
Cardiac tamponade	1/1089 (0.1)	1/1109 (0.1)	1.02 [0.06, 16.26]	1.00
Access site hemorrhage requiring intervention	3/1089 (0.3)	12/1109 (1.1)	0.25 [0.07, 0.90]	0.02
Clinically overt bleed	2/1089 (0.2)	4/1109 (0.4)	0.51 [0.09, 2.77]	0.69
Drop in hemoglobin or hematocrit	12/1089 (1.1)	34/1109 (3.1)	0.36 [0.19, 0.69]	0.001
Reoperation for bleeding	3/1089 (0.3)	0/1109 (0.0)	N/A	0.12
Blood transfusion	8/1089 (0.7)	24/1109 (2.2)	0.34 [0.15, 0.75]	0.005
Hemodynamic compromise	1/1089 (0.1)	2/1109 (0.2)	0.51 [0.05, 5.61]	1.00

* Patients may have experienced more than one event.

CI denotes confidence interval, GPI glycoprotein inhibitor, and NA not applicable.

Main Inclusion and Exclusion Criteria

- Patients presenting ≤ 12 h of symptom onset with a presumed diagnosis of STEMI
 - either ST-segment elevation ≥ 1 mm in 2 contiguous ECG leads, or
 - presumed new LBBB or ST-segment depression ≥ 1 mm in at least 2 leads in V1–V3 with a positive terminal T wave
- Scheduled for angiography with anticipated primary PCI < 2 h after first medical contact
- Excluded:
 - treatment with any injectable anticoagulant immediately before randomization
 - previous oral anticoagulation
 - recent surgery
 - bleeding history