One-Year Mortality for Bivalirudin vs Heparins Plus Optional Glycoprotein IIb/IIIa Inhibitor Treatment Started in the Ambulance for ST-Segment Elevation Myocardial Infarction

A Secondary Analysis of the EUROMAX Randomized Clinical Trial

Enrico Fabris, MD; Sinem Kilic, MD; Arnoud W. J. van't Hof, MD, PhD; Jurrien ten Berg, MD, PhD; Ana Ayesta, MD, PhD; Uwe Zeymer, MD; Martial Hamon, MD; Louis Soulat, MD; Debra Bernstein, PhD; Prodromos Anthopoulos, MD; Efthymios N. Deliargyris, MD; Philippe Gabriel Steg, MD

IMPORTANCE Uncertainty exists regarding potential survival benefits of bivalirudin compared with heparin with routine or optional use of glycoprotein IIb/IIIa inhibitors (GPIs) in patients with ST-segment elevation myocardial infarction (STEMI). Few data are available regarding long-term mortality in the context of contemporary practice with frequent use of radial access and novel platelet adenosine diphosphate P2Y12 receptor inhibitors.

OBJECTIVE To assess the effect of bivalirudin monotherapy compared with unfractionated or low-molecular-weight heparin plus optional GPIs on 1-year mortality.

DESIGN, SETTING, AND PARTICIPANTS This international, randomized, open-label clinical trial (EUROMAX [European Ambulance Acute Coronary Syndrome Angiography]) included 2198 patients with STEMI undergoing transport for primary percutaneous coronary intervention from March 10, 2010, through June 20, 2013, and followed up for 1 year. Patients were randomized (1:1) in ambulance to bivalirudin monotherapy vs unfractionated or low-molecular-weight heparin plus optional GPIs (control group). Analysis was based on intention to treat.

MAIN OUTCOMES AND MEASURES The primary outcome of this prespecified analysis was 1-year mortality. All deaths were adjudicated as cardiac or noncardiac by an independent, blinded clinical events committee. One-year mortality was assessed and examined across multiple prespecified subgroups.

RESULTS Of the 2198 patients enrolled (1675 men [76.2%] and 523 women [23.8%]; median [interquartile range] age, 62 [52-72] years), complete 1-year follow-up data were available for 2164 (98.5%). All-cause 1-year mortality occurred in 118 patients (5.4%). The number of all-cause deaths was the same for both treatment groups (59 deaths; relative risk [RR], 1.02; 95% CI, 0.72-1.45; $P = .92$). No differences were noted in the rates of 1-year cardiac death (44 [4.0%] for the bivalirudin group vs 48 [4.3%] for the control group; RR, 0.93; 95% CI, 0.63-1.39; $P = .74$) or noncardiac death (15 [1.4%] for the bivalirudin group vs 11 [1.0%] for the control group; RR, 1.39; 95% CI, 0.64-3.01; $P = .40$). Results were consistent across the prespecified patient subgroups. The rate of deaths occurring from 30 days to 1 year was also similar (27 [2.5%] in the bivalirudin group vs 25 [2.3%] in the control group; RR, 1.10; 95% CI, 0.64-1.88; $P = .73$).

CONCLUSIONS AND RELEVANCE In patients with STEMI who were being transported for primary percutaneous coronary intervention, treatment with bivalirudin or with heparin with optional use of GPI resulted in similar 1-year mortality. The reduced composite end point of death and/or major bleeding at 30 days in the bivalirudin arm of the EUROMAX trial did not translate into reduced cardiovascular or all-cause death at 1 year.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Arnoud W. J. van't Hof, MD, PhD, Department of Cardiology, Isala Hospital, Dokter van Heesweg 2, 8025 AB Zwolle, the Netherlands (a.w.j.vant.hof@isala.nl).

Debate persists as to whether heparin or bivalirudin results in superior clinical outcomes in patients undergoing primary percutaneous coronary intervention (PCI). Studies comparing bivalirudin with other antithrombotic strategies have produced inconsistently lower mortality findings.[1-5] In the EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trial,[1] bivalirudin therapy initiated during transport for primary PCI improved 30-day clinical outcomes, with a reduction in the primary composite end point of death and major bleeding because of a marked reduction in major bleeding without an obvious difference in 30-day mortality. Major bleeding is strongly associated with an increased risk for subsequent long-term mortality.[6] Long-term follow-up is important to assess the potential late benefits of bivalirudin therapy in primary PCI; we therefore assessed the effect of bivalirudin monotherapy compared with unfractionated or low-molecular-weight heparin plus optional glycoprotein IIb/IIIa inhibitors (GPIs) on 1-year mortality, a prespecified outcome of the EUROMAX trial.

Key Points

Question Does the reduced composite end point of death and/or major bleeding at 30 days in a randomized clinical trial of bivalirudin translate into fewer deaths at 1 year?

Findings In this secondary analysis of the EUROMAX randomized clinical trial of 2198 patients with ST-segment elevation myocardial infarction randomized during transport for primary percutaneous coronary intervention to bivalirudin or heparin with optional glycoprotein IIb/IIIa inhibitors, the number of all-cause deaths at 1 year was the same for both treatment groups.

Meaning In this patient population, treatment with bivalirudin or heparin with optional use of glycoprotein IIb/IIIa inhibitors resulted in similar 1-year mortality.

Methods

Study Design and Treatment

The EUROMAX study design and results have been described previously,[1,7] and the trial protocol is provided in Supplement 1. In brief, patients 18 years or older presenting with ST-segment elevation myocardial infarction (STEMI) and intended to undergo primary PCI within 2 hours of first medical contact were randomized (1:1) to bivalirudin or intravenous heparin (unfractionated or low-molecular-weight) with optional use of GPIs. Patients were enrolled and randomized from March 10, 2010, through June 20, 2013, and followed up for 1 year. All patients received aspirin and platelet adenosine diphosphate P2Y12 receptor (P2Y12) inhibitor as early as possible after the first medical contact. Decisions regarding access site, performance of thrombus aspiration, and stent type were left to physician preference. This study was approved by local ethics committees and health authorities. All patients provided written informed consent.

Study Outcomes

The present analysis aimed to evaluate the prespecified end point of 1-year mortality. All deaths were adjudicated as cardiac or noncardiac by an independent, blinded clinical events committee. Mortality was examined across multiple prespecified subgroups. Per protocol, nonfatal outcomes were not collected beyond the 30-day period.

Statistical Analysis

Analyses were performed in the intention-to-treat population, which was defined as all patients who underwent randomization and provided written informed consent. We compared categorical outcomes with the χ^2 test or Fisher exact test. We compared continuous variables with the Wilcoxon rank sum test. Time-to-event outcomes, determined with Kaplan-Meier methods, were compared with the log-rank test. For all analyses, a 2-sided $P < .05$ was considered to be statistically significant. All statistical analyses were performed using SAS software (version 9.2; SAS Institute Inc).

Results

A total of 2218 patients were enrolled in the trial. Of these patients, 2198 (1675 men [76.2%] and 523 women [23.8%]; median [interquartile range] age, 62 [52-72] years) provided formal written informed consent and were included in the intention-to-treat population. The baseline characteristics of patients were well matched between groups, although higher rates of diabetes (169 [15.3%] vs 127 [11.7%]) and previous myocardial infarction (113 [10.2%] vs 80 [7.4%]) were found in the control group (**Table**). Treatments and procedures are summarized in eTable 1 of Supplement 2. One-year follow-up data were available for 2164 patients (98.5%) (eFigure in Supplement 2).

Death from any cause at 1 year occurred in 59 patients (5.4%) in the bivalirudin group and 59 patients (5.3%) in the control group (relative risk [RR], 1.02; 95% CI, 0.72-1.45; $P = .92$) (eTable 2 in Supplement 2). A Kaplan-Meier curve for all-cause mortality to 1 year by treatment group is presented in **Figure 1**A.

No differences were noted in the rates of 1-year cardiac death, with 44 cardiac deaths (4.0%) in the bivalirudin group vs 48 (4.3%) in the control group (RR, 0.93; 95% CI, 0.63-1.39; $P = .74$). Noncardiac deaths occurred in 15 patients (1.4%) in the bivalirudin group vs 11 patients (1.0%) in the control group (RR, 1.39; 95% CI, 0.64-3.01; $P = .40$) (eTable 2 in Supplement 2). Kaplan-Meier curves for 1-year cardiac and noncardiac deaths by treatment group are presented in Figure 1B.

No differences were noted in the rates of deaths from 30 days to 1 year, with 27 deaths (2.5%) in the bivalirudin group and 25 (2.3%) in the control group (RR, 1.10; 95% CI, 0.64-1.88; $P = .73$). No difference was found in the rate of cardiac deaths, with 17 (1.6%) in the bivalirudin group and 15 (1.4%) in the control group (RR, 1.15; 95% CI, 0.58-2.39; $P = .68$), or in noncardiac deaths, with 10 (0.9%) in the bivalirudin group and 10 (0.9%) in the control group (RR, 1.02; 95% CI, 0.43-2.44; $P = .96$) (eTable 3 in Supplement 2). An analysis of the effect of bivalirudin in 12 prespecified subgroups showed no significant interactions with baseline or procedural variables, including the arterial access site and type of P2Y12 inhibitor that was administered (**Figure 2**).

Discussion

In this international, randomized, clinical open-label study, bivalirudin was compared with heparin with optional use of GPIs and was not associated with a reduction in 1-year all-cause or cardiac mortality, a result that was consistent across multiple subgroups. This information is potentially important given a lack of data regarding long-term outcomes of bivalirudin compared with heparin in patients with STEMI treated in the ambulance, with frequent use of radial access and novel P2Y12 inhibitors.

The HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial had a profound effect on the treatment of patients with STEMI, in part owing to its findings of a substantial reduction in cardiac mortality present at 30 days and maintained for 3 years of follow-up.[2] However, the precise mechanism by which bivalirudin reduced long-term mortality in the HORIZONS-AMI trial is uncertain.

The HEAT PPCI (How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) trial[3] used GPIs only for rescue situations, or bailout, in the bivalirudin and heparin arms and found no difference in bleeding complications or 30-day total mortality between the 2 groups. The higher bleeding rates seen in prior trials with heparin may have been attributable to the routine or high rate of use of GPIs in combination with heparin.[8] However, in the multicenter Chinese BRIGHT (Bivalirudin in Acute Myocardial Infarction vs Glycoprotein IIb/IIIa and Heparin) trial,[4] bleeding at 30 days was reduced by bivalirudin compared with heparin with GPIs or heparin without GPIs, but despite bleeding reduction, no clear difference was seen in 30-day mortality between groups. The recent MATRIX (Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX) trial,[5] the largest trial to explore bivalirudin in modern contemporary care, found a reduction in 30-day all-cause mortality with bivalirudin compared with heparin plus optional GPIs (1.7% vs 2.3%; $P = .04$) associated with a reduction in bleeding, although the primary outcome of the trial (a composite of death, myocardial infarction, or stroke) did not reach statistical significance. This finding appears to validate the findings of the HORIZONS trial; however, long-term data on mortality are still pending (eTable 4 in Supplement 2).

In the EUROMAX trial,[1] bivalirudin reduced the risk for the primary composite end point of death and/or bleeding not related to coronary artery bypass grafting at 30 days after PCI. However, although bivalirudin reduced major bleeding compared with treatment with heparin plus bailout GPIs and treatment with heparin and routine GPIs,[9] no reduction in mortality rates at 30 days (2.9% vs 3.1%) was observed. Some evidence suggests that bleeding affects short-[10] and long-term mortality (hazard ratio, 4.2)[6] and that the effect of nonprocedural bleeding is greater than that of access site bleeding and greater in the short term than in the long term.[10] In the EUROMAX trial,[11] substantial reductions in bleeding with bivalirudin were consistent for bleeding events related to access sites and nonrelated bleeding events. This reduction in bleeding did not translate into reduced cardiovascular or all-cause death at 1 year, a result in contrast with the HORIZONS-AMI and MATRIX trials. However, approximately two-thirds of the patients in HORIZONS-AMI and one-third of the patients in MATRIX randomized to the bivalirudin arm had received heparin before randomization.

Some important changes have occurred in clinical practice and trial design since the HORIZONS-AMI trial. First, the rates of major bleeding in the heparin arm were lower in the EUROMAX trial (6.0%) compared with the HORIZONS-AMI trial (8.3%),[2] which may be related to the lower rates of use of GPIs (98% in the HORIZONS-AMI trial[2] vs 69.1% in the EUROMAX trial[1]). The rate of use of GPIs, which was left to physician preference in the heparin group (as routine—started before PCI—or bailout), makes the EUROMAX trial unique; the other trials[2-5] have implemented GPI use as only a routine or as only a bailout strategy.

Second, the use of the radial access was frequent in the EUROMAX but not the HORIZONS trial. The reduction in the primary outcome seen in the EUROMAX trial at 30 days was consistent across radial and femoral access subgroups.[12] Third, in the EUROMAX trial, the use of new and more potent antiplatelet agents (ticagrelor and prasugrel) might have altered the balance between ischemic and bleeding risks[13] compared with the HORIZONS-AMI trial. Finally, the EUROMAX trial was

Table. Baseline Characteristics of the Intention-to-Treat Population[a]

Characteristic	Treatment Group, No./Total No. (%) of Patients	
	Bivalirudin (n = 1089)	Control (n = 1109)
Age		
Median (IQR), y	61 (52-71)	62 (52-72)
>65 y	394/1089 (36.2)	434/1109 (39.1)
Females	275/1089 (25.3)	248/1109 (22.4)
Cardiac-related history[b]		
Diabetes[b]	127/1088 (11.7)	169/1108 (15.3)
Hypertension	459/1088 (42.2)	504/1108 (45.5)
Hyperlipidemia[c]	398/1088 (36.6)	417/1108 (37.6)
Current smoker	453/1088 (41.6)	472/1108 (42.6)
Previous myocardial infarction[b]	80/1088 (7.4)	113/1108 (10.2)
Previous PCI	97/1088 (8.9)	108/1108 (9.7)
Previous CABG	18/1088 (1.7)	29/1108 (2.6)
Killip class II, III, or IV[d]	77/996 (7.7)	69/1000 (6.9)
Anemia	129/987 (13.1)	148/989 (15.0)
Creatinine clearance		
≤60 mL/min	147/1001 (14.7)	165/998 (16.5)
>60 mL/min	854/1001 (85.3)	833/998 (83.5)

Abbreviations: CABG, coronary artery bypass grafting; IQR, interquartile range; PCI, percutaneous coronary intervention.

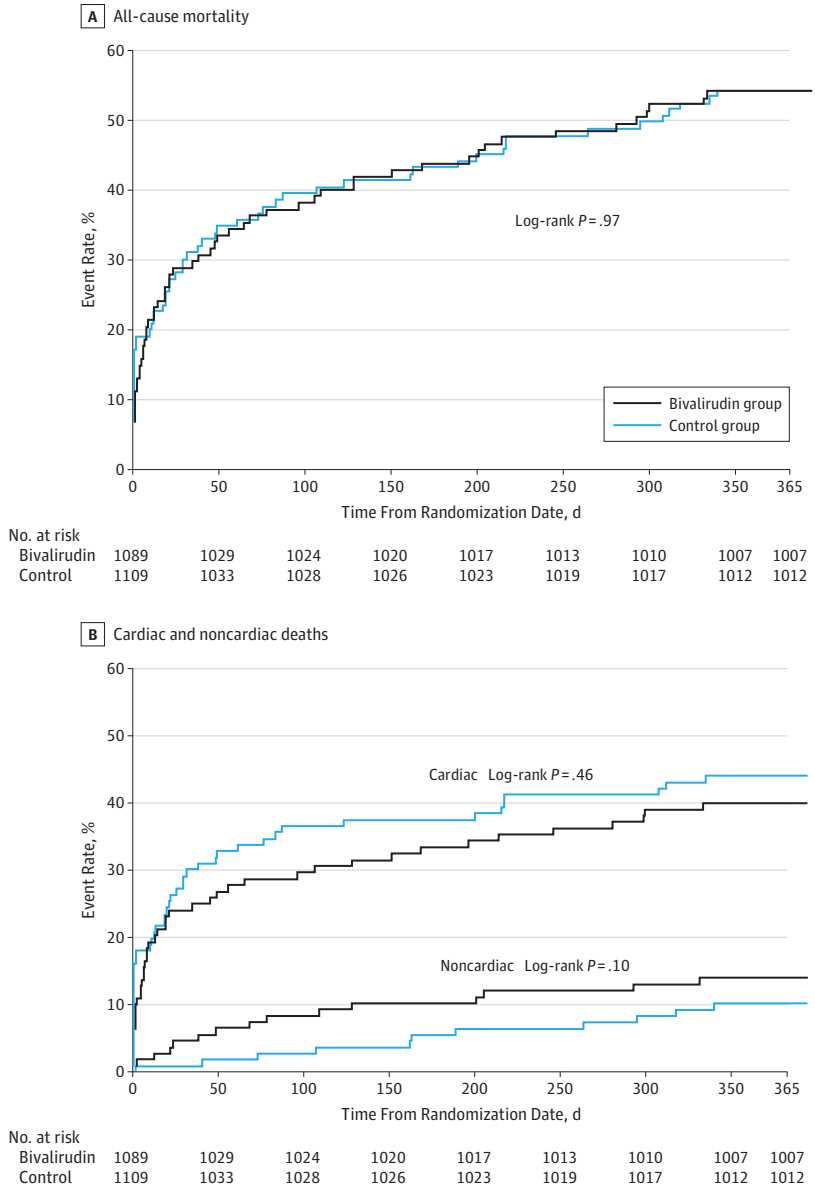
[a] No significant between-group differences were found except in the 2 categories noted.

[b] $P < .05$ for the between-group comparison.

[c] Defined as a diagnosis of hyperlipidemia or the use of therapy to lower lipid levels.

[d] Class I indicates no clinical signs of heart failure; class II, rales or crackles in the lungs, a third heart sound, and an elevated jugular venous pressure; class III, frank acute pulmonary edema; and class IV, cardiogenic shock or hypotension and evidence of peripheral vasoconstriction.

Figure 1. Kaplan-Meier Survival Curves



Analysis shows deaths to 1 year (365 days). The control group received unfractionated or low-molecular-weight heparin plus optional glycoprotein IIb/IIIa inhibitors. *P* values are calculated using the log-rank test.

slightly smaller and had lower statistical power than the HORIZONS-AMI trial.

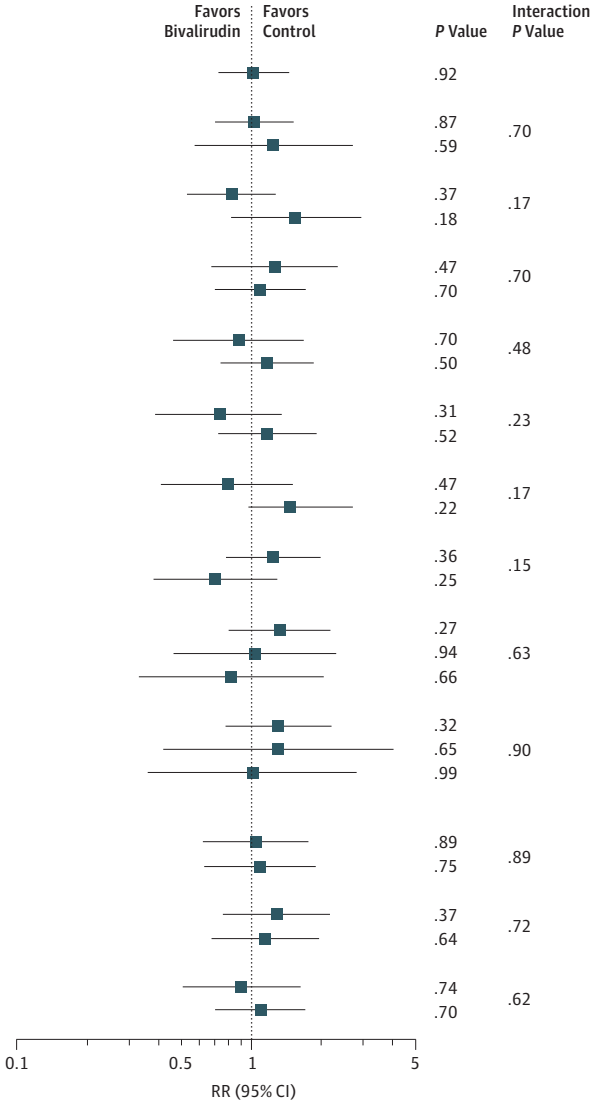
In the EUROMAX trial, a higher risk for acute stent thrombosis with bivalirudin was present. Although attributing the similar long-term mortality in the 2 treatment arms of the EUROMAX trial to contrary and offsetting effects of bivalirudin on bleeding and stent thrombosis is tempting, a patient-level analysis of the HORIZONS and EUROMAX trials[14] found that the mortality attributable to early STEMI was significantly lower after bivalirudin treatment than after heparin plus GPI treatment, possibly related to the timing of stent thrombosis, which occurred earlier in bivalirudin-treated patients. Additional studies are needed to find the optimal anticoagulant regimen to improve long-term mortality outcomes.

Limitations

Limitations of the EUROMAX trial have been previously described,[1] and some limitations of the present study should be considered. The present analysis was not designed to determine the possible mechanisms underlying deaths. Although this analysis was prespecified, the EUROMAX trial was not powered to examine 1-year mortality and its cardiac and noncardiac components, and therefore the 95% CI of the hazard ratio for mortality at 1 year cannot exclude a 28% reduction or conversely a 45% increase in mortality with bivalirudin. In that respect, no significant heterogeneity is evident between the EUROMAX and HORIZONS-AMI trials when analyzed at the patient level.[15]

Figure 2. Subgroup Analyses of 1-Year Mortality Outcome

Subgroup	No./Total No. (%) of Patients: Bivalirudin Group	Control Group	RR (95% CI)	P Value	Interaction P Value
All patients	59/1089 (5.4)	59/1109 (5.3)	1.02 (0.72-1.45)	.92	
Age, y					
>65	45/394 (11.4)	48/343 (14.0)	1.03 (0.70-1.51)	.87	.70
≤65	14/695 (2.0)	11/675 (1.6)	1.24 (0.57-2.70)	.59	
Sex					
Male	35/814 (4.3)	45/861 (5.2)	0.82 (0.53-1.27)	.37	.17
Female	24/275 (8.7)	14/248 (5.6)	1.55 (0.82-2.92)	.18	
Diabetes					
Yes	17/127 (13.4)	18/169 (10.7)	1.26 (0.67-2.34)	.47	.70
No	39/946 (4.1)	35/926 (3.8)	1.09 (0.70-1.71)	.70	
Arterial access site					
Radial	17/510 (3.3)	19/502 (3.8)	0.88 (0.46-1.67)	.70	.48
Femoral	37/558 (6.6)	33/582 (5.7)	1.17 (0.74-1.84)	.50	
No. of vessels with stenosis >50%					
1	17/591 (2.9)	22/556 (4.0)	0.73 (0.39-1.35)	.31	.23
≥2	31/407 (7.6)	30/462 (6.5)	1.17 (0.72-1.90)	.52	
Stent type					
≥1 drug-eluting stent	16/538 (3.0)	20/529 (3.8)	0.79 (0.41-1.50)	.47	.17
All bare metal stents	23/330 (7.0)	16/336 (4.8)	1.46 (0.79-2.72)	.22	
Killip class[a]					
I	38/919 (4.1)	31/931 (3.3)	1.24 (0.78-1.98)	.36	.15
II-IV	14/77 (18.2)	18/69 (26.1)	0.70 (0.38-1.29)	.25	
P2Y12 inhibitor loading dose					
Clopidogrel	33/524 (6.3)	26/545 (4.8)	1.32 (0.80-2.18)	.27	
Prasugrel	12/323 (3.7)	11/306 (3.6)	1.03 (0.46-2.31)	.94	.63
Ticagrelor	8/201 (4.0)	10/205 (4.9)	0.82 (0.33-2.03)	.66	
P2Y12 inhibitor maintenance dose					
Clopidogrel	29/377 (7.7)	24/407 (5.9)	1.30 (0.77-2.20)	.32	
Prasugrel	7/321 (2.2)	5/298 (1.7)	1.30 (0.42-4.05)	.65	.90
Ticagrelor	7/257 (2.7)	7/259 (2.7)	1.01 (0.36-2.83)	.99	
Duration of drug treatment to angiography, min					
<50	28/514 (5.4)	26/495 (5.3)	1.04 (0.62-1.74)	.89	.89
≥50	25/549 (4.6)	24/576 (4.2)	1.09 (0.63-1.89)	.75	
Baseline creatinine clearance					
≤60	25/147 (17.0)	22/165 (13.3)	1.28 (0.75-2.16)	.37	.72
>60	28/854 (3.3)	24/833 (2.9)	1.14 (0.67-1.95)	.64	
Target vessel					
LAD	21/425 (4.9)	23/423 (5.4)	0.91 (0.51-1.62)	.74	.62
No LAD	38/664 (5.7)	36/686 (5.2)	1.09 (0.70-1.70)	.70	



The control group received unfractionated or low-molecular-weight heparin plus optional glycoprotein IIb/IIIa inhibitors. LAD indicates left anterior descending; P2Y12, platelet adenosine diphosphate P2Y12 receptor; and RR, relative risk.

[a] Class I, no clinical signs of heart failure; class II, rales or crackles in the lungs, a third heart sound, and an elevated jugular venous pressure; class III, frank acute pulmonary edema; and class IV, cardiogenic shock or hypotension and evidence of peripheral vasoconstriction.

Conclusions

In patients with STEMI treated in the ambulance with frequent use of radial access and novel P2Y12 inhibitors, bivalirudin showed similar long-term mortality outcomes compared with heparin and optional GPIs. In this specific context, the reduced composite end point of death and/or major bleeding at 30 days in the bivalirudin arm of the EUROMAX trial did not translate into reduced cardiovascular or all-cause death at 1 year.

ARTICLE INFORMATION

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Author Affiliations: Department of Cardiology, Isala Hospital, Zwolle, the Netherlands (Fabris, Kilic, van't Hof); Cardiovascular Department, Azienda Sanitaria Universitaria Integrata, University of Trieste, Trieste, Italy (Fabris); Department of Cardiology, St Antonius Hospital, Nieuwegein, the Netherlands (ten Berg); Department of Cardiology, Hospital General Universitario Gregorio Marañon, Madrid, Spain (Ayesta); Department of Cardiology, Klinikum Ludwigshafen, Ludwigshafen, Germany (Zeymer); Department of Clinical Research, University of Caen, Caen, France (Hamon); Services d'Aide Médicale Urgente, Service Mobile d'Urgence et de Réanimation Urgences, Centre Hospitalier, Chateauroux, France (Soulat); The Medicines Company, Parsippany, New Jersey (Bernstein, Anthopoulos, Deliargyris); Institut National de la Santé et de la Recherche Medicale U-1148, Département Hospitalo-Universitaire FIRE (Fibrosis Inflammation Remodeling), Université Paris-Diderot, Paris, France (Steg); Hôpital Bichat, Assistance Publique–Hôpitaux de Paris, Paris,

France (Steg); National Heart and Lung Institute, Imperial College, Royal Brompton Hospital, London, England (Steg).

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Study concept and design: van't Hof, Zeymer, Hamon, Anthopoulos, Deliargyris, Steg.
Acquisition, analysis, or interpretation of data: Fabris, Kilic, ten Berg, Ayesta, Zeymer, Hamon, Soulat, Bernstein, Anthopoulos, Deliargyris, Steg.
Drafting of the manuscript: Fabris, Kilic, van't Hof.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Bernstein.
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Study supervision: Zeymer, Hamon, Anthopoulos, Deliargyris, Steg.

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