Kardiologia Polska 2018; 76, 4: 740–749; DOI: 10.5603/KP.a2018.0024

ORIGINAL ARTICLE

Patients treated with bivalirudin are still at higher risk of stent thrombosis: a comprehensive meta-analysis of randomised clinical trials of bivalirudin and heparin for percutaneous coronary interventions

Stefan Grajek[1], Michał Michalak[2], Adrian Gwizdała[1], Aleksander Araszkiewicz[1], Marek Grygier[1], Jarosław Hiczkiewicz[3], Maciej Lesiak[1]

[1]1st Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland
[2]Department of Computer Science and Statistics, Poznan University of Medical Sciences, Poznan, Poland
[3]Department of Cardiology of Specialised Hospital, Nowa Sol, Poland

Abstract

Background: Although the current practice guidelines recommend using both heparin and bivalirudin for percutaneous coronary interventions (PCI), the research data are ambiguous.

Aim: The aim of the study was to compare the impact of bivalirudin and heparin on major clinical endpoints in PCI patients with particular emphasis on periprocedural stent thrombosis.

Methods: A total of 18 randomised clinical trials involving 41,752 subjects were included. The endpoints comprised: net adverse clinical event (NACE: death, myocardial infarction [MI], unscheduled revascularisation, major bleeding), major adverse cardiovascular event (MACE: death, MI, or stroke), and acute/subacute stent thrombosis (ST). A subanalysis for planned and provisional glycoprotein IIb/IIIa inhibitor (GPI) use with heparin was performed. Results were presented as risk ratios (RR) and 95% confidence intervals (CI).

Results: Bivalirudin significantly reduced NACE risk (RR 0.85, 95% CI 0.76–0.96) and increased the incidence of MI (RR 1.09, 95% CI 1.01–1.18), ST (RR 1.50, 95% CI 1.13–1.99), and MACEs (RR 1.06, 95% CI 0.99–1.13). Comparing to heparin with provisional or planned GPI use, there was higher risk of acute ST with bivalirudin (RR 2.14, 95% CI 1.01–4.56 and RR 5.53, 95% CI 2.32–13.18, respectively). Comparing to heparin and provisional GPIs, bivalirudin failed to reduce NACEs and major bleeding. However, it decreased rates of NACEs (RR 0.81, 95% CI 0.69–0.96) and major bleeding (RR 0.64, 95% CI 0.48–0.85) compared with heparin and planned GPI use.

Conclusions: The advantages of bivalirudin are undoubtedly related to GPI use in the heparin arms. Bivalirudin-based regimens are more beneficial when compared with heparin and planned GPI use in terms of NACE and major bleedings; this was not observed when compared to heparin and provisional GPI use. Regardless of adjunctive GPI use, stent thrombosis episodes were significantly more common in bivalirudin-treated subjects. Therefore, the safety and economic issues may urge revision of this aspect of current clinical practice and guidelines.

Key words: acute coronary syndrome, bivalirudin, heparin, stent thrombosis

Kardiol Pol 2018; 76, 4: 740–749

Address for correspondence:
Adrian Gwizdała, MD, PhD, 1st Department of Cardiology, Poznan University of Medical Sciences, ul. Długa 1/2, 61–848 Poznań, Poland, e-mail: agwizdala@ump.edu.pl

Received: 17.07.2017 **Accepted:** 04.12.2017 **Available as AoP:** 12.01.2018

INTRODUCTION

Bivalirudin is an intravenous direct thrombin inhibitor. It is recommended as an alternative to heparin in patients undergoing percutaneous coronary interventions (PCIs) for acute coronary syndromes, in particular non-ST-segment elevation myocardial infarctions (NSTEMI) [1, 2]. The most recent European Society of Cardiology (ESC) practice guidelines on therapy of NSTEMI recommend the use of bivalirudin (0.75 mg/kg IV bolus, followed by 1.75 mg/kg/h for up to 4 h after the procedure) as an alternative to unfractionated heparin plus glycoprotein IIb/IIIa inhibitors (GPI) during PCI (class I, level A) [3]. Another guideline document issued by the ESC recommends the use of bivalirudin in the case of heparin-induced thrombocytopaenia (IC) or at high bleeding risk (IIaA) during PCI for stable coronary artery disease and for treatment of ST-segment elevation myocardial infarction (STEMI) (IIaA) [4]. The strength of recommendations may support more widespread use of bivalirudin in such clinical settings, but the results of some clinical studies raised safety concerns associated with this strategy. In various studies bivalirudin-based regimens significantly reduced bleeding complications compared to heparin [5–11]. The reduction of bleeding-related adverse events with bivalirudin observed in the ACUITY [5], HORIZONS-AMI [6], and EUROMAX [7] trials was potent enough to significantly decrease the overall rate of net adverse clinical events (NACEs) despite there being no impact on major adverse cardiovascular events (MACEs). However, similar NACE reduction by bivalirudin was not reproduced in the ISAR-REACT 3 [8], ISAR-REACT 4 [9], and BRAVE 4 [10] studies. In the HEAT-PPCI study [11], MACEs were significantly more common in patients treated with bivalirudin as compared to the heparin arm, but no significant differences in the bleeding rate were observed. On the other hand, the HORIZONS-AMI [10], EUROMAX [7], and HEAT-PPCI [11] studies documented considerably more frequent stent thrombosis (ST) in patients treated with bivalirudin-based regimens. The results of the latter trials greatly undermined the confidence in bivalirudin.

There was a tempestuous discussion between researchers in 2014 and 2015 on bivalirudin and heparin use, started by Cavender and Sabatine, who compared both regimens in patients scheduled for PCI [12]. They concluded that bivalirudin-based regimens were associated with increased risk of MACEs, myocardial infarction (MI), and ST, while the risk of serious bleeding was decreased. In addition, bivalirudin had no influence on mortality. Despite other reports, there is still ongoing controversy regarding the risk of individual MACEs. The latest randomised clinical trials presented different results regarding this endpoint (e.g. HEAT-PPCI vs. BRAVE 4). The most recent MATRIX trial showed that bivalirudin did not reduce MACE and NACE rates [13]. Additionally, there were no clear benefits from the prolongation of bivalirudin infusion after PCI when compared to heparin. The two most recent studies, including the largest one (i.e. BRAVE 4 and MATRIX), have not been included in previously published meta-analyses. Therefore, we present an updated meta-analysis comparing the effects of bivalirudin versus heparin in patients undergoing PCI, comprising all relevant trials and the largest number of subjects. Additionally, a unique sensitivity analysis was carried out to investigate the influence of individual studies on the overall meta-analysis summary estimate. Finally, a separate analysis was performed including trials that compared bivalirudin-based regimens with heparin-based regimens plus GPIs used in a provisional (up to 15% of subjects) or planned manner (at least 70% of study subjects).

METHODS

Literature search strategy

We systematically reviewed the literature databases for randomised trials comparing bivalirudin to heparin alone or with GPIs. The search criteria were limited to papers written in English, published in peer-reviewed journals before October 2015, and abstracts from the major cardiological conferences held between January and October 2015. We included prospective randomised clinical studies with a follow-up ranging between 48 h and 30 days, which were available in the Medline (PubMed), EBSCO, and Cochrane Central Register of Controlled Trials databases. The relevant trials comparing bivalirudin with either unfractionated or low molecular weight heparin were identified using the following keywords: "bivalirudin", "heparin", "glycoprotein IIb/IIIa inhibitor", "percutaneous coronary intervention", and "randomised trial". Studies that involved fibrinolytic therapy, did not provide clinical outcomes, or were conducted before the coronary stenting era were excluded from the analysis. The results of the literature search are summarised in Figure 1.

We analysed two composite endpoints: NACE (defined as all-cause death, recurrent MI, ischaemia-driven revascularisation, or major bleeding) and MACE (defined as all-cause death, recurrent MI, or stroke). Additionally, the following safety and efficacy endpoints were assessed: MI, all-cause death, major bleeding (defined based on the thrombolysis in myocardial infarction [TIMI] bleeding criteria) [14], non-coronary artery bypass grafting (CABG) major bleeding, and ischaemia-driven target vessel revascularisation/target lesion revascularisation (TVR/TLR), ST, including acute (≤ 24 h of index PCI) and subacute ST (between > 24 h and 30 days of index PCI). Based on the clinical urgency of PCI, studies having ST as an endpoint were divided into two groups: urgent PCI (STEMI/NSTEMI/acute MI/acute coronary syndrome [ACS]) and elective PCI (< 30% ACS in the study population).

Statistical analysis

The meta-analysis was performed in accordance with the guidelines set forward in the Cochrane Handbook for Systematic Reviews of Interventions [15], and we followed

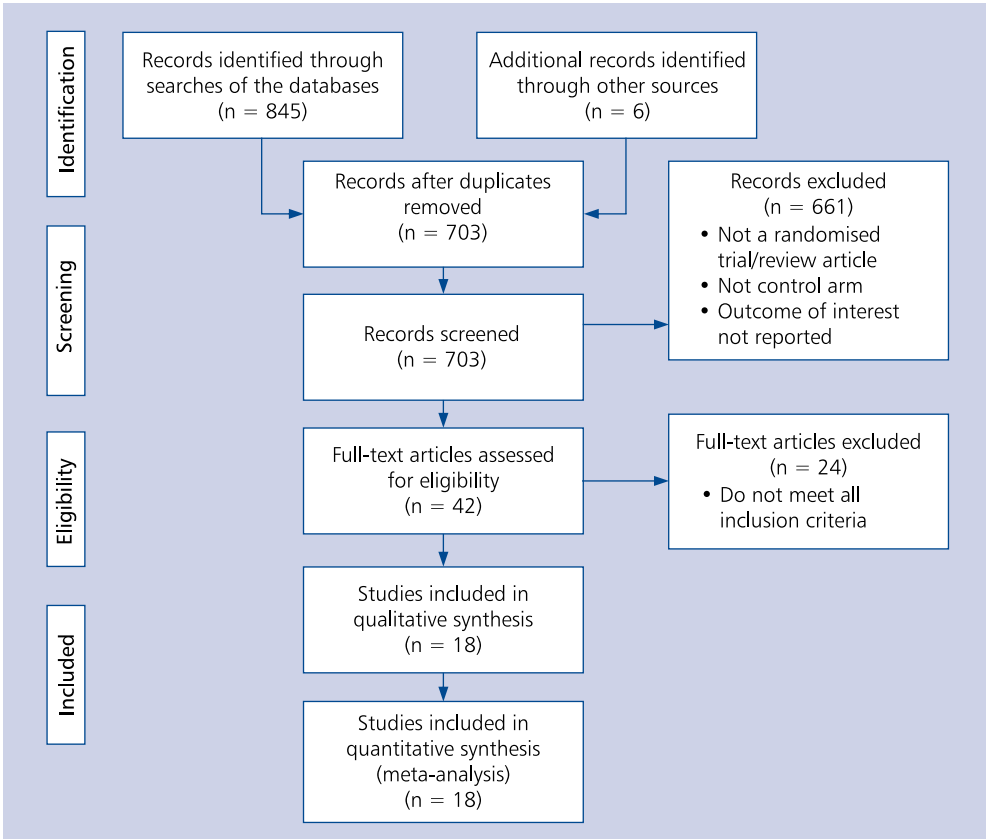

Figure 1. Flowchart of literature search

the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses. The data were analysed using the Mantel-Haenszel test, and the risk ratio (RR) was calculated using STATA software, version 13.1 (StataCorp LP, USA). The heterogeneity of the results between the studies was analysed using the Q and I^2 statistics, which presented the contribution of the variability resulting from study heterogeneity relative to the total. The significance level (p) for the Q statistics was deemed less than 0.10. Publication bias was analysed by visual inspection of funnel plots and by calculation of the Egger's test p value [16, 17]. The random-effects model described by DerSimonian and Laird [18] was used to aggregate the study data. In cases of 0 outcome events, continuity correction was performed by adding a correction factor of 0.5. Additionally, sensitivity analysis was performed to investigate the influence of each individual study on the overall meta-analysis summary estimate. All the p values were two-tailed with a statistical significance level at 0.05, and confidence intervals were calculated to 95% (95% CI). For three-arm trials (including bivalirudin, heparin alone, and heparin plus GPIs) the relevant pairwise comparisons were analysed separately. Except for the overall analysis, we stratified the results by provisional and planned GPI use in the heparin arm.

RESULTS

We identified 703 reports, of which 42 full-text contributions were assessed and reviewed for inclusion in the analysis. Ultimately, the meta-analysis criteria were met by 18 randomised, controlled trials (Fig. 1). The baseline characteristics of study populations, procedures, and medications are summarised in Table 1.

A total of 41,752 patients were included in the analysis: 21,671 patients received bivalirudin and 20,081 patients received heparin alone or heparin plus GPIs IIb/IIIa. GPIs were used in both arms (bivalirudin and heparin). In the bivalirudin arm, GPI was mostly administrated provisionally. Its use ranged between 1% and 15%. The use of GPIs in the heparin arm varied between < 1% and 100%. If used on a provisional basis, GPIs were administered in up to 15% of patients (ISAR-REACT 3 — 1%, ARMYDA-7 BIVALVE — 14%, BRIGHT [heparin alone] — 6%, HEAT PPCI — 15%, NAPLES III — 1%, BRAVE 4 — 6%, and MATRIX — < 1%); for planned use, GPIs were given in 70% to 100% of subjects (EUROMAX — 69%, REPLACE-2 and ACUITY-PCI — 97%, HORIZONS-AMI — 98%, NAPLES, TENACITY, ISAR-REACT, Deshpande et al. and BRIGHT [heparin plus GPIs] — 100%).

The CEs were observed in 2131 (9.8%) bivalirudin patients and 2384 (11.9%) heparin patients. The NACE rate

Table 1. Characteristics of included trials and study populations

Study	Biv (n)	Hep (n)	Population	ACS (%)	PCI (%)	Pretreatment with $P2Y_{12}$ inhibitors	Mean age [years]	GPI (%)		Gender		Diabetes		Prior MI	
								Biv	Hep	Biv (male)	Hep (male)	Biv	Hep	Biv	Hep
CACHET (2002) [29]	59	94	Elective PCI	0%	100%	N/A	63	31%	100%	44 (73%)	73 (77%)	N/A	N/A	N/A	N/A
REPLACE-2 (2003) [30]	2994	3008	Elective or urgent PCI	22%	98%	Encouraged (86% received)	63	7%	97%	2236 (75%)	2229 (74%)	840 (28%)	784 (26%)	1099 (37%)	1085 (37%)
REPLACE-1 (2004) [31]	532	524	Elective or urgent PCI	17%	100%	Encouraged (56% received)	64	71%	73%	368 (69%)	370 (71%)	167 (31%)	151 (29%)	205 (39%)	233 (45%)
PROTECT-TIMI 30 (2006) [32]	284	573	NSTE-ACS	100%	100%	Permitted	60	3%	99%	194 (68%)	378 (66%)	105 (37%)	252 (44%)	62 (22%)	114 (20%)
ACUITY-PCI (Biv alone, 2007) [5]	2619	2561	NSTE-ACS	100%	100%	69% received	63	9%	97%	1919 (73%)	1860 (73%)	721 (28%)	703 (28%)	798 (31%)	761 (30%)
ACUITY-PCI (Biv + GPI, 2007) [5]	2609	2561	NSTE-ACS	100%	100%	68% received	63	97%	97%	1919 (74%)	1860 (73%)	713 (27%)	703 (28%)	760 (30%)	761 (30%)
Horizons AMI (2008) [6]	1800	1802	STEMI	100%	93%	Mandated	60	8%	98%	1388 (77%)	1372 (76%)	281(16%)	312 (17%)	187 (10%)	205 (11%)
ISAR-REACT 3 (2008) [8]	2289	2281	Elective or urgent PCI	18%	100%	Mandated	67	1%	1%	1744 (76%)	1751 (77%)	176 (8%)	191 (8%)	734 (32%)	689 (30%)
NAPLES (2009) [33]	167	168	Elective or urgent PCI	15%	100%	Mandated	65	1%	100%	110 (66%)	108 (64%)	126 (75%)	116 (75%)	75 (45%)	75 (45%)
TENACITY (2011) [34]	185	198	Elective or urgent PCI	74%	100%	Encouraged	63	100%	100%	N/A	N/A	N/A	N/A	N/A	N/A
ISAR-REACT 4 (2011) [9]	860	861	NSTEMI	100%	98%	Mandated	68	0%	100%	661(77%)	661 (77%)	243 (28%)	257 (30%)	163 (19%)	188 (22%)
ARMYDA-7 BIVALVE (2012) [35]	198	203	Elective or urgent PCI	29%	93%	Mandated	70	12%	14%	141 (71%)	148 (72%)	134 (67%)	120 (59%)	74 (37%)	69 (34%)
Deshpande et al. (2012) [36]	49	52	Elective or urgent PCI	43%	100%	Mandated	56	100%	100%	44 (90%)	44 (85%)	18 (37%)	22 (42%)	12 (25%)	18 (35%)
EUROMAX (2013) [7]	1089	1109	STEMI	100%	86%	Mandated	62	12%	69%	814 (75%)	861 (78%)	127 (12%)	169 (15%)	80 (7%)	113 (10%)
BRIGHT (Hep + GPI, 2014) [37]	729	724	AMI	100%	97%	Mandated	58	4%	100%	603 (83%)	592 (82%)	166 (23%)	139(19%)	32 (4%)	33 (5%)
BRIGHT (Hep alone, 2014) [37]	729	725	AMI	100%	97%	Mandated	58	4%	6%	603 (83%)	596 (82%)	166 (23%)	160 (22%)	32 (4%)	33 (5%)
HEAT-PPCI (2014) [11]	905	907	STEMI	100%	82%	Mandated	63	13%	15%	662 (73%)	648 (71%)	114 (13%)	137 (15%)	122 (13%)	93 (10%)
NAPLES III (2014) [38]	418	419	Elective or urgent PCI	23%	100%	Not reported	78	1%	1%	218 (52%)	233 (56%)	189 (45%)	181 (43%)	181 (42%)	158 (38%)
BRAVE 4 (2014) [10]	275	269	STEMI	100%	100%	Mandated	61	3%	6%	205 (76%)	219 (79%)	45 (17%)	41 (15%)	22 (8%)	30 (11%)
MATRIX (2015) [13]	3610	3603	STEMI/NSTEMI	100%	100%	Encouraged (83% received)	65	0.1%	0.2%	2731 (76%)	2764 (77%)	815 (23%)	786 (22%)	530 (15%)	500 (14%)

Biv — bivalirudin; Hep — heparin; ACS — acute coronary syndrome; AMI — acute myocardial infarction; GPI — glycoprotein IIb/IIIa inhibitor; n — number of patients; N/A — not available; NSTE — non-ST-segment elevation; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction

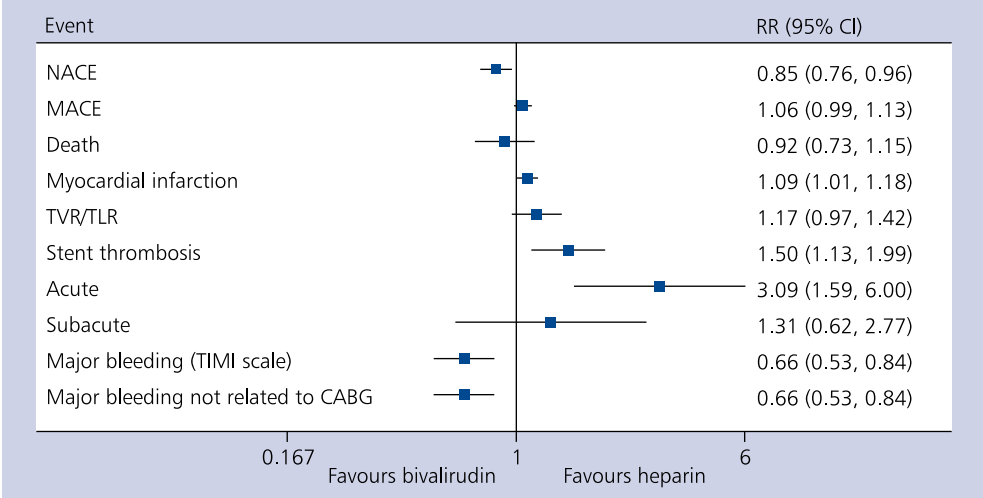

Figure 2. Net adverse clinical events (NACE), major adverse cardiovascular events (MACE), and individual cardiovascular events for overall analysis; CABG — coronary artery bypass grafting; CI — confidence interval; RR — risk ratios; TIMI — thrombolysis in myocardial infarction; TVR/TLR — target vessel revascularisation/target lesion revascularisation

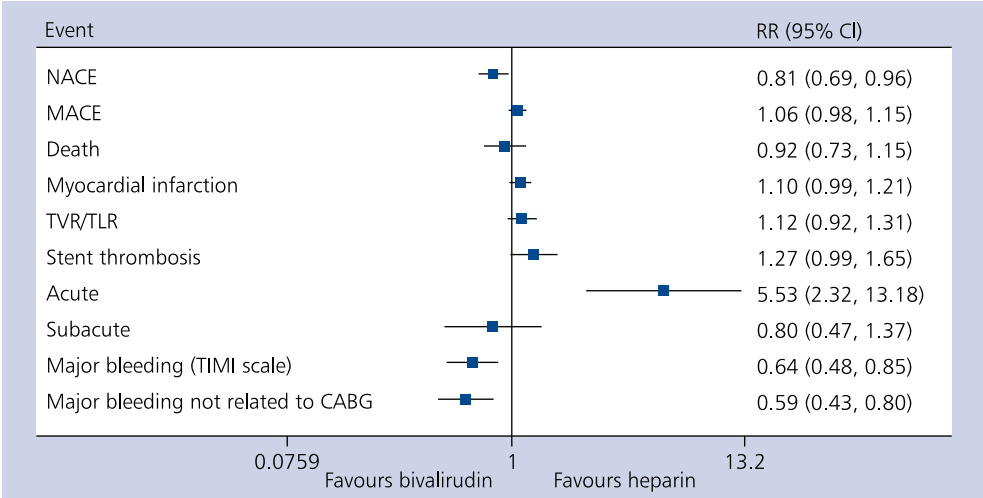

Figure 3. Net adverse clinical events (NACE), major adverse cardiovascular events (MACE), and individual cardiovascular events for heparin-based regimens with planned glycoprotein IIb/IIIa inhibitor (GPI) use; other abbreviations — see Figure 2

was lower in bivalirudin-based regimens (RR 0.85, 95% CI 0.76–0.96, p = 0.008, Fig. 2). However, a significant inter-study heterogeneity was observed (**Appendix — see journal website**). The stratified analysis revealed that this significantly lower risk pertains to the trials comparing bivalirudin to heparin-based regimens with planned GPIs (RR 0.81, 95% CI 0.69–0.96, p = 0.013, Fig. 3). The risk of NACE with bivalirudin-based regimens was similar to heparin-based regimens with provisionally used GPIs (RR 0.92, 95% CI 0.72–1.25; Fig. 4).

Another efficacy endpoint, MACEs, occurred in 1775 (7.9%) bivalirudin patients and 1697 (7.5%) heparin patients. The risk of MACEs was insignificantly higher for bivalirudin when compared with heparin (RR 1.06, 95% CI 0.99–1.13, p = NS, Fig. 2), heparin-based regimens with planned GPI use (RR 1.06, 95% CI 0.98–1.15, Fig. 3), and provisional GPIs (RR 1.11, 95% CI 0.93–1.32, p = NS, Fig. 4). Analysis of the MACE rate implies that better net clinical outcome with bivalirudin-based regimens was mainly driven by the bleeding component. Neither bivalirudin- nor heparin-based regimens increased the risk of death (RR 0.92, 95% CI 0.73–1.15; Fig. 2). The stratified analysis yielded similar results (Figs. 3, 4).

Myocardial infarction occurred in 1250 (5.6%) and 1138 (5.0%) patients treated with bivalirudin and heparin,

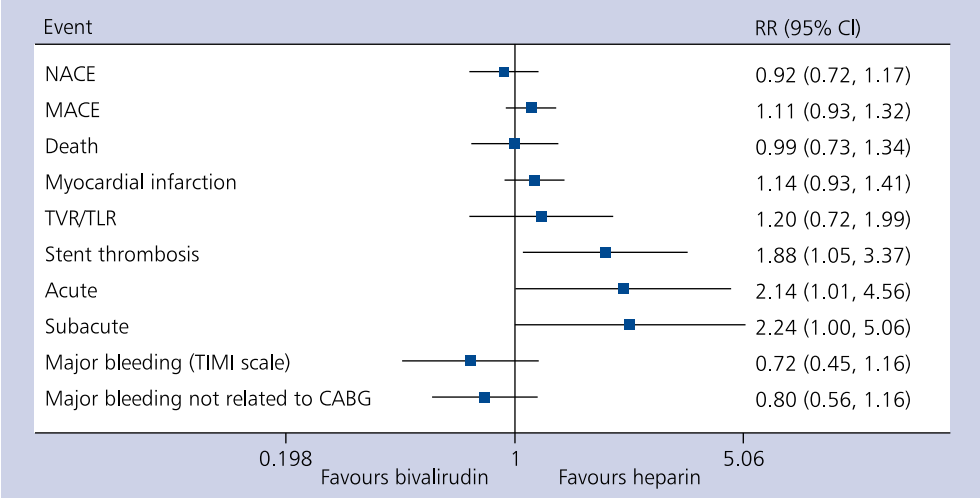

Figure 4. Net adverse clinical events (NACE), major adverse cardiovascular events (MACE), and individual cardiovascular events for heparin-based regimens with provisional glycoprotein IIb/IIIa inhibitor (GPI) use; other abbreviations — see Figure 2

respectively. Bivalirudin-based regimens were associated with significantly increased MI rate (RR 1.09, 95% CI 1.01–1.18, p = 0.032; Fig. 2). Such a trend was observed for both subanalyses. Insignificant differences were observed when comparing bivalirudin to heparin with planned GPI (RR 1.10, 95% CI 0.99–1.21, p = 0.075; Fig. 3, **Appendix — see journal website**) and provisional GPI use (RR 1.14, 95% CI 0.92–1.41, p = 0.211; Fig. 4).

There was no significant difference in the frequency of TVR/TLR between both analysed arms (Figs. 2–4).

Stent thrombosis was reported in 221 (1%) bivalirudin patients and 145 (0.6%) heparin patients. The risk of ST was considerably higher with bivalirudin-based regimens (RR 1.50, 95% CI 1.13–1.99, p = 0.005; Fig. 2). Significant differences were observed between bivalirudin and heparin with provisional GPI use (RR 1.88, 95% CI 1.05–4.80, p = 0.033; Fig. 4); however, no significant differences were observed between bivalirudin and heparin with planned GPI use (RR 1.27, 95% CI 0.99–1.65, p = 0.064; Fig. 3). More detailed analysis of ST, including the acute and subacute episodes, showed that only acute ST was associated with bivalirudin-based regimens (RR 3.09, 95% CI 1.59–6.00, p = 0.001; Fig. 2). This risk is similar in both subanalyses: bivalirudin vs. heparin with provisional GPI use (RR 2.14, 95% CI 1.01–4.56, p = 0.048; Fig. 4) and bivalirudin vs. heparin with planned GPI use (RR 5.53, 95% CI 2.32–13.18, p < 0.001; Fig. 3). There was no significant difference in the risk of subacute ST.

The subanalysis considering clinical classification of treated subjects (ACS vs. elective PCI) showed that ST was significantly more frequent in the patients presenting with ACS (RR 1.48, 95% CI 1.10–1.99, p = 0.009, random and fixed models; Fig. 5). Probably due to high heterogeneity (only three studies meeting criteria of elective PCI), no significant differences were found for elective patients in the random model (Fig. 5).

Both endpoints related to bleeding episodes, i.e. major bleeding by TIMI bleeding criteria and non-CABG related major bleeding, present in 260 (1.4%) and 671 (3.1%) bivalirudin patients and 384 (2.0%) and 972 (4.8%) heparin patients, respectively. The analysis of those safety endpoints favours bivalirudin- over heparin-based regimens (RR 0.66, 95% CI 0.53–0.84, p = 0.002 and RR 0.66, 95% CI 0.53–0.84, p = 0.002, respectively; Fig. 2). The sub-analysis shows that superiority of bivalirudin persists only when compared to heparin with planned GPI use (RR 0.64, 95% CI 0.48–0.85, p = 0.002 and RR 0.59, 95% CI 0.43–0.80, p = 0.001; Fig. 3).

Sensitivity analysis

The sensitivity analysis confirmed the above findings except for MACEs, MI, and TVR/TLR. The results regarding the risk of MACE depend on the MATRIX study. Exclusion of this study led to statistical significance with respect to the MACE risk (**Appendix, Table 8 — see journal website**). The MI risk is sensitive to the following studies: HEAT-PPCI, ISAR-REACT 3, ACUITY-PCI (bivalirudin alone), and REPLACE-2. Exclusion of either of these studies lresulted in non-significant differences with respect to the MI risk (**Appendix, Table 13 — see journal website**). Exclusion of one of two trials: ARMYDA-7 BIVALVE or REPLACE-2, led to statistical significance with respect to the TVR/TLR risk (**Appendix, Table 23 — see journal website**).

DISCUSSION

Bivalirudin, an intravenous monovalent thrombin inhibitor, is recommended in patients undergoing PCI. Recently, there has been a great deal of debate on the efficacy and safety of both

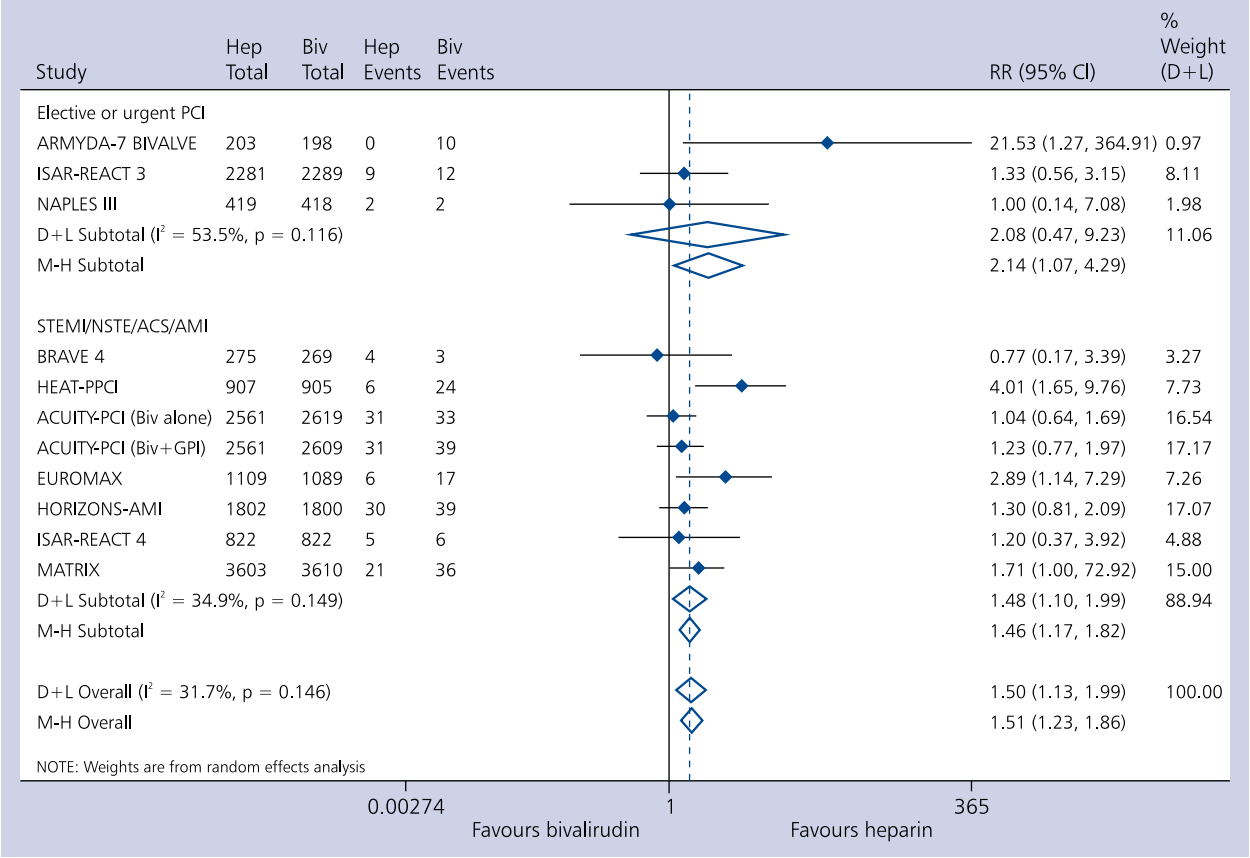

Figure 5. Forest plot of stent thrombosis for elective or urgent percutaneous coronary intervention (PCI) and ST-segment elevation myocardial infarction (STEMI)/non-ST-segment elevation (NSTE)/acute coronary syndrome (ACS)/acute myocardial infarction (AMI) group; Biv — bivalirudin; Hep — heparin; CI — confidence interval; GPI — planned glycoprotein IIb/IIIa inhibitor; RR — risk ratios

bivalirudin- and heparin-based regimens in this clinical setting. The results of our up-to-date meta-analysis are convergent with the previously published results regarding the majority of endpoints (i.e. MACE, NACE, major bleedings, ischaemic episodes) [12, 19–23]. However, the issue of increased stent thrombosis associated with the use of bivalirudin was equivocal and therefore is still under discussion.

Cavender and Sabatine [12] published in 2014 a meta-analysis comparing results of treatment with bivalirudin vs. heparin with or without concomitant use of GPIs in patients undergoing PCI. The authors documented that, compared to heparin, bivalirudin increased the risk of MI and ST while reducing the risk of bleeding complications. The significance of bleeding reduction depended on simultaneous use of GPIs. The meta-analysis including 16 randomised clinical studies (and total of 33,958 subjects) did not include two trials that were completed and published later, i.e. the BRAVE 4 (548 randomised subjects of 1240 planned; it was terminated earlier) and MATRIX studies (7213 subjects). We provided a comprehensive and, so far, the largest meta-analysis, including 41,752 patients. Uniquely, we analysed the incidence of ST in patients presenting with ACS (STEMI, NSTEMI, unstable angina) and in patients with predominating stable coronary artery disease and elective PCI.

Similarly to the previously mentioned meta-analysis [12], we observed a reduction in the bleeding episodes in the group treated with bivalirudin. Such a reduction resulted predominantly from a significant decrease in bleeding events as compared to the subjects receiving heparin and GPIs. As opposed to the group treated with intravenous heparin in monotherapy, there was no significant reduction in bleeding events with bivalirudin. The registry including PCI data from 47 American hospitals showed that bleeding adverse events were no longer reduced with bivalirudin if transradial interventions were involved [24]. For transfemoral interventions the incidence of bleeding with bivalirudin-based regimens was significantly better if compared to heparin. Because the included studies did not provide enough data, our meta-analysis could not reliably compare the results for transradial vs. transfemoral approach. Therefore, further studies are necessary to investigate that issue and to reassess the cost-effectiveness of bivalirudin treatment in the transradial cohort.

The overall risk of MI was significantly increased by 9% (RR 1.09, 95% CI 1.01–1.19) for bivalirudin. The entire bivalirudin group was also characterised by 50% higher risk of ST (RR 1.50, 95% CI 1.13–1.99). The increased risk of ST was still present if comparing to patients treated with heparin and planned GPIs (100% of subjects), as well as with heparin and provisional GPI use (up to 15% of subjects). We documented that ST was significantly more frequent in patients with ACS (random and fixed model; Fig. 5). The risk of ST was slightly less severe for the bivalirudin group undergoing elective PCIs (only a fixed model, not confirmed by a random model), but it was still marked despite the small size of this subgroup. The reasons for increased risk of ST for bivalirudin-based regimens are unknown. The postulated prolongation of bivalirudin infusion up to four (or even six) hours after the intervention failed to reduce the elevated risk of ST [13].

Higher incidence of ST in patients treated with bivalirudin compared to heparin and GPIs may reflect insufficient inhibition of activated platelets in the bivalirudin group. The ACUITY study [5] showed a significantly higher rate of composite endpoint, comprising ischaemic events in the bivalirudin group without the addition of supporting thienopyridine therapy, when compared with heparin plus GPIs. In patients with increased percentage of activated platelets despite the treatment with clopidogrel, the use of bivalirudin led to a significantly higher rate of cardiovascular events (MACEs), compared to subjects receiving heparin and abciximab infusion [25]. In patients with STEMI participating in the BRAVE 4 study [10], stent thrombosis was not significantly more frequent in the bivalirudin plus prasugrel strategy versus heparin plus clopidogrel regimen. Inadequate inhibition of the platelet activity in patients treated with bivalirudin may result in an increased risk of ST. The outcomes of the registry comprising 47 hospitals of the Michigan Cardiovascular Consortium also support the above hypothesis [24]. However, our meta-analysis documented that ST in patients treated with bivalirudin was also more frequent when compared with patients using heparin and provisional (up 15% of patients) GPIs.

Therefore, specific pharmacological properties of bivalirudin cannot be excluded. As is known, bivalirudin is an intravenous direct thrombin inhibitor. Other direct thrombin inhibitors include, but are not limited to, dabigatran, which is commonly used for the prevention of thrombotic events in patients with atrial fibrillation. In contrast to inhibitors of factor Xa (rivaroxaban and apixaban), dabigatran increases the risk of ACS [26]. A recently published meta-analysis documented that not only dabigatran but also the entire group of oral direct thrombin inhibitors increased the risk of ACS [27]. In the presence of high concentrations of tissue factor the medicine-to-thrombin binding is dissociated thus providing increased activation of both thrombin ("thrombin explosion") and platelets, with simultaneous blockage of the protective influence of protein C [27].

Hypothetically, in the presence of high tissue factor levels, it is possible that the ruptured (stented) plaque creates the above-described paradoxical "thrombin explosion" as a result of dissociation of the bivalirudin-thrombin complex. In particular, this mechanism may play a role in the formation of acute ST (up to 24 h of intervention). The increased risk of ST in patients treated with bivalirudin is now documented; however, the unknown cause of this phenomenon warrants further studies.

Recently, another bivalirudin-oriented registry-based trial was published: the VALIDATE-SWEDEHEART study [28]. Treatment with $P2Y_{12}$ inhibitors was mandatory, and radial access was used for most of the patients. The study documented that the use of $P2Y_{12}$ inhibitors was associated with elimination of one of the worst complications of bivalirudin monotherapy: stent thrombosis. However, the implementation of those agents diminished the beneficial effect of bivalirudin, i.e. reduction of bleeding rate. Overall, the complication rate was no lower for bivalirudin users than it was for heparin, thus making bivalirudin a better choice for special patients, e.g. with heparin-induced thrombocytopaenia.

The results of this meta-analysis are based on studies of different duration. The follow-up ranged between 48 h and 30 days. The included studies analysed a wide spectrum of patients. Data of individual patients would allow for analysis for homogenous patient subgroups, which could improve the accuracy of the analysis and lead to firm conclusions regarding specific groups of patients. Another limitation is the different use of GPIs in bivalirudin arms. Furthermore, a high heterogeneity of results occurred for some parameters, especially in a sub-analysis between bivalirudin- and heparin-based regimens with provisional GPI use.

The exact number of patients treated with transfemoral and transradial access are unknown for certain studies, so the detailed analysis comparing these two approaches would be unreliable.

The VALIDATE-SWEDEHEART study was not included in the analysis because of the non-randomised design and methodological issues (mostly radial access, mandatory use of $P2Y_{12}$ inhibitors).

The TIMI bleeding scale was used in this meta-analysis because it was employed in most of the studies. The BARC criteria were used only in some trials (e.g. MATRIX study). Therefore, we decided to use the most universal scale (TIMI) to avoid problems with data comparisons.

This meta-analysis did not stratify patients regarding the use of radial or femoral access. The source data were not available, and few studies reported the numbers.

In conclusion, notwithstanding the foregoing considerations, the results of our meta-analysis demonstrated that bivalirudin, while significantly reducing bleeding complications, does not improve the incidence of ischaemic events (MACE). Bivalirudin provides clinical benefits, measured by a significant

reduction in NACEs, if used as an alternative to heparin and concomitant GPIs. Bivalirudin, compared with heparin (without simultaneous use of GPIs), does not substantially reduce the risk of bleeding complications. Bivalirudin-based regimens are associated with a substantial risk of acute ST. Stent thrombosis was significantly more frequent in the patients presenting with ACS. This may result from specific properties of bivalirudin that produce a "thrombin explosion" originating from the plaque distortion caused by coronary intervention. Therefore, further research is warranted to investigate these mechanisms.

Conflict of interest: *none declared*

References

1. Windecker S, Kolh P, Alfonso F, et al. Authors/Task Force members. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014; 35(37): 2541–2619, doi: 10.1093/eurheartj/ehu278, indexed in Pubmed: 25173339.
2. Steg PhG, James SK, Atar D, et al. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012; 33(20): 2569–2619, doi: 10.1093/eurheartj/ehs215, indexed in Pubmed: 22922416.
3. Roffi M, Patrono C, Collet JP, et al. Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37(3): 267–315, doi: 10.1093/eurheartj/ehv320, indexed in Pubmed: 26320110.
4. Ibanez B, James S, Agewall S, et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2): 119–177, doi: 10.1093/eurheartj/ehx393, indexed in Pubmed:28886621.
5. Stone GW, White HD, Ohman EM, et al. Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial investigators. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. Lancet. 2007; 369(9565): 907–919, doi: 10.1016/S0140-6736(07)60450-4, indexed in Pubmed: 17368152.
6. Stone GW, Witzenbichler B, Guagliumi G, et al. HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med. 2008; 358(21): 2218–2230, doi: 10.1056/NEJMoa0708191, indexed in Pubmed: 18499566.
7. Steg PG, van 't Hof A, Hamm CW, et al. EUROMAX Investigators. Bivalirudin started during emergency transport for primary PCI. N Engl J Med. 2013; 369(23): 2207–2217, doi: 10.1056/NEJMoa1311096, indexed in Pubmed: 24171490.
8. Kastrati A, Neumann FJ, Mehilli J, et al. ISAR-REACT 3 Trial Investigators. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. N Engl J Med. 2008; 359(7): 688–696, doi: 10.1056/NEJMoa0802944, indexed in Pubmed: 18703471.
9. Kastrati A, Neumann FJ, Schulz S, et al. ISAR-REACT 4 Trial Investigators. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. N Engl J Med. 2011; 365(21): 1980–1989, doi: 10.1056/NEJMoa1109596, indexed in Pubmed: 22077909.
10. Schulz S, Richardt G, Laugwitz KL, et al. Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 Investigators. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. Eur Heart J. 2014; 35(34): 2285–2294, doi: 10.1093/eurheartj/ehu182, indexed in Pubmed: 24816809.
11. Shahzad A, Kemp I, Mars C, et al. HEAT-PPCI trial investigators. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet. 2014; 384(9957): 1849–1858, doi: 10.1016/S0140-6736(14)60924-7, indexed in Pubmed: 25002178.
12. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. Lancet. 2014; 384(9943): 599–606, doi: 10.1016/S0140-6736(14)61216-2, indexed in Pubmed: 25131979.
13. Valgimigli M, Frigoli E, Leonardi S, et al. MATRIX investigators. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. N Engl J Med. 2015; 373(11): 997–1009, doi: 10.1056/NEJMoa1507854, indexed in Pubmed: 26324049.
14. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011; 123(23): 2736–2747, doi: 10.1161/CIRCULATIONAHA.110.009449, indexed in Pubmed: 21670242.
15. Higgins JPT GS. Cochrane Collaboration: Cochrane handbook for systematic reviews of interventions. Version 5.1.0. 2011.
16. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109): 629–634, indexed in Pubmed: 9310563.
17. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. BMJ. 2001; 323(7304): 101–105, doi: 10.1136/bmj.323.7304.101, indexed in Pubmed: 11451790.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3): 177–188, doi: 10.1016/0197-2456(86)90046-2, indexed in Pubmed: 3802833.
19. Lee MS, Liao H, Yang T, et al. Comparison of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitors in patients undergoing an invasive strategy: a meta-analysis of randomized clinical trials. Int J Cardiol. 2011; 152(3): 369–374, doi: 10.1016/j.ijcard.2010.08.007, indexed in Pubmed: 20843568.
20. Ndrepepa G, Neumann FJ, Deliargyris EN, et al. Bivalirudin versus heparin plus a glycoprotein IIb/IIIa inhibitor in patients with non-ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention after clopidogrel pretreatment: pooled analysis from the ACUITY and ISAR-REACT 4 trials. Circ Cardiovasc Interv. 2012; 5(5): 705–712, doi: 10.1161/CIRCINTERVENTIONS.112.972869, indexed in Pubmed: 23048052.
21. Tarantini G, Brener SJ, Barioli A, et al. Impact of baseline hemorrhagic risk on the benefit of bivalirudin versus unfractionated heparin in patients treated with coronary angioplasty: a meta-regression analysis of randomized trials. Am Heart J. 2014; 167(3): 401–412.e6, doi: 10.1016/j.ahj.2013.11.013, indexed in Pubmed: 24576526.

22. Navarese EP, Schulze V, Andreotti F, et al. Comprehensive meta-analysis of safety and efficacy of bivalirudin versus heparin with or without routine glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndrome. JACC Cardiovasc Interv. 2015; 8(1 Pt B): 201–213, doi:10.1016/j.jcin.2014.10.003, indexed in Pubmed: 25616926.
23. Nairooz R, Sardar P, Amin H, et al. Meta-analysis of randomized clinical trials comparing bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitors in patients undergoing percutaneous coronary intervention and in patients with ST-segment elevation myocardial infarction. Am J Cardiol. 2014; 114(2): 250–259, doi: 10.1016/j.amjcard.2014.04.033, indexed in Pubmed: 24890986.
24. Perdoncin E, Seth M, Dixon S, et al. The comparative efficacy of bivalirudin is markedly attenuated by use of radial access: insights from Blue Cross Blue Shield of Michigan Cardiovascular Consortium. Eur Heart J. 2016; 37(24): 1902–1909, doi: 10.1093/eurheartj/ehv434, indexed in Pubmed: 26377400.
25. Sibbing D, Bernlochner I, Schulz S, et al. Prognostic value of a high on-clopidogrel treatment platelet reactivity in bivalirudin versus abciximab treated non-ST-segment elevation myocardial infarction patients. ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment-4) platelet substudy. J Am Coll Cardiol. 2012; 60(5): 369–377, doi: 10.1016/j.jacc.2012.02.044, indexed in Pubmed: 22682553.
26. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. 2012; 172(5): 397–402, doi: 10.1001/archinternmed.2011.1666, indexed in Pubmed: 22231617.
27. Artang R, Rome E, Nielsen JD, et al. Meta-analysis of randomized controlled trials on risk of myocardial infarction from the use of oral direct thrombin inhibitors. Am J Cardiol. 2013; 112(12): 1973–1979, doi: 10.1016/j.amjcard.2013.08.027, indexed in Pubmed: 24075284.
28. Erlinge D, Omerovic E, Fröbert O, et al. Bivalirudin versus Heparin Monotherapy in Myocardial Infarction. N Engl J Med. 2017; 377(12): 1132–1142, doi:10.1056/NEJMoa1706443, indexed in Pubmed: 28844201.
29. Lincoff AM, Kleiman NS, Kottke-Marchant K, et al. Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during percutaneous coronary revascularization: results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET). Am Heart J. 2002; 143(5): 847–853, doi: 10.1067/mhj.2002.122173, indexed in Pubmed: 12040347.
30. Lincoff AM, Bittl JA, Harrington RA, et al. REPLACE-2 Investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA. 2003; 289(7): 853–863, doi:10.1001/jama.289.7.853, indexed in Pubmed: 12588269.
31. Lincoff AM, Bittl JA, Kleiman NS, et al. REPLACE-1 Investigators. Comparison of bivalirudin versus heparin during percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events [REPLACE]-1 trial). Am J Cardiol. 2004; 93(9): 1092–1096, doi:10.1016/j.amjcard.2004.01.033, indexed in Pubmed: 15110198.
32. Gibson CM, Morrow DA, Murphy SA, et al. TIMI Study Group. A randomized trial to evaluate the relative protection against post-percutaneous coronary intervention microvascular dysfunction, ischemia, and inflammation among antiplatelet and antithrombotic agents: the PROTECT-TIMI-30 trial. J Am Coll Cardiol. 2006; 47(12): 2364–2373, doi: 10.1016/j.jacc.2005.12.077, indexed in Pubmed: 16781360.
33. Tavano D, Visconti G, D'Andrea D, et al. Comparison of bivalirudin monotherapy versus unfractionated heparin plus tirofiban in patients with diabetes mellitus undergoing elective percutaneous coronary intervention. Am J Cardiol. 2009; 104(9): 1222–1228, doi: 10.1016/j.amjcard.2009.06.035, indexed in Pubmed: 19840566.
34. Moliterno DJ. TENACITY Steering Committee and Investigators. A randomized two-by-two comparison of high-dose bolus tirofiban versus abciximab and unfractionated heparin versus bivalirudin during percutaneous coronary revascularization and stent placement: the tirofiban evaluation of novel dosing versus abciximab with clopidogrel and inhibition of thrombin (TENACITY) study trial. Catheter Cardiovasc Interv. 2011; 77(7): 1001—1009, doi:10.1002/ccd.22876, indexed in Pubmed: 21598351.
35. Patti G, Pasceri V, D'Antonio L, et al. Comparison of safety and efficacy of bivalirudin versus unfractionated heparin in high-risk patients undergoing percutaneous coronary intervention (from the Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty-Bivalirudin vs Heparin study). Am J Cardiol. 2012; 110(4): 478–484, doi: 10.1016/j.amjcard.2012.04.017, indexed in Pubmed: 22583760.
36. Deshpande NV, Pratiti R, Admane P, et al. Safety and efficacy of bivalirudin with glycoprotein IIb/IIIa for high-risk percutaneous coronary intervention. Indian Heart J. 2012; 64(5): 444–448, doi: 10.1016/j.ihj.2012.07.022, indexed in Pubmed: 23102380.
37. Han Y, Guo J, Zheng Y, et al. BRIGHT Investigators. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. JAMA. 2015; 313(13): 1336–1346, doi: 10.1001/jama.2015.2323, indexed in Pubmed:25775052.
38. Briguori C, Visconti G, Focaccio A, et al. Novel approaches for preventing or limiting events (Naples) III trial: randomized comparison of bivalirudin versus unfractionated heparin in patients at increased risk of bleeding undergoing transfemoral elective coronary stenting. JACC Cardiovasc Interv. 2015; 8(3): 414–423, doi: 10.1016/j.jcin.2014.10.015, indexed in Pubmed: 25703878.

Cite this article as: Grajek S, Michalak M, Gwizdała A, et al. Patients treated with bivalirudin are still at higher risk of stent thrombosis: a comprehensive meta-analysis of randomised clinical trials of bivalirudin and heparin for percutaneous coronary interventions. Kardiol Pol. 2018; 76(4): 740–749, doi: 10.5603/KP.a2018.0024.