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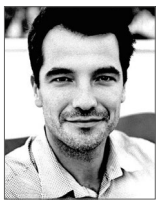
Myocardial damage after ST-segment elevation myocardial infarction by use of bivalirudin or heparin: a DANAMI-3 substudy



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Introduction

The benefits of bivalirudin or unfractionated heparin (UFH) during primary percutaneous coronary intervention (PCI) remain controversial. Bivalirudin rather than UFH plus a routine glycoprotein IIb/IIIa receptor inhibitor (GPI) has been shown to improve overall and cardiac survival and reduce bleeding complications in patients undergoing primary PCI. Several trials comparing bivalirudin and UFH±GPI have since questioned this survival advantage and created controversy related to bivalirudin-associated improved bleeding outcome and the risk of acute stent thrombosis. Recently, the VALIDATE-SWEDEHEART bivalirudin versus heparin monotherapy in myocardial infarction during PCI trial reported no differences in myocardial infarction, major bleeding, definite stent thrombosis and death[1]. Clinically meaningful reduced efficacy of either regimen in antithrombotic protection during primary PCI is likely to lead to increased myocardial damage. Therefore, the present analysis evaluated myocardial salvage, infarct size, microvascular obstruction (MVO) and left ventricular ejection fraction (LVEF) by cardiac magnetic resonance (CMR), according to the antithrombotic strategy.

Methods

This is a non-randomised *post hoc* analysis of the DANAMI-3 trial programme in patients with available CMR[2]. Patients (n=730) were evaluated with an acute CMR after primary PCI during the index admission and with a second examination at 90-day follow-up. We first stratified patients by the administration of GPI. In the DANAMI-3 trial, the choice of antithrombotic regimen was left to the operator. The decision to administer bail-out GPI in bivalirudin-treated patients was associated with the event of a complicated procedure, illustrated by prolonged procedure duration and a higher frequency of distal embolisation and no or slow reflow in the culprit artery. The decision to administer provisional GPI was associated with randomisation to the DEFER study in the DANAMI-3

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trial programme **(Supplementary Table 1, Supplementary Table 2)**. Patients with provisional or bail-out GPI treatment (n=166, 26.7%) were therefore excluded from the present analysis.

Results

In patients without GPI treatment (n=564, 77.3%) and with very similar area at risk (% of LV) at index CMR (32.5 [±11.8] vs 33 [±11.3] [p=0.72]), we did not find significant differences in acute or final infarct size, myocardial salvage index (MSI), LVEF **(Figure 1)** or MVO (% of LV) (1.62 [±3.6] vs 2.04 [±3.4] [p=0.30]) according to the mono-comparison of UFH versus bivalirudin. Multivariable analysis adjusted for differences (p<0.1) in baseline and procedural characteristics and bivalirudin was forced into the models. Male gender, heart rate, anterior myocardial infarction, Killip class ≥2, preprocedural TIMI flow 0/1, and symptom onset to PCI were associated with acute and final infarct size (IS), MSI and LVEF, whereas bivalirudin versus UFH treatment was not **(Table 1, Table 2)**. A sensitivity analysis in patients (bivalirudin n=234, UFH n=40) randomised to the conventional treatment groups in the DANAMI-3 trial programme without GPI treatment confirmed the above results.

Discussion

The present study is the first to compare bivalirudin and UFH according to indices of myocardial damage in a large CMR population of patients undergoing primary PCI. The use of bivalirudin alone compared to UFH alone is not associated with IS, MSI, LVEF or MVO. Our results indicate that bivalirudin and heparin have comparable outcome regarding indices of myocardial injury, when used as adjunctive pharmacotherapy during primary PCI. Our study therefore does not provide pathophysiological explanatory factors of myocardial damage, which could substantiate previously observed mortality benefits in patients treated with bivalirudin compared to UFH.

Limitations

The operators' choice of antithrombotic strategy during primary PCI holds treatment attribution biases, which we attenuated by excluding GPI-treated patients and performing multivariate and sensitivity analyses. Potential selection biases affect the extrapolation of the present results to a general ST-segment elevation myocardial infarction (STEMI) population. Compared to CMR participants, randomised patients who dropped out before acute

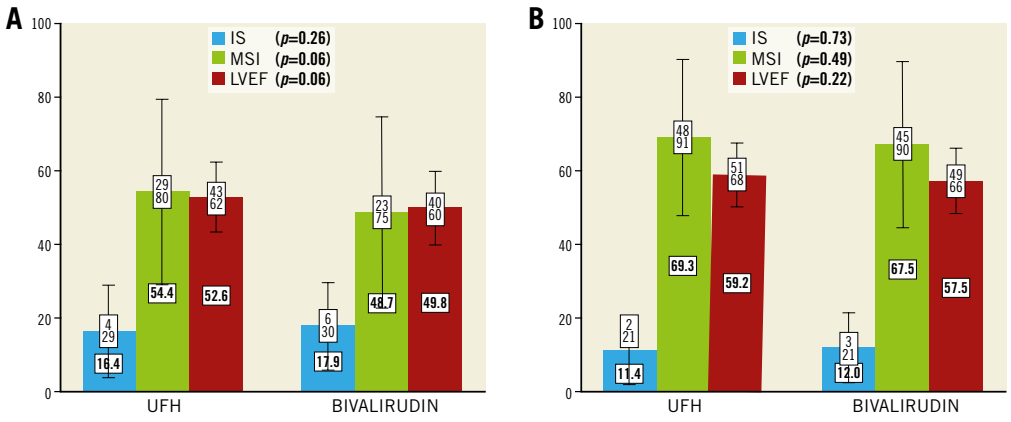

Figure 1. *Infarct size (IS) (%±1 SD), myocardial salvage index (MSI) (±1 SD) and left ventricular ejection fraction (LVEF) (%±1 SD) at index (A) and follow-up (B) according to bivalirudin and unfractionated heparin (UFH). P-values are shown for the comparison of IS, MSI and LVEF according to bivalirudin and UFH.*

Table 1. Multivariable linear regression analysis for the endpoints of infarct size (IS), myocardial salvage index (MSI) and left ventricular ejection fraction (LVEF), evaluated at index cardiac magnetic resonance.

	Acute infarct size			Acute MSI			Acute LVEF		
	B	95% CI	*p*-value	B	95% CI	*p*-value	B	95% CI	*p*-value
Bivalirudin	0.60	–1.67-2.88	0.61	–0.04	–0.09-0.01	0.15	–1.24	–3.18-0.7	0.21
Male gender	3.56	1.5-5.6	0.001	–0.08	–0.12-–0.03	0.001	–3.72	–5.45-–2.0	<0.001
TIMI 2/3	–9.43	–11.2-–7.7	<0.001	0.22	0.18-0.26	<0.001	3.97	2.51-5.43	<0.001
Heart rate	0.04	–0.002-0.09	0.06	–0.001	–0.01-0.00	0.035	–0.10	–0.14-–0.06	<0.001
Anterior MI	6.21	4.5-7.9	<0.001	–0.04	–0.08-–0.01	0.025	–5.51	–6.98-–4.05	<0.001
Killip class 2-4	13.55	9.1-18.1	<0.001	–0.25	–0.36-–0.15	<0.001	–12.77	–16.46-–9.09	<0.001
Symptom to PCI	0.005	0.00-0.01	0.07	0.001	0.00-0.01	0.001	0.001	–0.003-0.006	0.57

Table 2. Multivariable linear regression analysis for the endpoints of infarct size (IS), myocardial salvage index (MSI) and left ventricular ejection fraction (LVEF), evaluated at final cardiac magnetic resonance at 3-month follow-up.

	Final infarct size			Final MSI			Final LVEF		
	B	95% CI	*p*-value	B	95% CI	*p*-value	B	95% CI	*p*-value
Bivalirudin	–0.057	–2.05-1.93	0.96	–0.02	–0.07-0.03	0.52	–0.64	–2.57-1.29	0.52
Male gender	2.13	0.34-3.92	0.020	–	–	–	–3.81	–5.55-–2.07	<0.001
TIMI 2/3	–6.98	–8.47-–5.49	<0.001	0.15	0.11-0.19	<0.001	4.47	3.03-5.91	<0.001
Anterior MI	3.58	2.11-5.06	<0.001	–	–	–	–3.03	–4.46-–1.60	<0.001
Killip class 2-4	15.09	10.96-19.21	<0.001	–0.30	–0.41-–0.18	<0.001	–14.54	–18.54-–10.54	<0.001
Symptom to PCI	0.005	0.00-0.01	0.041	–	–	–	–0.004	–0.01-0.00	0.067
BMI	–0.21	–0.38-–0.03	0.021	–	–	–	0.21	0.18-0.35	0.018

CMR assessment had a worse clinical risk profile upon admission[3], and study participants in the DANAMI-3 trial had lower mortality compared to contemporary non-participants with STEMI from unselected registries[4].

Conclusion

In a non-randomised analysis of patients undergoing primary PCI, the use of bivalirudin compared to UFH was not associated with myocardial damage.

Impact on daily practice

Bivalirudin and heparin during primary PCI have comparable outcomes regarding indices of myocardial injury. Our results do not provide pathophysiological explanatory factors of myocardial damage in terms of differences in infarct size, myocardial salvage, microvascular obstruction or LVEF that could substantiate previously observed survival advantages in patients treated with bivalirudin compared to UFH.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Baseline and procedural characteristics, stratified by the administration of a provisional glycoprotein IIb/IIIa inhibitor (GPI).

Supplementary Table 2. Baseline and procedural characteristics.

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Supplementary data

Supplementary Table 1. Baseline and procedural characteristics, stratified by the administration of a provisional glycoprotein IIb/IIIa inhibitor (GPI).

	No GPI (n=564)	GPI (n=166)	*p*-value
Age	58.9 (10.7)	58.4 (10.8)	0.57
BMI	27.2 (4)	26.9 (3.9)	0.50
Male	445 (78.9)	138 (83.1)	0.28
Diabetes	43 (7.6)	14 (8.4)	0.74
Hypertension	199 (35.3)	55 (33.1)	0.60
Dyslipidaemia	195 (34.6)	65 (39.2)	0.28
Current smoking	307 (54.4)	87 (52.4)	0.65
Family disposition	271 (48.7)	82 (50)	0.76
Previous MI	20 (3.5)	8 (4.8)	0.45
Previous PCI	21 (3.7)	11 (6.6)	0.11
Previous stroke	20 (3.5)	5 (3.0)	0.74
Killip class 2-4	20 (3.5)	8 (4.9)	0.43
Pre-hospital UFH	537 (95.2)	160 (96.4)	0.52
Aspirin	551 (97.7)	165 (100)	0.049
Clopidogrel	30 (5.3)	15 (9.1)	0.08
Prasugrel	424 (75.2)	134 (81.2)	0.11
Ticagrelor	108 (19.1)	15 (9.1)	0.002
Multivessel disease	232 (41.1)	67 (40.4)	0.86
POSTCON	319 (56.6)	48 (28.9)	<0.001
DEFER	311 (55.1)	134 (80.7)	<0.001
PRIMULTI	209 (37.1)	64 (38.6)	0.73
Anterior STEMI	226 (40.1)	68 (41.0)	0.84
Pre-PCI TIMI 0/1	201 (35.6)	69 (41.6)	0.16
Distal embolism	36 (6.4)	23 (13.9)	0.002
No/low reflow	11 (2)	3 (1.8)	0.91
Procedure duration (min)	30.5 (15.5)	31.1 (17.9)	0.68
Symptom to PCI (min)	217.9 (157.3)	201.8 (121.6)	0.72

Continuous variables are presented as mean value (±SD), categorical variables as count (%).

BMI: body mass index; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction; UFH: unfractionated heparin

Supplementary Table 2. Baseline and procedural characteristics.

	No GPI (n=564)			GPI (n=166)		
	UFH (n=93)	**Bivalirudin (n=471)**	***p*-value**	**UFH (n=112)**	**Bivalirudin (n=54)**	***p*-value**
Age	60.9 (11.7)	58.6 (10.4)	0.09	59.4 (11)	56.5 (10.2)	0.10
BMI	26.3 (3.9)	27.3 (4.1)	0.022	26.3 (3.8)	28.2 (3.9)	0.005
Male	65 (69.9)	380 (80.7)	0.020	89 (79.5)	49 (90.7)	0.07
Diabetes	2 (2.2)	41 (8.7)	0.030	10 (8.9)	4 (7.4)	0.74
Hypertension	36 (38.7)	163 (34.7)	0.46	39 (34.8)	16 (29.6)	0.51
Dyslipidaemia	32 (34.4)	163 (34.6)	0.97	47 (42)	18 (33.3)	0.29
Current smoking	55 (59.1)	252 (53.5)	0.32	58 (54.1)	29 (53.7)	0.82
Family disposition	43 (46.7)	228 (49)	0.69	56 (50.5)	26 (49.1)	0.87
Previous MI	2 (2.2)	18 (3.8)	0.43	6 (5.4)	2 (3.7)	0.65
Previous PCI	4 (4.3)	17 (3.6)	0.75	8 (7.1)	3 (5.6)	0.70
Previous stroke	4 (4.3)	16 (3.4)	0.76	2 (1.8)	3 (5.6)	0.33
Killip class 2-4	4 (4.3)	16 (3.4)	0.67	5 (4.5)	3 (5.8)	0.72
Pre-hospital UFH	88 (94.6)	449 (95.3)	0.77	111 (99.1)	49 (90.7)	0.007
Aspirin	91 (97.8)	460 (97.7)	0.91	112 (100)	53 (100)	N/A
Clopidogrel	9 (9.8)	21 (4.5)	0.038	12 (10.7)	3 (5.7)	0.39
Prasugrel	68 (73.1)	356 (75.6)	0.61	89 (79.5)	45 (85.9)	0.40
Ticagrelor	16 (17.2)	92 (19.5)	0.60	10 (8.9)	5 (9.4)	0.92
Multivessel disease	29 (31.2)	203 (43.1)	0.033	42 (37.5)	25 (46.3)	0.28
POSTCON	45 (48.4)	274 (58.2)	0.08	28 (25)	20 (37)	0.11
DEFER	59 (63.4)	252 (53.5)	0.08	97 (86.6)	37 (68.5)	0.006
PRIMULTI	30 (32.3)	179 (38)	0.29	45 (40.2)	19 (35.2)	0.54
Anterior STE	23 (46)	122 (45.2)	0.91	30 (42.3)	12 (30)	0.20
Pre-PCI TIMI 0/1	55 (59.1)	308 (65.4)	0.25	62 (55.5)	35 (64.8)	0.25
Distal embolism	5 (5.4)	31 (6.6)	0.66	13 (11.6)	10 (18.5)	0.23
No/low reflow	0 (0)	11 (2.3)	0.14	0 (0)	3 (5.6)	0.012
Procedure duration (min)	33.1 (18.5)	30 (14.9)	0.13	26.8 (15.4)	40.3 (19.3)	<0.001
Symptom to PCI (min)	244.8 (199.8)	212.6 (147.2)	0.144	196.7 (119.1)	212.4 (126.9)	0.450

Continuous variables are presented as mean value (±SD), categorical variables as count (%).

BMI: body mass index; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction; UFH: unfractionated heparin