Unfractionated heparin versus bivalirudin in patients undergoing primary percutaneous coronary intervention: a SWEDEHEART study

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Abstract

Aims: The aim of the study was to compare outcomes in unfractionated heparin (UFH) and bivalirudin-treated patients undergoing primary percutaneous coronary intervention (PPCI).

Methods and results: This observational study contained 20,612 PPCI patients treated with either UFH monotherapy or bivalirudin with or without concomitant UFH. Patients with oral anticoagulant or glycoprotein IIb/IIIa inhibitor (GPI) treatment were excluded. The primary outcome measure was definite early stent thrombosis (ST) that occurred at low and similar rates in UFH only and bivalirudin-treated patients: 0.9% vs. 0.8% (adjusted hazard ratio [HR] 1.08, 95% confidence interval [CI]: 0.7-1.65). All-cause death at 30 days occurred in 6.9% vs. 5.4% of patients (adjusted HR 1.23, 95% CI: 1.05-1.44) and within 365 days in 12.1% vs. 8.9% (adjusted HR 1.34, 95% CI: 1.19-1.52) in the two groups, respectively. The incidence of major bleeding within 30 days was 0.8% vs. 0.6% (adjusted HR 1.54, 95% CI: 0.97-2.45). The incidence of reinfarction within 365 days and stroke within 30 days was similar between groups.

Conclusions: In this large, nationwide observational study we found low and similar rates of early ST in UFH only and bivalirudin-treated patients undergoing primary PCI. Mortality was higher in UFH compared with bivalirudin-treated patients.

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Abbreviations

ACS	acute coronary syndrome
CABG	coronary artery bypass graft
CI	confidence interval
GPI	glycoprotein IIb/IIIa inhibitor
HR	hazard ratio
MI	myocardial infarction
NPR	National Patient Register
PPCI	primary percutaneous coronary intervention
RCT	randomised clinical trial
SD	standard deviation
ST	stent thrombosis
STEMI	ST-elevation myocardial infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
UFH	unfractionated heparin

Introduction

Potent adjunctive antithrombotic agents are crucial for the treatment of ST-elevation myocardial infarction (STEMI) with primary PCI (PPCI). Periprocedural parenteral antithrombotic treatment choices include anticoagulation with bivalirudin, unfractionated heparin (UFH) or enoxaparin, and antiplatelet treatment with cangrelor and glycoprotein IIb/IIIa inhibitors (GPI). Bivalirudin, as compared to UFH with or without GPI, improved event-free survival at 30 days and reduced major bleeding, but also increased the risk of acute stent thrombosis (ST) in a pivotal PPCI STEMI trial[1]. Mainly based on these results, the American College of Cardiology/American Heart Association and European Society of Cardiology have included bivalirudin in STEMI treatment guidelines[2-4]. The majority of subsequent trials have shown that bivalirudin as compared with UFH with or without GPI results in lower bleeding risk but increased rates of ST[5-7].

Editorial, see page 1930

One open-label, single-centre trial that evaluated UFH alone as compared with periprocedural bivalirudin alone showed a lower rate of major adverse ischaemic events, including ST at 30 days, with UFH[8]. Interestingly, bleeding rates were similar with UFH and bivalirudin. As a result of that trial, the advantages of bivalirudin vs. UFH in PPCI have been questioned. In this observational study, we compared ST, reinfarctions, stroke, all-cause mortality and major bleeding in a large contemporary Swedish PPCI STEMI population treated with either UFH only or bivalirudin (with or without concomitant UFH).

Methods

STUDY POPULATION AND OUTCOME MEASURES

Patients were identified using the Swedish Coronary Angiography and Angioplasty Register (SCAAR), part of the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) register[9]. We included all STEMI patients undergoing PPCI, treated with bivalirudin and/or UFH in Sweden, from January 2007 until December 2014. Exclusion criteria were concomitant GPI or oral anticoagulant treatment. The study population (n=20,612) was divided into two groups, those treated with bivalirudin, with or without concomitant UFH (n=16,891), and those treated with UFH only (n=3,721) **(Figure 1)**. The primary outcome measure was definite stent thrombosis within 30 days of PPCI (early ST). Secondary outcome measures included all-cause mortality within 30 and 365 days, reinfarction within 365 days, stroke within 30 days and major bleeding within 30 days. Drug dosage and duration are not registered in SCAAR and not reported in this study.

DATA COLLECTION

The SCAAR/SWEDEHEART registry includes baseline characteristics, angiographic findings, procedural data and index hospitalisation medications. The interventionist enters all information. Restenosis and ST are actively recorded by mandatory questions for each stent at any subsequent coronary angiography. Data from SWEDEHEART were merged with the National Board of Health and Welfare's Cause of Death Register and the National Patient Register (NPR)[10], providing mortality, stroke and major bleeding data. The study complies with the Declaration of Helsinki. Uppsala regional ethics committee approved the protocol (reference number 2011/333/2).

DEFINITIONS

SCAAR applies the universal definition of myocardial infarction and the Academic Research Consortium definition of definite ST[11].

Major bleeding was defined as any major bleeding reported in the NPR as a hospitalisation discharge diagnosis of: intracerebral, subarachnoidal or subdural haematoma; gastrointestinal tract bleeds including oesophageal, gastric, duodenal, lower gastrointestinal tract and rectal bleeds; haematemesis or melena. Stroke was defined as any stroke reported in the NPR as cerebral infarction, intracerebral haematoma or subarachnoidal haemorrhage.

STATISTICAL ANALYSES

Continuous variables were presented as mean±SD or median (interquartile range) and categorical variables as numbers (percentages). Incidences were estimated by the proportion of patients with an outcome. Corresponding 95% confidence intervals were calculated using normal approximation. Adjusted analyses were performed using:

1) propensity scores as covariate in the Cox model with multiple imputation on missing data;
2) propensity score-matched cases with multiple imputed data sets using robust sandwich estimators to estimate the variance of the coefficients accounting for the matched pairs (sensitivity analyses).

When analysing reinfarction within 365 days, an initial 28-day blanking period was applied at discharge in order to avoid multiple inclusion of one event[12]. From 2010, the registry was modified
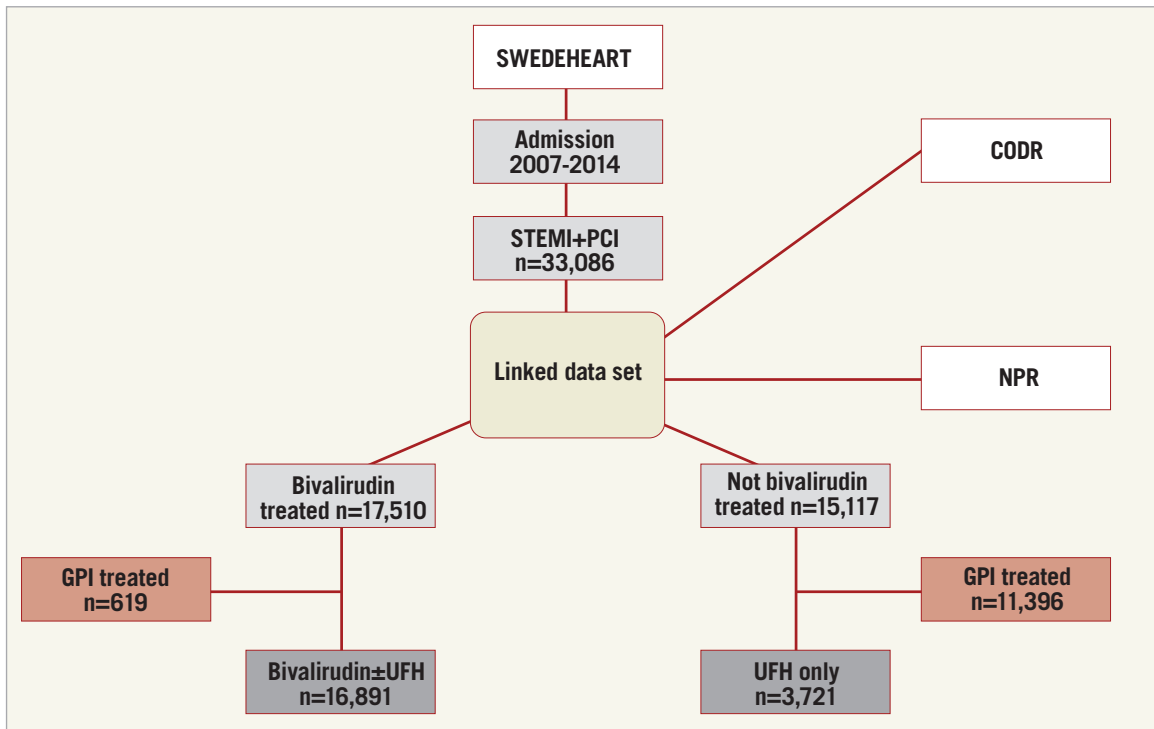
Figure 1. *Patient population flow chart. CODR: National Board of Health and Welfare's Cause of Death Register; GPI: glycoprotein IIb/IIIa inhibitor; NPR: National Patient Register; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; UFH: unfractionated heparin*

to overcome the uncertainty whether a new hospitalisation for myocardial infarction was a true recurrent event or merely a registration related to inter-hospital transfer. A separate sensitivity analysis for reinfarction within 365 days was added for the period 2010-2014. Statistical analyses were performed using R statistical programme version 3.1.3 (The R Foundation, Vienna, Austria).

Results

BACKGROUND CHARACTERISTICS

The treatment groups differed in baseline and procedural variables. UFH only treated patients were older, less likely to be male and generally at higher risk with more prior MI, PCI, CABG and longer time delays to PPCI. Thrombus aspiration and direct stenting were less frequently used. On the other hand, they were less often smokers and tended to have less severe lesions. Propensity score matching with imputed data sets generated very similar data groups **(Table 1)**.

EARLY STENT THROMBOSIS

The crude incidence of early ST was low and similar in UFH only (0.91%, n=34) and bivalirudin (0.78%, n=131) treated patients **(Figure 2, Table 2)**. Acute ST (day 0-1 post PCI) (0.32%, n=12 vs. 0.29%, n=49) and subacute ST (0.61%, n=22, vs. 0.50%, n=82) also occurred at similar rates. After multivariable adjustment using propensity score matching with an imputed data set, there was no difference in early ST: HR 1.08 (95% CI: 0.7-1.65). Also, using

propensity score-matched groups with an imputed data set, there was no difference between the groups: HR 1.03 (95% CI: 0.54-1.94). Event numbers were too low to perform adjusted analyses for acute and subacute ST separately.
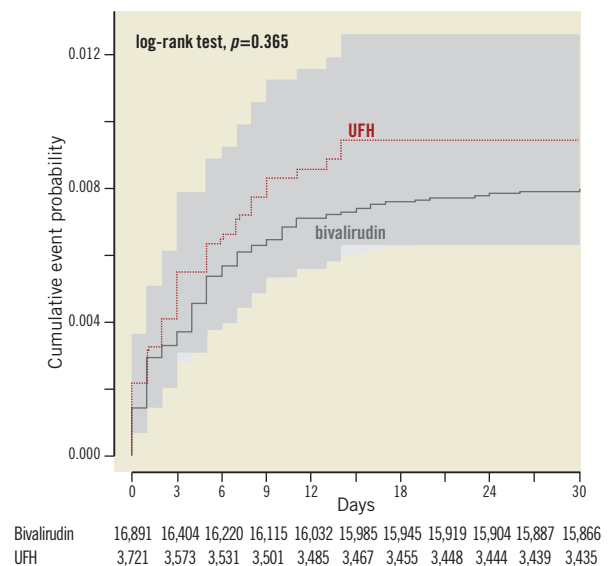

Bivalirudin	16,891	16,404	16,220	16,115	16,032	15,985	15,945	15,919	15,904	15,887	15,866
UFH	3,721	3,573	3,531	3,501	3,485	3,467	3,455	3,448	3,444	3,439	3,435

Figure 2. *Stent thrombosis within 30 days of PPCI. Kaplan-Meier curve of early stent thrombosis. UFH: unfractionated heparin; x-axis: number of days post PPCI; y-axis: proportion of individuals with stent thrombosis*

Table 1. Background characteristics.

		Entire cohort			Matched cohort	
		Bivalirudin n=16,891	UFH n=3,721	*p*-value	Bivalirudin n=3,250	UFH n=3,250
Patient and clinical factors						
Male gender (%)		70.1	67.9	0.008	68.1	68.2
Age, years±SD		67.7±12	68.7±12	<0.001	68.8±12	68.8±12
Body mass, mean (kg)		80±16	79±16	0.001	79.4±16	79.4±16
Diabetes (%)		14.3	14.6	0.669	14.4	14.4
Insulin-treated DM (%)		5.6	7.2	<0.001	6.6	6.7
Hypertension (%)		44	47	0.002	47	47.7
Hyperlipidaemia Tx (%)		21	24	<0.001	23.9	25.1
Prior AMI (%)		11.9	16.6	<0.001	15.5	16.5
Prior PCI (%)		8.0	10.7	<0.001	10.0	10.7
Prior CABG (%)		2.7	4.3	<0.001	4.3	4.5
GFR, median (mL/min)		83.7	78.5	<0.001	84.6±37	82.4±38
Current smoker (%)		30.9	27.9	<0.001	27.3	27.3
Cardiogenic shock (%)		2.3	2.9	0.057	1.8	2.9
No. of diseased vessels	1 (%)	49.5	46.6	<0.001	48.2	48.3
	2 (%)	28.7	28.8	<0.001	28.9	28.4
	3 (%)	16.6	19.2	<0.001	17.9	17.8
Left main disease (%)		4.6	4.7	<0.001	4.6	5
No. of vessels treated	One, no LM (%)	92	90	<0.001	90.8	89.9
	Two, no LM (%)	6.0	7.6	<0.001	7.0	7.5
	Three, no LM (%)	0.3	0.7	<0.001	0.4	0.7
	One incl. LM (%)	1.0	1.2	<0.001	1.2	1.3
	Two incl. LM (%)	0.4	0.5	<0.001	0.5	0.5
	Three incl. LM (%)	0.02	0	<0.001	0	0
Lesion variables						
Restenosis treated (%)		2.6	3.3	0.018	3.1	3.3
CABG graft treated (%)		1.2	1.8	0.007	1.8	1.9
B2/C lesion treated (%)		64	60	<0.001	57.9	58
CTO treated (%)		1.8	1.8	1	1.5	1.9
Stent variables, mean						
Total stent length (mm)		29.0±17	28±19	0.014	28.7±19	28.5±19
Stent diameter (mm)		3.1±0.5	3.0±0.5	<0.001	3.0±0.5	3.0±0.5
Min. stent diameter, mm		3.0±0.5	3.0±0.5	<0.001	3.0±0.5	3.0±0.5
No. of stents inserted, median		1	1	*	*	
Any DES inserted (%)		52.3	51.4	0.343	58.2	54.9
Only BMS (%)		47.1	48.1	*	41.4	44.5
Only DES (%)					56.4	
Mix BMS/DES (%)		51	49.6	*	1.7	53
		1.2	1.8	*		1.9
Access						
Femoral access (%)		36	39	0.006	30.2	31.7
Radial access (%)		63	61	*	60.8	59.2
Time delays						
Symptom start to PCI, median (hrs)		3.25	3.62	*	*	
ECG to start of PCI, median (hrs)		1.22	1.33	*	*	

Table 1. Background characteristics. (cont'd)

	Entire cohort			Matched cohort	
	Bivalirudin **n=16,891**	**UFH** **n=3,721**	*p*-value	**Bivalirudin** **n=3,250**	**UFH** **n=3,250**
Technical variables					
Thrombus aspiration (%)	29.8	14.0	<0.001	*	*
Direct stenting (%)	30	27	0.001	*	*
Procedural success (%)	98	98	0.082	*	*
Complete revascularisation (%)	58	60	0.075	*	*
Pharmacological variables					
P2Y$_{12}$ inhibitor prior to/during PCI	98	96	<0.001	*	*
UFH prior to/at PCI	78	100	<0.001	*	*

AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; CTO: chronic total occlusion; DES: drug-eluting stent; DM: diabetes mellitus; GFR: glomerular filtration rate; LM: left main; PCI: percutaneous coronary intervention; Tx: treatment; UFH: unfractionated heparin; *: variable not calculated

MORTALITY, REINFARCTION, STROKE AND MAJOR BLEEDING

The crude incidence of all-cause death at 30 days was higher in the UFH only as compared with bivalirudin-treated patients (6.93%, n=256 vs. 5.43%, n=916) **(Figure 2-Figure 4, Table 2)**. The difference remained after adjustment: HR 1.23 (95% CI: 1.05-1.44) and with matched groups: HR 1.2 (95% CI: 0.97-1.49). Similarly, the crude incidence of all-cause death at 365 days was higher in the UFH only as compared with bivalirudin-treated patients (12.1%, n=256 vs. 8.94%, n=1,472). The difference remained with adjustment: HR 1.34 (95% CI: 1.19-1.52) and with matched groups: HR 1.35 (95% CI: 1.07-1.72) **(Table 2)**.

The crude incidence of reinfarction within 365 days was higher in UFH only (3.05%, n=101) than bivalirudin-treated patients (2.41%, n=377) but with adjustment (HR 1.14 [95% CI: 0.88-1.46]) and with matched groups (HR 1.04 [95% CI: 0.73-1.48]) no significant difference remained **(Table 2)**. A separate sensitivity analysis for reinfarction within 365 days was added for the period 2010-2014, with no difference between treatment groups: adjusted HR 1.13 (95% CI: 0.86-1.47).
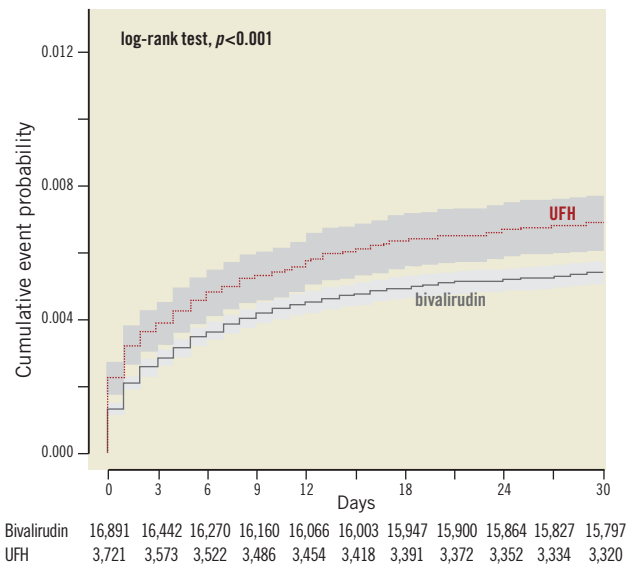

Bivalirudin	16,891	16,442	16,270	16,160	16,066	16,003	15,947	15,900	15,864	15,827	15,797
UFH	3,721	3,573	3,522	3,486	3,454	3,418	3,391	3,372	3,352	3,334	3,320

Figure 3. *All-cause death within 30 days of PPCI. Kaplan-Meier curve of all-cause mortality within 30 days of PPCI.*
UFH: unfractionated heparin; x-axis: days post PPCI;
y-axis: proportion of individuals diseased

Table 2. Outcomes.

	UFH % (n) n=3,721	Bivalirudin % (n) n=16,891	Unadjusted HR (95% CI) n=20,612	Adjusted HR (95% CI) n=20,612	PS matched (95% CI) n=5,942
Early ST	0.91% (34)	0.78% (131)	1.19 (0.82-1.74)	1.08 (0.7-1.65)	1.03 (0.54-1.94)
Acute ST day 0-1	0.32% (12)	0.29% (49)	*	*	*
ST day 2-30	0.61% (22)	0.50% (82)	*	*	*
All-cause death at 30 days	6.93% (256)	5.43% (916)	1.29 (1.12-1.48)	1.23 (1.05-1.44)	1.2 (0.97-1.49)
All-cause death at 365 days	12.1% (415)	8.94% (1,472)	1.37 (1.23-1.53)	1.34 (1.19-1.52)	1.35 (1.07-1.72)
MI at 365 days	3.05% (101)	2.41% (377)	1.27 (1.02-1.58)	1.14 (0.88-1.46)	1.04 (0.73-1.48)
Stroke at 30 days	1.17% (41)	1.02% (165)	1.16 (0.82-1.63)	1.08 (0.73-1.59)	1.12 (0.62-2.02)
Major bleeding at 30 days	0.8% (28)	0.62% (100)	1.31 (0.86-1.98)	1.54 (0.97-2.45)	1.40 (0.72-2.69)
Death, MI, stroke at 365 days	16.9% (568)	12.6% (2,065)	1.37 (1.25-1.5)	1.34 (1.2-1.49)	1.27 (1.07-1.5)

Hazard ratio displayed is for UFH vs. bivalirudin treatment groups. Acute ST: stent thrombosis day 0-1 post PCI; CI: confidence interval; Early ST: stent thrombosis day 1-30 post PCI; HR: hazard ratio; MI: myocardial infarction; UFH: unfractionated heparin; *: variable not calculated
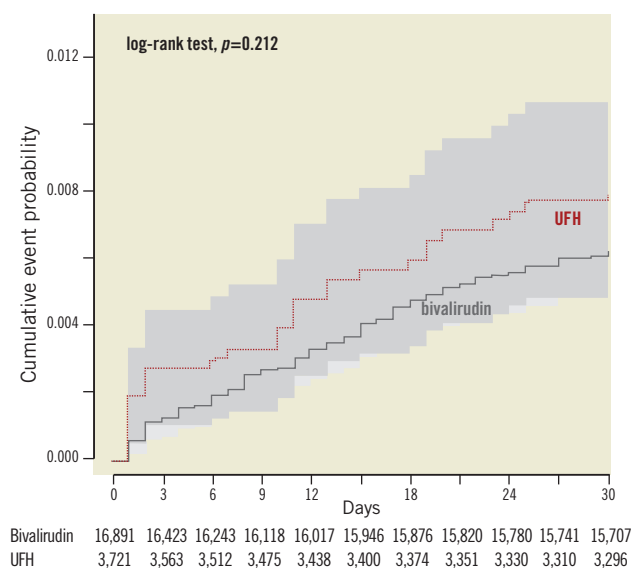
Figure 4. *Major bleeding within 30 days of PPCI. Kaplan-Meier curve of major bleeding within 30 days of PPCI. UFH: unfractionated heparin; x-axis: days post PPCI; y-axis: proportion of individuals with major bleeding*

The crude incidence of stroke within 30 days of PCI was similar with UFH (1.17%, n=41) and bivalirudin (1.02%, n=165), with no difference after adjustment (HR 1.08 [95% CI: 0.73-1.59]) or with matched groups (HR 1.12 [95% CI: 0.62-2.02]) **(Table 2)**.

The crude incidence of major bleeding within 30 days was higher in the UFH only (0.80%, n=28) as compared with the bivalirudin-treated patients (0.62%, n=100), but the difference did not remain after adjustment (HR 1.54 [95% CI: 0.97-2.45]) or with matched groups (HR 1.40 [95% CI: 0.72-2.69]) **(Table 2)**.

Discussion

In this large, nationwide observational study we found low and similar rates of early ST in UFH only and bivalirudin-treated patients undergoing primary PCI. Mortality was higher in UFH only compared with bivalirudin-treated patients. There were no differences in major bleeding, reinfarction or stroke.

Although randomised clinical trials are the gold standard for efficacy and safety, they have inherent limitations of selected enrolment and often limited sample size. Post-approval real-world registries may provide valuable supplementary data and important external validity to findings of randomised trials. SCAAR is a high-quality register, providing reliable data from a nationwide population, reflecting contemporary real-world practice in a high-risk, all-comer population. A mix of planned and bail-out GPI use in study arms limits many trials comparing UFH and bivalirudin.

MORTALITY

A recent meta-analysis of 14,000 randomised PPCI STEMI patients showed that bivalirudin, as compared to UFH with or without GPI, reduced the risk of all-cause mortality, cardiac mortality and major bleeding, but yielded comparable rates of major adverse cardiac events and net adverse clinical events at 30 days[13]. This meta-analysis contains several studies with marked differences in GPI use between study arms. Other meta-analyses with more balanced GPI exposure yield results with no mortality benefit for bivalirudin[14-16]. A recent UK registry report of more than 60,000 PPCI patients treated with either UFH/GPI or bivalirudin could not detect any mortality advantage with bivalirudin[17]. However, the study found a higher mortality in patients treated with UFH only. Our study results are consistent with the UK report, as we found higher all-cause mortality at 30 and 365 days associated with UFH only, compared with bivalirudin treatment.

STENT THROMBOSIS

A majority of randomised trials[1,5,6,8] and several meta-analyses[14-16] have shown increased ST rates with bivalirudin compared to UFH/GPI treatment. In our observational study, we found a very low incidence of early ST in both groups. Noted differences in ST rates between other trials and our study probably relate to pre- and post-randomisation patient characteristics, hospital treatment, downstream adverse event management, adherence to and continuation of key medications. Patient characteristics such as diabetes, smoking status, degree of coronary disease, previous AMI and PCI, parenteral antithrombotic treatment strategy, type or absence of $P2Y_{12}$ inhibition, stent properties and appropriate stent deployment are all factors of documented importance.

Ticagrelor reduces ST rates as compared with clopidogrel across all ACS modalities[18]. Prehospital ticagrelor loading is common in Sweden[19], and may partly explain the low ST rates[20]. The unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention trial (HEAT-PPCI) used only in-hospital ticagrelor loading and reported higher ST rates than other randomised clinical trials comparing UFH and bivalirudin[8]. Moreover, no concomitant UFH was used with bivalirudin, a practice that has been linked to increased ST rates in clinical trials and registries[5,21,22]. Bivalirudin was stopped at termination of PCI in HEAT-PPCI. Post-PCI continuation of bivalirudin, at PCI dose, is common in Sweden, but not reported in SCAAR. In the bivalirudin vs. heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction (BRIGHT) trial, prolonged bivalirudin infusion at PCI dose was postulated as an explanation for the similar ST rates observed with UFH and bivalirudin[7]. Risk of ST was not affected by prolonged bivalirudin infusion in the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) trial[6]. An exploratory analysis of the MATRIX trial suggested a relationship between dose during prolonged infusion and ST risk. A *post hoc* analysis of the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial suggested that prolonging the bivalirudin infusion at PCI dose mitigates the risk of ST[23]. Optimal dose/duration to minimise ST remains to be ascertained.

The HEAT-PPCI combination of in-hospital ticagrelor loading, bivalirudin without UFH and absence of prolongation may allow

ST, as platelet inhibition may not have reached sufficient levels of inhibition at bivalirudin termination.

Frequent prehospital ticagrelor, concomitant UFH with bivalirudin (78%) and bivalirudin prolongation may reduce Swedish ST rates. Future use of the parenteral platelet inhibitor cangrelor with a predictable fast onset may further reduce acute ST[24].

BLEEDING

Trials with major differences in GPI exposure to treatment arms have consistently shown decreased bleeding rates with bivalirudin, as compared with UFH/GPI[1,5,6]. Trials with balanced GPI exposure yield diverging results, with less clear bleeding advantages or even disadvantages for bivalirudin[7,8]. A recent real-world registry reported numerically higher bleeding rates in UFH monotherapy compared with bivalirudin-treated patients[25]. We excluded all GPI-treated patients and found no statistically significant differences in major bleeding. However, there was a trend towards more major bleeding in the UFH only treated patients. Although residual confounding may be the full explanation, we speculate that bleeding may be a contributing factor to our observed higher all-cause mortality in UFH only treated patients.

Limitations

The bivalirudin and UFH subgroups were different in clinical baseline characteristics. Despite propensity score adjustment and matching, residual confounding cannot be excluded. Inherent to all observational studies, there is a chance of under-reporting of events such as stent thrombosis and bleeding. Probable and possible ST events have not been included.

Exact drug dosage and duration are unknown in this study since they are not reported in SCAAR, although assumed to follow national and European guidelines. Unknown dosage is a major limitation, particularly for UFH with its narrow therapeutic range. Activated clotting time measurements are unknown. The exclusion of GPI-treated patients is a potential limitation, our primary reason being uncertainty as to whether GPI was a primary strategy or bail-out option. We acknowledge that bail-out GPI may have been used more frequently in either the UFH or bivalirudin-treated patients, which may have introduced a selection bias. In addition, bail-out GPI is used in high-risk cases with presumably large thrombus burden, possibly more exposed to stent thrombosis and other adverse events, leaving us with a lower-risk population. We recently published a descriptive report on ST rates in Sweden 2007-2014, reporting low early ST rates regardless of UFH, bivalirudin or GPI treatment[26]. Thus, excluding GPI in this study does not seem to have greatly affected rates of ST.

Conclusions

This large nationwide observational study shows overall low ST rates without any signals of increased ST rates associated with bivalirudin treatment. We found higher all-cause mortality in the UFH only as compared to bivalirudin-treated patients. Further randomised trials are needed to settle the uncertainty of optimal antithrombotic strategy in PPCI.

Impact on daily practice

This contemporary, large, nationwide observational study provides reassuring real-world data for the use of bivalirudin in STEMI patients treated with PPCI. We found that UFH compared with bivalirudin was associated with higher mortality at 30 and 365 days. The rates of early ST were low and similar with UFH and bivalirudin, and there were no differences in the rates of stroke, reinfarction and major bleeding.

Conflict of interest statement

P. Grimfjärd reports institutional grants from The Medicines Company and lecture fees from AstraZeneca. D. Erlinge reports speaker fees from The Medicines Company and AstraZeneca. S. Koul reports lecture fees from AstraZeneca. B. Lagerqvist reports institutional grants from AstraZeneca. B. Svennblad reports institutional grants from AstraZeneca, The Medicines Company and Novartis. C. Varenhorst reports institutional grants from AstraZeneca and The Medicines Company, lecture and advisory board fees from AstraZeneca, The Medicines Company and Boehringer Ingelheim, lecture fees from Bayer, CSL Behring, Bristol Myers Squibb, Pfizer and is on the Clinical Endpoint Committee for Pfizer, Bristol Myers Squibb, Philips and AstraZeneca. S.K. James reports institutional grants and honoraria from AstraZeneca, The Medicines Company, Abbott and Boston Scientific.

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