Circulation

ORIGINAL RESEARCH ARTICLE

Prehospital Heparin Administration in Patients With STEMI Undergoing Primary PCI: HEPARIN-STEMI Randomized Controlled Trial

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BACKGROUND: Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for patients with ST-segment–elevation myocardial infarction (STEMI). We investigated the benefits and safety of pretreatment with unfractionated heparin (UFH) in patients with STEMI referred to primary PCI.

METHODS: In HEPARIN-STEMI (Pretreatment With Unfractionated Heparin for ST Elevation Myocardial Infarction)—a single-center, open-label, randomized controlled trial—patients with STEMI with ≤6 hours symptom duration were assigned to receive either a 70- to 100-IE/kg bolus of UFH at first prehospital medical contact plus a supplemental dose before PCI, adjusted to activated clothing time ≥250 seconds, or to a control group receiving standard UFH at the time of PCI. The primary efficacy end point was TIMI (Thrombolysis in Myocardial Infarction) flow grade 2–3 in the infarct-related artery at initial coronary angiography. The primary safety end point was BARC (Bleeding Academic Research Consortium) type 3–5 bleeding during the index hospital stay.

RESULTS: From March 2022 to February 2025, 298 patients were randomized to UFH pretreatment and 295 to the control group. The groups were comparable in age, sex, risk factors, previous cardiovascular events, and median delay from symptoms to coronary angiography (145 versus 150 minutes; P=0.814). The median time from UFH pretreatment to coronary angiography was 60 minutes (25th–75th interquartile range, 47–55 minutes). TIMI flow grade 2–3 in the infarct-related artery was documented in 43% of patients with UFH pretreatment and 27% of patients in the control group (relative risk, 1.59 [95% CI, 1.27–1.98]; P<0.001), with no significant difference in BARC type 3–5 bleeding (2.4% versus 2.0%; relative risk, 1.16 [95% CI, 0.39–3.45]; P=0.789).

CONCLUSIONS: In patients with STEMI undergoing primary PCI, in a mature STEMI network, pretreatment with UFH at first prehospital medical contact was associated with an absolute 16% increase in infarct-related artery patency without an increased risk of bleeding.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT05247424.

Key Words: heparin ■ percutaneous coronary intervention ■ ST elevation myocardial infarction

Editorial, see p 1535

Primary percutaneous coronary intervention (PCI) is the standard reperfusion strategy for patients with ST-segment–elevation myocardial infarction (STEMI).[1,2] Because a patent infarct-related artery (IRA) at initial coronary angiography is associated with an improved outcome,[3] several pharmacologic agents have been attempted—including unfractionated heparin (UFH), bivalirudin, glycoprotein IIb/IIIa inhibitors, and oral $P2Y_{12}$ inhibitors—with mixed success.[4–10] Subcutaneous pretreatment with a novel glycoprotein IIb/IIIa inhibitor,

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Clinical Perspective

What Is New?

- In patients with ST-segment–elevation myocardial infarction referred for primary percutaneous coronary intervention, an intravenous bolus of unfractionated heparin (70–100 IU/kg) administered at the first prehospital medical contact increased the patency of the infarct-related artery by an absolute 16%.
- The increased infarct-related artery patency was achieved without an excess risk of bleeding.

What Are the Clinical Implications?

- UFH-STEMI (Pretreatment With Unfractionated Heparin for ST Elevation Myocardial Infarction) supports routine unfractionated heparin administration at the first medical contact in patients with ST-segment–elevation myocardial infarction referred for primary percutaneous coronary intervention.
- Prehospital unfractionated heparin administration is effective, safe, inexpensive, and widely available.

Nonstandard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
cTnI	cardiac troponin I
DANAMI-2	Danish Trial in Acute Myocardial Infarction-2
FMC	first medical contact
HEAP	Heparin in Early Patency
HELP-PCI	Early Administration of Heparin at First Medical Contact for PPCI of STEMI Patients
IRA	infract-related artery
PCI	percutaneous coronary intervention
STEMI	ST-segment–elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
UFH	unfractionated heparin
UFH-STEMI	Pretreatment With Unfractionated Heparin for ST Elevation Myocardial Infarction

zalunfiban, was recently found to improve IRA patency, but was associated with increased mild to moderate bleeding.[11]

Pretreatment with UFH, a predominant intravenous anticoagulant used during primary PCI for STEMI, was first investigated in DANAMI-2 (Danish Trial in Acute Myocardial Infarction-2).[12] After a 10 000-IU bolus of UFH on the way to primary PCI, a 32% IRA patency rate was documented at first coronary angiography. This is in accordance with several retrospective observational studies demonstrating improved IRA patency and better clinical outcome.[7,8,10] In contrast, in the HEAP randomized trial (Heparin in Early Patency),[9] a high UFH dose (300 IE/kg) compared with low-dose or no UFH did not increase IRA patency (22% versus 21%; $P>0.1$) and was associated with a strong trend toward increased need for transfusion (10% versus 6%; $P=0.07$). The HELP-PCI randomized study (Early Administration of Heparin at First Medical Contact for PPCI of STEMI Patients) recently demonstrated that UFH pretreatment significantly improved TIMI (Thrombolysis in Myocardial Infarction) flow grade 3 at initial coronary angiography from 17.6% to 23.6%.[13] In this study, however, <5% of patients received prehospital UFH at the first medical contact (FMC); the rest of the patients were pretreated later on the way to primary PCI.

In the current study, we investigated UFH pretreatment at the FMC in a contemporary high-volume primary PCI network characterized by systematic prehospital ECG STEMI diagnosis and direct transfer to a single high-volume primary PCI center with 24-hour, 7-day availability.[1]

METHODS

Data Availability

Data, analytic methods, and study materials will be available to other researchers upon request by contacting the first or the last author of the study.

Study Design

UFH-STEMI (Pretreatment With Unfractionated Heparin for ST Elevation Myocardial Infarction) was an investigator-initiated, single-center, open-label, randomized controlled trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT05247424) funded by the University Medical Center Ljubljana (grant 20220075). The trial was approved by the National Ethics Committee (approval 0120-591/2021/3), which granted a waiver for informed consent at the time of randomization. Written informed consent was therefore obtained during hospitalization with timing depending upon the mental condition of the patient. In case of death, the National Ethics Committee granted approval for data utilization without patient consent. Data were collected by the investigators and analyzed by an independent statistician (Appendix in the Supplemental Material). The manuscript was drafted by the first and the second author and edited by coauthors, who agreed to manuscript submission and vouch for the accuracy and completeness of the data. A detailed protocol of the study has been published previously.[14]

Patients

UFH-STEMI enrolled consecutive patients with STEMI referred for primary PCI within the Ljubljana STEMI network.[15] Patients were >18 years old, had obvious STEMI on 12-lead ECG[8]

recorded at the prehospital FMC, and had symptom duration of ≤6 hours. Pregnant women, comatose survivors of out-of-hospital cardiac arrest, and patients in cardiogenic shock were excluded.

Randomization

After documenting STEMI on 12-lead ECG recorded at the prehospital FMC, the emergency physician informed the acute cardiac care physician at the Center for Intensive Internal Medicine, University Medical Center Ljubljana, Slovenia, and sent the 12-lead ECG. After confirming the STEMI diagnosis and fulfillment of inclusion criteria, the patient was randomized 1:1 to either UFH pretreatment administered at the FMC on the field or the control group without UFH pretreatment. Randomization was performed using random permutated blocks with a secure online randomization service (www.sealedenvelope.com).

Procedures

At the prehospital FMC, all patients received acetylsalicylic acid (250–500 mg per os) and no P2Y12 inhibitor. Patients randomized to UFH pretreatment received a 70- to 100-IE/kg intravenous bolus[1] at the prehospital FMC plus a supplemental dose after initial coronary angiography and before primary PCI, which was adjusted to an activated clotting time of ≥250 seconds. The control group received a 70- to 100-IE/kg UFH bolus after initial coronary angiography and before primary PCI. Primary PCI was performed by one of the attending interventional cardiologists at the University Medical Center Ljubljana, Slovenia, who was blinded to the group assignment. Eptifibatide or cangrelor were given only during primary PCI, at the discretion of the interventional cardiologist. The patients were then admitted to the cardiac intensive care unit for monitoring and further care. Repeat 12-lead ECG was recorded immediately on admission.

Outcomes

All coronary angiograms were evaluated by an experienced interventional cardiologist who was blinded to the group assignment.

The primary efficacy end point was TIMI flow grade 2 or 3 in the IRA at initial coronary angiography. The primary safety end point was occurrence of BARC (Bleeding Academic Research Consortium) type 3–5 bleeding during the index hospital stay.[16]

Secondary end points were postprocedural TIMI flow grade 3, early ST-segment resolution according to the baseline, peak cardiac troponin I (cTnI), cTnI after 24 hours, progression to cardiogenic shock after primary PCI, and 30-day all-cause mortality. ST-segment resolution was measured from digitalized ECG recordings using digital calipers by a single noninvasive cardiologist who was blinded to group assignment. The lead with the highest ST-segment elevation on initial ECG was identified and the ST-segment elevation was measured 40 ms after QRS, using the TP segment as baseline.[17] ST-segment elevation was measured in the same lead from the second ECG recorded on admission to the coronary care unit after primary PCI. Based on these 2 measurements, the percent change was calculated.

The prespecified subgroup analysis included sex, age (≤65 or >65 years), IRA (left anterior descending, left circumflex, right coronary, or side branch), time from symptom onset to prehospital UFH administration (<2, 2–4, or >4 hours), and time from prehospital UFH administration to coronary angiography (≤1 or >1 hour).

Additional nonprespecified study end points were 1-year all-cause mortality and primary and safety end points according to radial or femoral access site.

Statistical Analysis

The study was designed as a superiority trial testing the hypothesis that UFH pretreatment increases IRA patency at initial coronary angiography compared with the current standard of care (UFH given after coronary angiography and before primary PCI). Sample size calculation was based on the primary end point with an expected absolute difference of 11.5% in IRA TIMI flow grade 2 or 3 in favor of prehospital UFH pretreatment.[7–10] Based on this assumption, 538 patients were needed to achieve a statistical power of 80% at a 2-sided significance level of 0.05. Considering an expected dropout of ≈2.5% in each group, the total sample size was increased to 600. Sample size calculations were performed using the Sealed Envelope 2012 power calculator for binary outcome superiority trials (https://www.sealedenvelope.com/power/binary-superiority).

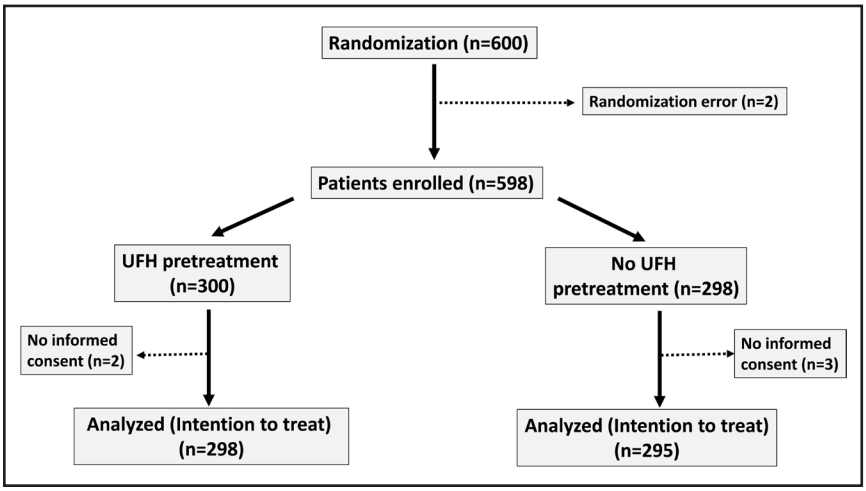

Figure 1. Study flowchart.
UFH indicates unfractionated heparin.

Table 1. Characteristics, Prehospital Treatment, and Periprocedural Details of Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Pretreatment With or Without Unfractionated Heparin Pretreatment

Characteristics	UFH pretreatment (n=298)	No UFH pretreatment (n=295)	*P* value
Age, y	64.2±11.7	63.0±11.6	0.186
Male sex	215 (72)	225 (76)	0.215
Body mass index	27.8±4.3	28.2±4.2	0.257
Hypertension	151/298 (51)	159/295 (54)	0.431
Diabetes	52/298 (17)	49/295 (17)	0.786
Hypercholesterolemia	98/298 (33)	101/295 (34)	0.727
Current smoking	127/298 (43)	117/295 (41)	0.464
Previous MI	30/298 (10)	38/295 (13)	0.282
Previous stroke	15/298 (5)	11/295 (4)	0.438
PAD	11/298 (4)	13/295 (4)	0.658
Previous PCI	36/298 (12)	45/295 (15)	0.260
Previous CABG	2/298 (0.7)	2/295 (0.7)	1.000
ACE inhibitor/sartan	117/298 (39)	132/295 (45)	0.748
Statin	77/298 (26)	79/295 (27)	0.796
B-blocker	67/298 (23)	63/295 (21)	0.740
Calcium channel blocker	53/298 (18)	61/295 (21)	0.371
Furosemide	5/298 (2)	4/295 (1)	1.000
Acetylsalicylic acid	53/298 (18)	66/295 (22)	0.163
Clopidogrel	6/298 (2)	3/295 (1)	0.505
Prasugrel	2/298 (0.7)	1/295 (0.3)	1.000
Ticagrelor	1/298 (0.3)	1/295 (0.3)	1.000
Anticoagulation	8/298 (3)	13/295 (4)	0.275
Prehospital treatment			
Symptoms to FMC, min	70 (35–135)	66 (35–120)	0.986
FMC to catheterization laboratory, min	69 (50–95)	66 (49–100)	0.853
Symptoms to catheterization laboratory, min	145 (107–210)	150 (104–220)	0.814
Acetylsalicylic acid at FMC	296/298 (99.3)	294/295 (99.7)	0.569
UFH pretreatment at FMC	291/298 (97.7)	5/295 (1.7)	<0.001
Primary PCI			
Coronary angiography	296/298 (99.3)	292/295 (99.0)	0.645
Radial access	229/296 (77.4)	233/292 (79.8)	0.473
Obvious IRA	285/296 (96.3)	280/292 (95.9)	0.806
LM	6 (2.1)	2 (0.7)	
LAD	97 (34.0)	120 (42.9)	
LCX	35 (12.3)	32 (11.4)	
RCA	121 (42.5)	113 (40.4)	
Side branch	26 (9.1)	13 (4.6)	
Multivessel disease	108/296 (36.5)	107/292 (36.6)	0.968
PCI, with stenting	287/296 (97.0)	280/296 (94.6)	0.153
Total UFH, IE/kg	163 (146–181)	92 (83–100)	<0.001
Eptifibatide	44/287 (15.3)	43/280 (15.4)	0.993
Cangrelor	13/287 (4.5)	16/280 (5.7)	0.522
Oral $P2Y_{12}$ inhibitor			0.282
Clopidogrel	43/287 (15.0)	32/280 (11.4)	

(*Continued*)

Table 1. Continued

Characteristics	UFH pretreatment (n=298)	No UFH pretreatment (n=295)	*P* value
Ticagrelor	156/287 (54.4)	169/280(60.4)	
Prasugrel	88/287 (30.7)	79/280 (28.2)	
Hemostasis at puncture site			0.102
Radial band	228/296 (77.0)	232/292(79.5)	
Femoral closure device	49/296 (16.6)	53/292 (18.2)	
Femoral manual compression	10/296 (3.4)	3/292 (1.0)	
Radial band and femoral closure device	8/296 (2.7)	3/292 (1.0)	

Values are mean±SD, n/N (%), or median (25th–75th interquartile range). ACE indicates angiotensin-converting enzyme; CABG, coronary artery bypass graft; FMC, first prehospital medical contact; IRA, infarct-related artery; LAD, anterior descending artery; LCX, left circumflex artery; LM, left main; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; and UFH, unfractionated heparin.

Numeric data are shown as mean and SD or median with 25th and 75th interquartile ranges. Categorical data are shown as numbers and proportions in percentages. Between-group comparisons for numeric variables were performed using unpaired *t* tests for normally distributed variables and Mann-Whitney *U* tests for non-normally distributed variables. Categorical variables were compared by the Fisher exact test or χ^2 test. All statistical tests were 2-sided, and a significance threshold (α) of 0.05 was used for primary analyses.

Primary analysis was performed according to the intention to treat. Additional sensitivity analyses were performed per protocol and as treated for evaluation of data robustness (Appendix in the Supplemental Material). The per-protocol population was defined as patients who fulfilled all inclusion and exclusion criteria, received treatment as randomized, underwent coronary angiography, had STEMI, and had no protocol deviations affecting the primary outcome. The as-treated population was defined according to the actual treatment. Effect sizes regarding secondary outcomes are presented as relative risks (RRs) with corresponding 95% CIs, calculated using generalized linear models with a log link and binomial distribution. Forest plots of the RR for the primary outcome with 95% CI were computed for prespecified subgroups. Corresponding $P_{interaction}$ values were derived from logistic regression models including interaction terms between treatment and each subgroup variable. An overview of data availability, eligibility, and reasons for nonassessment is provided in the Appendix in the Supplemental Material (Table S8). SPSS 22.0.0.0 was used for statistical analysis.

RESULTS

From March 10, 2022, to February 5, 2025, among 1162 consecutive patients with STEMI referred for primary PCI at the University Medical Center Ljubljana, 600 (52%) were randomized. Because of 2 randomization errors and inability to obtain informed consent from 5 patients, 298 patients were ultimately enrolled in the UFH pretreatment group and 295 in the control group (Figure 1). There was no significant difference in age,

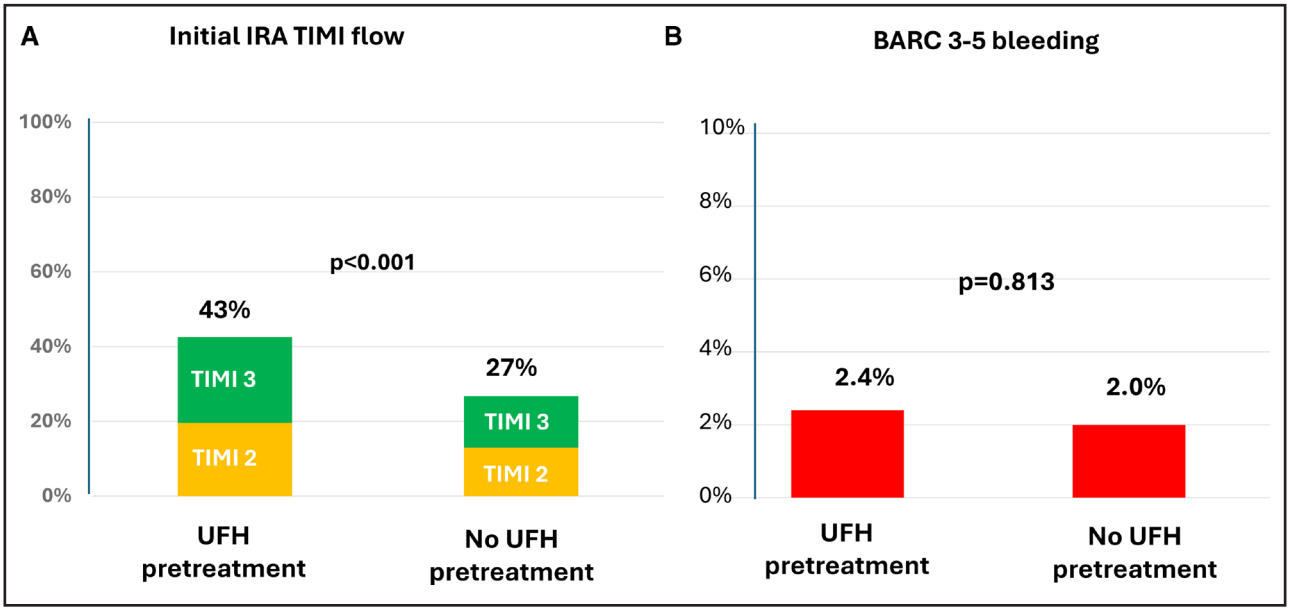

Figure 2. Primary efficacy and safety end points in patients with or without unfractionated heparin pretreatment.
A, Initial TIMI (Thrombolysis in Myocardial Infarction) flow grade 2 or 3 in the infarct-related artery (IRA) at coronary angiography. **B**, BARC (Bleeding Academic Research Consortium) type 3–5 bleeding. IRA indicates infarct-related artery; and UFH, unfractionated heparin.

sex, body mass index, cardiovascular risk factors, previous history of atherosclerotic events, revascularization procedures, or medical therapy (Table 1). There was also no difference between the UFH pretreatment and control groups in previous treatment with acetylsalicylic acid (18% versus 22%), P2Y12 inhibitors (3% versus 1.6%), or anticoagulants (3% versus 4%). Delays between symptom onset and prehospital FMC (70 versus 66 minutes; *P*=0.986) and from FMC to catheterization laboratory arrival were also comparable. The median time from prehospital UFH administration to coronary angiography was 60 minutes (25th–75th interquartile range, 47–55 min) and the average prehospital dose of UFH was 97 IU/kg (25th–75th interquartile range, 92–100 IU/kg).

Radial access was used in 77.4% of the UFH pretreatment group and in 79.8% of the control group (*P*=0.473; Table 1). Obvious IRA was documented in >95% of cases, without a significant difference between the groups. Primary PCI with IRA stenting was performed in 97% of the pretreatment group and 94.6% of the standard group (*P*=0.153). Periprocedural medication included eptifibatide, cangrelor, and oral P2Y12 inhibitors, without significant differences between the groups. The cumulative dose of UFH including prehospital UFH was significantly greater in the pretreatment group (163 versus 92 IE/kg; *P*>0.001).

TIMI flow grade 2 or 3 in the IRA at initial coronary angiography was documented in 43% of the UFH pretreatment group and 27% of the control group (RR, 1.59 [95% CI, 1.27–1.98]; *P*<0.001; Figure 2A and Table 2). BARC type 3–5 bleeding was documented in 2.4% of the UFH pretreatment group and 2.0% of the control

Table 2. Study End Points

End points	UFH pretreatment (n=298)	No UFH pretreatment (n=295)	Relative risk (95% CI)	*P* value
Primary end point				
Initial TIMI flow grade 2 or 3	126/296 (42.6)	78/292 (26.7)	1.59 (1.27–1.98)	<0.001
Initial TIMI flow grade				<0.001
0	137/296 (46.3)	191/292 (65.4)		
1	33/296 (11.1)	23/292 (7.9)		
2	58/296 (19.6)	38/292 (13.0)		
3	68/296 (23.0)	40/292 (13.7)		
Safety end point				
BARC type 3–5 bleeding	7/297 (2.4)	6/295 (2.0)	1.16 (0.39–3.45)	0.789
BARC type 0–5 bleeding*				0.077
No bleeding	219/297 (73.7)	236/295 (80.0)		
1	51/297 (17.2)	38/295 (12.9)		
2	20/297 (6.7)	15/295 (5.1)		
3a	3/297 (1.0)	2/295 (0.7)		
3b	1/297 (0.3)	1/295 (0.3)		
3c	1/297 (0.3)	0/295 (0.0)		
4	2/297 (0.7)	3/295 (1.0)		
5	0/297 (0.0)	0/295 (0.0)		
Final TIMI flow grade				0.863
0	3/296 (1.0)	4/292 (1.4)		
1	3/296(1.0)	5/292 (1.7)		
2	50/296 (16.9)	47/292 (16.1)		
3	240/296 (81.1)	236/292 (80.8)		
ST-segment resolution,%	65 (42–88)	59 (30–80)		0.047
Troponin I 24 h, ng/L	30.357 (10.272–66.828)	41.795 (17.550–71.396)		0.036
Peak troponin I, ng/L	43.126 (13.133–96.592)	46.971 (20.152–94.839)		0.318
Cardiac arrest	11/298 (3.7)	14/295 (4.7)		0.523
Shock	46/298 (15.4)	41/295 (13.9)	1.11 (0.75–1.64)	0.597
Death at 30 d	7/294 (2.4)	7/282 (2.5)	0.96 (0.34–2.70)	0.937

Values are n/N (%) or median (25th–75th interquartile range). TIMI indicates Thrombolysis in Myocardial Infarction; and UFH, unfractionated heparin.

*Mann-Whitney *U* test comparing ordinal BARC (Bleeding Academic Research Consortium) bleeding severity.

group (RR, 1.16 [95% CI, 0.39–3.45]; *P*=0.789; Figure 2B and Table 2). These findings were consistent with per-protocol (Appendix in the Supplemental Material [Table S6]) and as-treated analyses (Appendix in the Supplemental Material [Table S7]).

Postprocedural TIMI flow grade 3 was documented in 81.1% of the UFH pretreatment group and in 80.8% of the control group (*P*=0.863) (Table 2). Early ST-segment resolution was better in the UFH pretreatment group (65% versus 59%; *P*=0.047). There was no significant difference in peak cTnI between the groups. However, cTnI at 24 hours was significantly decreased in the UFH pretreatment group compared with the control group (30.357 versus 41.795 ng/L; *P*=0.036). There was no significant difference in incidence of cardiac arrest, progression to cardiogenic shock, or 30-day all-cause mortality between the groups.

Prespecified subgroup analyses are shown in Figure 3. The RR estimates were directionally consistent across subgroups defined by sex, age, culprit artery, symptom-to-heparin time, and time from heparin administration to coronary angiography. Formal tests for interaction were not statistically significant for any subgroup (all $P_{interaction}$>0.05), indicating no evidence of heterogeneity of treatment effect.

The 1-year all-cause mortality rate was 4.1% in the UFH pretreatment group and 2.8% in the control group (*P*=0.397). The primary efficacy end point was in favor of UFH pretreatment when patients were stratified according to radial (RR, 1.58 [95% CI, 1.21–2.05]; *P*=0.001) or femoral access (RR, 1.73 [95% CI, 1.04–2.88]; *P*=0.039). BARC type 3–5 bleeding was comparable in the UFH pretreatment and control groups in both radial (RR, 1.44 [95% CI, 1.00–2.07]; *P*=0.064) and femoral access (RR, 0.97 [95% CI, 0.59–1.59]; *P*=1.000).

DISCUSSION

The main finding of our study is that UFH administration at the dose of 70 to 100 IE/kg at prehospital FMC in patients with STEMI with direct transfer to primary PCI significantly improves IRA patency from 27% to 43% at initial coronary angiography without increasing the risk of significant bleeding. Because UFH is a standard anticoagulation drug used during primary PCI, administration at prehospital FMC with additional adjustments according to activated clotting time before primary PCI seems reasonable, although unequivocal proof of reduced infarct size and improved clinical outcome is lacking.

The rate of IRA patency after prehospital UFH in our study was comparable to pretreatment with bivalirudin[4] or abciximab[18] and notably higher than after ticagrelor.[5,6] However, pretreatment with those agents may be associated with excess bleeding,[5,18–20] which was not the case in our study.

Subgroup	Early heparin	Control	RR (95% CI)	p	P for interaction
Sex					0.273
Male	93/214 (43.5)	56/222 (25.2)	1.72 (1.31-2.26)	**<0.001**	
Female	33/82 (40.2)	22/70 (31.4)	1.28 (0.83-1.98)	0.260	
Age					0.468
<65 years	61/158 (38.6)	42/162 (25.9)	1.49 (1.07-2.06)	**0.015**	
≥65 years	65/138 (47.1)	36/130 (27.7)	1.70 (1.22-2.36)	**0.001**	
Culprit artery					0.745
LM	5/6 (83.3)	0/2 (0.0)		0.035	
LAD	39/97 (40.2)	24/120 (20.0)	2.01 (1.30-3.10)	**0.001**	
LCX	18/35 (51.4)	13/32 (40.6)	1.27 (0.75-2.15)	0.376	
RCA	40/121 (33.1)	25/113 (22.1)	1.50 (0.97-2.29)	0.062	
Side branch	13/26 (50.0)	4/13 (30.8)	1.63 (0.66-4.00)	0.254	
Symptoms to heparin (time - h)					1.000
<2	87/184 (47.3)		1.77 (1.39-2.26)	**<0.001**	
2-4	30/84 (35.7)	78/292 (26.7)	1.34 (0.95-1.89)	0.108	
>4	9/28 (32.1)		1.20 (0.68-2.13)	0.537	
Heparin to coronary angiography (time - h)					1.000
≤1	50/144 (34.7)	78/292 (26.7)	1.30 (0.97-1.74)	0.084	
>1	76/152 (50.0)		1.87 (1.46-2.40)	**<0.001**	

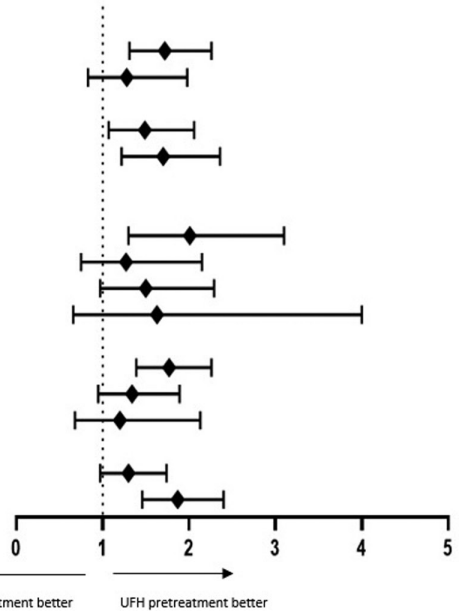

Figure 3. Forest plot for the primary end point in prespecified subgroups.
The forest plot shows relative risk (RR) and 95% CI, for the primary end point (TIMI [Thrombolysis in Myocardial Infarction] flow grade 2 or 3 at initial coronary angiography) in prespecified subgroups. No unfractionated heparin (UFH) group was used as a common reference category for estimated RR. LAD indicates left anterior descending artery; LCX, left circumflex artery; LM, left main coronary artery; and RCA, right coronary artery.

Our findings are in accordance with the recent HELP-PCI randomized trial from China, which showed significantly improved IRA-TIMI flow grade 3 from 17.6% to 23.5%.[13] However, when pooling together TIMI flow grade 2 and 3, the benefits in HELP-PCI (32.2% versus 27.9%) are less obvious than in our patients (43% versus 27%). This difference is best explained by shorter delay from symptom onset to FMC in our patients (70 versus 161 minutes), which is likely to be associated with less organized coronary thrombus more prone to UFH dissolution.

Although statistically significant treatment effects were observed in certain prespecified subgroups, there was no evidence of heterogeneity across the subgroups, with nonsignificant $P_{interaction}$. These findings therefore do not provide evidence of differential treatment effect and may be at best hypothesis-generating.

Limitations

The primary end point—IRA patency at initial coronary angiography—was evaluated by a single experienced interventional cardiologist who was blinded to UFH assignment and not by a core laboratory or another independent interventional cardiologist. We addressed only IRA patency without measuring infarct size, although significantly improved ST-segment resolution and lower cTnI at 24 hours in the UFH pretreatment group may point to smaller infarct size. Our protocol did not specify more troponin measurements, which would enable calculation of the area under the curve to better estimate an infarct size. Furthermore, echocardiography during the follow-up, which could provide a signal for better left ventricular function in UFH-pretreated patients, was not one of the study end points. Our study was underpowered to address clinical end points such as 30-day and 1-year mortality as well as incidence and degree of heart failure, which may be more sensitive indicators to show potential benefits of UFH pretreatment. Our study also excluded high-risk patients with STEMI, such as late presenters, comatose survivors of cardiac arrest, and patients with cardiogenic shock.

CONCLUSION

In patients with STEMI undergoing primary PCI at a high-volume center with 24-hour, 7-day availability within a contemporary STEMI network, pretreatment with UFH at prehospital FMC improved IRA patency at initial coronary angiography without increasing clinically significant bleeding. This safe, inexpensive treatment has the potential to reduce infarct size and improve clinical outcome.

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Disclosures

None.

Supplemental Material

Checklists
Appendix
Tables S1–S8
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