Effect of Fixed-Bolus (5,000 Units) Unfractionated Heparin Before Primary Percutaneous Coronary Intervention on Activated Clotting Time, Time Flow, and All-Cause Mortality

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The American College of Cardiology Foundation /American Heart Association guidelines recommend a weight-based dose of unfractionated heparin (UFH) for primary percutaneous coronary intervention (PCI). However, it is convention to administer a fixed-bolus dose of 5,000 units of UFH. It is unclear if 5,000 units are sufficient to achieve a therapeutic first activated clotting time (ACT). We conducted a retrospective cohort study to determine the proportion of therapeutic first ACT in patients who received 5,000 units of UFH before primary PCI. We examined the association of therapeutic first ACT with clinical outcomes, including post-PCI Thombolysis in Myocardial Infarction (TIMI) grade flow, myocardial infarction, bleeding, and mortality. Among the 269 included patients, 74.7% were men, and 61.4% were overweight or obese. The mean first ACT was 243.4 (SD = 61.5) seconds. Most patients (56.1%) had an infratherapeutic first ACT, 21.9% had a therapeutic first ACT, and 21.9% had a supratherapeutic first ACT. Furthermore, 44.6% of patients who achieved the American College of Cardiology Foundation/American Heart Association target weight-based dosing had an infratherapeutic ACT. The proportion of patients with post-PCI TIMI grade flow 0 to 2 was 14.6% among those with a first ACT that was infratherapeutic versus 6.8% among those with a first ACT that was not infratherapeutic (relative risk 2.15, 95% CI 0.99 to 4.65). In conclusion, over half of patients with ST-elevation myocardial infarction administered 5,000 units of UFH have an infratherapeutic first ACT and the high rate of poor TIMI grade flow in patients with an infratherapeutic ACT is concerning. **(Am J Cardiol 2017;119:178−185)**

Intravenous (IV) unfractionated heparin (UFH) is routinely administered before primary percutaneous coronary intervention (PCI) to prevent acute vessel closure and poor post-PCI Thombolysis in Myocardial Infarction (TIMI) grade flow.[1−4] The 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines recommend a 50 to 70 unit/kg bolus of UFH if glycoprotein IIb/IIIa inhibitors (GPIs) are administered and a 70 to 100 unit/kg bolus of UFH if GPIs are not administered.[3] Despite these weight-based recommendations, it is common practice to administer a fixed dose of 5,000 units of UFH in all patients before primary PCI. However, it is unclear if 5,000 units of UFH is adequate to achieve a therapeutic first activated clotting time (ACT) measured in the cardiac catheterization laboratory. Much of this controversy stems from evidence suggesting that acute myocardial infarction (MI) triggers an acute phase protein response, leading to a hypercoagulable state and transient heparin resistance.[5,6] We conducted a retrospective cohort study to determine if a fixed 5,000-unit bolus of UFH before primary PCI leads to a majority of patients achieving a therapeutic first ACT.

Methods

We conducted a hospital-based, retrospective cohort study of patients aged ≥18 years who were diagnosed with ST-elevation myocardial infarction (STEMI), received a fixed 5,000-unit bolus of UFH and subsequently underwent primary PCI from January 2008 to December 2012 at the Jewish General Hospital in Montreal, Quebec, Canada. Ethics approval for this study was granted by the Research Ethics Committee of the Jewish General Hospital.

All consecutive patients who were diagnosed with STEMI and underwent primary PCI were identified in the cardiac catheterization laboratory database. We identified these patients by searching cardiac catheterization reports for the term "STEMI." Patients with potential STEMI were defined as

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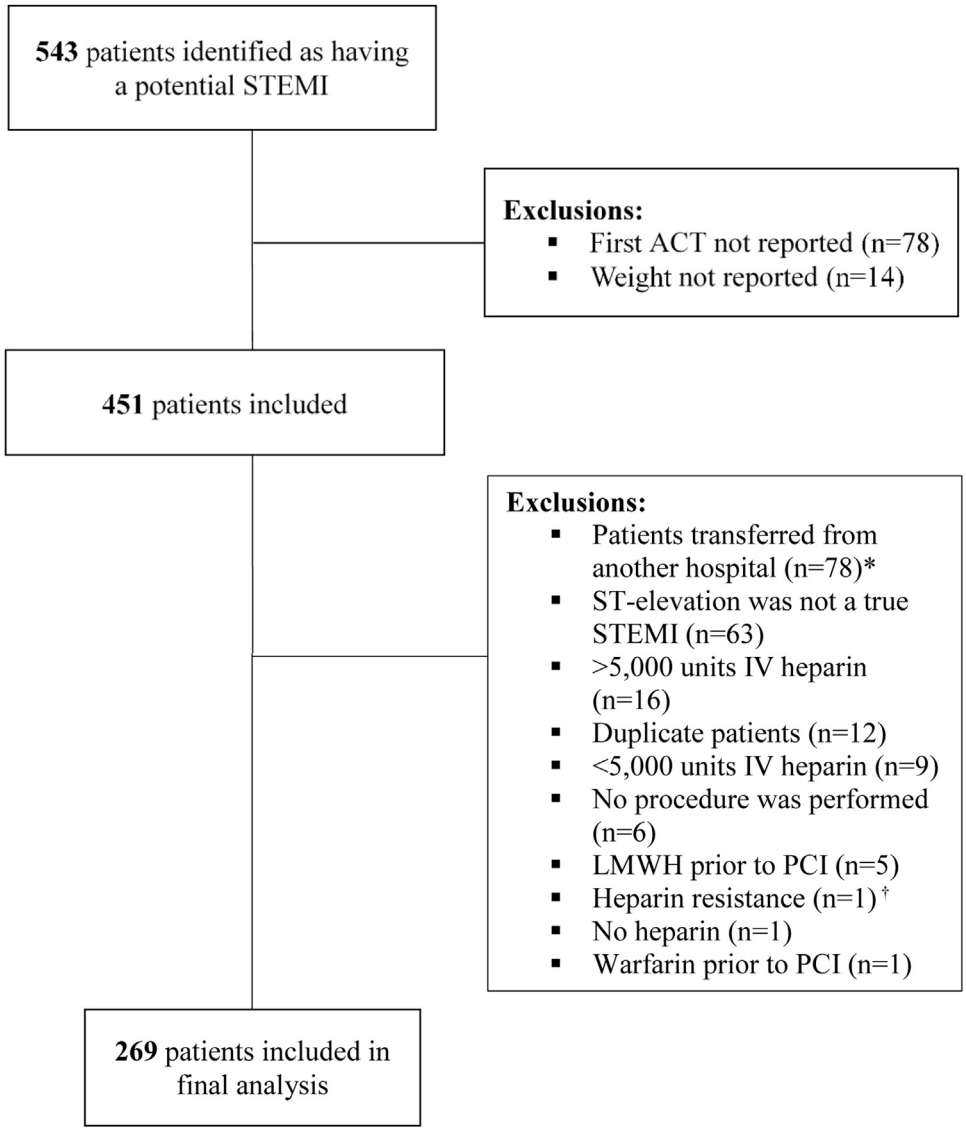

Figure 1. Flow diagram describing construction of study cohort. *Patients from another hospital were excluded since we could not verify their heparin dosing. †Patients with a known history of heparin resistance or with an ACT that did not increase despite additional heparin boluses. LMWH = low molecular weight heparin.

those who presented to the emergency room (ER) with symptoms of MI and who had ST elevations on their electrocardiogram, thus requiring immediate cardiac catheterization laboratory activation by the ER physician. All STEMIs were confirmed by angiogram during the procedure, thereby excluding false STEMI diagnoses made by the ER physician.

Inclusion was restricted to patients with STEMI who underwent primary PCI, defined as any potential patient with STEMI who underwent emergency angioplasty with or without stenting and with no previous administration of fibrinolytics or GPIs.[7] Inclusion was further restricted to patients administered a fixed bolus of 5,000 units of IV UFH before PCI, either in the ER or the cardiac catheterization laboratory. Exclusion criteria were the following: (1) patients transferred from another hospital (since we could not verify their heparin administration); (2) patients diagnosed with heparin resistance, defined as patients with a known history of heparin resistance or patients with an ACT that did not increase despite additional UFH boluses; (3) patients who received or were regularly taking warfarin or low molecular weight heparin; and (4) patients with missing data on first ACT and/or weight.

Data were extracted from cardiac catheterization laboratory reports by first converting the Microsoft Word formatted reports to plain text, followed by extraction on textual information using a custom Python script. These data were then supplemented with information extracted from patient charts for the hospitalization due to STEMI. The following data were extracted for each patient: (1) baseline characteristics, (2) PCI characteristics, (3) UFH dosing, and (4) in-hospital complications.

The primary outcome was the proportion of patients with a first ACT that was therapeutic, infratherapeutic, or supratherapeutic. The first ACT was defined as the initial ACT measured during PCI in the cardiac catheterization

Table 1
Baseline characteristics

Baseline characteristics	Infra-therapeutic (n=151)	Therapeutic (n=59)	Supra-therapeutic (n=59)	Total (n= 269)
Age, mean (SD) [years]	64.8 (14.5)	61.7 (11.2)	64.2 (12.4)	64.0 (13.4)
Men	114 (75.5%)	46 (78.0%)	41 (69.5%)	201 (74.7%)
BMI, mean (SD) [kg/m^2]	26.5 (4.7)	27.8 (4.6)	25.8 (3.5)	26.6 (4.5)
BMI category* (kg/m^2)				
<18.5	5 (3.3%)	1 (1.7%)	0	6 (2.2%)
18.5-24.9	52 (34.4%)	19 (32.2%)	27 (45.8%)	98 (36.4%)
25.0-29.9	62 (41.1%)	25 (42.4%)	24 (40.7%)	111 (41.3%)
30.0-34.9	24 (15.9%)	10 (17.0%)	8 (13.6%)	42 (15.6%)
35.0-39.9	7 (4.6%)	4 (6.8%)	0	11 (4.1%)
≥40.0	1 (0.7%)	0	0	1 (0.4%)
Weight, mean (SD) [kg]	77.3 (17.3)	82.5 (17.1)	72.6 (11.3)	77.4 (16.4)
Weight category (kg)				
40.0-59.9	29 (19.2%)	6 (10.2%)	8 (13.6%)	43 (16.0%)
60-79.9	61 (40.4%)	21 (35.6%)	38 (64.4%)	120 (44.6%)
80.0-99.9	49 (32.5%)	26 (44.1%)	12 (20.3%)	87 (32.3%)
100.0-119.9	10 (6.6%)	5 (8.5%)	1 (1.7%)	16 (6.0%)
≥120.0	2 (1.3%)	1 (1.7%)	0	3 (1.1%)
Height, mean (SD) [cm]	170.1 (9.4)	171.8 (9.2)	167.7 (9.9)	170.0 (9.5)
Comorbidities				
CVA/TIA	2 (1.3%)	0	1 (1.7%)	3 (1.1%)
Diabetes mellitus	28 (18.5%)	15 (25.4%)	12 (20.3%)	55 (20.5%)
Hypertension	63 (41.7%)	23 (39.0%)	22 (37.3%)	108 (40.2%)
Previous CABG	2 (1.3%)	1 (1.7%)	1 (1.7%)	4 (1.5%)
Previous MI	24 (15.9%)	4 (6.8%)	7 (11.9%)	35 (13.0%)
Previous PCI	20 (13.3%)	5 (8.5%)	6 (10.2%)	31 (11.5%)
Smoker				
Current	60 (44.8%)	21 (38.2%)	20 (34.5%)	101 (40.9%)
Former	20 (14.9%)	9 (16.4%)	11 (19.0%)	40 (16.2%)
Never	54 (40.3%)	25 (45.5%)	27 (46.6%)	106 (42.9%)

BMI = body mass index; CABG = coronary artery bypass graft; CVA = cerebrovascular accident; MI = myocardial infarction; N = number; PCI = percutaneous coronary intervention; SD = standard deviation; STEMI = ST segment elevation MI; TIA = transient ischemic attack.
* World Health Organization classification of obesity.

laboratory using a Hemochron device.[8] In accordance with the 2013 ACCF/AHA STEMI guidelines,[3] therapeutic first ACT was defined as 200 to 250 seconds if a GPI was administered during PCI and 300 to 350 seconds if no GPI was administered. Any value below and above these cutoffs was considered infratherapeutic and supratherapeutic, respectively. The decision to administer a GPI was physician dependent based on individual experience and the perceived severity of MI and bleeding risk of the patient.

Secondary outcomes included the proportion of patients who achieved the ACCF-/AHA-recommended weight-based dosing of UFH (50 to 70 units/kg with GPI administration and 70 to 100 units/kg without GPI administration). We also determined the total UFH administration during PCI. We examined the association of first ACT with clinical variables, including UFH administration in the ER and weight. We also examined the association between ACT category and complication rates, as well as post-PCI TIMI grade flow 0 to 2 (as reported by the interventional cardiologist conducting the PCI). TIMI grade flow is a score used to assess coronary blood flow before and after PCI; where 0 = no flow, 1 = penetration without perfusion, 2 = partial reperfusion, and 3 = normal flow.[9] Bleeding complications were defined as mild (does not require medical intervention or follow-up); moderate (requires nonsurgical medical intervention and/or close monitoring); or severe (hemoglobin decrease of 3 g/dl or requiring transfusions, surgery, or vasopressors).[10]

Descriptive analyses were used to compare baseline characteristics, PCI characteristics, UFH dosing, and complications by ACT category. Continuous variables were described as mean ± SD and dichotomous variables as number (%). Continuous variables with a skewed distribution were described as medians (interquartile range).

To determine the association between clinical variables with first ACT, we conducted a multiple linear regression. Models were adjusted for age, smoking, gender, UFH administration in the ER, and weight. The crude relative risks (RRs) and corresponding 95% CIs of TIMI grade flow 0 to 2 and complications were calculated using count data for patients with an infratherapeutic first ACT compared with those without an infratherapeutic first ACT. Analyses were performed using StataSE 13.1 (StatCorp, College Station, Texas).

Results

A total of 543 patients were identified as having a potential STEMI in the cardiac catheterization laboratory database (Figure 1). Of these patients, 269 were included in

Table 2
Procedural characteristics

PCI characteristic	Infra-therapeutic (n=151)	Therapeutic (n=59)	Supra-therapeutic (n=59)	Total (n=269)
Pre-PCI antiplatelet administration				
Aspirin	144 (95.4%)	56 (94.9%)	51 (86.4%)	251 (93.3%)
Clopidogrel	140 (92.7%)	52 (88.1%)	46 (78.0%)	238 (88.5%)
Radial approach to PCI	58 (38.4%)	34 (57.6%)	26 (44.1%)	118 (43.9%)
Door-to-balloon time, median (IQR) [minutes]	83.0 (70-103)	80.5 (61.5-96.5)	76.5 (59.5-101.5)	82.0 (65-100)
< 90	87 (57.6%)	34 (57.6%)	37 (62.7%)	158 (58.7%)
≥ 90	51 (33.8%)	22 (37.3%)	19 (32.2%)	92 (34.2%)
Missing	13 (8.6%)	3 (5.1%)	3 (5.1%)	19 (7.1%)
Door-to-therapeutic ACT time, median (IQR) [minutes]	83.9 (67.2-117.9)	86.1 (55.7-123.7)	73.0 (49.2-102.1)	78.9 (56.8-116.5)
< 60.0	18 (11.9%)	5 (8.5%)	19 (32.2%)	42 (15.6%)
60.0-79.9	22 (14.6%)	2 (3.4%)	17 (28.8%)	41 (15.2%)
80.0-99.9	10 (6.6%)	4 (6.8%)	8 (13.6%)	22 (8.2%)
100.0-119.9	16 (10.6%)	2 (3.4%)	4 (6.8%)	22 (8.2%)
≥120	20 (13.3%)	5 (8.5%)	11 (18.6%)	36 (13.4%)
Missing	65 (43.1%)	41 (69.5%)	0	106 (39.4%)
In-PCI antiplatelet administration				
Aspirin	9 (6.0%)	7 (11.9%)	7 (11.9%)	23 (8.6%)
Clopidogrel	22 (14.6%)	14 (23.7%)	17 (28.8%)	53 (19.7%)
Glycoprotein IIb/IIIa inhibitors	38 (25.2%)	49 (83.1%)	52 (88.1%)	139 (51.7%)
In-PCI bivalirudin	1 (0.7%)	0	0	1 (0.4%)
Culprit coronary artery				
Left circumflex	6 (4.0%)	4 (6.8%)	11 (18.6%)	21 (7.8%)
Left anterior descending	65 (43.1%)	31 (52.5%)	22 (37.3%)	118 (43.9%)
Left main	2 (1.3%)	0	0	2 (0.7%)
Right coronary	65 (43.1%)	21 (35.6%)	20 (33.9%)	106 (39.4%)
Missing	13 (8.7%)	3 (5.1%)	6 (10.2%)	22 (8.2%)
Total stents placed				
0	19 (12.6%)	5 (8.5%)	2 (3.4%)	26 (9.7%)
≥1	132 (87.4%)	54 (91.5%)	57 (96.6%)	243 (90.3%)
Pre-PCI TIMI grade flow				
0-2	86 (57.0%)	37 (62.7%)	34 (57.6%)	157 (58.4%)
3	23 (15.2%)	6 (10.2%)	4 (6.8%)	33 (12.3%)
Missing	42 (27.8%)	16 (27.1%)	21 (35.6%)	79 (29.4%)
Post-PCI TIMI grade flow				
0-2	22 (14.6%)	4 (6.8%)	4 (6.8%)	30 (11.2%)
3	119 (78.8%)	51 (86.4%)	50 (84.8%)	220 (81.8%)
Missing	10 (6.6%)	4 (6.8%)	5 (8.5%)	19 (7.1%)

TIMI grade flow[9] is used to assess coronary blood flow during PCI: 0 = no flow, 1 = penetration without perfusion, 2 = partial reperfusion, 3 = normal flow.

ACT = activated clotting time; IQR = interquartile range; N = number; PCI = percutaneous coronary intervention; TIMI grade flow = Thrombolysis in Myocardial Infarction grade flow.

the final analysis. Exclusions were primarily due to missing data on first ACT (n = 78), patients transferred from other hospitals (n = 78), and a final diagnosis other than STEMI (n = 63). Approximately, 3/4 of included patients were men (n = 201), and the mean age was 64.0 (SD = 13.4) years (Table 1). A total of 61.4% of patients were overweight or obese. Excluded patients had similar characteristics to those included in our study. Specifically, 74.8% of excluded patients were men; mean age was 65.9 (SD = 14.5) years; and mean weight was 80.4 kg (SD = 21.3).

The vast majority of patients were administered aspirin (93.3%) and clopidogrel (88.5%) before PCI, and 51.7% received a GPI during PCI (Table 2). No patients received prasugrel or ticagrelor before PCI. Only 1 patient was administered bivalirudin; however, the bivalirudin was administered during PCI and after UFH. A total of 43.9% of patients underwent PCI using a radial approach, and 58.7% had a door-to-balloon time of <90 minutes. Approximately, 60% of patients had a pre-PCI TIMI flow grade 0 to 2.

All 269 patients were administered 5,000 units of UFH before PCI; however, this dose was not adequate to achieve the ACCF/AHA target weight-based dosing in 84 patients (31.2%; Table 3; Figure 2). Among these patients, 86.9% had an infratherapeutic first ACT versus 44.6% in those with the target weight-based dosing and 34.8% in those above the target (Figure 3). When combining the pre-PCI 5,000-unit bolus of UFH and UFH administered during PCI, 65.4% received over 5,000 units of UFH (i.e., >1 bolus of UFH) and 92.6% received a dose of UFH greater than the ACCF/AHA target weight-based dosing.

Table 3
Heparin dosing

Heparin dosing	Infra-therapeutic (n=151)	Therapeutic (n=59)	Supra-therapeutic (n=59)	Total (n=269)
Pre-PCI*				
1st bolus administered in ER	143 (94.7%)	52 (88.1%)	47 (79.7%)	242 (90.0%)
Units of heparin / kg body weight, median (IQR)	64.9 (55.6-76.9)	61.3 (52.5-73.5)	68.0 (63.0-78.7)	64.9 (56.5-76.0)
<50.0	12 (8.0%)	6 (10.2%)	1 (1.7%)	19 (7.1%)
50.0-69.9	87 (57.6%)	37 (62.7%)	32 (54.2%)	156 (58.0%)
70.0-99.9	43 (28.5%)	15 (25.4%)	25 (42.4%)	83 (30.9%)
>100.0	9 (6.0%)	1 (1.7%)	1 (1.7%)	11 (4.1%)
Pre-PCI + In-PCI†				
Total units of heparin, median (IQR)	8,000 (7,000-9,000)	6,000 (5,000-7,000)	5,000 (5,000-5,000)	7,000 (5,000-8,000)
5,000	25 (16.6%)	20 (33.9%)	48 (81.4%)	93 (34.6%)
5,001-9999	90 (59.6%)	35 (59.3%)	9 (15.3%)	134 (49.8%)
≥10,000	36 (23.8%)	4 (6.8%)	2 (3.4%)	42 (15.6%)
Total units of heparin / kg body weight, median (IQR)	100 (84.7-130.7)	76.0 (66.7-91.9)	72.0 (63.3-83.5)	88.2 (70.5-112.8)
<50.0	0	0	1 (1.7%)	1 (0.4%)
50.0-69.9	19 (12.6%)	20 (33.9%)	25 (42.4%)	64 (23.8%)
70.0-99.9	55 (36.4%)	28 (47.5%)	28 (47.5%)	111 (41.3%)
>100.0	77 (51.0%)	11 (18.6%)	5 (8.5%)	93 (34.6%)
Total number of heparin boluses				
1	26 (17.2%)	19 (32.2%)	48 (81.4%)	93 (34.6%)
2	93 (61.6%)	36 (61.0%)	9 (15.3%)	138 (51.3%)
3	27 (17.9%)	3 (5.1%)	2 (3.4%)	32 (11.9%)
4	5 (3.3%)	1 (1.7%)	0	6 (2.2%)
Heparin drip in-PCI	5 (3.3%)	1 (1.7%)	3 (5.1%)	9 (3.4%)

ER = emergency room; IQR = interquartile range; N = number.
* Heparin administered strictly pre-PCI (before first ACT measurement).
† Total heparin administered before and in PCI.

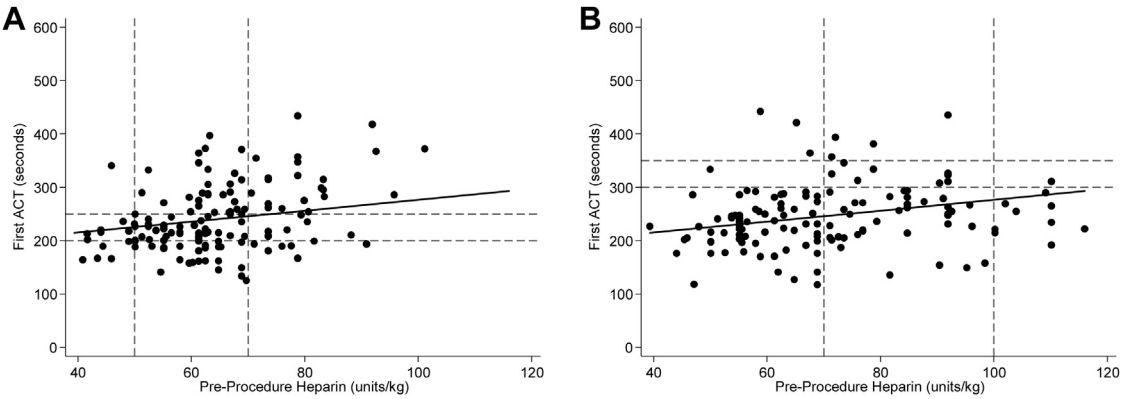

Figure 2. First ACT with pre-PCI UFH. *(A)* Pre-PCI UFH with GPI; *(B)* Pre-PCI UFH without GPI. *Dashed lines* represent ACCF/AHA-recommended UFH dosing (50 to 70 units/kg with GPI; 70 to 100 units/kg without GPI) and target ACT (200 to 250 seconds with GPI; 300 to 350 seconds without GPI).

The mean first ACT for the entire cohort was 243.4 (SD = 61.5) seconds. Over half of patients had an infratherapeutic first ACT (56.1%). The proportion of patients with a therapeutic and supratherapeutic first ACT was 21.9% each. Only 35.3% of patients had a first ACT within the ACCF/AHA targets of 200 to 250 seconds with GPI (Figure 2), and 7.7% had a first ACT within the ACCF/AHA targets of 300 to 350 seconds without GPI (Figure 2). Important differences existed between first ACT group and post-PCI TIMI grade flow (Table 2). Compared with patients with therapeutic or supratherapeutic first ACT, patients with an infratherapeutic first ACT were more likely to have post-PCI TIMI grade flow 0 to 2 (14.6% vs 6.8%, RR 2.15, 95% CI 0.99 to 4.65).

A total of 94.7% of patients with infratherapeutic first ACT were administered a first bolus of UFH in the ER compared with 88.1% and 79.7% in patients with therapeutic and supratherapeutic ACT, respectively (Table 3). After adjusting for age, current smoking status, first heparin bolus administered in the ER, gender, and weight, first UFH

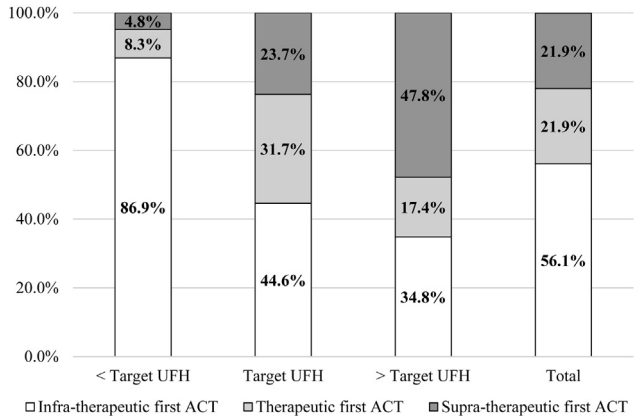

Figure 3. Proportion of infratherapeutic, therapeutic, and supratherapeutic first ACTs by ACCF/AHA weight-based pre-PCI target UFH dosing. ACCF/AHA target weight-based dosing UFH dosing is 50 to 70 units/kg and 70 to 100 units/kg for patients with and without GPI, respectively.

Table 4
Association of clinical variables and first activated clotting time

Clinical variables	Unadjusted		Adjusted*	
	Change in first ACT (seconds)	95% CI	Change in first ACT (seconds)	95% CI
1st heparin bolus in ER	-58.1	(-81.7, -34.5)	-55.8	(-80.0, -31.7)
Age (per10 years)	6.4	(0.9, 11.9)	-1.6	(-8.0, 4.7)
BMI (per 5 kg/m^2)	-9.9	(-18.1, -1.7)	-9.2	(-17.7, -0.8)
Current smoker	-17.6	(-33.4, -1.7)	-10.9	(-26.5, 4.8)
Door-to-balloon time (per 10 minutes)	-0.04	(-1.5, 1.6)	0.08	(-1.6, 1.8)
Male sex	-31.0	(-47.6, -14.3)	-16.7	(-35.7, 2.4)
Post-PCI TIMI III flow	11.6	(-11.9, 35.2)	9.1	(-14.4, 32.6)
Pre-PCI heparin bolus/ body weight (per 10 units/kg)	10.3	(5.5, 15.0)	9.3	(3.4, 15.1)
Weight (per 10 kg)	-10.1	(-14.5, -5.8)	-9.1	(-14.1, -4.0)

TIMI grade flow[9] is used to assess coronary blood flow during PCI: 0 = no flow, 1 = penetration without perfusion, 2 = partial reperfusion, 3 = normal flow.

ACT = activated clotting time; BMI = body mass index; CI = confidence interval; ER = emergency room; TIMI grade flow = Thrombolysis in Myocardial Infarction grade flow.

* Multiple linear regression adjusted for age, current smoking status, first heparin bolus administered in the ER, gender, and weight.

bolus administered in the ER, as opposed to the cardiac catheterization laboratory, was associated with lower ACT (difference, −55.8 seconds; 95% CI −80.0 to −31.7; Table 4). Furthermore, pre-PCI UFH per body weight was also associated with greater first ACT (difference per 10 units per kg, 9.3 seconds; 95% CI 3.4 to 15.1; Table 4). In contrast, higher body weight was associated with lower first ACT (difference per 10 kg change, −9.1 seconds; 95% CI −14.1 to −4.0).

A total of 9.9% of patients in the infratherapeutic first ACT group died compared with 3.4% of patients in the group that was not infratherapeutic (RR 2.93, 95% CI 1.00 to 8.60; Table 5). There was only 1 patient who had a radial bleed in patients with radial access for PCI. Among patients with femoral access for PCI (n = 151), 4.0%, 10.8%, and 18.2% had an inguinal bleed in the therapeutic, infratherapeutic, and supratherapeutic first ACT groups, respectively.

Discussion

Our study was designed to determine whether a fixed 5,000-unit bolus of UFH administered to patients before primary PCI is adequate to achieve a first therapeutic ACT. Our results indicate that 5,000 units of fixed-dose UFH is inadequate in achieving therapeutic first ACT, and consequently, may be associated with low post-PCI TIMI grade flow. Patients with an infratherapeutic ACT had a higher risk of all-cause mortality without any perceived benefit in bleeding risk. However, these clinical outcomes need to be interpreted with caution given the small sample size of our study. Nevertheless, it is well established that a TIMI grade flow of 0 to 2 after primary PCI for STEMI is associated with a higher risk of mortality at 1 year compared with patients with a TIMI grade flow 3.[11–13] Consequently, the large proportion of patients receiving 5,000 units of UFH with an infratherapeutic first ACT and poor TIMI grade flow is concerning. Increasing the initial bolus dose of UFH may be beneficial. This may be achieved by administering weight-based dosing with a higher maximum dose or by administering a higher fixed-dose bolus for all patients undergoing primary PCI.

UFH, which binds to antithrombin to improve the inhibition of thrombin and factor Xa,[14] remains the recommended anticoagulant to be used during primary PCI.[2,3] However, defining the optimal dose of UFH has remained a challenge.[15,16] This challenge is due in part to the prothrombotic state inherent to patients with acute MI, which may minimize the anticoagulant effects of UFH. Studies suggest that patients with acute MI mount an acute phase response and may therefore be more resistant to UFH compared with normal volunteers or patients with stable coronary artery disease.[5,6] Specifically, it has been shown that the mean activated partial thromboplastin time for heparin-treated plasma samples from patients with acute MI is approximately 230 (SD = 120) seconds versus 443 (SD = 137) seconds in healthy volunteers.[5] This variation may account for the sizable proportion of patients with an infratherapeutic first ACT despite achieving the ACCF/AHA target weight-based dosing.

Defining optimal UFH dosing for primary PCI is also challenging due to the multiple clinical variables that may alter its efficacy.[16,17] First, with an observed association between increased UFH units per kg and higher first ACT, our study demonstrated that the efficacy of UFH is highly dependent on patient weight. With over half of patients with STEMI being classified as overweight or obese, it is particularly important to consider weight when dosing UFH in this population. For example, a 5,000-unit bolus of UFH in a female weighing 45 kg is more likely to be therapeutic than the same bolus in a man weighing 110 kg. Second, our regression analyses demonstrated that first administration of UFH boluses in the ER was associated with lower first ACT compared with first administration in the cardiac catheterization laboratory. The half-life for IV UFH ranges from 1 to

Table 5
Complications by first activated clotting time

Complications, n (%)	Infra-therapeutic (n=151)	Therapeutic (n=59)	Supra-therapeutic (n=59)	Total (n=269)	RR (95% CI)*
All-cause mortality	15 (9.9)	3 (5.1)	1 (1.7)	19 (7.1)	2.93 (1.00, 8.60)
Cardiogenic shock	6 (4.0)	1 (1.7)	0 (0.0)	7 (2.6)	4.69 (0.57, 38.41)
Inguinal bleed†	10 (10.8)	1 (4.0)	6 (18.2)	17 (11.3)	1.12 (0.44, 2.85)
Mild	7 (7.5)	0 (0.0)	4 (12.1)	11 (7.3)	1.37 (0.41, 4.56)
Moderate	2 (2.2)	1 (4.0)	2 (6.1)	5 (3.3)	0.52 (0.09, 3.07)
Severe	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.7)	-
Mild radial bleed‡	0 (0.0)	1 (2.9)	0 (0.0)	1 (0.8)	-
Repeat PCI	1 (0.7)	2 (3.4)	0 (0.0)	3 (1.1)	0.39 (0.04, 4.23)
Other complications§	9 (6.0)	5 (8.5)	5 (8.5)	19 (7.1)	0.70 (0.30, 1.68)

ACT = activated clotting time; CI = confidence interval; N = number; PCI = percutaneous coronary intervention; RR = relative risk.

* RR is comparing cumulative incidence for patients with an infratherapeutic first ACT to that in patients without an infratherapeutic first ACT.

† Percentages of inguinal bleed calculated in cases with femoral access for PCI (n = 151). Bleeding classification[10]: mild bleed = does not require medical intervention or follow-up; moderate bleed = overt bleed that requires nonsurgical medical intervention and/or close monitoring; severe bleed = overt bleed with hemoglobin decrease of 3 g/dl or requiring transfusions or surgery or vasopressors.

‡ Percentages of mild radial bleed calculated in cases with radial access for PCI (n = 118).

§ Other complications include arrhythmias, coronary artery dissection, gastrointestinal bleed, infections, pericarditis, pulmonary edema, sepsis, and thrombocytopenia.

2 hours.[17] Consequently, patients receiving UFH early on arrival to the ER may be more likely to have an infratherapeutic first ACT.

While infratherapeutic UFH dosing may lead to acute vessel closure and poor TIMI grade flow, supratherapeutic dosing may lead to bleeding complications.[17] Consequently, defining optimal target ACT cutoffs has been difficult.[15] The cutoffs recommended in the 2013 ACCF/AHA STEMI guidelines with GPI (first ACT 200 to 250 seconds) and without GPI (first ACT 300 to 350 seconds) were used in our study.[3] Common practice is to target these values; however, interventional cardiologists frequently aim for higher levels.[18] Several studies have suggested that higher first ACT levels than those currently recommended may be needed to optimally prevent ischemic events.[19–22] In addition, as a growing number of interventional cardiologists favor a radial approach as opposed to a femoral approach to PCI, patients may tolerate higher doses of UFH without bleeding events.[23,24] Consequently, UFH dosing can potentially be increased safely to help prevent ischemic complications without a substantial increase in bleeding complications.

There are some potential limitations to our study. First, we were missing data for ACT and/or UFH dosing in a small proportion of patients who potentially had STEMI (n = 92; 16.9%). Missing data, along with patients transferred from other hospitals led to exclusions (n = 170) from our cohort. However, these excluded patients appeared to have similar patient characteristics as those included in our study. Second, approximately half of patients in our cohort were administered a GPI during PCI. However, with the advent of newer antiplatelet drugs, the use of GPIs during primary PCI has fallen out of favor.[25] In our cohort, most patients (74.8%) with an infratherapeutic first ACT were not administered a GPI. Consequently, as the proportion of patients not administered a GPI increases, so may the proportion of patients with an infratherapeutic first ACT. Third, our results suggest an association between infratherapeutic first ACT and poor TIMI grade flow; however, there is the potential for confounding as patients with STEMI may be sicker and more heparin resistant to begin with, thus leading to a lower first ACT. Fourth, this study uses a retrospective cohort design. Consequently, unmeasured variables may differ between subgroups of patients, and unlike in a randomized controlled trial, there is no way to control for these possible differences. Finally, a larger sample size would be needed to conclusively examine the association between infratherapeutic first ACT and adverse clinical events, such as repeat MI and repeat revascularization.

Disclosures

The authors have no conflicts of interest to disclose.

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