Higher initial weight-based heparin dosing is required with direct oral anticoagulants during catheter ablation for atrial fibrillation

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Abstract

Background Heparin dosing of patients anticoagulated with direct oral anticoagulants (DOACs) undergoing atrial fibrillation (AF) ablation can be challenging as they require more heparin than those on warfarin therapy. We sought to compare periprocedural activated clotting times (ACTs) of patients on warfarin vs. DOAC and determine an optimal weight-based heparin dosage strategy.

Methods Patients who underwent AF ablation over 28 months were reviewed for type of anticoagulation, intraprocedural heparin dosing, ACTs, and adverse outcomes. A heparin dosing strategy was then tested in a prospective validation cohort.

Results There were 89 patients in the DOAC group and 43 in the warfarin group. Demographics, comorbidities, and complication rates were similar. Mean ACT and percentage of therapeutic ACTs were lower in the DOAC group, most significantly in those with a weight > 90 kg. In DOAC patients, a higher initial heparin bolus ≥ 150 units/kg yielded a higher percentage of therapeutic intraprocedural ACTs (49% ± 10 vs. 29% ± 7, $p = 0.0008$). In a prospective validation cohort of 25 patients administered an initial heparin bolus ≥ 150 units/kg, the mean ACT was 295 ± 33 and 49% of the ACTs collected were therapeutic, similar to findings of our high-dose retrospective subgroup.

Conclusion Patients on DOACs require more heparin during AF ablation to achieve therapeutic ACT. We suggest an initial heparin dose of at least 150 units/kg in this subset of patients, particularly in those with a weight > 90 kg.

Keywords Atrial fibrillation ablation · Intraprocedural anticoagulation · Heparin dosing

1 Introduction

Periprocedural management of oral anticoagulation therapy for atrial fibrillation has evolved. Initial strategies called for discontinuation of oral anticoagulation prior to ablation due to a perceived increased bleeding risk with the administration of intraprocedural heparin in patients on long-term oral anticoagulation. Subsequent studies have shown the safety of heparin during ablation in the setting of uninterrupted warfarin therapy [1, 2]. Similarly, studies have shown that uninterrupted, or minimally interrupted, direct oral anticoagulants (DOACs) are equally safe as warfarin with low bleeding and thromboembolic rates [3–6]. Current guidelines reflect the findings of these studies, with recommendations for uninterrupted oral anticoagulation with intraprocedural administration of heparin prior to or immediately after transseptal puncture to achieve consistent intraprocedural activated clotting times (ACTs) of > 300 s [7]. Current guidelines also suggest the continuation of oral anticoagulation for at least 2 months post-ablation regardless of their stroke risk.

Despite an approximate decade of experience with periprocedural management of DOACs, intraprocedural dosing of heparin remains challenging, even with weight-based dosing [13–19]. In addition, it has been widely reported that patients on DOACs require more heparin and take longer to achieve therapeutic ACT [8–14]. There is little evidence showing the impact of weight, body mass index (BMI), or obesity on heparin dosing for patients on a DOAC. The primary aims of this study were to compare periprocedural ACT between patients on warfarin and patients on a DOAC and to determine a baseline weight-based heparin dosage to achieve therapeutic ACT during AF ablation for patients on a DOAC.

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2 Methods

In this retrospective, observational single-center study, charts of consecutive patients who underwent AF ablation by a single operator from September 01, 2015, to January 31, 2018, were reviewed after institutional review board approval. Data collected included patient demographics, comorbidities, periprocedural oral anticoagulation use, intraprocedural dosing of heparin, and intraprocedural ACTs. Patients were divided and analyzed into two groups, those on warfarin and those on DOAC.

All patients underwent a similar protocol for atrial fibrillation ablation under general anesthesia by a single operator. Techniques for transspetal access, RF ablation, venous access, electroanatomical mapping, and hemostasis were consistent throughout the study. All patients received 4 h of bedrest post-procedure.

Patients on warfarin continued the medication uninterrupted through the ablation procedure. DOAC use was minimally interrupted, as patients were instructed to hold the medication for 12–24 h prior to the procedure. Baseline ACT was obtained regardless of OAC (oral anticoagulant) type. Intraprocedural anticoagulation was performed per guidelines with an initial weight-based dose of at least 120 units/kilogram (kg) intravenous unfractionated heparin bolus [7]. A repeat ACT was drawn every 30 min with intervals maintained by a timer function of the electrophysiology lab recording system and measured by a Hemochron® system (Accriva Diagnostics). Additional heparin boluses were administered as required with a goal ACT of ≥ 300 s.

Major bleeding events were reported as defined by the International Society on Thrombosis and Hemostasis (ISTH) [15]. Major bleeding events were reported for up to 8 weeks after ablation, as also stroke, transient ischemic attacks, and systemic embolism. Minor bleeding events were defined as clinical bleeding events that did not fulfill ISTH criteria for major bleeding events.

Twenty-five consecutive patients anticoagulated with DOAC for were then enrolled in a prospective validation cohort using an initial heparin bolus of 150 units/kg. The procedural technique for pulmonary vein isolation, protocol for periprocedural anticoagulation management, intraprocedural heparin administration after an initial bolus, and patient information collected were identical to the retrospective study as detailed above. Results were compared with patients in the retrospective DOAC group.

All data was analyzed using Stata 13 software (StataCorp, Texas, USA). Categorical variables were presented as frequencies and percentages while continuous variables were presented as mean ± standard deviation (SD) if normally distributed, or median with interquartile range (IQR) if not. The Shapiro-Wilk normality test was used to assess the distribution of continuous variables. Continuous variables with normal distribution were compared using Student's t test and linear regression. The Wilcoxon rank-sum test was used to compare continuous variables with non-parametric distribution. Categorical variables were compared using chi-square and Fischer's exact tests. All significance tests were 2-sided, and the results were considered statistically significant if the p value was lower than 0.05.

3 Results

A total of 132 patients underwent ablation in the 28-month period and were included in our analysis. There were 89 patients in the DOAC group (group A) and 43 patients in the warfarin group (group B). In group A, there were 11 patients on dabigatran, 39 on apixaban, 36 on rivaroxaban, and 3 on edoxaban. Patient demographics including age, gender, weight, renal function, and comorbidities were similar between the two groups (Table 1). There was no difference in mean procedural duration between the two groups (228 ± 64 min in group A vs. 242 ± 79 min in group B, $p = 0.06$). While mean procedural ACT was not related to procedural duration ($p = 0.48$), total heparin dose was proportional to procedural duration.

International normalized ratio (INR) on the day of procedure and baseline ACT were significantly higher in group B as expected (2.01 ± 0.4 vs. 1.10 ± 0.3, $p < 0.001$ and 164.6 ± 23.8 vs. 124.45 ± 26, $p < 0.001$, respectively). Mean ACT and the percentage of ACTs within therapeutic range (> 300 s) were higher in group B despite higher initial and total heparin doses in group A (Table 2).

There were no significant differences in complications between the two groups. One pericardial effusion occurred in group A that required pericardiocentesis. There were 2 thromboembolic events in group A (1 stroke on apixaban at 4 weeks, and 1 pulmonary embolism on dabigatran on the second postoperative day). There were 2 minor bleeds, small hematomas, in group A and 1 in group B. A small AV fistula also occurred in group B, which was managed conservatively.

3.1 Weight

For ease of analysis, patients were divided into quartiles based on weight. On comparison between the two anticoagulation groups within the weight quartiles, mean procedural ACT was similar in quartile 1 (weight ≤ 89.65 kg). There was, however, a significant difference between the two groups in quartiles 2–4, with weights > 89.5 kg, with higher mean ACTs in group B (Fig. 1). Similarly, the percentage of procedural ACTs within therapeutic range was comparable between the two groups for weights ≤ 89.65 kg but were significantly higher in group B in weight quartiles 2–4 (weights > 89.5 kg) (Fig. 2).

Table 1 Patient demographics

	Group A (n = 89)	Group B (n = 43)	p value
Male	60 (67%)	25 (58%)	0.114
Age (years)	63 ± 9	66 ± 10	0.278
Weight (kg)	106 ± 23	103 ± 20	0.72
BMI	34 ± 7	34 ± 7	0.998
Creatinine (mg/dL)	1.0 ± 0.3	0.96 ± 0.2	0.552
GFR (mL/min)	74 ± 21	73 ± 19	0.99
Hypertension	74 (83%)	40 (93%)	0.13
Diabetes	27 (30.34%)	16 (37%)	0.176
Heart failure	29 (33%)	19 (44%)	0.079
Coronary artery disease	24 (27%)	17 (40%)	0.34
Coronary artery bypass grafting	10 (11%)	8 (19%)	0.504
Chronic obstructive pulmonary disease	20 (22%)	9 (21%)	0.425

BMI, body mass index; *kg*, kilograms; *mg*, milligrams; *mL*, milliliters; *dL*, deciliters; *min*, minutes

3.2 Determination of optimal heparin dosage

To determine an optimal initial heparin dose for patients anticoagulated with DOACs, we retrospectively divided patients in group A into two subgroups: a high-dose cohort who received a dose ≥ 150 units/kg (n = 28 patients), and a low-dose cohort who received a dose < 150 units/kg (n = 61). This value was derived from the cutoff of the highest quartile of initial heparin boluses. While the percentage of 1st ACT within therapeutic range was similar between the two groups (23% in the low-dose group vs. 20% in the high-dose group), there was a significant difference in the total percentage of therapeutic ACTs (49% in the high dose vs. 29% in the low dose, $p = 0.0008$). Additionally, the mean procedural ACT was > 300 s in the high-dose cohort, compared with 282 s in the low-dose cohort (Table 3).

3.3 Prospective validation cohort with initial heparin dosage ≥ 150 units/kg

All 25 patients in the prospective validation cohort were anticoagulated with either apixaban or rivaroxaban, held for

1 dose prior to AF ablation. Demographic data including age, weight, gender, and co-morbidities were similar to the retrospective group A (Table 4). The initial heparin bolus dose was more tightly regulated in the validation, with mean dose 160.1 ± 12.5 units/kg therefore being lower than the corresponding retrospective DOAC high-dose heparin cohort. The validation cohort also had lower total heparin dose per weight. The mean procedural ACT was just below therapeutic range (295.45 ± 32.84) but not statistically different compared with the retrospective group. Although the percentage of 1st ACT within therapeutic range was lower in the validation cohort, the percentage of 2nd ACT within therapeutic range was similar (Table 4).
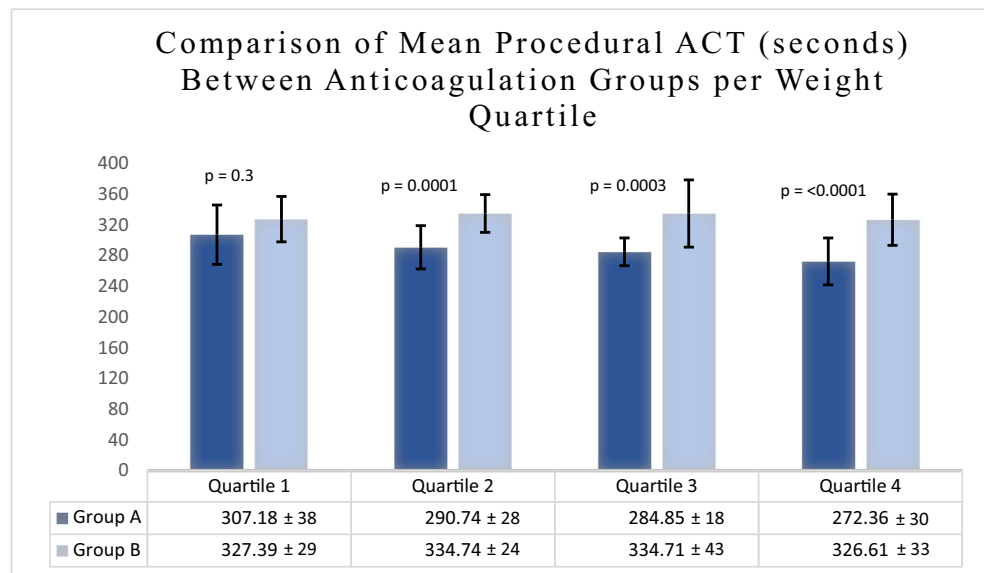
4 Discussion

Our results corroborate other studies that found that more heparin is required to achieve a therapeutic ACT during AF ablation in patients on DOACS [8–14]. Only one previous study has shown weight to be a factor influencing heparin dosage in this patient population. In this study of 417 patients comparing

Table 2 Procedural anticoagulation

	Group A (n = 89)	Group B (n = 43)	p value
INR day of procedure	1.1 ± 0.27	2 ± 0.4	< 0.001
Baseline ACT (s)	124.4 ± 25.8	164.6 ± 23.8	< 0.001
Initial heparin dose per kg	138.68 ± 26.25	112.5 ± 27.72	< 0.001
Total heparin dose per kg	227.23 ± 57.77	158.11 ± 41.66	< 0.001
Initial heparin dose per BMI	432.27 ± 87.36	343.22 ± 93.46	< 0.001
Total heparin dose per BMI	713.4 ± 205.58	483.27 ± 143.31	< 0.001
Mean procedural ACT (s)	288.11 ± 31.4	330.77 ± 32.27	< 0.001
% ACTs in therapeutic range (≥ 300 s)	35.37 ± 27.58	69.77 ± 24.59	< 0.001
Mean procedural duration (min)	203.25 ± 59.9	205.11 ± 63.1	1

INR, international normalized ratio; *ACT*, activated clotting time; *kg*, kilograms

Fig. 1 Comparison of mean procedural ACT (s) between anticoagulation groups per BMI and weight quartiles

Comparison of Mean Procedural ACT (seconds) Between Anticoagulation Groups per Weight Quartile

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Group A	307.18 ± 38	290.74 ± 28	284.85 ± 18	272.36 ± 30
Group B	327.39 ± 29	334.74 ± 24	334.71 ± 43	326.61 ± 33

patients on uninterrupted rivaroxaban to uninterrupted warfarin, body weight was found to be a strong predictor of total heparin dose on multivariable analysis with platelet count and INR being weaker predictors. Based on their data, an initial heparin dose of 120 mg/kg was used in a small ($n = 25$) prospective validation study, with 88% achieving a therapeutic ACT (> 300 s) prior to septal puncture [12]. This recommendation is concordant with current guidelines suggesting the same initial bolus for patients who are taking a DOAC and have held one or two doses [7]. However, our data suggests that a dose of 120 units/kg is insufficient, with equivalent and insufficient mean procedural ACT, total percentage ACT ≥ 300 s, and percentage of 1st and 2nd ACT within therapeutic range compared with the < 120 units/kg group (Table 5). Even with our proposed higher initial bolus, the percentage of 1st and overall

ACT values within therapeutic range was suboptimal, as evidenced by our findings in the validation cohort using initial heparin dosage > 150 units/kg. Regardless, an initial bolus of at least 150 units/kg heparin appears to be a more appropriate starting point to achieve therapeutic ACT during ablation, with particular consideration for patients weighing ≥ 89.65 kg. It is possible that an even higher initial heparin weight-based bolus might be required with increasing weight.

Achieving therapeutic intra-operative ACT during AF ablation is of paramount importance. Although a low occurrence of stroke (< 1%) has been reported even in patients who are sub-optimally anticoagulated, stroke can be debilitating with a risk that can be easily modulated with heparin administration [16, 17]. An ACT > 300 has been associated with lower risk of thromboembolic events regardless of oral anticoagulant type

Fig. 2 Comparison of percentage procedural ACT ≥ 300 s between anticoagulation groups per BMI and weight quartiles
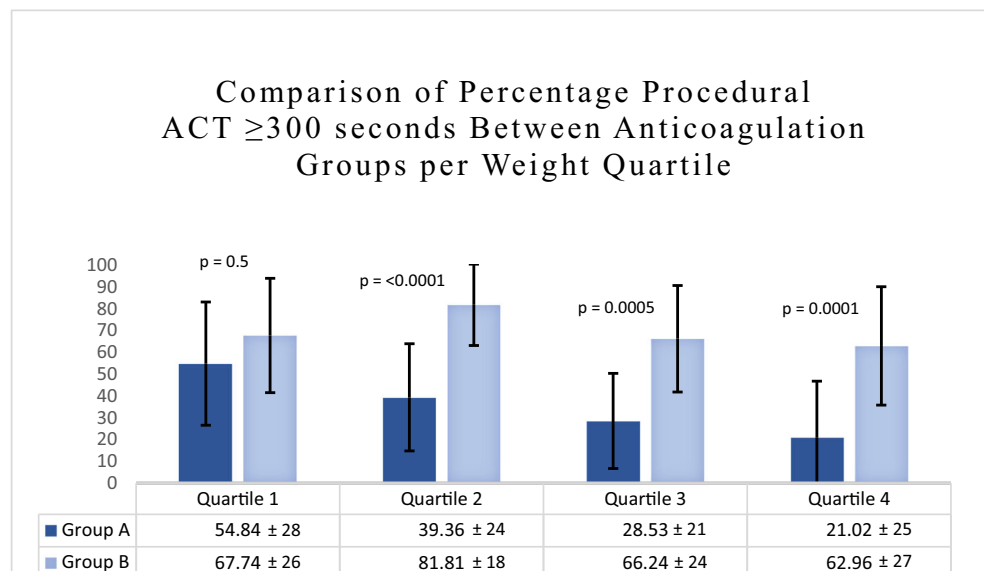

Comparison of Percentage Procedural ACT ≥ 300 seconds Between Anticoagulation Groups per Weight Quartile

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Group A	54.84 ± 28	39.36 ± 24	28.53 ± 21	21.02 ± 25
Group B	67.74 ± 26	81.81 ± 18	66.24 ± 24	62.96 ± 27

Table 3 Initial heparin dosage in DOAC group by body weight

Initial heparin dose (units/kg)	≥ 150 (n = 28)	< 150 (n = 61)	p value
Mean initial dose (U/kg)	169 ± 13.6	124.7 ± 17.3	< 0.001
Percentage of 1st ACT ≥ 300 s (n, %)	20 (71.4)	23 (37.7)	0.003
Percentage of 2nd ACT ≥ 300 s (n, %)	17 (60.7)	15 (24.5)	0.001
Total percentage ACT ≥ 300 s (n, %)	49.4 ± 25.9	28.9 ± 26	0.0008
Mean procedural ACT (s)	300.8 ± 32.5	282.2 ± 29.3	0.009
Baseline ACT (s)	125.1 ± 21	124.1 ± 27.9	0.88
BMI	32.7 ± 7.1	34.7 ± 6.7	0.21
Weight (kg)	100.9 ± 25.3	108.9 ± 20.9	0.12
INR day of procedure	1.01 ± 0.1 (n = 23)	1.15 ± 0.3 (n = 44)	0.04

kg, kilogram; *ACT*, activated clotting time; *BMI*, body mass index; *INR*, international normalized ratio

[10, 18]. As DOACS are being used more readily, it is important to note the differences in heparin dosing requirements. As we now show, this is especially important in patients who also have weight ≥ 90 kg.

Although the trend of patients on DOACS requiring more heparin to achieve therapeutic ACT during AF ablation than patients on warfarin is well established, little literature exists as to why this occurs. Warfarin acts upon multiple enzymes in the clotting cascade including elements in the intrinsic, extrinsic, and common pathways while DOACs are more specific in their actions, working more downstream in the common pathway. Dabigatran is a direct thrombin inhibitor while the other DOACs are direct factor Xa inhibitors. It would be expected that DOACs would have a similar effect on ACT, which is primarily an evaluation of the intrinsic clotting cascade; however, different variations in ACT values have been reported. It has been suggested that this may be a function

Table 4 Comparison of patients receiving an initial heparin dose ≥ 150 U/kg in the validation cohort compared with the retrospective cohort

	Prospective cohort (n = 25)	Retrospective cohort (n = 28)	p value
Age	65.2 ± 8.56	65.67 ± 9.23	0.84
Weight	98.2 ± 23.14	100.97 ± 25.33	0.68
BMI	31.36 ± 7.49	32.79 ± 7.1	0.47
Male gender	18 (72%)	16 (57.14%)	0.26
Hypertension	19 (76%)	23 (82.14%)	0.58
Diabetes mellitus	7 (28%)	6 (21.43%)	0.57
Heart failure	1 (4%)	12 (42.86%)	0.001
Coronary artery disease	6 (24%)	8 (28.57%)	0.7
Coronary artery bypass grafting	1 (4%)	3 (10.71%)	0.35
Chronic obstructive pulmonary disease	2 (8%)	7 (25%)	0.1
Creatinine	1.05 ± 0.3	1.04 ± 0.31	0.88
GFR	71.05 ± 20.74	67.79 ± 18.98	0.55
INR day of procedure	1.06 ± 0.22 (n = 8)	1.01 ± 0.1 (n = 23)	0.41
Baseline ACT	125.72 ± 19.01	125.07 ± 21	0.9
Mean ACT	295.45 ± 32.84	300.8 ± 32.54	0.55
Percentage ACT ≥ 300 (%)	49.1 ± 33.61	49.54 ± 25.98	0.96
1st ACT ≥ 300 s (n, %)	11 (44%)	20 (71%)	0.043
2nd ACT ≥ 300 s (n, %)	14 (56%)	17 (60.7%)	0.72
Total heparin per weight	217.74 ± 49.1	250.37 ± 63.12	0.04
Initial heparin per weight	160.08 ± 12.5	169.03 ± 13.63	0.01
Total heparin per BMI	691.87 ± 207.4	772.12 ± 230.49	0.19
Initial heparin per BMI	506.01 ± 82.92	518.58 ± 64.87	0.53

BMI, body mass index; *GFR*, glomerular filtration rate; *INR*, international normalized ration; *ACT*, activated clotting time

Table 5 Initial heparin dosage of < 120 units/kg compared with ≥ 120 units/kg in patients anticoagulated with a DOAC (group A)

Initial heparin dose (units/kg)	≥ 120 (n = 73)	< 120 (n = 16)	p value
Mean initial dose (U/kg)	146.4 ± 20.7	103.4 ± 19.4	< 0.001
Percentage of 1st ACT ≥ 300 s (n,%)	34 (46.58)	9 (56.25)	0.48
Percentage of 2nd ACT ≥ 300 s (n,%)	29 (39.7)	3 (18.7)	0.113
Total percentage ACT ≥ 300 s (%)	35.5 ± 27.8	34.4 ± 26.9	0.88
Mean procedural ACT (s)	287.5 ± 33.2	290.6 ± 21.6	0.72
Baseline ACT (s)	120.4 ± 21.8	142.9 ± 34.2	0.001
BMI	33.9 ± 6.7	34.7 ± 7.5	0.7
Weight (kg)	105.6 ± 23	109.9 ± 20.7	0.4
INR day of procedure	1.04 ± 0.17 (n = 54)	1.33 ± 0.42 (n = 23)	0.04

kg, kilogram; *ACT*, activated clotting time; *BMI*, body mass index; *INR*, international normalized ratio

of variable ACT sensitivity [19, 20]. In our study, the number of patients on dabigatran was small (n = 11) and there were no differences otherwise between the ACT values of the patients on different DOAC medications.

In addition, although its use is widespread, ACT may not be the best modality to access the level of anticoagulation. There is more than one ACT testing system, and there are reports of a decline in correlation and reproducibility with higher doses of heparin [21, 22]. The use of alternative modalities such as anti-Xa and thromboelastogram (TEG) testing is limited by turnaround time and lack of proximity to the procedural theater. Advancements in these or other technologies are needed to replace ACT.

5 Limitations

The primary limitation of this study is its retrospective and non-randomized nature, which can lead to potential selection bias. External validity may be limited by a single-center, single-operator study. Our results may also not be generalizable to all patients on a DOAC as dabigatran and edoxaban were under-represented; however, this is consistent with general prescription trends of DOACs with apixaban and rivaroxaban being more commonly prescribed [23]. Additionally, pre-procedure DOAC usage was non-uniform due to differences in half-lives and labeled dosing. This may have contributed to ACT variability within this group of patients.

Baseline ACT and INR were not used in our analysis of optimal heparin dosage or our validation cohort. While these additional variables have been used to predictably achieve therapeutic levels in patients anticoagulated with warfarin [24], their significance is less understood in patients anticoagulated with a DOAC. Further studies should consider the determination of the initial heparin dose using a combined formula to accommodate both weight, baseline INR, and baseline ACT in these patients.

6 Conclusion

Patients on direct oral anticoagulants require significantly higher procedural heparin dosage during ablation for atrial fibrillation to achieve a therapeutic ACT of > 300 s in patients weighing ≥ 89.5 kg. We suggest an initial heparin dose of at least 150 units/kg in this subset of patients to achieve an initial therapeutic ACT of > 300 s.

Conflict of interest The authors declare that they have no conflict of interest.

Compliance with ethical standards

This was a retrospective, observational study conducted after institutional review board approval.

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