Weight Based Heparin Dosage with Activated Clotting Time Monitoring Leads to Adequate and Safe Anticoagulation in Non-Cardiac Arterial Procedures

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Background: Unfractionated heparin has an unpredictable effect in an individual patient. The activated clotting time (ACT) can be used to measure the effect of heparin in the individual patient and guide additional heparin dosages. Previous cohort studies showed that a standardized bolus of 5,000 IU during noncardiac arterial procedures (NCAP) does not lead to an adequate ACT in the vast majority of patients. The aim of this study was to investigate whether an initial heparin dose of 100 IU/kg leads to an adequate but safe ACT, from 200 to 300 s.

Methods: In this multicenter prospective study, 186 patients undergoing NCAP were enrolled and received an initial heparin dose of 100 IU/kg. Target ACT was set at $\geq$250 s initially; during the course of the study the target ACT was lowered to $\geq$200 s. After the initial heparin dose, additional heparin dosages were administered depending on the ACT values following a heparin dose protocol. ACT measurements and complications were monitored.

Results: The mean baseline ACT was 134 ± 17 s. The mean ACT 5 minutes after the initial heparin dose was 227 ± 37 s. After the initial dose of heparin, 78 and 46% of patients reached an ACT of 200 and 250 s, respectively. Seven patients (4%) reached an ACT of 300 s or more. Ninety-four patients (51%) received at least one additional dose of heparin. After one additional dose of heparin, 91% of patients reached an ACT of 200 s and 13 patients (7%) reached an ACT of 300 s or more. Arterial thromboembolic complications occurred in 4.3% and bleeding complications occurred in 9.7%.

Conclusions: A bolus of 100 IU/kg of heparin during NCAP results in adequate coagulation in most patients. ACT measurements enable accurate additional dosing, ensuring the individual patient tailored and safe coagulation.

Key words: anticoagulants; heparin; blood coagulation tests; vascular surgical procedures; peripheral vascular disease

INTRODUCTION

Unfractionated heparin (in short: heparin) is administered to prevent arterial thromboembolic complications (ATEC) when major vessels are cross-clamped during noncardiac arterial procedures (NCAP). A wide variation for periprocedural heparin therapy is reported, including fixed dose, body weight based dose with a variation between 50 and 100 IU/kg, and the use of additional heparin dosages depending on the duration of the procedure.[1,2] Current guidelines on NCAP do not provide

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evidence based recommendations for periprocedural heparin therapy.[3–5] The anticoagulatory effect of heparin is multifactorial and is unpredictable in the individual patient.[6–12] To ascertain adequate periprocedural anticoagulation in the individual patient, the effect of heparin should be monitored.

The activated clotting time (ACT) can be used to measure the anticoagulant effect of heparin in the individual patient.[13] Little clinical data are available defining the optimal periprocedural ACT associated with the lowest number of ATEC and bleeding complications in NCAP.[1] Studies on interventions of the carotid artery recommend a target ACT of 200–250 s during carotid endarterectomy (CEA) and a target ACT of 250–300 s during carotid stenting.[14–16] In a study in patients undergoing peripheral vascular interventions, an ACT of $\geq$250 s was associated with an increased periprocedural drop in hemoglobin and a higher number of red blood cell (RBC) transfusions when compared to an ACT $<$250 s.[17]

However, till now, no randomized controlled trials have been performed that investigated the association between ACT during NCAP and clinical outcomes. Based on sparse literature and our own experience, the optimal ACT might be between 200 and 300 s. Previous cohort studies showed that ACT-guided heparinization is feasible, safe, and that an initial bolus of 5,000 IU of heparin, irrespective of patient body weight, was too low to reach desired ACT levels.[1,12,18] The aim of this prospective study was to investigate whether an initial heparin dose of 100 IU/kg leads to an adequate patient-tailored and safe ACT, from 200 to 300 s.

METHODS

Data Collection, Design, and Patients

The MANCO registry (measuring the ACT during non-cardiac arterial procedures, Clin. Trials.gov NCT 03426293) is an ongoing, prospective, multicenter registry for patients undergoing NCAP in two high-volume hospitals (Amsterdam University Medical Center, location VU Medical Center, Amsterdam, the Netherlands [VU] and the Dijklander Ziekenhuis, Hoorn, the Netherlands [DLZ]). Surgical procedures included carotid endarterectomy, standard and complex endovascular aneurysm repair, open aortic surgery, open and endovascular procedures for peripheral arterial occlusive disease, and other (Table I). Consecutive patients were included from January 2018 till May 2019. The MANCO registry is registered at clinicaltrials.gov (NCT number: NCT03426293) and at the Dutch trial registry (NTR ID: NL6788). The protocol was approved by the local ethics committee. Data were collected from the electronic patient system files and were stored in the cloud-based electronic data capture platform Castor EDC® (Castor Electronic Data Capture; CIwIt BV, Amsterdam, I.C. Netherlands, 2018). Patients older than 18 years who underwent open or endovascular NCAP were enrolled in this prospective analysis. Exclusion criteria were a known coagulation disorder, documented heparin allergy, preprocedural unfractionated heparin therapy (except preventive use of low molecular weight heparin), and chronic renal failure with a clearance less than 30 mL min^{-1}. Patients with renal clearance were excluded because unfractionated heparin undergoes renal clearance.[19] Patient demographic variables including age, gender, body weight, height, medical history, preprocedural and postprocedural antithrombotic therapy, and also variables related to the surgical procedure were collected. Patient data were checked by two authors (O.D. and A.W.).

Anticoagulation Monitoring

ACT measurements were performed as a point-of-care test using the Hemostasis Management System Plus (HMS Plus, Medtronic Inc., Minneapolis, MN, USA). Blood samples were drawn from the radial artery catheter. High-range cartridges (HR-ACT) containing kaolin were used. The ACT was measured at the following time points: after anesthetic induction (T0), 5 minutes after the administration of the initial heparin bolus (T1), 5 minutes after every additional dose of heparin, and at 30 min intervals after the desired ACT was reached, until the end of the procedure or until new heparin administration was required.

Heparin Dose Protocol

All patients received a heparin bolus of 100 IU/kg based on the real weight of body weight intravenously prior to cross-clamping or after insertion of the sheath in case of endovascular procedures. An additional dose of heparin was administered depending on the ACT. Initially, the target ACT was set at $\geq$250 s. During the course of the study the target ACT was lowered to $\geq$200 s because a high dose of heparin was required to reach an ACT $\geq$250 and a possible trend of increased bleeding. Dose protocols for both hospitals VU and DLZ are depicted in Figure 1, with the main difference being the administration of an additional standard dose of heparin (2,500 or 5,000) or weight depended (30

Table I. Patient demographics and procedure details

	n (total = 186)
Age, y (range)	71 ± 8 (48−88)
Gender	
Male, *n* (%)	133 (72)
Female, *n* (%)	53 (28)
BMI, kg/m^2 (range)	26 ± 5 (14−39)
Cardiac history, *n* (%)	75 (40)
Cardiac intervention, *n* (%)	59 (32)
Hypertension, *n* (%)	138 (74)
Hypercholesterolemia, *n* (%)	68 (37)
COPD/pulmonary fibrosis, *n* (%)	55 (30)
TIA/CVA, *n* (%)	58 (31)
Malignancy, *n* (%)	33 (18)
Diabetes Mellitus, *n* (%)	34 (18)
Impaired renal function, *n* (%)	10 (5)
PAOD, *n* (%)	96 (52)
Type of intervention−open	
CEA, *n* (%)	38 (20)
AAA[a], *n* (%)	31 (17)
Femorodistal[b], *n* (%)	38 (20)
Other, *n* (%)	14 (8)
Type of intervention−endovascular	
EVAR, *n* (%)	19 (10)
FEVAR, *n* (%)	7 (4)
TEVAR, *n* (%)	5 (3)
Other, *n* (%)	2 (1)
Type of intervention−hybrid	
Carotid	3 (2)
THAAA, *n* (%)	1 (1)
Femorodistal[c], *n* (%)	25 (13)
Other	3 (2)
Preoperative laboratory variables	
Platelets (*n* = 108, range)	244 ± 83 (101−511)
INR (*n* = 43, range)	1.4 ± 1.1 (1.0−8.0)
APTT (*n* = 27, range)	28.7 ± 7.2 (12−45)

Mean ± SD (range).

BMI, body mass index; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; CVA, cerebrovascular accident; PAOD, peripheral arterial occlusive disease; CEA, carotid endarterectomy; AAA, Abdominal Aortic Aneurysm repair; EVAR, Endovascular Aneurysm repair; FEVAR, Fenestrated Endograft; TEVAR, Thoracic Endovascular Aortic repair; THAAA, Thoraco-abdominal Aortic Aneurysm repair.

[a]Including supra, juxta, and infrarenal AAA.

[b]Femoral interventions including endarterectomy common femoral artery and supra-genual and infra-genual femoropopliteal bypass.

[c]Endarterectomy with combined endovascular procedure.

IU/kg or 60 IU/kg). At the end of surgery, target ACT was ≤180 s. Protamine was administered if ACT was >180 s. Protamine could be used at the completion of a procedure to neutralize any residual heparin effect by using a dose of 25 to 100 mg per patient. The decision to administer protamine was left to the discretion of the attending vascular surgeon. Local flushing of arteries with heparin solution was routinely performed. This was performed using a solution of 10,000 IU heparin in 1,000 mL 0.9% sodium chloride. For flushing, a maximum of 30 mL was used for each procedure, equaling to 300 IU of heparin.

Preprocedural and Postprocedural Antithrombotic Therapy and Protamine

Preprocedural monotherapy with acetylsalicylic acid (ASA) or clopidogrel was continued during the procedure. In some cases, especially in patients receiving epidural anesthesia, clopidogrel was switched to acetylsalicylic acid preoperatively. In case of preprocedural dual antiplatelet therapy,

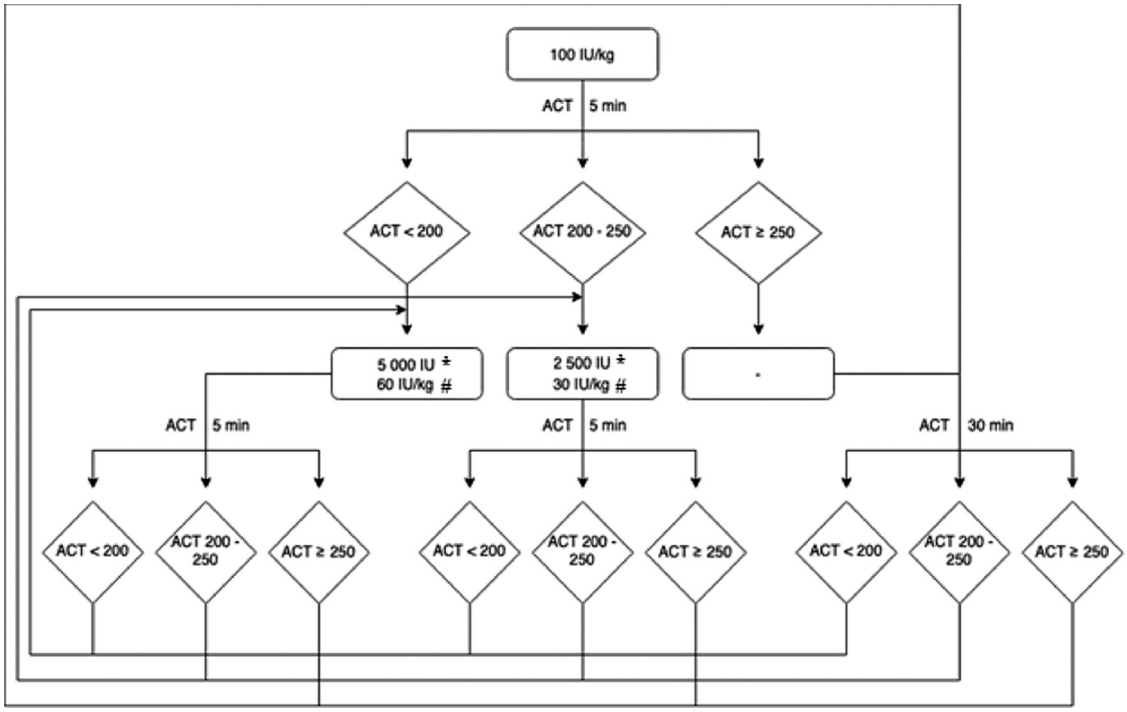

Fig. 1. Heparin dose schedule in institution VU and DLZ.

one of the antiplatelet therapies was discontinued, except for CEA, when a dual antiplatelet therapy was continued. Preprocedural direct oral anticoagulation drugs (DOAC) and vitamin K antagonists (VKA) were discontinued as per the National Guideline on Antithrombotic Therapy: two to five days preprocedurally.[20] If required (CHA_2DS_2-Vasc > 8), bridging therapy was started using low molecular weight heparin.[21]

Outcome Measurements

The main endpoint of this study was to investigate if an initial heparin dose of 100 IU/kg leads to an adequate ACT: from 200 to 300 s. Secondary study endpoints were the amount of additional heparin dosages administered, the effect of these additional heparin dosages on the ACT, and the incidence of complications during the same admission or during a 30-day follow-up. Complications were categorized as:

I) ATEC such as graft thrombosis, embolism, myocardial infarction, minor and major stroke, pulmonary embolism, and bowel ischemia.

II) Bleeding complications as per the E-CABG classification grade 2 or higher (transfusion of 5−10 units of RBC or reoperation for bleeding).[22] To explore an optimal ACT value, patients were divided in three groups for all endpoints: ACT <200 s, ACT between 200 and 250 s, and ACT >250 s.

III) All other complications. Renal injury was defined as per RIFLE criteria (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) at least double increased serum creatinine level or a reduction of the glomerular filtration rate of more than 50%.[19]

Statistical analysis was performed using the SPSS statistical software package 26.0 (IBM, New York, USA). A normality test was performed to the set of multiple ACT measurements. Based on the number of patients the Shapiro−Wilk test was used and the data were normally distributed. Continuous, normally distributed variables were expressed as mean ± standard deviation or percentage. Descriptive statistics were used to report and determine the distribution of the ACT. The paired *t*-test was used to test normally distributed data. The Mann−Whitney *U*-test was used to test

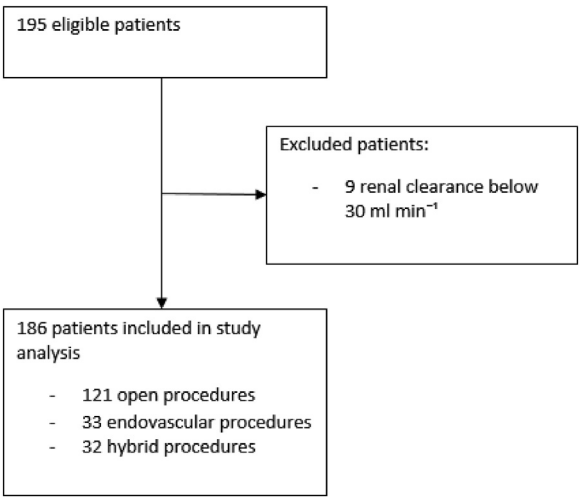

Fig. 2. Flow diagram illustrating the patient selection process.

skewed and ordinal data. The chi-squared and Fisher's exact tests were used to analyze categorical variables and the outcomes were expressed as counts and percentages. Test results were reported as *t*-statistics (degrees of freedom), followed by the *P* value. A *P* value less than 0.05 was considered as statistically significant.

RESULTS

During the study period, 195 patients underwent NCAP and were per procedurally heparinized using an initial heparin dose of 100 IU/kg. Nine patients were excluded because of a renal clearance less than 30 mL min^{-1}. In total, 186 eligible patients were enrolled and the ACT measurements of these patients were analyzed. One-hundred and twenty-one (65%) patients underwent an open procedure, 33 (18%) an endovascular procedure, and 32 (17%) a hybrid procedure. A flowchart of patient inclusion in this study is depicted in Figure 2. The patient characteristics and procedure details are depicted in Table I. The preprocedural and postprocedural anticoagulation therapy is depicted in Table II.

Activated Clotting Time

The ACT at T0 is the baseline ACT before the administration of heparin and the ACT at T1 is 5 min after administration of the initial dose of heparin. The mean ACT at T0 was 134 ± 17 s (range 70−198 s) and the mean ACT at T1 was 227 ± 37 s (range 117−348 s). The ACT measurements at T0 were performed in 183 patients and at T1 were performed in 184 patients. The mean initial heparin dose was 7,798 ± 1,581 IU (range 4,000−13,000 IU) and the mean initial heparin dose per kg of body weight was 99 ± 3 IU/kg (range 91−109 IU/kg). Figure 3 illustrates the distribution of the ACT at T0 and T1.

After the initial heparin bolus (T1), 40 patients (21.74%) reached an ACT <200 s, 100 patients (54.35%) an ACT 200−250 s, and 44 patients (23.91%) an ACT >250 s. At T1, 7 patients (4%) reached an ACT of ≥300 s. At T1 in 145 patients (80%) the ACT reached 1.5 times the baseline ACT and in 25 patients (14%) the ACT reached 2 times the baseline ACT.

The maximum ACT reached during all procedures were again categorized in three groups: 10 patients (5.38%) reached an ACT <200 s, 105 patients (56.45%) an ACT 200−250 s, and 71 patients (38.17%) an ACT >250 s.

Additional Heparin Dose Protocol

In Center VU, 28 of 46 patients (61%) received at least one additional dose of heparin. After the first additional dose of heparin, 42 (91%) and 19 (41%) patients reached an ACT of 200 and 250 s, respectively. Four patients (9%) reached an ACT more than 300 s. In Center DLZ, 66 of 140 patients (47%) received at least one additional dose of heparin. After the first additional dose, 128 (91%) and 42 (30%) patients reached an ACT of 200 and 250 s, respectively. Nine patients (6%) reached an ACT more than 300 s. In total, using an additional dose protocol in 177 (95%) patients an ACT ≥200 s was reached, in 73 (39%) patients ACT was ≥250 s, and in 13 (7 %) patients ACT was ≥300 s. The mean total periprocedural heparin dose was 9,769 ± 3,333 IU (range 4,000−28,700 IU). Details of the effect on the ACT for the different additional heparin dosages are depicted in Table III. In the patient who received an initial heparin dose of 13,000, the ACT increased from 123 to 195 s and after an additional dose of 3,900 IU the ACT increased to 224 s.

Complications

Complications are depicted. ATEC occurred in 8 patients (4.3%). In 6 patients (3.2%), postprocedural graft thrombosis occurred. Those 6 patients underwent reoperation for embolectomy (Table IV). One patient (0.5%) developed a transient ischemic attack (TIA) 3 days after an open repair procedure of an infrarenal abdominal aortic aneurysm. One patient (0.5%) developed bowel ischemia 3 days

Table II. Preprocedural and postprocedural details on antithrombotic therapy

	$n = 186$ (n, %)
Preprocedural anticoagulants	
Acetylsalicylic acid	64 (34)
Clopidogrel	61 (33)
Dual antiplatelet	13 (7)
VKA	19 (10)
DOAC	8 (4)
Combination	8 (4)
Other	1 (1)
None	12 (7)
Postprocedural anticoagulants	
Acetylsalicylic acid	35 (19)
Clopidogrel	75 (40)
Dual antiplatelet	33 (18)
VKA	19 (10)
DOAC	10 (5)
Combination	7 (4)
Other	2 (1)
Missing	5 (3)

VKA, vitamin K antagonists; DOAC, direct oral anticoagulants.

postoperatively and underwent surgical resection. Seven patients (4%) developed renal injury. In none of these patients hemodialysis was necessary. Three patients (2%) died: one because of postprocedural aortic dissection after an open repair of abdominal aortic aneurysm, one because of hemorrhagic stroke after an open repair for aorto-iliac disease, and one because of sepsis based on necrotizing fasciitis.

Bleeding complications (RBC transfusion 5 unit or more) occurred in 18 patients (9.7%): 1/18 with ACT <200 s, 10/18 with ACT 200−250 s, and 7/18 with ACT ≥250 s.

There is no significant relationship between hemorrhagic complications and the three ACT groups, X^2 (1, $n = 186$) = 0.007, $P = 0.997$.

Of the 13 patients who reached an ACT ≥300 s, none developed postprocedural graft thrombosis; one patient developed a TIA and one patient developed renal injury. Four of these 13 patients (31%) developed a bleeding complication (E-CABG grade 1 in two patients and grade 2 in two patients).

DISCUSSION

ACT measurements are not yet a common practice in NCAP and a standard starting dose of 5,000 IU is still often used by many vascular surgeons. In a previous cohort study, we found that a heparin dose protocol with a starting dose of 5,000 IU does not lead to adequate anticoagulation; however, several additional heparin dosages are required to reach an ACT >200 s.[18] In this study, we evaluated 186 patients who received heparinization using an initial dose of 100 IU/kg. An ACT of 200 was reached in 78% of patients. After the necessary additional dosages of heparin this increased to 91%.

A lower incidence of ATEC was found after using the additional heparin dose protocol with an initial heparin bolus of 100 IU/kg and a target ACT >200 s, in comparison to the earlier cohort of a standardized heparin bolus of 5,000 IU, 4.3 vs. 9.0%, respectively. However, the cohorts cannot directly be compared to each other because the type of procedures included varies. Future studies need to be performed using more homogenous patient groups in large numbers to determine an optimal ACT. Compared to the 5,000 IU cohort there was an increased incidence of severe bleeding (grade 2 or more as per the E-CABG classification[22]) in the 100 IU/kg cohort: 9.7 vs. 2.6%.[18] Furthermore, a high quantity of heparin with often more than one additional dosage was required to reach an ACT >250 s. Therefore, during the study the target ACT was lowered to ≥200 s.

Interestingly, despite the dosing heparin on body weight, resulting ACT values varied widely after the initial dose of heparin (117−348 s). This wide variation in ACT values was also observed after the administration of additional heparin dosages. The additional heparin dosages of 2,500 IU and 30 IU/kg resulted in a mean ACT increase of 25 and 31 s, respectively. However, these ACT values varied from −52 s to +88 s for an additional dose of 2,500 IU and from −12 s to +131 s for an additional dose of 30 IU/kg. The additional heparin dosages of 5,000 IU and 60 IU/kg resulted in a mean ACT increase of 53 and 86 s, respectively.

Notably, in some patients a decrease in ACT was observed after administration of an additional dose of heparin. These findings are supported by the earlier literature on the unpredictable effect of heparin in the individual patient. There are many factors influencing the effect of heparin. Heparin has a low volume of distribution and does not enter muscle or fat tissue.[23,24] It has also been found that the distributions of body weight and body surface area−corrected heparin response were similar in comparison to standard heparin dosing.[25] There is an individual difference in the biological availability of heparin due to its binding to plasma proteins, macrophages, platelets, and endothelial cells.[7] Age, thrombocytosis (platelet count >300,000/mL),

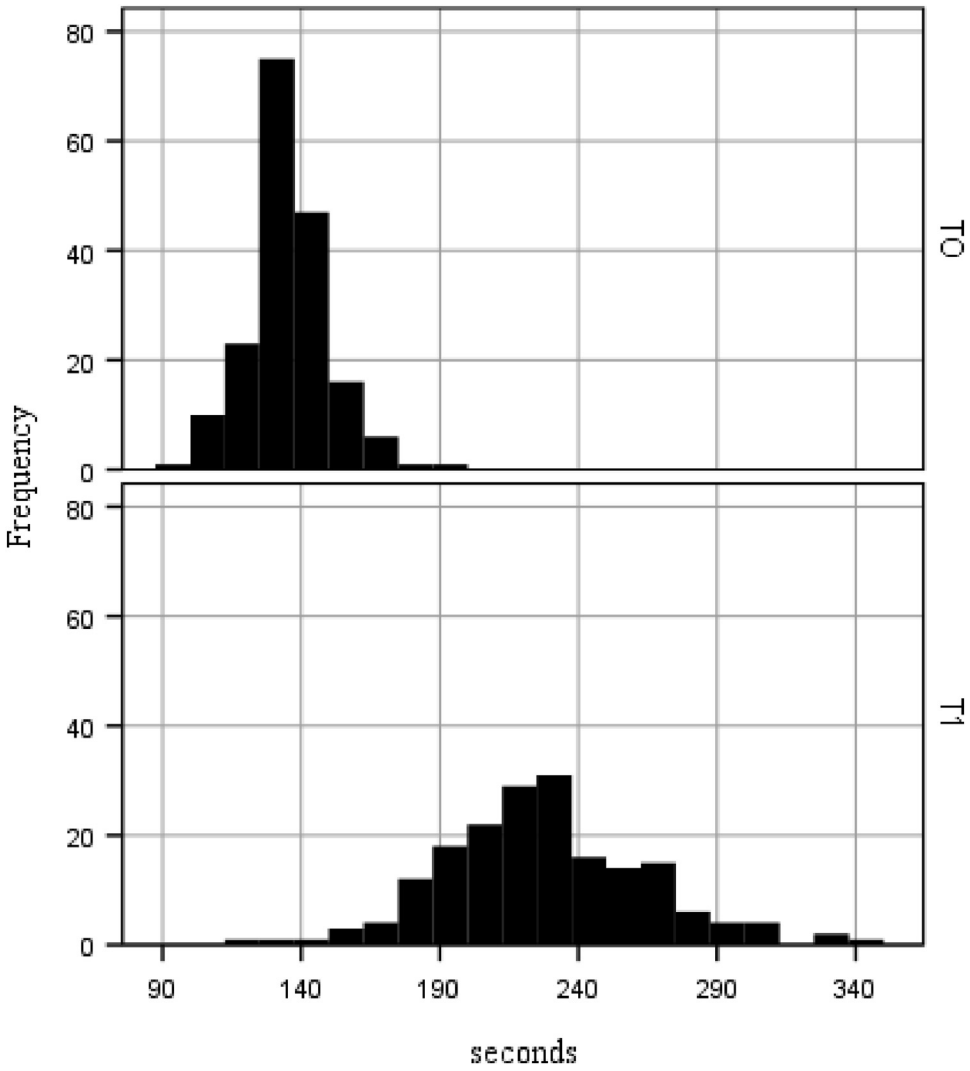

Fig. 3. Distribution of the baseline ACT (T0) and ACT 5 min after the initial 100 IU/kg. Dose of heparin (T1).

Table III. The effect of the different first additional heparin dosages administered

Type of additional heparin dose	*n*[a]	Mean ACT effect (s.), (range)
Fixed		
~2,500 IU	19	+25 (−52; +88)
~5,000 IU	6	+53 (−22; +107)
Body weight based		
~30 IU/kg.	43	+31 (−12; +131)
~60 IU/kg.	18	+86 (+26; +223)

This was defined by the mean ACT difference before and after the administration of the first additional heparin dose.
[a]These were the patients in which the ACT was measured before and after the additional dose of heparin.

preprocedural heparin therapy, impaired liver function, low antithrombin III levels (<60%), high levels of platelet factor 4, elevated factor VIII levels, hemodilution, temperature, anesthesia, and surgery also may be contributing factors.[6–11] An empiric, fixed, or body weight based heparin dose without measuring the anticoagulatory effect may result in inadequate or excessive anticoagulation. Therefore,

Table IV. Incidence of clinical complications during 30 day follow-up

Complications	$n = 186$
ATEC, *n* (%)	8 (4.3)
Local graft thrombosis, *n* (%)	6 (3.2)
Myocardial infarction, *n* (%)	-
Stroke, *n* (%)	1 (0.5)
Bowel Ischemia, *n* (%)	1 (0.5)
Other Complications	
Renal injury, *n* (%)	7 (3.7)
Spinal cord ischemia, *n* (%)	1 (0.5)
Wound infection, *n* (%)	14 (7.5)
E-CABG bleeding severity classification	
Grade ≥1, *n* (%)	42 (22.6)
Grade ≥2, *n* (%)	18 (9.7)
Grade ≥3, *n* (%)	1 (0.5)
Total periprocedural blood loss (mL)	
Open, mean ± S.E.M.	881 ± 997
Endovascular, mean ± S.E.M.	308 ± 692
Hybrid, mean ± S.E.M.	446 ± 360
Death, *n* (%)	3 (1.6)

Renal injury was classified following the RIFLE criteria.[19]
ATEC, arterial thrombo-embolic complications.

the measurement of the effect of heparin by using the ACT seems indispensable.

The main strengths of this study are that patients were enrolled prospectively, patient data were double checked by two authors (O.D. and A.W.), and an analysis of a body weight based heparin dose has not been described in such a large group of patients yet. Limitations of this study are that the group of patients was heterogeneous and that this study was not a dose finding study. In addition, a periprocedural flush solution was used and a minor systemic effect of a heparin flush solution cannot be excluded. In this study, open and peripheral endovascular procedures were included, the same heparin protocol, and therefore dosages were used in both type of interventions which could lead to overanticoagulating patients who undergo peripheral endovascular interventions. This study was not designed to determine the optimal ACT associated with the least amount of ATEC and bleeding complications, neither to relate ACT to clinical outcomes, such as ATEC or bleeding complications. The target ACT was adjusted during the inclusion period and in the two centers different additional dosages were administered. During the present study, the HMS Plus was used for the ACT measurements. Importantly, a significant variability in ACT values between different brands of ACT devices has been reported.[26–29] Therefore, the findings of the present study cannot be extrapolated on a 1:1 basis to the measurements performed with ACT devices from different brands with a different type of cartridges.

In conclusion, an initial heparin dose of 100 IU/kg results in an adequate ACT (200 to 300 s) in 74% of patients. Nevertheless, ACT measurements are essential to monitor the effect of heparin and thereby ensuring the individual patient of safe and tailor-made anticoagulation. Future studies are needed to investigate an optimal ACT in NCAP with a lowest incidence of ATEC without a significant increase in bleeding complications.

DISCLOSURES

None.

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