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Dose adjusted heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin

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Summary. Two studies have been done to establish recommendations for dosage and dose adjustment in the treatment of deep vein thrombosis (DVT) with low molecular weight heparin (LMWH). In the first, 56 patients were randomized in a double blind study to be treated either with unfractionated heparin (UFH) or LMWH s.c. every 12 h. Initial doses were given according to age and sex, disregarding bodyweight, and the dose was then adjusted when the peak plasma heparin concentration fell outside the desired range of 0.5–0.8 anti-FXa U/ml.

There were fewer dose adjustments in the LMWH group. The correlation between injected dose (U/kg bodyweight) and the heparin concentration was higher in the LMWH group ($r = 0.59$) than in the UFH group ($r = 0.38$). The results suggest that, in order to obtain the desired heparin concentration, the initial dose of LMWH should be about 100 U/kg bodyweight every 12 h.

In the second, open study, this dosage plan was followed in 15 patients. The peak heparin concentration on Day 2 ranged from 0.40 to 0.75 anti-FXa U/ml and adjustment was only required in 3 patients. Day to day variation in peak heparin activity in the individual patient varied little (CV 11–22%), and there was no accumulation.

The results indicate that plasma heparin concentration is more predictable using LMWH than UFH, and they point to definite advantages in the use of LMWH in a bodyweight adjusted dosage.

Key words: Heparin, dose adjustment; LMW heparin, deep vein thrombosis, plasma level

Heparin has been used in the treatment and prophylaxis of thrombosis for the past 50 years. The usual commercial preparations contain unfractionated heparin (UFH), of molecular weight (MW) 3000–30000 dalton (D). The effect on the activated partial thromboplastin time (APTT), and the ability to accelerate the inhibition of thrombin, requires heparin molecules of a minimum size of about 5000 D [1–3]. The ability to accelerate inhibition of activated coagulation factor X (F-Xa), on the other hand, is retained by molecules of MW in the 2000–5000 D range [1, 3, 4]. Heparin fractions in that range are called low molecular weight heparins (LMWH).

In animal experiments, LMWH fractions (with high anti-F Xa and low anti-thrombin activity) are reported to combine a good antithrombotic effect with a low bleeding tendency [5–7]. Because bleeding is the main complication of heparin treatment, clinicians are tempted to test the hypothesis that the use of LMW heparin will reduce the risk of bleeding in patients. During the past few years, LMWH from several producers has become available for clinical investigation in prophylaxis against thrombosis [8–12], in haemodialysis [13–15] and also in the treatment of deep venous thrombosis (DVT); [16–18].

Compared to UFH, LMWH has a longer duration after intravenous injection [19, 20], and greater biological availability after subcutaneous injection [19–21].

Pharmakokinetic data based on the clinical use of LMWH are relatively limited, and recommendations for dosage in treatment of DVT have not been established.

The present study describes the determination of plasma heparin concentrations in patients treated for DVT, with emphasis on the use of dose adjustment to obtain the desired heparin level. In the first study, 56 patients were randomised to s.c. treatment with UH or LMWH SC. The initial dose was chosen according to sex and age criteria, disregarding bodyweight. Based on those results, a second, open study was performed in 15 patients, testing the

Table 1. Age, sex and bodyweight of the patients (Studies I and II)

	Study I		Study II
	UFH	LMWH	LMWH
Age (years)			
mean (SD)	62 (13.9)	61 (14.7)	56 (18.9)
range	25–85	23–85	20–90
No of males/females	17/10	16/13	6/9
Weight (kg)			
mean (SD)	75.6 (13.9)	72.6 (12.4)	73.8 (12.7)
range	35–95	42–100	48–90

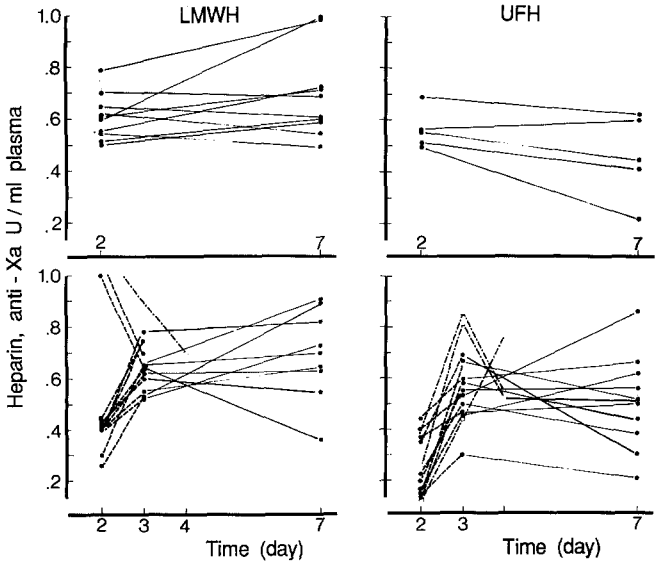

Fig. 1. Individual peak concentration of heparin (Study I). Upper two panels: no adjustment. Lower panels: adjustments. LMW heparin in left panels, UF heparin in right panels

dose regimen suggested by the findings in the first study. The main clinical findings of both studies have previously been reported [17, 22].

The present report is focused on the relation between dosage, bodyweight and anticoagulant effect, and examines the effectivenes of a dose adjustment system according to laboratory monitoring.

Materials and subjects

Patients

In Study I 56 patients (33 males and 23 females), and in Study II 15 patients (6 males and 9 females), all with venographically proven DVT were included (Table 1). Patients were excluded if they had evidence of pulmonary embolism, thrombus extension above the groin, symptoms lasting more than 14 days, a history of cerebral haemorrhage, surgical treatment within the last 6 days, signs or history of bleeding tendency, severe hypertension, pregnancy, antithrombin (AT) deficiency or other serious coexistent disease [17].

Heparin preparations

Low molecular weight heparin (LMWH; Fragmin, KABI, Sweden), was prepared by nitrous acid degradation of porcine mucosal heparin, and fractionated to obtain mean MW of 4000–6000 D. The specific activity was 160 anti-Xa IU/mg (S-2222 assay) and 40 $U \cdot mg^{-1}$ by APTT assay. The solution for SC injection, 10000 anti-Xa IU/ml, was provided in vials of 1 ml (Lot no 86992).

Unfractionated heparin (UFH). A sodium heparin of porcine mucosal origin with a mean MW of about 13000 D (KABI, Sweden). The specific activity was 160 anti-Xa IU/mg (S-2222 assay) and 160 $U \cdot mg^{-1}$ by APTT assay. The solution for SC injection, 20000 anti-Xa $U \cdot ml^{-1}$, was provided in vials of 1 ml (Lot no 88132).

Pre-study drug. Unfractionated heparin for IV administration. Sodium heparin of porcine mucosa origin, 5000 $U \cdot ml^{-1}$ (Nycomed, Norway).

Laboratory analyses

Plasma heparin (anti-Xa) activity was determined in samples taken 3 h after SC injection on Day 2 (morning) and Day 7 (morning), and on days in between if the dose had been adjusted. In 8 patients (Study II) 13 samples were collected at intervals between a morning and an evening injection (see Fig. 5). A simplified assay based on the Coatest Heparin kit using chromogenic substrate S-2222 (KabiVitrum) was developed [23] and was used throughout the study. In this assay AT is added as the reagent and the result of the assay essentially reflects the heparin concentration [24].

Thrombotest (TT) was determined daily from Day 3 according to instructions from the producer (Nycomed, Norway).

Phlebography/Marder score

Ascending venography [25] was done to verify the diagnosis of DVT and was repeated after 7 days of treatment. The evaluation was performed as described previously [17], using the system of Marder et al. [26].

Statistical analysis

The data were analysed using SAS version 82.3. Non-parametric Wilcoxon-Rank two sample tests were used to examine statistical significance. $P < 0.05$ was considered significant.

Study design

Definition of desired therapeutic range

Based on earlier studies [27] the appropriate mean plasma heparin concentration was considered to lie in the range 0.3–0.5 U/ml for UFH. For LMWH, data on the relationship between clinical effect and plasma concentration were scarce when Study I was designed, so it was decided to apply the same therapeutic range as for UFH. It was also decided to base dosage adjustment on the peak heparin concen-

Table 2. Study I. Initial dosage according to age and sex. Distribution of the patients by dose

	UFH ($n = 27$)			LMWH ($n = 29$)		
Age (y)	male (*n*)	female (*n*)	Initial dose anti Xa $U \cdot 12\ h^{-1}$	male (*n*)	female (*n*)	Initial dose anti Xa $U \cdot 12\ h^{-1}$
< 60	10	4	15,000	7	3	7500
60–69	2		15,000	4		7500
		1	10,000		2	5000
⩾ 70	5		10,000	5		5000
		5	8,000		8	4000

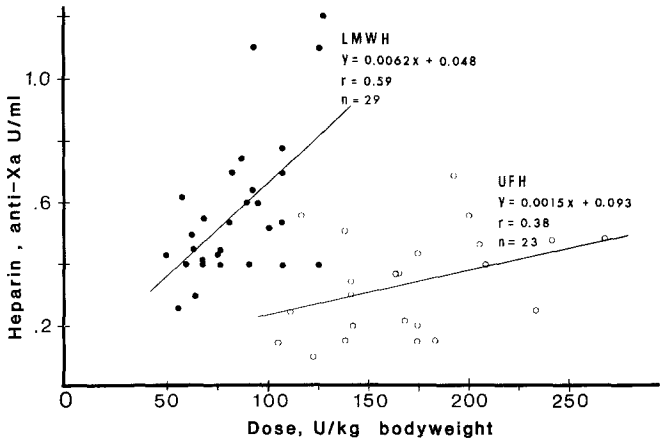

Fig. 2. The relation between dose of heparin $\cdot kg^{-1}$ bodyweight and the peak concentration (Study I). Blood was sampled on Day 2, 3 h after injection of heparin. ● LMW heparin ○ UF heparin

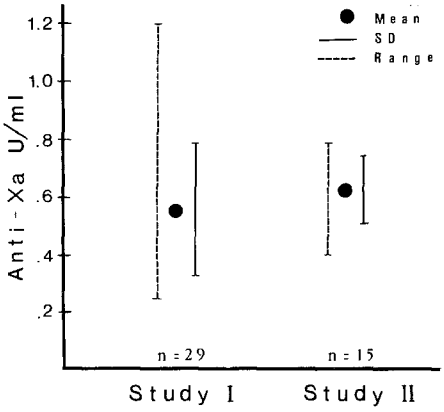

Fig. 3. Peak LMW heparin concentration in plasma. Blood was sampled Day 2, 3 h after injection, in the 29 patients of Study I (standard dose), and in the 15 patients in Study II (dose according to bodyweight)

tration after the SC injection. In order to study the relation between the mean and peak concentration of heparin in plasma, 4 healthy volunteers were given a total of eleven injections of various doses (5000–10000 U) of LMWH and UFH by subcutaneous injection, and the plasma heparin concentration was determined every hour for 12 h. For both UFH and LMWH, the peak concentrations was reached 2–3 h after injection. The ratio between the peak and the mean concentrations in the 12 h period averaged 1.66 (range 1.4–1.8). Using this ratio, the recomended mean range (0.3–0.5 U $\cdot$ ml^{-1}) corresponds to a peak range of 0.5–0.8 U $\cdot$ ml^{-1} in plasma sampled 2–3 h after SC injection.

Selection of initial subcutaneous dose of heparin

In the first study, the two initial SC injections were given to each patient according to defined age and sex categories (regardless of bodyweight, bw), as shown in Table 2. The reasons for this were that a previous study of the intravenous treatment of DVT had shown that the rate of heparin elimination was lower both in patients more than 70 years of age and in females [28]. Major bleeding was mainly observed in females older than 70 y [28].

The initial dose of LMWH was chosen to be half the dose of UFH, employing anti-FXa units. This was done because LMWH has greater bioavailability than UFH. In fact, our pilot experiments had suggested that availability was about three-times higher for LMWH, but a lower ratio had also been reported [29]. With apparently a more limited action on the coagulation system, it was also considered more important to try to avoid underdosage with LMWH than with UFH. The two heparins were supplied in vials containing 10000 (LMWH) and 20000 (UFH) anti-FXa U $\cdot$ ml^{-1}, respectively.

Dose adjustment

Dose adjustment was performed on Day 2, and if necessary on subsequent day(s) until peak heparin anti Xa activity was within the desired range of 0.5–0.8 U/ml plasma (see Results). The following system for dose adjustment was recommended: plasma level (pl) < 0.3 U/ml – increase dose 50%; pl 0.3–0.5 U $\cdot$ ml^{-1} – increase dose 25%; pl 0.5–0.8 U $\cdot$ ml^{-1} – unchanged dose; pl 0.8–1.0 U $\cdot$ ml^{-1} – reduce dose 25%; pl > 1.0 U $\cdot$ ml^{-1} – reduce dose 50%. The new doses were chosen to the nearest 0.05 ml. In a few cases dose adjustments deviated somewhat from the recommendations.

Treatment

Prestudy medication. Upon admission to the Department of Internal Medicine with suspected DVT, each patient was given an IV bolus injection (5000 U) and an IV contineous infusion (about 400 U $\cdot$ kg^{-1} bw/24 h) of UF heparin according to the standard hospital routine. After DVT had been venographically verified, and the patient randomized to treatment with UFH or LMWH, the IV infusion was stopped 2 h prior to the first SC injection of UFH or LMWH. On average, the IV infusion lasted for 17 h (range 1–48 h).

In all patients treatment with Warfarin 10–12.5 mg was started on Day 1.

Study medication. SC injections of LMWH or UFH were given every 12 h, starting in the evening on Day 1. In Study I, the initial dose was given according to age and sex criteria (Table 2), and in Study II, the dose was 100 U $\cdot$ kg^{-1} bw $\cdot$ 12^{-1} h.

Heparin was discontinued when Warfarin treatment was effective, defined as a Thrombotest value below 9%.

Results

Study I. Comparison between LMWH and UFH

The two patient groups were well matched in age, sex and bodyweight (Table 1). About half the LMWH patients (14/27), and 80% of the UFH patients (20/25) required dose adjustment (Table 3). That was less successful in the UFH than in the LMWH group (Table 3). A second adjustment was required in 6/25 in the UFH group, but in

Table 3. Dose adjustments in Study I

	UFH	LMWH
	(number of patients)	
Heparin conc. determined day 2	25	27
Heparin conc. within desired range	5 (20%)	13 (48%)
One dose adjustment sufficient	10	12
Two dose adjustments sufficient	6	2
Desired range not obtained[a]	4	0

[a] In these 4 patients, plasma heparin concentration (anti-FXa activity) day 2 was below the desired range: In 3 patients, maximum dosage was insufficient to obtain desired concentration. In one patient, heparin was discontinued day 3

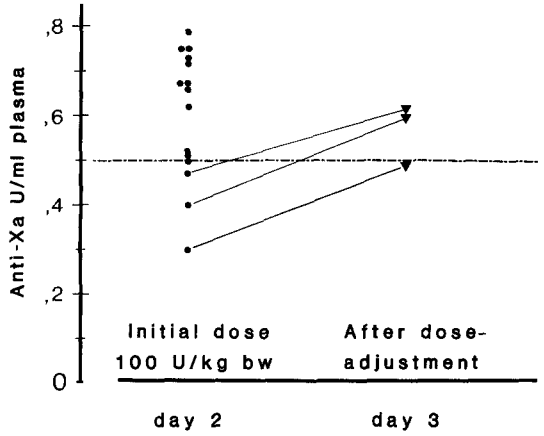

Fig. 4. Individual peak plasma heparin concentrations on Day 2. (Study II). Blood was sampled 3 h after injection. Dose adjustment and new heparin determination Day 3 in 3 patients

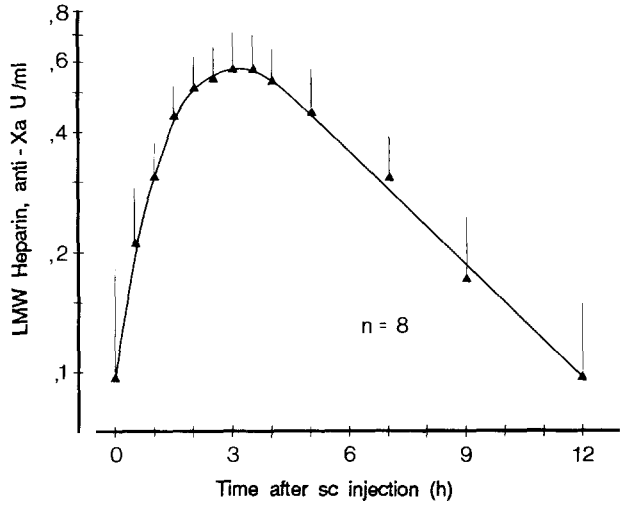

Fig. 5. Plasma concentration determined in 8 patients who received 100 U·kg^{-1} bw of LMW heparin (Study II). Blood was sampled as indicated. Mean (SD)

only 2/27 of the LMWH group. Patients in the UFH group on average had lower heparin concentrations than those in the LMWH group. The difference was reduced but not eliminated by the dose adjustments (Fig. 1).

Relation between dose and plasma concentration

The bodyweight of the 56 patients ranged from 35–100 kg. As the initial doses in the study were given regardless of bodyweight (bw), a large range of dose/kg bw were obtained (Fig. 2). The mean doses given after final adjustment, expressed as anti-FXa U·kg^{-1} bw·12 h^{-1} were 219 (UFH group) and 90 (LMWH group), respectively (Table 4).

The correlation between the dose/kg and plasma concentration were calculated assuming a linear relationship; r was 0.59 (LMWH) and 0.38 (UFH), respectively (Fig. 2). Applying the equation describing the linear LMWH dose/concentration relation (Fig. 2), 97 U·kg^{-1} bw·12 h^{-1} of LMWH was chosen as the dose required to produce a mid-therapeutic concentration as defined here study, i.e. a peak value of 0.65 U·ml^{-1} plasma. For UFH the regression line suggested a dose of 371 U·kg^{-1} bw·12 h^{-1} to obtain a similar peak value, but this was only a tentative figure because the linear dose/concentration relationship for UFH was not statistically significant.

Study II. Testing the new dose recommendations for LMWH

In order to test the hypothesis that about 100 U·kg^{-1} bw·12 h^{-1} LMWH would produce the desired plasma concentration, this regimen was employed in 15 patients (Table 1) in an open study (Study II). The average peak concentration on Day 2 of 0.63 U·ml^{-1} was close to the desired mid-therapeutic value of 0.65 U·ml^{-1}. The *range* of peak concentrations, 0.40–0.79, was only 36% of that in the LMWH group in Study I (Fig. 3). A single dose adjustment was required in 3 patients (Fig. 4).

In the 8 patients in whom plasma concentrations were determined at short intervals, the mean half-time ($t_{1/2}$) was 3 h (Fig. 5). The LMW heparin concentration on Day 3 was subtherapeutic (< 0.2 U·ml^{-1}) in 4 of the 12 h (Fig. 5).

Clinical and venographic results in Studies I and II

One patient had a symptomatic, non fatal pulmonary embolism (LMWH group, Study I). There was one major bleed (Study II): a 90 year old man died from an undiagnozed rupture of a popliteal artery aneurysm. The plasma heparin concentration in samples taken 3 h after injection on Days 1 (evening) 2 and 3 (morning and evening) were 0.49, 0.50, 0.46, 0.54 and 0.43 anti-Xa U/ml, respectively. Control venography showed similar results in the two patient groups in Study I (Table 5). In both groups half the patients showed improvement and the other half was essentially unchanged; 1 patient in the LMWH group and 2 in the UFH group had a moderate increase in the thrombosis (Table 5). In Study II, there was a tendency (NS) towards better results (Table 5).

Table 4. Study I. Initial and final doses after adjustment in the UFH and LMWH groups

	UFH (n = 27)		LMWH (n = 29)	
	mean (SD)	range	mean (SD)	range
Initial dose				
U·kg^{-1} bw·12 h^{-1}	170 (42)	105–268	85 (22)	49–127
U·12 h^{-1}	12800	8000–15000	6050	4000–7500
Final dose				
U·kg^{-1} bw·12 h^{-1}	219 (44)	116–279	90 (17)	61–121
U·12 h^{-1}	16550	8000–20000	6550	4000–10000

Table 5. The results of control venography in the three patient groups (see Methods)

		Study I		Study II
Fate of the thrombus	Score before/ after	UFH n	LMWH n	LMWH n
Improved	decrease ≥ 2	12	11	10
Unchanged	difference < 2	11	14	4
Deteriorated	increase ≥ 2	2	1	0
Not evaluable		2	3	1

Discussion

The biological effects of heparin are related to the dose administered [28, 30], but knowing the plasma concentration gives additional information about the likelihood of bleeding [31], as well as of rethrombosis [27]. This is the main reason for recommending laboratory monitoring of patients treated for thrombosis [32]. The definition of a "therapeutic range" of plasma heparin concentrations is a compromise, because both the antithrombotic effect and the risk of bleeding tend to increase as the heparin concentration in blood is increased.

The venographic findings reported here indicate a satisfactory antithrombotic effect compared to other clinical studies [16, 33]. The single major bleeding episode – the unrecognized rupture of an arterial aneurysm – may be related to heparin, but a coincidence seems more likely.

Because LMWH was used, the laboratory monitoring depended on an anti-FXa assay and a desired therapeutic range defined in anti-FXa units. In the absence of recommended plasma levels for LMWH, it was decided to aim at similar levels as those defined for UFH, and to use the anti-FXa assay for both preparations. The ratio between the peak and mean plasma concentrations was very similar in a pilot study in normal volunteers (1.66) and in 8 patients (1.59). The patient groups treated were small and the findings do not permit conclusions about the optimal LMWH level in the treatment of DVT. But with venographic improvement as good as or better than in the UFH treated group [17], the results do not call for a major change in the "therapeutic range" of a mean plasma level of 0.3–0.5 anti-FXa $U \cdot ml^{-1}$. The conclusion is supported by clinical findings with another LMWH preparation [34].

Not surprisingly, the results have confirmed that the plasma concentration of heparin tends to vary proportionally with the dose and inversely with the bodyweight. Even so bodyweight is ignored in many dosage recommendations.

The use of a standard initial dose (ignoring bodyweight) in the first study resulted in a wide range of plasma concentrations and afforded the opportunity to test a dose adjustment system. In 29 out of 56 patients (58%), the first measured heparin concentration was outside the desired range, and it took 1–2 and in a few cases 3 adjustments, to obtain that range. The greater need for dose adjustment in the UFH groups was partly explained by use of too low an initial dose of UFH.

There are few reports on the efficacy of dose adjustment of heparin. Both prospective [35] and retrospective [28] work has shown that after dose adjustment the majority of plasma values were still outside the therapeutic range.

The present have shown that more predictable plasma levels are obtained after SC injection of LMWH than of UFH. With LMWH the correlation between dose/kg bw and plasma concentration was stronger than for UFH.

Although the relationship between the amount of *intravenously* administered heparin and the plasma concentration is fairly well understood [36], much less is known about the plasma concentration resulting from various of *subcutaneous* doses UFH. Some reports have indicated that after SC LMWH, 80–90% enters the blood [37, 38], whereas only 10–30% of UFH enters the blood [21, 38]. The capillary wall in the subcutaneous tissue permits entrance by passive diffusion of small molecules with an upper limit of about MW 5000 [39]. This makes LMWH the drug of choice when SC injection is used. The closer correlation found between the dose and the plasma concentration of LMWH may be explained by its much higher bioavailability.

From the findings in the first study, it was calculated that doses of about 100 anti-FXa $U \cdot kg^{-1}$ of LMWH every 12 h should be used to obtain plasma concentrations as close as possible to those believed to be optimal (mean 0.3–0.5 $U \cdot ml^{-1}$; peak 0.5–0.8 $U \cdot ml^{-1}$). For UFH, the calculated dose of about 370 anti-FXa $U \cdot kg^{-1}$ $bw \cdot 12\ h^{-1}$ is uncertain, since it is based on a statistically nonsignificant correlation and it is also higher than the usual dose [35]. In the second study this dose of LMWH gave plasma concentrations in the desired range in 12 out of 15 patients, and the average of the 15 peak concentrations (0.63 anti-FXa $U \cdot ml^{-1}$) was almost identical to the mid-therapeutic value. Even if new findings were to lead to a change in what is regarded as the "therapeutic range", the relation described between dose and plasma concentration may provide a base for dosage recommendations.

Subcutaneous administration of heparin is less expensive than intravenous infusion and may permit treatment outside hospital. LMWH seems particularly well suited for subcutaneous administration. In view of the more predictable plasma concentration obtained with LMWH, the need for laboratory monitoring may be less acute than for UFH. This topic should be explored in new studies.

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