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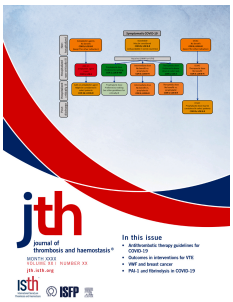

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Results of an international survey on the management of therapeutic-intensity unfractionated heparin: communication from the SSC of the ISTH

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ABSTRACT

Unfractionated heparin (UFH) remains the anticoagulant of choice in critically ill patients. However, its laboratory monitoring and clinical management are particularly challenging.

Between November 2023 and February 2024, we surveyed 142 clinicians and laboratory medicine specialists from 15 countries involved in the care of patients receiving therapeutic-intensity UFH. Our objective was to describe current practices and variations among centers. UFH monitoring was based on an anti-Xa assay or on activated partial thromboplastin time in 54% and 46% of respondents, respectively. Different therapeutic ranges were used depending on local protocols and indications; the 0.3-0.7 IU/mL anti-Xa range was commonly used, except for patients on mechanical circulatory support with a lower range, mostly 0.3-0.5 IU/mL. Most respondents managed therapeutic UFH administration with weight-based dosing (88%), while fewer used a nomogram (57%) for dose adjustment. When a nomogram was used, it was primarily based on anti-Xa monitoring (86%). The situations when respondents administered antithrombin varied widely; 22% reported using it when antithrombin levels were below 60IU/dL(%) and 20% reported never using it.

Our survey results revealed considerable heterogeneity in UFH management approaches, reflecting a knowledge gap and a paucity of evidence to guide decision-making. Key issues requiring well-designed up-to-date studies were identified that include optimal approaches to heparin monitoring, assays and reagents to be used, therapeutic range based on indications, the use of weight-adjusted nomograms for initial dosing and titrating of UFH infusion, and indications for antithrombin supplementation. Survey results provide a strong rationale for the development of international guidance addressing these issues.

INTRODUCTION

Unfractionated heparin (UFH) has been used since the 1930s to treat thromboembolic events and prevent increased thrombotic burden in patients [1,2]. Currently, UFH remains the anticoagulant of choice for the treatment of acute venous or arterial thromboembolism, or for thromboprophylaxis in selected patient groups that include cardiac surgery, mechanical circulatory support, intensive care unit (ICU), and severe renal impairment. These patients also have a hypercoagulable state, characterized by hemostatic activation leading to excessive thrombin generation and/or increased fibrin mass [3,4]. Because they are also at high risk of bleeding, their management is particularly challenging.

Many key issues related to the monitoring and management of therapeutic-intensity UFH are far from resolved [5]. Initial dosing and adjustment of UFH infusions are based on limited data and low clinical relevance, which likely contributes to heterogeneity in practice, especially in settings beyond acute VTE. Close monitoring of UFH is mandatory due to its unpredictable pharmacokinetics and pharmacodynamics, but there is still no consensus on the optimal approach to UFH monitoring in clinical practice.

The International Society on Thrombosis and Haemostasis (ISTH) Control of Anticoagulation and Perioperative and Critical Care Thrombosis and Hemostasis Scientific and Standardization Committee (SSC) Subcommittees sought to gain insight into current practice regarding UFH monitoring and prescription patterns.

We conducted an international cross-sectional online survey of clinicians and laboratory medicine specialists involved in the management of patients receiving therapeutic-intensity UFH. Our primary objective was to describe current practices and variations in practices. Our secondary objective was to provide a basis for the development of guidance addressing key issues related to the monitoring and management of therapeutic-intensity UFH.

METHODS

Three authors (IGT, TL, FM) developed the initial questionnaire. Negative questions were avoided. The chairs of the Control of Anticoagulation (AC) and the Perioperative and Critical Care Thrombosis and Hemostasis (JMC) SSCs reviewed the questionnaire for clarity and relevance. Adjustments were made based on their feedback. The final questionnaire (Supplementary) consisted of 37 questions (3 questions on clinic demographics, 1 question on the indications for therapeutic-intensity UFH, 12 questions on preanalytical and analytical

issues related to UFH monitoring, and 21 indication-specific questions on prescription patterns). For prescription patterns questions, each respondent could answer more than once based on the indication for UFH use. In some cases, participants had the opportunity to write free text to provide explanations. The survey was posted online using the SurveyMonkey software, and then distributed via email invitation to all members of the respective subcommittees from November 8, 2023 to February 28, 2024, with a link directing individuals to a webpage with more information and the option to consent and proceed to the questionnaire. The survey was also promoted on the "My ISTH Community" website, posted to the ISTH Twitter page, and could be distributed by the SSC members to respective National Societies. The target population was physicians involved in the management of patients receiving therapeutic intensity UFH. Participation was voluntary. Respondents were asked to participate only once, and responses were collected anonymously. No financial incentives were offered for completing the survey.

Survey results were summarized as proportions of the total number of responses per question. Percentages were presented with their 95% Wilson confidence intervals (CI). Missing responses were excluded from the analysis. All statistical analyses were performed using SAS software.

RESULTS

General questions

A total of 142 respondents from 15 countries completed the survey, representing 73 unique institutions.

Demographics

Most respondents were from France (47.9%, 95%CI 39.8-56.1%), followed by the United States (21.1%, 95%CI 15.2-28.6%) and Belgium (11.3%, 95%CI 7.1-17.5%). Forty percent (95%CI 31.3-49.1%) of respondents were laboratory medicine specialists, of whom 53% (95%CI 39.1-67.1%) had clinical expertise, primarily within thrombosis/hemostasis/coagulation clinics (75%, 95%CI 55.1-88%). Sixty percent (95%CI 51-68.7%) of respondents had only clinical expertise. Among them, 27% (95%CI 18.8-37%) were specialists in thrombosis/hemostasis/coagulation clinics, 25.8% (95%CI 17.9-35.8%) in intensive care or cardiac intensive care units, while the other main areas of specialties were

vascular medicine, cardiology, internal medicine, emergency medicine, anesthesiology, cardiac surgery, vascular surgery, geriatrics.

The distribution was slightly different among the three most represented countries.

In France, most respondents were laboratory medicine specialists (57.9%, 95%CI 44.9-69.8%) with clinical expertise for 57% (95%CI 40.8-72.7%) of them. Among the clinicians (42.1%, 95%CI 30.1-55%), 41.9% (95%CI 26.4–59.2%) were intensive care specialists or anesthesiologists

Only 10 % (95%CI 3.5-25.6%) of respondents in the United States, were laboratory medicine specialists. Among the clinicians (90%, 95%CI 33-70.7%), 51.8% (95%CI 33.9-69.2%) were specialists in hematology and/or in a thrombosis/hemostasis/coagulation clinics.

Finally in Belgium, 37.5% (95%CI 38.6-81.5%) of respondents were laboratory medicine specialists. Clinicians (62.5%, 95%CI 38.6-81.5%) were specialists intensive care or cardiac intensive care units (51.8%, 95%CI 33.9-69.2%).

UFH indications

Therapeutic UFH was mainly prescribed for the following six indications: acute venous thromboembolism (n=74), mechanical circulatory support [including Extra Corporeal Membrane Oxygenation (ECMO), Left Ventricular Assist Device (LVAD), and other intravascular cardiac assist devices)] (n=74), mechanical heart valves (n=57), acute limb ischemia (n=54), atrial fibrillation (n=38), and acute coronary syndrome (n=37).

UFH monitoring: tube collection, tests and reagents

Most respondents (84.5%, 95%CI 75.3-90.7%) reported using sodium citrate-containing tubes rather than CTAD (citrate-theophylline-adenosine-dipyridamole) tubes (15.5%, 95%CI 9.3-24.7%) to collect blood samples for UFH monitoring. Of the 96 respondents who reported use of a tube transport system at their institution, 77 (80.2%, 95%CI 71.1-86.9%) reported using a pneumatic transport system.

The maximum acceptable time interval between blood collection and centrifugation ranged from 30 minutes to 6 hours (Table 1). The maximum acceptable time interval between centrifugation and running laboratory tests ranged from 15 minutes to 6 hours, with 53.1% (95% CI 39.4-66.3%) of respondents reporting a maximum acceptable time interval ≤ 1h.

For UFH monitoring, the proportion of respondents who used an anti-Xa assay was slightly higher (53.9%, 95%CI 46-61.7%) than those using an aPTT assay (46.1%, 95%CI 37.3-53%); and 3 (1.9%, 95%CI 0.6-5.5%) respondents reported using both anti-Xa and aPTT assays (Figure 1). When an aPTT assay was used, the results were equally expressed in seconds or as a ratio (Figure 1).

The proportion in the three most represented countries for anti-Xa assay use was as follows: 60% (95%CI 35.7-80.2%) in Belgium, 58.8% (95%CI 46-61.7%) in France and 50% (95%CI 32.1-67.9%) in United States. Interestingly, the proportion varied widely among the countries concerning the use of aPTT assays expressed in seconds: 42.3% (95%CI 35.7-80.2%) in United States, 8.2% (95%CI 4.0-16.0%) in France and 0% in Belgium.

Among the 53 respondents who reported their reagent, Liquid anti-Xa®, Stago (n=20), Anti-Xa Biophen LRT®, Hyphen (n=9) and HemosIL anti-Xa, Werfen® (n=6) were the most commonly used reagents for anti-Xa measurement. For the aPTT assay, two reagents were reported: PTT Automate, Stago® (n=12); HemosIL Synthasil®, Werfen (n=4).

The responses regarding knowledge of the systematic differences between anti-Xa assays containing or not containing dextran (higher values with dextran) were almost equally divided between YES (51.4%, 95%CI 41.9-60.7%) and NO (48.6%, 95%CI 39.2-58%).

Respondents mentioned that the effect of dextran was to prevent neutralization of UFH by Platelet Factor 4 (PF4) released during blood collection (21.7%, 95%CI 12.2-35.6%), to dissociate UFH from circulating interactants other than antithrombin (28.3%, 95%CI 17.3-42.5%) or both (50%, 95%CI 36.1-63.9%).

Only 6 centers reported that laboratory testing for UFH monitoring was performed at another institution or laboratory, and only 2 centers mentioned plasma sample preparation and storage prior to shipping.

Therapeutic ranges

With regard to the therapeutic range for acute venous thromboembolism, responses varied widely (Figure 2), although the 0.3-0.7 IU/mL anti-Xa range was most common (54.5%, 95%CI 37.9-70.1%).

All (n=14) but one respondent used anti-Xa assays to monitor UFH in patients with mechanical circulatory support. However, the target anti-Xa level varied, with the 0.3-0.5 IU/mL target being the most common target used (40%, 95%CI 19.8-64.2%) (Figure 3).

Very few responses were received for the other indications, with variation between the respondents (Table 2).

Nomograms-Dose adjustments

Of 74 respondents, the large majority administered UFH using an initial bolus (83.1%, 95%CI 72.7-90.1%) and weight-based dosing (87.9%, 95%CI 78.5-93.5%), but fewer used a nomogram [n=42, 57% (95%CI 46.1-68.2%)]. The nomograms used were more often based on anti-Xa monitoring (n=36) than on aPTT (n=6) monitoring. Only 8 centers provided their nomogram. All but one were based on anti-Xa. All were adapted from published nomograms, mainly by Smith et *al* (weight-based UFH dosing nomogram using anti-Xa monitoring) and/or Raschke *et al* (weight-based UFH dosing nomogram using aPTT monitoring) [6,7].

Resistance to heparin

As illustrated in Figure 4, responses regarding the definition of heparin resistance varied widely, with no consensus and no country specific results. A dose of heparin >35 000 IU/d was considered as an "altered response to UFH" by approximately 30% of respondents, while about 15 % considered a dose of >20 IU/kg/h as much greater than expected and 28% defined heparin resistance without any threshold, and yet another 28% with other definitions.

Administration of antithrombin

The situations where respondents administer antithrombin (AT) varied widely, with no country specific results: never, based on UFH dose required (>20 IU/kg/h or >35000 IU/day) or based on AT level expressed in IU/dL (corresponding to %) (50 IU/dL, 60 IU/dL, 70 IU/dL, 80 IU/dL or other AT level). The full range of responses is presented in Figure 5.

DISCUSSION

In this study, we surveyed clinicians and laboratory medicine specialists involved in the management of patients receiving therapeutic-intensity UFH around the world to gain insight into their current practices. We found considerable heterogeneity in approaches to UFH monitoring and prescription patterns among respondents. This may reflect both a clear knowledge gap and a paucity of high-quality evidence to guide decision making.

Regarding blood collection for UFH monitoring, most respondents (>80%) reported collecting blood samples into sodium citrate-containing tubes, which is consistent with available recommendations [8–10]. Several studies have reported only small differences in anti-Xa levels between samples collected into sodium citrate tubes *versus* CTAD tubes [11–13]. CTAD limits *ex-vivo* platelet activation and the release of heparin neutralizing proteins such as PF4 [14,15]. However, the extent to which this mixture limits platelet activation, PF4 release, and heparin neutralization remains unclear. Most respondents (80.2%) reported using pneumatic tube systems to transport blood samples to the laboratory, which is consistent with available recommendations and reduces overall turnaround time [8–10]. The maximum acceptable time-interval from blood collection, centrifugation, and analysis varied from 15 minutes to 6 hours. This time interval may affect the amount of PF4 released from platelets in the sample prior to testing [5]. PF4 release reduces the anticoagulant effect of UFH in the collection tube and may lead to underestimation of the anticoagulant activity of heparin [16]. Of note, none of the published studies evaluating sample stability for UFH monitoring adhere to all 20 items in the Checklist for Reporting Stability Studies (CRESS), which were released in 2020 by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) to allow transferability of the data [17]. Thus, dedicated rigorous studies adhering to stringent criteria are still required to provide strong evidence on preanalytical issues such as collection tube (is there any benefit of CTAD in some situations?), blood sample transport to the laboratory, maximum acceptable time-intervals between blood draw and centrifugation, and between centrifugation and analysis.

Regarding the assay used for UFH monitoring, 53.9% of respondents reported using an anti-Xa assay, , and 46.1% an aPTT assay. In the setting of mechanical circulatory support, all but one respondent used anti-Xa assays, consistent with the observation that anti-Xa level monitoring improves the precision of the anticoagulation compared to aPTT monitoring [18]. Interestingly, the use of an anti-Xa assay for monitoring UFH was consistent across the three countries, eventhough it was slightly lower in the United States (50%) than in France (59%) and Belgium (60%). However, the practices differed regarding the use of aPTT in seconds, reported by 42.3% of respondents from the United States compared to 8% and 0% in France and Belgium in which aPTT is more often expressed as a ratio.

The most recent American College of Chest Physicians (ACCP) consensus group recommended against the use of a fixed aPTT therapeutic range and that the therapeutic range should be calibrated, specifically for each reagent batch/coagulometer, against anti-Xa levels (0.30–0.70 IU/mL) [19], because of the variability in reagent-coagulometer sensitivity to UFH [19–22]. The issue of selecting an adequate anti-Xa assay for this purpose remains to be resolved (see below).

Despite the lack of robust validation, UFH levels determined by anti-Xa levels have often been considered a better option for UFH monitoring than resorting to aPTT [20,23–25]. In fact, the aPTT is highly sensitive to many conditions unrelated to the anticoagulant effect of UFH that are common in critically ill patients: defects in the contact system, interference of C-reactive protein at least with certain aPTT reagents, and the presence of a lupus anticoagulant, which prolong the aPTT. Conversely, high levels of factor VIII, which are common in case of inflammatory syndrome, shorten the aPTT, making it less sensitive to UFH [20,26–28]. Moreover, the use of an anti-Xa assay rather than aPTT has been reported to be associated with a faster time to reach the therapeutic range [25,29–31]. Despite its limitations, aPTT continues to be widely used for UFH monitoring due to cost and availability as evidenced by our survey results [2,29,32–34].

Anti-Xa assays also have important limitations which should be considered. First, limited agreement between anti-Xa assays (the respondents reported 6 different anti-Xa assays) has been repeatedly reported, and may lead to a change in treatment decisions [24,35–38].

This is due, at least in part, to the presence or absence of dextran sulfate (DS) in the anti-Xa assay. DS is used to displace UFH from proteins released *in vitro* from platelets into plasma after blood sampling, especially PF4, to recover UFH activity [39,40]. DS also can displace UFH from complexes formed *in vivo* with various proteins (the so-called interactome), contributing to higher anti-Xa levels and likely overestimating true UFH anticoagulant activity [24,36–38,40,41]. The magnitude of differences between anti-Xa values measured using reagents with or without DS may exceed 50 % in samples spiked with UFH or from patients receiving UFH. This discrepancy could lead to changes in dosage decisions in up to 46% of patients [24,35,36,38,40,42].

The presence or absence of DS in anti-Xa reagents and the mechanisms of action of DS were known only by half of respondents to the present survey. In addition to the presence of DS, the type of blood collection tube, the addition of exogenous antithrombin, the calibrator, and

the calibration curve mathematical processing may also contribute to disparities in anti-Xa levels [24]. A total of six different anti-Xa assays were used by respondents to the survey. Efforts are needed to better understand the differences between types of anti-Xa assays, which will require concerted action among professional societies and reagent manufacturers. Second, anti-Xa levels do not provide information about the effect of UFH on hypercoagulability and inflammation. Similarly, an underlying coagulopathy is not detected by the anti-Xa assay.

This survey shows that clinicians use different therapeutic ranges, depending on local protocol and indication. The anti-Xa range of 0.3 to 0.7 IU/mL, reported by 54% of the respondents, has been widely accepted for decades as the therapeutic range of UFH for treating acute VTE [19]. However, it is based on limited evidence.

The UFH therapeutic range for an acute episode of VTE was first established in the 1970s as an aPTT ratio (using an APTT method with locally prepared reagents) between 1.5 and 2.5 [43]. Subsequently, heparin levels were also assessed by protamine titration [44]. The transition to chromogenic anti-Xa assay with a therapeutic range of 0.35 to 0.67 IU/mL, using a reagent not containing DS (Stachrom Heparin®, Stago), was based on a single study published in 1994 [25]. Since then, no clinical studies have challenged the therapeutic range (rounded to 0.3-0.7 IU/mL), and no evidence supports that a specific therapeutic range is associated with optimal clinical outcomes. The reagents used at that time are no longer, or rarely, used today, and the applicability of the results to reagents currently in widespread use remains unknown.

The target anti-Xa for managing UFH in ECMO patients varied among respondents, with 0.3-0.5 IU/mL being the most common response. This lower therapeutic range is explained by the goal of anticoagulation to prevent clotting in the circuit and oxygenator and thrombosis in the ECMO-treated patient while minimizing bleeding complications. Guidance from the ISTH on anticoagulation in ECMO patients has recently been published and highlights the lack of robust data for heparin monitoring for this indication [45].

Beyond VTE and circulatory support, respondents used therapeutic doses of UFH in patients with mechanical heart valves, acute limb ischemia, atrial fibrillation, and acute coronary syndrome. For these indications, there was heterogeneity among respondents. Doses and monitoring were derived from those considered appropriate for acute VTE. The heterogeneity

of responses is not surprising given the low level of evidence for therapeutic use of UFH in those clinical settings [19,46]. To the best of our knowledge, there are few data to support the use of UFH in patients with mechanical heart valves, who are managed based on clinical experience [47].

The results of this survey highlights the lack of consensus regarding the definition of 'heparin resistance' [19,48] and are consistent with those of a recent survey on the definition of "heparin resistance" conducted by the ISTH SSC on Perioperative and Critical Care Thrombosis and Hemostasis in June 2023 [49]. Authors concluded that there is still a need to identify a common definition of reduced responsiveness to heparin [49]. The 9th edition of the ACCP recommendations on antithrombotic treatment, but not in the subsequent updates, suggested that a dose > 35,000 IU/day of UFH could be considered 'abnormally high' [19], based on the study by Levine et al [25]. While this threshold has subsequently been widely used in the literature to define heparin resistance, it has several limitations, one of which is that it does not take into account the patient's weight. In the previous ISTH survey, 17.4% of practitioners reported using the >35,000 U/day threshold to define an 'abnormally high' dose of heparin [49], in ours the proportion was even higher (29.5 %).

The need to increase the dose of UFH to reach the target therapeutic interval is a common situation in the ICU. To adjust doses, most of the respondents managed UFH with weight-based dosing but fewer used a nomogram. The nomograms used were based on anti-Xa monitoring. A randomized controlled trial conducted by Raschke *et al* in 1993 showed that a significantly higher proportion of patients reached the aPTT therapeutic range of 1.5 to 2.3 times control within 24 hours and had less recurrent thromboembolic events when using a weight-based nomogram compared to standard care [7]. Several studies demonstrated the benefit of weight-adapted nomograms derived from Raschke one, when it is necessary to achieve the desired anticoagulation quickly [6,29,30,50]. These nomograms reduced the time needed to reach the target therapeutic range, and increased the proportion of patients reaching this target zone, but their clinical benefit has not been demonstrated [6,29,30,50].

However, the nomograms differ in the number of patients and indications of UFH in their validation, the initial dose, the presence or absence of an initial bolus, and the dose adjustments based on anti-Xa results.

Variability in indications for antithrombin supplementation may be explained by the paucity of evidence supporting its benefit. AT deficiency can occur due to several causes, inherited or acquired, in the latter case due to reduced synthesis related to liver dysfunction or accelerated clearance/consumption associated with mechanical devices (cardiopulmonary bypass, ventricular assist device, ECMO), nephropathy (renal losses), disseminated intravascular coagulation, extensive deep venous thrombosis/pulmonary embolism, or L-asparaginase administration [51,52]. The question is whether AT deficiencies can impact the capacity of UFH to exert its anticoagulant activity *in vivo* and, ultimately patient outcomes. The plasma level of AT required for the full desired anticoagulant effect of UFH is not well known and likely depends on the assay used to monitor UFH, with no threshold to define a "resistance"/"altered response" to UFH [53–57]. In clinical practice, particularly in patients on ECMO, AT supplementation is often arbitrarily considered when concentrations are below 50-60 IU/dL, while no relationship has been established between UFH response and AT level [58,59]. Moreover, no studies have demonstrated any benefit of AT administration in this setting or others [58–62].

Our survey has several limitations. First, the relatively small sample size and the uneven geographic representation of the respondents may have introduced some bias. However, it is always a significant challenge to obtain comprehensive and representative practices across a wide array of indications, considering the variations in healthcare systems and available ressources. Second, respondents voluntarily chose to participate in the survey. We cannot exclude the possibility that those who responded to our survey are more frequently involved in the management of patients receiving therapeutic-intensity UFH than those who did not respond, and therefore are more aware of research and evidence regarding UFH monitoring and management. Finally, another limitation is that some respondents were from the same institution but not the same department. This could skew responses to questions about institutional practices. Future studies should address these limitations to help strengthen and generalize the findings.

CONCLUSION

This survey was designed to describe current worldewide practices regarding the monitoring and management of therapeutic UFH. Our results revealed considerable heterogeneity in

approaches to UFH monitoring and prescription patterns, reflecting both a knowledge gap and a paucity of evidence to guide decision-making.

This provides a strong rationale for developing guidance from the SSCs aimed at offering standardized approaches and practical support for clinicians. The guidance based on a Delphi process, including the optimal approach to UFH monitoring (assays and reagents to be used), the therapeutic range to be achieved depending on the indication, the use of weight-adjusted nomograms for initial dosing and adjustment of UFH infusions, the use of antithrombin supplementation and the issue of altered response to UFH, is currently being developed and will be released soon by the SSCs. Moreover, the key issues identified in the survey could be addressed in future clinical research under the aegis of the SSCs.

AUTHOR CONTRIBUTIONS

IGT, FM, and TL designed the survey and performed the analysis. Feedback on the initial survey was obtained from JMC, AC, CF, JHL and LAC. All authors performed critical revision, reviewed the manuscript, and approved the submitted version.

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Communication from the ISTH SSC Subcommittees on Control of Anticoagulation and Perioperative and Critical Care Thrombosis and Hemostasis. The preliminary results of the survey were presented at the session of the ISTH SSC on Control of Anticoagulation during the 32nd ISTH Congress in Bangkok, Thailand.

DECLARATION OF COMPETING INTERESTS

IGT serves as a consultant for Aguettant, Bayer, BMS-Pfizer, Leo-Pharma, Sanofi, Viatris

LAC's research institution has received honoraria from Bayer, BMS-Pfizer Alliance, The Academy for Continued Advancement in Healthcare Education, Amag Pharmaceutical, LEO Pharma, Sanofi, Valeo Pharma, and Servier. LAC holds a Tier 2 research Chair in Thrombosis and Anticoagulation Safety from the University of Ottawa.

AC has served as a consultant for MingSight, Pfizer, Sanofi, and Synergy and has received authorship royalties from UpToDate.

JHL serves on steering and research committees for Bayer, Octapharma, Takeda, and Werfen.

JC, MH, AM, VS, CF, TL and FM declare no conflicts interest.

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Figure legends

- Figure 1: Test(s) and its units used to monitor UFH (n=155).
Bars represent % of responses and upper value of 95% Wilson confidence intervals.
Anti-Xa: IU/mL
*: two aPTT expressed in seconds, one in ratio.

- Figure 2: Therapeutic ranges for APTT (sec), APTT (ratio) and anti-Xa (IU/mL) used to monitor UFH in acute venous thromboembolism (n=33). Bars represent % of responses and upper value of 95% Wilson confidence intervals.

- Figure 3: Therapeutic ranges for APTT (sec), APTT (ratio) and anti-Xa (IU/mL) used to monitor UFH in mechanical circulatory support (n=14). Bars represent % of responses and upper value of 95% Wilson confidence intervals.

- Figure 4: Definitions of heparin resistance (n=44).
Bars represent % of responses and 95% upper value of Wilson confidence intervals.

- Figure 5: Situations where antithrombin is administered (n=69).
Bars represent % of responses and 95% upper value of Wilson confidence intervals.

Table 1: Maximal time-interval between blood drawing and centrifugation (n=65). Percentage of responses and 95% Wilson confidence intervals.

		%	95% CI
Maximal time-interval between blood drawing and centrifugation (n=65)	**≤ 1h**	26.2	17-37.9
	≤ 2h	36.9	26.2-49.1
	≤ 4h	32.3	22.2-44.4
	≤ 6h	4.6	1.6-12.8

Table 2: Therapeutic ranges for APTT (sec), APTT (ratio) and anti-Xa (IU/mL) used to monitor unfractionated heparin in other indications (n=11).

Indications	Ranges
Stroke, n=1	Anti-Xa: 0.3-0.6 IU/mL
Acute limb ischemia, n=1	Anti-Xa: 0.3 - 0.7IU/mL
Severe renal insufficiency, n=1	Anti-Xa: 0.3-0.6 IU/mL
Atrial fibrillation, n=2	Anti-Xa: 0.2-0.5IU/mL; 0.3-0.7 IU/mL
All indications, n=1	Anti-Xa: 0.3-0.7IU/mL
Mechanical heart valves, n=1	APTT ratio: 2-3
During PCI, n=2	APTT ratio: 2-3
ICU post cardiac surgery, n=1	APTT, sec: 60-100
Atrial fibrillation ablation, perprocedure, n=1	APTT, sec: 250-300