# How to monitor and manage unfractionated heparin in practice (Part 1): guidance from the SSC of the ISTH

**Key Words:** unfractionated heparin; aPTT; anti-Xa; venous thromboembolism; arterial thromboembolism; nomogram, antithrombin; monitoring.

**Word Lengths:** 4983

**Abstract**

The International Society on Thrombosis and Haemostasis (ISTH) recently published a survey on the management of unfractionated heparin (UFH), which revealed substantial heterogeneity in practice and highlighted the need to develop evidence-based guidance. This document summarizes evidence and provides consensus guidance, developed through a Delphi process, for preanalytical, analytical, and clinical aspects of UFH management.

For preanalytical issues, optimal practice includes centrifuging blood samples within one hour of collection and testing within ten minutes of centrifugation, though a one-hour interval is acceptable. Standard 3.2% buffered trisodium citrate tubes are recommended, with no routine use of CTAD tubes due to cost and uncertain benefit.

Analytically, anti-Xa assays are preferred over aPTT for UFH monitoring, as they are less affected by interferences and do not require local calibration. Assays without dextran sulphate or added antithrombin are optimal, especially to avoid overestimating UFH activity after protamine reversal. Establishing a local heparin therapeutic range (HTR) is essential if aPTT is used.

Clinically, a target anti-Xa level of 0.30–0.70 U/mL is suggested for most indications, including venous thromboembolism, arterial events, and mechanical heart valves. Weight-based nomograms are recommended for dosing, though no single nomogram is preferred due to limited outcome data. Antithrombin supplementation is generally not advised for acquired deficiency.

The guidance highlights critical evidence gaps and calls for further research to optimize UFH monitoring and dosing, with future documents addressing special populations and periprocedural management.

## 1.Introduction

The International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committees (SSC) on Thrombosis and Antithrombotic Therapies and on Perioperative and Critical Care Thrombosis and Hemostasis recently published the results of an international cross-sectional survey, which revealed substantial heterogeneity in unfractionated heparin (UFH) monitoring and dosing strategies [1], highlighting the urgent need for developing evidence-based guidance.

This document summarizes the limited available evidence and provides expert guidance on the monitoring and management of therapeutic UFH. Additional guidance recommendations will be provided in a subsequent manuscript, including recommendations pertaining to special populations (e.g., children, pregnant women, obese patients, patients with renal failure, and patients with chronic liver disease), periprocedural anticoagulation (e.g., cardiac surgery, extracorporeal circulation and hemodialysis), and implementation guidance for low-resource settings. The use of the activated clotting time (ACT) will be addressed in this future document.

## 2. Methodology

A detailed description of the methodology is provided in **Supplementary Material**. Briefly, after conducting a comprehensive literature review, 8 experts (all coauthors of this guidance document) developed provisional guidance statements addressing 11 key questions on the monitoring and management of therapeutic-UFH across three domains: preanalytical, analytical, and clinical issues. Provisional guidance statements were evaluated using a structured two-round Delphi consensus process. Members of the UFH working group were contacted by email and asked to rank their agreement with the provisional guidance statements on a 5-point Likert scale (ranging from strongly disagree to strongly agree). All responses were collected anonymously via SurveyMonkey® and analyzed accordingly. Consensus was defined as ≥70% agreement (combining agree and strongly agree). Statements failing to reach consensus in the first round were revised and resubmitted in a second round, following the same procedure. Statements still lacking consensus after the second round were excluded from the final guidance.

To ensure transparency, all experts and members of the working group submitted declarations of competing interests, which were reviewed by the Guidelines and Guidance (G&G) Committee.

Consistent with ISTH guidance documents, "we advise" indicates a strong guidance statement with the availability of high-quality evidence that the clinician should consider adopting into practice in most cases, whereas "we suggest" indicates a weak guidance statement with the availability of lower-quality evidence that the clinician may or may not adopt. Additionally, three categories were defined for each statement: optimal, acceptable, and not acceptable, corresponding to consensus levels of strongly agree/agree, neither agree nor disagree, and strongly disagree/disagree, respectively.

**3. Preanalytical issues specific to tests used for monitoring therapeutic-intensity UFH**

*Q1. What is the maximum acceptable time interval between blood collection and centrifugation, and between centrifugation and performing laboratory tests for monitoring UFH (if fresh samples are used)?*

Guidance Statements

- We suggest as optimal a time interval of no more than 1 hour between blood collection and centrifugation (for aPTT and anti-Xa assays).
- We suggest as optimal a time-interval of no more than 10 min between centrifugation and laboratory testing (for aPTT and anti-Xa assays)
- We suggest as acceptable a time-interval of no more than 1 hour between centrifugation and laboratory testing (for aPTT and anti-Xa assays)
- If a pneumatic transport system is used, we suggest local validation of the absence of clinical impact of pneumatic transport on laboratory assays results.

The Clinical & Laboratory Standards Institute and the International Council for Standardisation in Haematology recommend centrifugating samples collected in citrate tubes within 1 hour of blood collection [2,3]. The British Committee for Standards in Haematology recommends centrifugation within 1 to 2 hours of blood collection [4]. Both societies recommended performing laboratory tests to monitor UFH within 4 hours at most [2–4].

None of the stability studies on UFH monitoring adhered to the 20 items of the Checklist for Reporting Stability Studies (CRESS) released in 2020 by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), limiting data transferability [5].

More specifically, regarding acceptability criteria, the maximum acceptable difference should be derived from outcome data: direct (impact of the analytical performance on clinical outcomes) or indirect outcome studies (effect of the analytical performance on clinical classifications or decisions). Regarding anti-Xa assays, only two studies provided sufficient data to assess the effect of delayed centrifugation of blood collected in evacuated tubes beyond the one-hour reference time-interval on clinical classification (within or below the therapeutic range). When non-separated unseparated plasma was assayed within 10 minutes after centrifugation, delaying centrifugation from one hour to four hours caused a shift from within to below the therapeutic range in 10% of patients [6,7].

In addition in Toulon *et al*. [6], 67 blood samples were centrifuged within one hour after collection and kept capped without separation of the plasma at room temperature for four hours. As illustrated in Table S1, a significant reduction in APTT and anti-Xa values was observed when the time-interval between centrifugation and analysis was increased from 10 minutes to one and four hours.

Although those studies adequately reported on blood collection, laboratory assays, and time-intervals from blood collection to centrifugation and from centrifugation to testing, the number of included patients was modest [6,7]. None complied with basic specifications, including the indication for therapeutic UFH, number of samples per patient, modalities of sample transportation, and/or room temperature. Furthermore, the authors did not report individual data [7] or only reported statistical impact and did not report impact on patient outcomes [6].

When interpreting stability studies of anti-Xa levels, the presence or absence of dextran sulphate (DS) in the assay should be considered. DS can dissociate heparin from platelet factor 4 (PF4) [8], at least in part, thereby extending the time permitted to perform the assay. A single study addressed the potential impact of DS. Anti-factor Xa testing was performed using two analyzer/reagent pairs [Stago and reagent without DS (n=31); Siemens and reagent with

DS (n=33)] after 1, 4, and 6 hours of sample storage as whole blood or as separated plasma. No significant differences were observed between assays with and without DS, though lack of individual data precludes firm conclusions [7].

Studies that adhere to CRESS or similar criteria are still needed to provide strong evidence about preanalytical variables. Notably, a turnaround time of less than one hour is possible for both aPTT and anti-Xa assays. [9]. Although a pneumatic transport system (PTS) is an option, it may alter aPTT and anti-Xa results during UFH therapy [10], platelet function, and other parameters [11–13]. Thus, we recommend validating its clinical impact on laboratory assays, which may be challenging. At a minimum, we suggest comparing the aPTT and anti-Xa results of UFH-treated patients on at least 20 paired samples (transported manually and by PTS to the laboratory).

*Q2. What type of blood collection tube is most appropriate for monitoring UFH?*

Guidance Statements

- We suggest using blood collection tubes containing 109 mM (3.2%) buffered trisodium citrate.
- We suggest using a small residual air space in the tube once blood is added, achieved mainly with a predetermined vacuum, when using trisodium citrate blood collection tubes to monitor UFH.
- We do not advise the systematic use of citrate, theophylline, adenosine, and dipyridamole (CTAD) tubes.

Blood samples for monitoring UFH should be collected in tubes containing 109mM (3.2%) buffered trisodium citrate according to current guidelines [3]. Tubes containing 129mM (3.8%) buffered citrate, which could factitiously prolong the prothrombin time and aPTT, are no longer readily available.

As illustrated in Table S1, there are no published data showing that type S-Monovette® without vacuum, not buffered, and containing 106 mM (3.1%) citrate are adequate for UFH monitoring. Two studies reported stability data for APTT samples but not for patients receiving heparin [14,15].

Thus, dedicated studies using S-Monovette® containing 106 mM (3.2%) citrate and adhering to CRESS criteria are required.

There should be only a small residual air space in the tube once blood is added, achieved mainly with a predetermined vacuum [4,16,17].

Blood collection tubes containing citrate and the platelet inhibitory cocktail of theophylline, adenosine, and dipyridamole (TAD) are intended to prevent platelet activation and PF4 release in the collecting tube; PF4 binds and neutralizes UFH, potentially leading to underestimation of anticoagulant effect [18–20]. However, the extent to which TAD limits platelet activation, PF4 release and heparin neutralization is uncertain, as is the appropriate time following collection before centrifugation and testing [21]. Differences in anti-Xa levels between samples collected in CTAD versus citrate tubes (109mM, 3.2%) have been reported and are, on average, modest [7,20,21]. In the DEXHEP study, higher anti-Xa levels were found (from +8% up to +24%) in CTAD samples versus citrate samples [22]. CTAD tubes are not widely available, are more expensive than citrate tubes, and require adequate conditions to protect against photochemical decomposition of dipyridamole [23].

**4. Analytical issues**

*Q3. Which test should be used for routine monitoring of UFH and assessment of its anticoagulant effect, the activated partial thromboplastin time (aPTT assay), the anti-Xa assay, or a combination of both based on the situation?*

Guidance Statements

- We suggest using an anti-Xa assay as optimal.
- We suggest using the aPTT as acceptable.
- We advise using an anti-Xa assay for monitoring UFH when the baseline aPTT is greater than the upper limit of the locally defined normal range.
- No guidance can be formulated about the added value of aPTT to anti-Xa assay to adjust UFH doses, because there is no clear direction on responding to divergent values.

For UFH laboratory monitoring, there is not yet any other option than relying on tests performed with platelet poor plasma, *i.e.,* aPTT or anti-Xa assay. Anti-Xa assays are now

considered a better option for monitoring UFH over aPTT [24–26], despite the lack of robust validation data.

The aPTT test is influenced by many conditions, including defects in the contact system, interference between C-reactive protein and certain aPTT reagents, and the presence of a lupus anticoagulant. Since those conditions do not reflect a procoagulant effect, aPTT is not a reliable indicator of overall procoagulant and anticoagulant balance.

Conversely, high factor VIII levels, common in inflammatory conditions, shorten the aPTT, making it less sensitive to UFH [18,20–23], but this can be considered a useful insight into the patient's coagulation status.

Above all, the sensitivity of the aPTT to UFH is highly variable and reagent-dependent [25,27–30]. Therefore, using the aPTT to monitor UFH requires establishing a heparin therapeutic range (HTR) for each aPTT reagent-coagulometer pair and each new reagent lot. Obtaining a baseline aPTT before initiating UFH is warranted [4], and if it is prolonged (or shortened), then the aPTT is unsuitable for monitoring UFH, and anti-Xa assay is the only option [4].

Despite its limitations, the aPTT continues to be widely used for UFH monitoring, mainly due to cost and availability. In contrast, anti-Xa assays are much less affected by interferences than aPTT and do not require re-establishment of the HTR. They are not specific for UFH, as they can be influenced by the presence of other anticoagulants that act on Factor Xa (FXa) and by endogenous glycosaminoglycans. They are prone to the same preanalytical issues as the aPTT, and can be influenced by plasma levels of hemoglobin, bilirubin, and lipid.

So far, large prospective studies have not investigated whether monitoring UFH with either an aPTT or an anti-Xa assay results in better outcomes. Therefore, there is insufficient data to demonstrate either approach's superiority. However, it has been reported that using an anti-Xa assay, rather than an aPTT, is associated with a faster time to reach the therapeutic range [31–34]. The per-test cost of anti-Xa assays varies between countries and is higher than that of the aPTT [35,36], but fewer monitoring tests and dose adjustments are required with anti-Xa assays.

Many retrospective studies have reported that aPTT and anti-Xa levels are often discordant in clinical practice, with the most common discordant pattern being a high aPTT value relative to the anti-Xa level. Therefore, we suggest to avoid parallel measurement of anti-Xa and aPTT in the same specimen because there is no clear direction on responding to discordant values [37]. However, there are situations where parallel measurement may be acceptable, and it is required to validate local therapeutic aPTT ranges (see #Q5).

*Q4. Which anti-Xa assay should be used for UFH monitoring?*

Guidance Statements

- We suggest as optimal use of assays with no addition of DS.
- We suggest as optimal using assays with no addition of antithrombin (if one-stage assay).
- In the specific setting of reversal by protamine, we advise not using an assay with DS to confirm that full neutralization of UFH has been achieved.

The Stachrom Heparin® two-stage anti-Xa assay without DS, which can be considered the reference assay since 1994 (see below), is seldom used today [34].

Currently, the most widely used anti-Xa assays (chromogenic) are based on competition (FXa and chromogenic substrate are added together). Limited agreement between those anti-Xa assays for monitoring therapeutic UFH has been repeatedly reported [15,28–30], with clinically relevant implications (up to 46% of changes in dosing decisions) [38].

One substantial difference among anti-Xa assays is the presence or absence of DS in the reagent. The type of DS and its concentration might vary among manufacturers and are often undisclosed. DS is used to displace, at least in part, UFH from heparin-neutralizing proteins released *in vitro* by platelets into plasma after blood sampling, to recover all UFH [39,40]. DS would also displace UFH from complexes formed *in vivo* with various proteins (heparin interactome), at least in part, contributing to an overestimation of anti-Xa levels [22,26,38,40–43].

Other assay-related parameters are likely to contribute to discrepancies in anti-Xa levels when using competition assays, including plasma dilution, the ratio of plasma to reagent volumes,

addition of exogenous antithrombin (AT), calibrator and calibration curve mathematical processing, and the optical density measurement device [26]. There are both clinical (study with Stachrom Heparin® [see below Q5]; none with the other assays after careful literature review) and theoretical (see above) reasons to choose an assay without DS. However, studies on the clinical impact of using assays without DS *versus* with DS and on their analytical performance are lacking. Moreover, the preanalytical phase is then more critical, and there may be disagreements about whether citrate alone is used or citrate plus a TAD mixture (CTAD) to limit platelet activation, and, thus, PF4 release.

Most anti-Xa assays currently used are performed without added AT [26]. Assays with the addition of exogenous AT are, by design, insensitive to variations in endogenous AT levels and would mask a decreased sensitivity to UFH due, at least in part, to low AT levels.

After UFH-neutralization by protamine, *in-vitro* and *ex-vivo* studies have shown that DS contained in anti-Xa assays would displace UFH from complexes formed *in vivo* with protamine, leading to higher anti-Xa values and overestimation of active UFH [22,40].

*Q5. How to establish the Heparin Therapeutic Range (HTR) for aPTT?*

Guidance Statements

-We advise against the use of a fixed HTR for aPTT

-We advise that each laboratory locally defines the sensitivity to UFH (HTR) of the specific aPTT in use for each batch of reagent

- There is insufficient data to advise one method to establish the HTR for aPTT over another among those available.

Due to the variability of reagent-coagulometer sensitivity to UFH [19,25,27–29], the American College of Chest Physicians consensus group recommended against the use of a fixed aPTT therapeutic range and suggested that the therapeutic aPTT range at a particular institution should be adapted to the responsiveness of the reagent and coagulometer used [27]. However, there is no general agreement on how such a calibration should be performed.

The most recent British Society for Haematology Guideline suggests using a locally validated aPTT ratio (patient/mean normal aPTT) corresponding to heparin anti-Xa levels of 0.30 to 0.70 U/mL, when using aPTT for monitoring UFH, without providing a specific method [4].

Marlar RA *et al.* suggested to determine the HTR for aPTT in seconds, using the *ex-vivo* method as follows: collect appropriate samples (minimum 20) from patients on therapeutic UFH with INR < 1.3 (without any further specification); process the blood sample according to the above-mentioned guidelines; determine aPTT on fresh samples; determine heparin level on either fresh or frozen sample; plot heparin level on X-axis and aPTT value on Y-axis; determine best fit line using linear regression; determine aPTT value for both 0.30 U/mL heparin and 0.70 U/mL heparin [44]. They also recommended against using the "spiked curve" method. Indeed, *in-vitro* methods to determine HTR lead to values that differ from those obtained with the *ex vivo* method, with lower HTR reported when *ex-vivo* method is used [45]. This is due to the differential clearances of UFH chains according to their lengths: the longer and more active chains, the faster the clearance.

Using a similar approach, other investigators expressed aPTT as the clotting time (in seconds) and the patient-to-control ratio. The control clotting time was defined as the geometric mean aPTT measured in plasma from at least 30 healthy individuals. The aPTT therapeutic range was calculated by plotting aPTT (y-axis) *vs*. anti-Xa levels evaluated with plasma samples from 60 patients on therapeutic UFH and corresponding to anti-Xa levels between 0.30 and 0.70 U/mL [6]. The added value of using a ratio is uncertain though, since it does not harmonize results across the many reagent-coagulometer pairs.

However, selection of the blood samples from UFH-treated patients, which is critical since it must reflect actual use, as well as the choice of an anti-Xa reagent, were not specified in these approaches.

**5. Clinical issues**

*Q6. What is the optimal therapeutic range in patients receiving UFH for treatment of acute venous thromboembolism (VTE), using anti-Xa levels?*

Guidance Statement

- We suggest the optimal therapeutic range using an anti-factor Xa assay is 0.30 to 0.70 U/mL.

In the 1970s, a prospective study suggested that achieving an aPTT (Dade Actin thromboplastin) of 1.5 to 2.5 times the value of the pooled normal plasma, may reduce the risk of recurrent VTE in patients receiving UFH for the treatment of acute VTE [46]. Based on

the results of this study, an aPTT of 1.5 to 2.5 times the control value was long accepted as the HTR, without further prospective studies evaluating patient outcomes.

UFH preparations, aPTT reagents, and coagulometers have changed over time. It is well established that the sensitivity of different commercial aPTT reagents to UFH varies considerably. As highlighted above (see Q3), an arbitrary therapeutic aPTT range for UFH monitoring is no longer recommended and may lead to inappropriate UFH dosing. Brill-Edwards *et al*. first reported that a therapeutic aPTT range with a lower limit set at an aPTT ratio of 1.5 times the control value consistently resulted in subtherapeutic heparin levels when protamine titration heparin concentrations of 0.2 to 0.4 U/mL were used as the reference standard [34].

A single study by the same Canadian group supported the transition from protamine titration of heparin concentrations of 0.2 to 0.4 U/mL to chromogenic anti-Xa levels of 0.35 to 0.67 U/mL. Patients treated for VTE who required a daily UFH dose greater than 35,000 U/day during the previous 24 hours were randomized to aPTT or anti-Xa levels monitoring. An aPTT of 60 to 85 seconds (reagent Actin FS®, Dade) or anti-Xa levels of 0.35 to 0.67 U/mL (reagent Stachrom Heparin®, Stago) were determined beforehand as corresponding to UFH concentrations of 0.2 to 0.4 U/mL measured by the protamine titration assay. The incidence of recurrent VTE and bleeding did not differ between the groups. However, patients randomized to aPTT monitoring required higher doses of UFH than patients randomized to anti-Xa level monitoring [34].

Since then, a rounded target anti-factor Xa level of 0.30-0.70 U/mL has been widely accepted as the therapeutic range to be achieved in patients receiving UFH to treat acute VTE, without further prospective studies challenging this range. Nonetheless, physicians should be aware that variable equivalence has been reported between UFH concentrations measured by the protamine titration assay and those measured by heparin anti-factor Xa assays [47,48].

Large-scale VTE trials evaluating patient outcomes based on monitoring anti-Xa levels are warranted.

*Q7. What is the optimal therapeutic range in patients receiving UFH for treatment of acute arterial thromboembolic events, using anti-Xa levels?*

Guidance Statement

- We suggest achieving a target anti-factor Xa level of 0.30 to 0.70 U/mL is acceptable.

No specific therapeutic range for UFH has been validated in patients receiving UFH for acute arterial thrombotic events.

In patients with acute coronary syndrome (ACS), the 2023 European Society of Cardiology (ESC) [49] and the 2025 American College of Cardiology (ACC)/American Heart Association (AHA)/ American College of Emergency Physicians (ACEP)/ National Association of EMS Physicians (NAEMSP)/ Society for Cardiovascular Angiography & Interventions (SCAI) guidelines [50] strongly recommended the use of parenteral anticoagulation at the time of diagnosis and during percutaneous coronary intervention (PCI). Compared to patients with VTE, patients with ACS are at increased risk of bleeding due to concomitant use of dual antiplatelet therapy (DAPT). The ESC guidelines recommended an initial intravenous bolus of 70-100 U/kg UFH followed by an intravenous infusion titrated to achieve an aPTT of 60-80 s [49]. The ACC/AHA/ACEP/NAEMSP/SCAI guideline recommended a loading dose 60 U/kg, with an initial infusion 12 U/kg per hour adjusted to achieve an aPTT of 60-80 s [50]. This lower UFH dosing was based primarily on the results of the ISAR-REACT-3A study, which demonstrated a net clinical benefit with a loading dose of 100 U/kg compared to a loading dose of 140 U/kg [51]. However, an aPTT target range of 60-80 s is not appropriate due to the high variability in the sensitivity of aPTT reagents to UFH. Indeed, most large cardiology trials did not report the aPTT reagents used or the target therapeutic range for aPTT. In the OASIS-2 trial, patients with aPTT values <60 s for more than 48 hours were at increased of recurrent cardiovascular events (RR 1.84; 95% CI 1.25-2.70), while every 10-s increase in aPTT was associated with an increased risk of major bleeding of 7% (95% CI 3% to 11%) [52].

Anticoagulation is also mandatory for the initial treatment of patients with acute limb ischemia awaiting revascularization. The 2020 European Society for Vascular Surgery (ESVS) Clinical Practice Guidelines on the Management of Acute Limb Ischemia recommended the use of intravenous UFH at an initial dose of 5,000 U or 70 to 100 U/kg, followed by an intravenous infusion with a dose adjustment according to patient response and monitored

with activated clotting time or aPTT. The target range achieved in this setting was not specified [53]. We suggest a therapeutic range derived from that used to treat acute VTE, with the preferred use of an anti-Xa assay.

*Q8. What is the optimal therapeutic range in patients with mechanical prosthetic heart valves receiving UFH, using anti-Xa levels?*

Guidance Statement

- We suggest that achieving an anti-factor Xa level between 0.30 and 0.70 U/mL is an acceptable target goal.

Patients with mechanical prosthetic heart valves (MHVs) require lifelong treatment with vitamin K antagonists (VKAs). The target INR depends on the thrombogenicity of the prosthesis (valve site, valve type, and manufacturer) and patient-related risk factors [54]. In those patients, UFH bridging may be required immediately after MHV replacement until the target INR is achieved or during temporary VKA discontinuation for a surgery/procedure.

When bridging anticoagulation is indicated, the 2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease recommend using therapeutic doses of UFH without specifying the therapeutic range to be achieved [54]. In contrast, the American College of Chest Physicians Clinical Practice (ACCP) Guideline on the Perioperative Management of Antithrombotic Therapy recommends full-dose UFH to achieve a target aPTT of 1.5 to 2 times the control value or a target anti-Xa level of 0.35-0.70 U/mL [55] and 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease recommends full-dose UFH to achieve a target aPTT of 2 times the control value (without information on the way the control value is defined) [56].

There is a paucity of evidence to guide decision-making regarding the optimal therapeutic range in this setting. A retrospective study compared two UFH dosing strategies in patients with mitral MHVs requiring temporary VKA discontinuation. The low-intensity UFH dosing strategy consisted of UFH infusion starting at 12 U/(kg x h) (maximum initial dose of 1000 U/h) with nomogram adjustments to maintain a target anti-Xa level of 0.2-0.5 U/mL (no information on anti-Xa reagent provided), whereas the high-intensity UFH dosing strategy consisted of UFH infusion starting at 18 U/(kg x h) (maximum initial dose of 1800 U/h) to

maintain a target anti-Xa level of 0.3-0.7 U/mL. The study was not powered to detect differences between groups regarding bleeding and thrombotic events [57].

Patient characteristics such as the type and position of the valve, bleeding risk, and previous thrombotic or bleeding events should be taken into account. Patients with one or more risk factors, such as first-generation mechanical valves (Starr Edwards, ball and cage valves), mitral position, atrial fibrillation, or prior stroke, might require a target anti-Xa in the upper level of the therapeutic range.

*Q9. How should UFH be initiated and adjusted?*

Guidance Statement

- We suggest, as optimal, using a weight-based nomogram that includes a weight-based initial bolus of UFH, and further dose adjustments *versus* not using a nomogram.

Data in the 1990's showed that patients who failed to achieve the therapeutic threshold by 24h and those who were subtherapeutic for 24h were at increased risk of subsequent recurrent venous thromboembolism [58–60]. Although the importance of achieving an early therapeutic aPTT on recurrence was controversial, authors agreed that best efforts should be made to achieve a therapeutic aPTT in a timely manner [58,59,61].

In 1993, Raschke *et al.* demonstrated, in a randomized controlled trial, that weight-based dose adjustments, including an initial bolus (to saturate the binding of UFH to non-AT proteins) and repeated boluses as needed, resulted in a significantly higher proportion of patients reaching the therapeutic aPTT range within 24 h when compared with standard care [60]. Moreover, recurrent VTE was more common in the standard care group [60].

Subsequently, several studies have demonstrated the benefit of weight-adapted nomograms derived from Raschke *et al*, especially those based on anti-Xa levels, in achieving therapeutic levels more rapidly and with fewer dose adjustments per 24-hour period. Still, their benefit has not been proven with respect to improvement in clinical outcomes [31,32,62,63].

*Q10. Which anticoagulation nomogram should be used for adjusting UFH?*

Guidance Statement

- There is insufficient data to advise the use of one nomogram over another.

Weight-based UFH nomograms were developed over three decades ago to standardize dosing. Published weight-based UFH nomograms, displayed in Tables S2 and S3, include two aPTT-based nomograms [31,60] and five anti-Xa levels-based nomograms [31,62–64]. The target population, bolus dose, infusion dose, and need for bolus administration differ among nomograms. The Raschke study is the only randomized controlled trial, with the primary outcomes being the time to exceed the therapeutic threshold and the time to achieve the therapeutic range [60]. None of the weight-based UFH nomograms have been validated using clinical events as the primary outcome. Therefore, we cannot advise the use of one nomogram over another.

Q11. When should antithrombin supplementation be used to improve the efficacy of UFH?

Guidance Statement

- We suggest that antithrombin administration in patients with acquired antithrombin deficiency may not be needed to improve UFH efficacy.

Although adult antithrombin reference values are 80 to 120 IU/dL [65], acquired AT deficiency is common in patients receiving UFH due to multiple causes that include reduced synthesis from hepatic dysfunction, increased clearance/consumption associated with mechanical circulatory support (cardiopulmonary bypass, ventricular assist devices, ECMO) nephropathy, disseminated intravascular coagulation, extensive deep venous thrombosis/pulmonary embolism, or L-asparaginase administration [66].

An antithrombin level of at least 50 IU/dL has been suggested to support a heparin effect as assessed by anti-Xa assays that do not contain exogenous AT without strong evidence to support this assumption [41]. Few *in vitro* studies have shown that the impact of AT varies depending on the assay used to monitor UFH [67,68]. So far, the plasma level of AT required to achieve the full desired anticoagulant effect of UFH is not known or established and is likely dependent on the patient's condition. Moreover, increasing UFH doses using a weight-based nomogram (see above) may overcome the poor response to UFH related to a decrease in AT level [69].

Although AT supplementation can improve anticoagulation based on altered dose-responses, clinical benefits to this approach have not been demonstrated. Most available studies on AT

administration are from cardiac surgery studies, have shown that AT supplementation improves the heparin anticoagulant effect as measured by the activated clotting time (ACT) [70,71]. However, randomized controlled trials have failed to demonstrate any benefit of AT supplementation on patient outcomes, with rising concerns about higher rates of bleeding or acute kidney injury [71].

The issue of congenital antithrombin deficiency is quite different and is beyond the scope of this guidance.

## 6. Conclusions

Despite its widespread use, critical gaps persist in the monitoring and optimal dosing of UFH. Current evidence remains limited regarding fundamental aspects such as sample stability, reagent performance, therapeutic ranges, and nomogram validation, underscoring the urgent need for rigorous, standardized investigations.

Future clinical studies should prioritize the following research objectives: 1) defining the maximum acceptable time intervals between blood collection, centrifugation, and analysis to ensure reliable UFH monitoring, 2) comparing the performance of reagents with and without DS to determine their impact on assay accuracy and clinical decision-making, 3) redefining and updating the HTR across diverse clinical settings while accounting for modern assays, and contemporary clinical practice; 4) validating UFH nomograms through large-scale, multicenter studies incorporating robust surrogate outcomes and, ideally, patient-centered clinical endpoints, including thrombotic and bleeding events.

Additional recommendations addressing special populations (e.g., pediatric, pregnant, obese, and patients with renal or hepatic impairment), periprocedural anticoagulation management, and implementation strategies for low-resource settings will be provided in a forthcoming guidance document.

## Author contributions

I.G.-T., C.F., T.L., and F.M drafted the manuscript. All authors provided critical revisions and agreed to the guidance recommendations. All authors read and approved the final document.

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REFERENCES


1 Gouin-Thibault I, Castellucci LA, Connors JM, Hardy M, Mansour A, Siguret V, Frere C, Levy JH, Cuker A, Lecompte T, Mullier F. Results of an international survey on the management of therapeutic intensity unfractionated heparin: communication from the SSCs of the ISTH. *J Thromb Haemost JTH* 2025; : S1538-7836(25)00108-4.

2 Adcock DM, Hoefner DM, Kottke-Marchand K, Marlar RA, Szamosi DI, Warunek DJ. CLSI Document H21-A5. Collection, transport, and processing of blood specimens for testing plasma-based coagulation assays and molecular hemostasis assays. *Approv Guidel-Fifth Ed Clin Lab Stand Inst* 2008; **28**.

3 Kitchen S, Adcock DM, Dauer R, Kristoffersen A-H, Lippi G, Mackie I, Marlar RA, Nair S. International Council for Standardisation in Haematology (ICSH) recommendations for collection of blood samples for coagulation testing. *Int J Lab Hematol* 2021; **43**: 571–80.

4 Baker P, Platton S, Arachchillage DJ, Kitchen S, Patel J, Riat R, Gomez K, BSH Committee. Measurement of heparin, direct oral anti-coagulants and other non-coumarin anti-coagulants and their effects on haemostasis assays: A British Society for Haematology Guideline. *Br J Haematol* 2024; **205**: 1302–18.

5 Cornes M, Simundic A-M, Cadamuro J, Costelloe SJ, Baird G, Kristensen GBB, von Meyer A, Nybo M, Gómez Rioja R, on behalf of the Working Group for the Preanalytical Phase (WG-PRE) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). The CRESS checklist for reporting stability studies: on behalf of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group for the Preanalytical Phase (WG-PRE). *Clin Chem Lab Med CCLM* 2021; **59**: 59–69.

6 Toulon P, Appert-Flory A, Fischer F, Buvat S, Jambou D, Mahagne M-H. Monitoring unfractionated heparin therapy. 4 hour-stability of anti-Xa activity in unspun citrated tubes. *Thromb Res* 2020; **186**: 7–12.

7 Gremillet M, Talon L, Lebreton A, Sinegre T. Monitoring heparin therapy: stability of two different anti-Xa assays using blood samples collected in citrate-containing and CTAD tubes. *Thromb J* 2023; **21**: 21.

8 Gouin-Thibault I, Mansour A, Hardy M, Gueret P, demaistre emmanuel, Siguret V, Cuker A, Mullier F, Lecompte T. Management of therapeutic-intensity unfractionated heparin: a narrative review on critical points. *TH Open* 2024; : a-2359-0987.

9 Chandler WL. Anticoagulation without monitoring. *Am J Clin Pathol* 2013; **140**: 606–7.

10 Lebreton A, Casini A, Bulla O, Fontana P. Impact of pneumatic tube system transport for the monitoring of heparin therapy. *Thromb Res* 2017; **158**: 35–7.

11 Wang H, Wang L, Liang H, Wei J, Wu Y, Wang X, Xu J. Falsely decreased FVIII activity following pneumatic tube transport. *Int J Lab Hematol* 2021; **43**: 305–10.

12 Lorenzen H, Frøstrup A, Larsen AS, Fenger MS, Dahdouh S, Zoel-Ghina R, Nielsen LK. Pneumatic tube transport of blood samples affects global hemostasis and platelet function assays. *Int J Lab Hematol* 2021; **43**: 1207–15.

13 Poletaev AV, Koltsova EM, Ignatova AA, Kuprash AD, Gitelson PG, Sepoyan AM, Balandina AN, Novichkova GA, Panteleev MA. Alterations in the parameters of classic, global, and innovative assays of hemostasis caused by sample transportation via pneumatic tube system. *Thromb Res* 2018; **170**: 156–64.

14 Quirke W, Toomey S, Sheikhi A. The stability of 'add-on' coagulation assays in refrigerated citrated plasma stored on a packed cellular fraction. *Int J Lab Hematol* 2021; **43**: 779–85.

15 Lima-Oliveira G, Lippi G, Salvagno GL, Montagnana M, Picheth G, Guidi GC. Sodium citrate vacuum tubes validation: preventing preanalytical variability in routine coagulation testing. *Blood Coagul Fibrinolysis* 2013; **24**: 252–5.

16 Ray MJ. An artefact related to the ratio of sample volume to the blood collection vial size which effects the APTTs of specimens taken to monitor heparin therapy. *Thromb Haemost* 1991; **66**: 387–8.

17 Ray MJ, Carroll PA, Just SJ, Hawson GA. A low volume specimen container suitable for monitoring the aPTT of heparinized patients. *Blood Coagul Fibrinolysis Int J Haemost Thromb* 1993; **4**: 805–7.

18 Contant G, Gouault-Heilmann M, Martinoli JL. Heparin inactivation during blood storage: its prevention by blood collection in citric acid, theophylline, adenosine, dipyridamole-C.T.A.D. mixture. *Thromb Res* 1983; **31**: 365–74.

19 van den Besselaar AM, Meeuwisse-Braun J, Jansen-Grüter R, Bertina RM. Monitoring heparin therapy by the activated partial thromboplastin time--the effect of pre-analytical conditions. *Thromb Haemost* 1987; **57**: 226–31.

20 Savard P, Curis E, Gouin-Thibault I, Toussaint-Hacquard M, Delassasseigne C, Bauters A, Flaujac C, Eschwège V, Mouton C, Lecompte T, de Maistre E, Lasne D, Siguret V. Laboratory Monitoring of UFH in Different Settings (DEXHEP Study): Association between Anti-Xa Levels, Platelet Factor 4 (PF4) Plasma Levels and Dextran Sulfate. *Thromb Haemost* 2025; .

21 Billoir P, Clavier T, Guilbert A, Barbay V, Chrétien MH, Fresel M, Abriou C, Girault C, Le Cam Duchez V. Is citrate theophylline adenosine dipyridamole (CTAD) better than citrate to survey unfractionated heparin treatment? Has delayed centrifugation a real impact on this survey? *J Thromb Thrombolysis* 2019; **48**: 277–83.

22 Lasne D, Toussaint-Hacquard M, Delassasseigne C, Bauters A, Flaujac C, Savard P, Mouton C, De Maistre E, Stepanian A, Eschwège V, Delrue M, Georges J-L, Gros A, Mansour A, Leroy G, Jouffroy R, Mattei M, Beurton A, Pontis A, Neuwirth M, et al. Factors influencing anti-Xa assays: a multicenter prospective study in critically ill and non-critically ill patients receiving unfractionated heparin. *Thrombosis and Haemostasis*. 2023; : 1105–15.

23 van den Besselaar AMHP. Photochemical decomposition of dipyridamole in aqueous solution and the utilization of citrate-theophylline-adenosine-dipyridamole anticoagulant for monitoring of heparin. *Int J Lab Hematol* 2010; **32**: 265–7.

24 Cuker A. Unfractionated heparin for the treatment of venous thromboembolism: best practices and areas of uncertainty. *Semin Thromb Hemost* 2012; **38**: 593–9.

25 Arachchillage DRJ, Kamani F, Deplano S, Banya W, Laffan M. Should we abandon the APTT for monitoring unfractionated heparin? *Thromb Res* 2017; **157**: 157–61.

26 Hollestelle MJ, van der Meer FJM, Meijer P. Quality performance for indirect Xa inhibitor monitoring in patients using international external quality data. *Clin Chem Lab Med* 2020; **58**: 1921–30.

27 Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: e24S-e43S.

28 Baluwala I, Favaloro EJ, Pasalic L. Therapeutic monitoring of unfractionated heparin - trials and tribulations. *Expert Rev Hematol* 2017; **10**: 595–605.

29 Gouin-Thibaut I, Martin-Toutain I, Peynaud-Debayle E, Marion S, Napol P, Alhenc-Gelas M, AGEPS Hemostasis Group. Monitoring unfractionated heparin with APTT: a French collaborative study comparing sensitivity to heparin of 15 APTT reagents. *Thromb Res* 2012; **129**: 666–7.

30 Eikelboom JW, Hirsh J. Monitoring unfractionated heparin with the aPTT: time for a fresh look. *Thromb Haemost* 2006; **96**: 547–52.

31 Whitman-Purves E, Coons JC, Miller T, DiNella JV, Althouse A, Schmidhofer M, Smith RE. Performance of Anti-Factor Xa Versus Activated Partial Thromboplastin Time for Heparin Monitoring Using Multiple Nomograms. *Clin Appl Thromb Off J Int Acad Clin Appl Thromb* 2018; **24**: 310–6.

32 Rosborough TK. Monitoring unfractionated heparin therapy with antifactor Xa activity results in fewer monitoring tests and dosage changes than monitoring with the activated partial thromboplastin time. *Pharmacotherapy* 1999; **19**: 760–6.

33 Zhu E, Yuriditsky E, Raco V, Katz A, Papadopoulos J, Horowitz J, Maldonado T, Ahuja T. Anti-factor Xa as the preferred assay to monitor heparin for the treatment of pulmonary embolism. *Int J Lab Hematol* 2024; **46 (2)**: 354–61.

34 Levine MN, Hirsh J, Gent M, Turpie AG, Cruickshank M, Weitz J, Anderson D, Johnson M. A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. *Arch Intern Med* 1994; **154**: 49–56.

35 Vandiver JW, Ritz LI, Lalama JT. Chemical prophylaxis to prevent venous thromboembolism in morbid obesity: literature review and dosing recommendations. *J Thromb Thrombolysis* 2016; **41**: 475–81.

36 Guervil DJ, Rosenberg AF, Winterstein AG, Harris NS, Johns TE, Zumberg MS. Activated partial thromboplastin time versus antifactor Xa heparin assay in monitoring unfractionated heparin by continuous intravenous infusion. *Ann Pharmacother* 2011; **45**: 861–8.

37 Price EA, Jin J, Nguyen HM, Krishnan G, Bowen R, Zehnder JL. Discordant aPTT and anti-Xa values and outcomes in hospitalized patients treated with intravenous unfractionated heparin. *Ann Pharmacother* 2013; **47**: 151–8.

38 Smahi M, De Pooter N, Hollestelle MJ, Toulon P. Monitoring unfractionated heparin therapy: Lack of standardization of anti-Xa activity reagents. *J Thromb Haemost* 2020; **18**: 2613–21.

39 Lyon SG, Lasser EC, Stein R. Modification of an amidolytic heparin assay to express protein-bound heparin and to correct for the effect of antithrombin III concentration. *Thromb Haemost* 1987; **58**: 884–7.

40 Hardy M, Cabo J, Deliège A, Gouin-Thibault I, Lecompte T, Mullier F. Reassessment of dextran sulfate in anti-Xa assay for UFH laboratory monitoring. *Research and Practice in Thrombosis and Haemostasis*. 2023; : 1–9.

41 Amiral J, Amiral C, Dunois C. Optimization of Heparin Monitoring with Anti-FXa Assays and the Impact of Dextran Sulfate for Measuring All Drug Activity. *Biomedicines* 2021; **9**: 700.

42 Mouton C, Calderon J, Janvier G, Vergnes M-C. Dextran sulfate included in factor Xa assay reagent overestimates heparin activity in patients after heparin reversal by protamine. *Thromb Res* 2003; **111**: 273–9.

43 Hammami E, Stiel L, Palpacuer C, Harzallah I. Heparin monitoring during extracorporeal membrane oxygenation: the effect of dextran sulfate on anti-Xa assay. *Res Pract Thromb Haemost* 2023; **7**: 102196.

44 Marlar RA, Clement B, Gausman J. Activated Partial Thromboplastin Time Monitoring of Unfractionated Heparin Therapy: Issues and Recommendations. *Semin Thromb Hemost* 2017; **43**: 253–60.

45 Chen Z, Xu Q, Song D, Bayartaikishigtai D, Pei S, Cheng G, Wang X, Zhang Y, Zhou Z. Comparative study and relevant exploration on methods for establishing unfractionated heparin therapeutic range (HTR) based on APTT. *Clin Chim Acta* 2025; **577**: 120435.

46 Basu D, Gallus A, Hirsh J, Cade J. A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. *N Engl J Med* 1972; **287**: 324–7.

47 Smythe MA, Mattson JC, Koerber JM. The heparin anti-Xa therapeutic range: are we there yet? *Chest* 2002; **121**: 303–4.

48 Kitchen S, Theaker J, Preston FE. Monitoring unfractionated heparin therapy: relationship between eight anti-Xa assays and a protamine titration assay. *Blood Coagul Fibrinolysis Int J Haemost Thromb* 2000; **11**: 137–44.

49 Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan G-A, Dweck MR, Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Jüni P, Kimura T, Kunadian V, Leosdottir M, Lorusso R, Pedretti RFE, Rigopoulos AG, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J Acute Cardiovasc Care* 2024; **13**: 55–161.

50 Rao SV, O'Donoghue ML, Ruel M, Rab T, Tamis-Holland JE, Alexander JH, Baber U, Baker H, Cohen MG, Cruz-Ruiz M, Davis LL, de Lemos JA, DeWald TA, Elgendy IY, Feldman DN, Goyal A, Isiadinso I, Menon V, Morrow DA, Mukherjee D, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2025; **151**: e771–862.

51 Schulz S, Mehilli J, Neumann F-J, Schuster T, Massberg S, Valina C, Seyfarth M, Pache J, Laugwitz K-L, Büttner H-J, Ndrepepa G, Schömig A, Kastrati A, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 3A Trial Investigators. ISAR-

REACT 3A: a study of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention. *Eur Heart J* 2010; **31**: 2482–91.

52 Anand SS, Yusuf S, Pogue J, Ginsberg JS, Hirsh J. Relationship of Activated Partial Thromboplastin Time to Coronary Events and Bleeding in Patients With Acute Coronary Syndromes Who Receive Heparin. *Circulation* American Heart Association; 2003; **107**: 2884–8.

53 Björck M, Earnshaw JJ, Acosta S, Bastos Gonçalves F, Cochennec F, Debus ES, Hinchliffe R, Jongkind V, Koelemay MJW, Menyhei G, Svetlikov AV, Tshomba Y, Van Den Berg JC, Esvs Guidelines Committee null, de Borst GJ, Chakfé N, Kakkos SK, Koncar I, Lindholt JS, Tulamo R, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia. *Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg* 2020; **59**: 173–218.

54 Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2022; **43**: 561–632.

55 Douketis JD, Spyropoulos AC, Murad MH, Arcelus JI, Dager WE, Dunn AS, Fargo RA, Levy JH, Samama CM, Shah SH, Sherwood MW, Tafur AJ, Tang LV, Moores LK. Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline. *Chest* 2022; **162**: e207–43.

56 Writing Committee Members, Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2021; **77**: e25–197.

57 Olsen M, Adie SK, Divens A, Popova K, Brancaccio A. Low-Intensity Heparin Infusion Compared With High-Intensity Heparin Infusion Dosing in Patients With Mechanical Mitral Valves: A Retrospective Cohort Study. *J Cardiovasc Pharmacol* 2024; **84**: 383–8.

58 Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis. *Arch Intern Med* 1997; **157**: 2562–8.

59 Hull RD, Raskob GE, Hirsh J, Jay RM, Leclerc JR, Geerts WH, Rosenbloom D, Sackett DL, Anderson C, Harrison L. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1986; **315**: 1109–14.

60 Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. *Ann Intern Med* 1993; **119**: 874–81.

61 Anand SS, Bates S, Ginsberg JS, Levine M, Buller H, Prins M, Haley S, Kearon C, Hirsh J, Gent M. Recurrent venous thrombosis and heparin therapy: an evaluation of the importance of early activated partial thromboplastin times. *Arch Intern Med* 1999; **159**: 2029–32.

62 Smith ML, Wheeler KE. Weight-based heparin protocol using antifactor Xa monitoring. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm* 2010; **67**: 371–4.

63 Jimaja WE, Stirnemann J, Fontana P, Blondon KS. Improving safety of unfractionated heparin: a retrospective, quasi-experimental, observational study of the impact of a pocket card and a computerised prescription aid tool in the University Hospitals of Geneva - PubMed. *BMJ Open* 2023; **12**: e056912.

64 Mansour A, Berahou M, Odot J, Pontis A, Parasido A, Reizine F, Launey Y, Garlantezec R, Flecher E, Lecompte T, Nesseler N, Gouin-Thibault I. Antithrombin levels and heparin responsiveness during veno-arterial extracorporeal membrane oxygenation: a prospective single-center cohort study. *Anesthesiology* 2024; **140**: 1153–64.

65 Van Cott EM, Orlando C, Moore GW, Cooper PC, Meijer P, Marlar R, Subcommittee on Plasma Coagulation Inhibitors. Recommendations for clinical laboratory testing for antithrombin deficiency; Communication from the SSC of the ISTH. *J Thromb Haemost JTH* 2020; **18**: 17–22.

66 Levy JH, Sniecinski RM, Welsby IJ, Levi M. Antithrombin: anti-inflammatory properties and clinical applications. *Thromb Haemost* 2016; **115**: 712–28.

67 Lehman CM, Rettmann JA, Wilson LW, Markewitz BA. Comparative Performance of Three Anti–Factor Xa Heparin Assays in Patients in a Medical Intensive Care Unit Receiving Intravenous, Unfractionated Heparin. *Am J Clin Pathol* 2006; **126**: 416–21.

68 Croles FN, Lukens MV, Mulder R, de Maat MPM, Mulder AB, Meijer K. Monitoring of heparins in antithrombin-deficient patients. *Thromb Res* 2019; **175**: 8–12.

69 Gueret P, Mansour A, Pontis A, Gallin M, Maucorps L, Nedelec-Gac F, Lecompte T, Gouin-Thibaut I. Laboratory response to unfractionated heparin at low antithrombin levels: an in-vitro study. *Res Pract Thromb Haemost* 2024; **8**: e102504.

70 Finley A, Greenberg C. Review article: heparin sensitivity and resistance: management during cardiopulmonary bypass. *Anesth Analg* 2013; **116**: 1210–22.

71 Ranucci M, Baryshnikova E, Pistuddi V, Di Dedda U. The Rise and Fall of Antithrombin Supplementation in Cardiac Surgery. *Anesth Analg* 2023; **136**: 1043–51.

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