Activated Partial Thromboplastin Time Monitoring of Unfractionated Heparin Therapy: Issues and Recommendations

Richard A. Marlar, PhD[1,2] Bernadette Clement, BS[3] Jana Gausman, MT(ASCP)[1]

[1] Pathology and Laboratory Medicine Service, Oklahoma City VA Health Care System, Oklahoma City, Oklahoma
[2] Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma
[3] College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

Address for correspondence Richard A. Marlar, PhD, Lab Services #113, Oklahoma City VA Health Care System, 921 13th Street, Oklahoma City, OK 73104 (e-mail: Richard-Marlar@ouhsc.edu).

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Abstract

When administering unfractionated heparin (UFH), therapeutic levels of anticoagulation must be achieved rapidly and maintained consistently in the therapeutic range. The basic assays for monitoring UFH therapy are the activated partial thromboplastin time (APTT) and/or the chromogenic antifactor Xa or antithrombin assays. For many laboratories, the APTT is the preferred standard of practice; however, the APTT is a surrogate marker that only estimates the heparin concentration. Many factors, including patient variation, reagents of the APTT, UFH composition, and concentration can influence the APTT result. This article reviews various methods to determine the heparin therapeutic range and presents recommendations for the laboratory to establish an APTT heparin therapeutic range for all sizes of hospitals.

Keywords
- heparin
- APTT
- thrombosis
- antifactor Xa assay

Intravenous unfractionated heparin (UFH) therapy is commonly used for the treatment of venous thromboembolic disease and acute coronary syndrome.[1–5] When administering UFH, therapeutic levels of anticoagulation must be achieved rapidly and maintained consistently in the therapeutic range.[2–6] Inadequate or overanticoagulation is associated with increased risks of thrombosis or bleeding, respectively.[1–6] UFH has a narrow therapeutic range and significant inter- and intraindividual variation in pharmacokinetics and pharmacodynamic properties, such that UFH therapy must be closely monitored.[1,3,6]

The main assays for monitoring UFH therapy are the activated partial thromboplastin time (APTT) and/or the chromogenic antifactor Xa or antithrombin assays.[1–5,7,8] For many laboratories, the APTT is the preferred standard of practice; however, the APTT is a surrogate marker that only estimates the heparin concentration.[1–5,8] Many factors, including patient variation, APTT reagents, UFH composition, and concentration can influence the APTT result.[6,9–14] This article will review the laboratory parameters of APTT assessment of UFH therapy and recommend the best methods for establishing the most accurate and reliable APTT heparin therapeutic range (HTR).

UFH is used for the initial treatment or prophylaxis of venous thromboembolism or acute coronary syndrome, and the UFH infusion protocols may be different as they can be dependent on the individual provider's preference or the use of the hospital's approved protocol.[4,5,8] The amount of the bolus dosage, the dose administered and the duration of treatment or prophylaxis are dependent on the protocol used.[4,5,8] Numerous guidelines for treatment and prophylaxis with UFH have been published; and providers and hospitals have established their protocols based on one of the published guidelines.[4,5,8,15] Detailing the use of UFH for treatment or prophylaxis is beyond the scope of this article. Although not absolute, the most commonly used protocols for adult and pediatric usage of UFH are presented in ►**Table 1**.[4,5,8,15] One important aspect of monitoring

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Table 1 Summary of UFH treatment and prophylaxis dosing for adults with venous thromboembolism or acute coronary syndrome and pediatric thrombosis

Treatment	Bolus	Infusion rate	Target (APTT)	Target (anti-FXa) (U/mL)
Adult (VTE and ACS)	80 U/kg (maximum 5,000 U)	18 U/kg/h (maximum 1,200 U/h and maximum 1,800 U/h for obese)	HTR	0.3–0.7
Children				
> 12 y	80 U/kg (maximum 5,000 U)	18 U/kg/h (maximum 1,200 U/h and maximum 1,800 U/h for obese)	HTR	0.3–0.7
> 1 y	75 U/kg (maximum 5,000 U)	20 U/kg/h (maximum 1,200 U/h)	Do not use	0.3–0.7
0–12 mo	75 U/kg (maximum 5,000 U)	28 U/kg/h (maximum 1,200 U/h)	Do not use	0.3–0.7
Prophylaxis	5,000 U SQ every 8–12 h		APTT 1–5 above reference interval	

Abbreviations: ACS, acute coronary syndrome; APTT, activated partial thromboplastin time; FXa, factor Xa; HTR, heparin therapeutic range; SQ, subcutaneous; UFH, unfractionated heparin; VTE, venous thromboembolism.

heparin administration is the caveat to not use the APTT to monitor UFH administration in children under the age of 12 years as the potential for the APTT to not reflect the true heparin therapy level resulting in erroneous therapeutic results. For children < 12 years of age and infants, the antifactor Xa assay for heparin must be used (►**Table 1**). No matter what protocol is used, collecting of a blood specimen for monitoring (either by APTT or antifactor Xa chromogenic methods) should be 4 to 6 hours after starting UFH (bolus infusion), 4 to 6 hours after dose changes, or 4 to 6 hours after prophylactic administration (subcutaneous injection).[4,5,8]

Preanalytical Variables

Plasma-based coagulation test results are affected by many variables during the collection, transport, processing, and storage processes.[16] The most concerning variables affecting the APTT monitoring and heparin assays are the time from draw to testing and residual platelets in the plasma.[16–18] Time as whole blood before processing should not exceed 1 hour for specimens collected in sodium citrate.[16,17] Longer times can cause heparin neutralization by platelet factor 4.[17] Extending time as whole blood will cause a decrease in the heparin concentration and will shorten the APTT, potentially underestimating in vivo heparin concentration.[16]

The residual platelet count in the plasma sample can also significantly affect the APTT and heparin results.[16,17] The centrifugation of the whole blood specimen must be at an appropriate speed and duration to reduce the platelet count to < 10,000/μL.[16] Verification of centrifugation must be performed at least every 6 months.[16] Platelet counts that exceed 10,000/μL are not acceptable for the APTT and heparin testing if the sample is frozen or left as plasma for more than 4 hours.[16,17] Freeze-thawing of samples or plasma left for > 4 hours with > 10,000/μL platelets cause the release of PF4, a potent inhibitor of heparin activity resulting in erroneous results.[17]

Ex Vivo Method for Heparin Therapeutic Range Determination

The most common method for determining the APTT HTR using the ex vivo heparin method is outlined in ►**Table 2**.[19–21] Details of the protocol for APTT HTR determination by the ex vivo method are also presented in the Clinical and Laboratory Standards Institute guideline H47.[19] Basically, the HTR is determined from the best fit line comparing the APTT and heparin concentrations in patient samples with the APTT lower limit corresponding to a heparin level of 0.3 U/mL and the upper limit of the APTT corresponding to 0.7 U/mL, as determined by an antifactor Xa chromogenic heparin assay.[19–21]

Correlation of Activated Partial Thromboplastin Time Results with Heparin Concentration

Even when the ex vivo method is used to determine the APTT HTR, there is poor correlation of APTT value to the heparin concentration.[1,12,22] In our data (►**Fig. 1**), the APTT and heparin concentration correlated only 57% of the time. Overall, the APTT is not the most accurate method for monitoring heparin therapy despite its popularity in most clinical laboratories. The poor correlation between APTT and antifactor Xa heparin assay may be attributed to several different variables.[1,23–27] Biological (patient) variation among samples (increased acute phase proteins [factor VIII and fibrinogen], concurrent use of oral anticoagulants, pregnancy, and pathologic conditions) can contribute to this reduced correlation.[1,19,22,23] The observed discordance may also be due to preanalytical variables (drawing and processing of sample, time spent as whole blood or freezing the sample with residual platelets).[1,19,22–26] Analytical variables can also contribute to this poor correlation, including APTT reagent used, type of heparin assay, AT level in the patient's plasma, heparin calibrators used, or type of heparin molecules present in the blood.[27–30]

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Table 2 Summary of the method to determine the heparin therapeutic range by ex vivo method[19]

	Ex vivo method for heparin therapeutic range determination
1	Collect appropriate samples (minimum 20) from patients on UFH
2	Process using guidelines, such as CLSI (H21)
3	Determine APTT on fresh samples
4	Determine heparin level on either fresh or frozen sample
5	Plot heparin level on X-axis and APTT value on Y-axis
6	Determine best fit line using linear regression
7	Determine APTT value for both 0.3 U/mL heparin and 0.7 U/mL heparin
8	Heparin therapeutic range is the APTT range between 0.3 and 0.7 U/mL
9	All data and calculations must be available for evaluation

Abbreviations: APTT, activated partial thromboplastin time; CLSI, Clinical and Laboratory Standards Institute; UFH, unfractionated heparin.

Variability of Reagents and Different Lots of the Same Reagent

Not only do different APTT reagents have different HTR values (►**Fig. 2**), different lots of the same reagent can also exhibit variability in their sensitivity to the UFH concentration and have a different HTR (►**Fig. 3**).[23,31] This variability between lots may be seen with all commercial reagents so far evaluated. Therefore, the HTR must be redetermined or verified for each new lot of APTT.[19,23,31]

Variation Associated to Same Hospital and Same Reagent Lot Used in Different Hospitals

In studies where the HTR was determined multiple times with the same lot of reagent on the same instrument in the same laboratory, there were no apparent significant clinical differences in the HTR.[22] This lack of clinical difference may be attributed to the shared environment of the instrument-reagent system (same maintenance, reagent procedures, sample collection, and technologists).[23] When using two different instrument models (primary and backup), with the same detection method and the same lot of reagent and same patient samples, no clinical differences were observed.[23] To minimize differences, the recommended method is to average the HTR determined from the two different instruments ranges and use the averaged HTR as the reported range.[23] However, the differences between the two instruments should not exceed the averaged value by 3 seconds.[23]

When using the same lot of APTT reagent and same instrument model in different laboratories, clinically significant differences in the upper and lower limits of the HTR have been observed.[19,23] As appealing as using the same lot in different laboratories may appear, HTR determinations should not be shared among laboratories even with the same lot number and the same instrument.[19,23] A possible workaround for multihospital networks using the same APTT reagent lot and instruments models is to perform an ex vivo HTR at more than two laboratories and if the

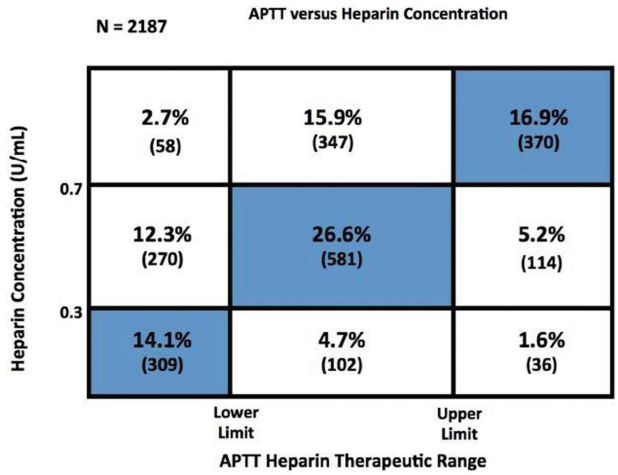

Fig. 1 Comparison of APTT Values to the heparin concentration in samples from patients receiving unfractionated heparin. The APTT value in relation to the determined APTT heparin therapeutic range is plotted against the plasma heparin concentration in relation to the heparin therapeutic dose. The percentage of samples and the total number of samples within each square is presented. The shaded areas (58% of samples) represent the values where the heparin concentration correlates with the APTT value in relation to the heparin therapeutic range. The total number of samples evaluated is 2,187. APTT, activated partial thromboplastin time.

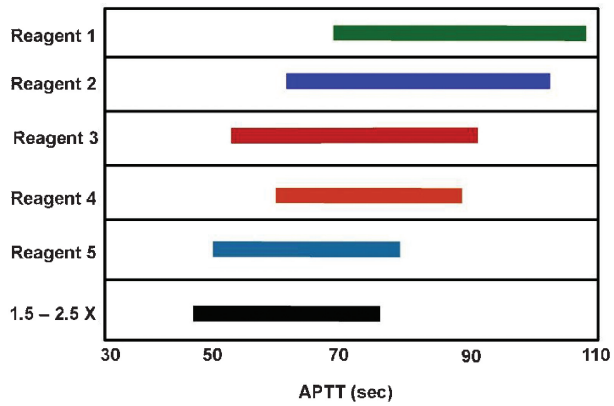

Fig. 2 Comparison of the heparin therapeutic ranges for five different APTT reagents and the 1.5–2.5× control values. APTT, activated partial thromboplastin time.

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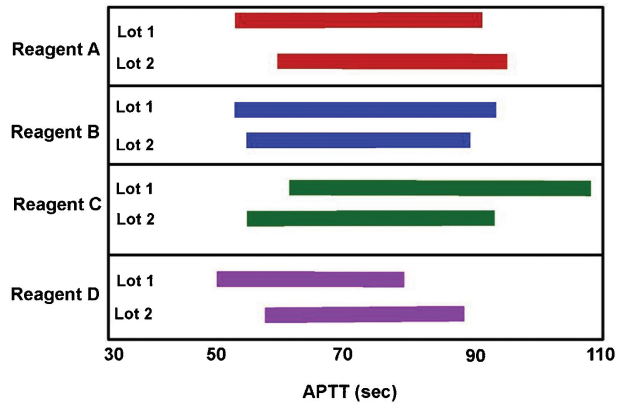

Fig. 3 Comparison of heparin therapeutic ranges for different lots of four different APTT reagents. APTT, activated partial thromboplastin time.

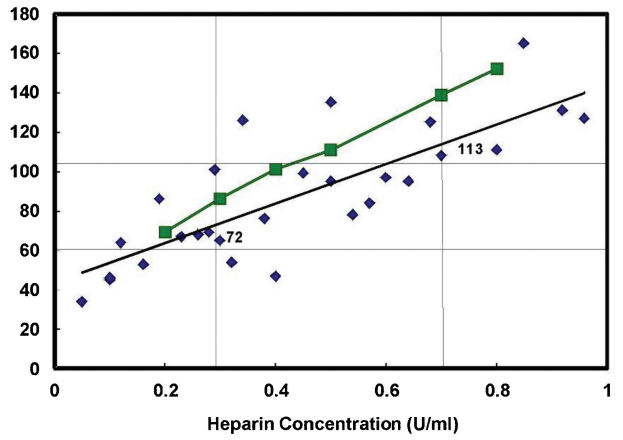

Fig. 4 Example of an in vitro spiked curve compared with HTR determined by antifactor Xa heparin assay. HTR, heparin therapeutic range.

averaged HRT does not differ by ± 10%, then it could be adapted across the network (E. Favaloro, written communication, January 2016). The observed differences have been attributed to preanalytical and analytical variables that occur in different hospitals.[19,23]

Characteristics of Samples Used for Heparin Therapeutic Range Determination Samples

A variety of factors may influence the accuracy of an ex vivo APTT HTR.[19,26,31] Based on published studies, the ex vivo method may be used to establish an accurate HTR determination by (1) using a minimum of 20 plasma samples, with (2) less than 10% from the same individual, and (3) less than 50% of samples with an international normalized ratio (INR) between 1.3 and 1.5.[19,26,31] Some of the newer anticoagulant drugs, such as dabigatran, rivaroxaban, or apixaban, may also affect the HTR as these drugs can prolong the APTT and samples containing these drugs should be avoided.[24,25] The optimum number and acceptable types of samples will ensure the accuracy and precision necessary for the HTR (►**Table 2**).

Spiked Curves

The in vitro or "spiked curve" method is not an accurate method to determine the true HTR.[29] The in vitro technique produces a statistically significant and clinically significant increase in the upper and lower limits of the APTT HTR and a wider range of the HTR (►**Fig. 4**).[29] On average, the in vitro method produces a lower limit that is increased by at least 10% and the upper limit increased by at least 17%, and a widening of the range by approximately 27%. More patient samples will be reported as underheparinized with the "spiked curve" method (►**Fig. 4**).[19,29]

Fresh versus Frozen Activated Partial Thromboplastin Time

Frozen samples may be used to determine the HTR if the appropriate protocol is followed.[17,18] As shown in ►**Fig. 5**, frozen samples with increasing platelet counts will reduce both the APTT value and the heparin concentration as measured by the antifactor Xa chromogenic assay.[17,18] This is attributed in part to the release of platelet factor 4 from the frozen platelets that have lysed with thawing.[17,18] If the APTT value of the frozen samples is compared with the results of the fresh samples, then the APTT HTR can be determined using frozen samples. In properly prepared samples, the APTT

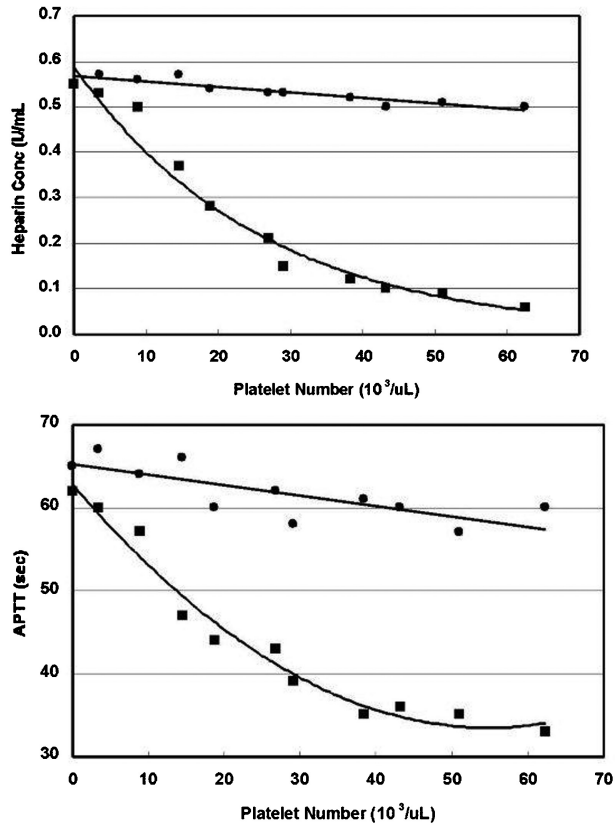

Fig. 5 Comparison of the heparin concentration (upper panel) and the APTT value (lower panel) remaining in fresh samples (solid circles) and frozen plasma (solid squares) with increasing platelet concentrations. APTT, activated partial thromboplastin time.

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of fresh samples compared with the APTT of a frozen sample, the two values are usually not significantly different (►**Fig. 6**). A small difference in the APTT between fresh and frozen samples is seen, but the resulting HTR is still accurate. Frozen samples may be used if the platelet count is < 10,000/µL and no significant difference between fresh and frozen results is found.[17,18]

Cumulative Summary Method

The cumulative summary method is considered by some to be an acceptable method for establishing the HTR when comparing different lots of the same reagent and not a different APTT reagent; however, very little information is available and evidence-based studies have not been reported.[10,19] The cumulative summary method is an APTT-based only evaluation in which the APTT values of heparinized patients are compared between the current lot of APTT reagent with the new lot of APTT reagent.[10,19] The new APTT reagent lot is considered to have the same HTR if the mean of the APTT using the new reagent is within 5 seconds of the old mean results.[10,19] This technique has not been investigated in-depth and evidence-based guidelines for implementation and acceptable criteria have not been developed. By providing only a vague set of rules, the cumulative summary method allows individual laboratories to extrapolate, as they deem appropriate.

Many problems arise when using the cumulative summary method to determine the HTR. This method uses the average of all the APTT values rather than values around the upper and lower limits of the HTR range. This can result in a variety of reagents with the same mean APTT value while the HTR itself may be drastically different (►**Fig. 7**). For example, an upper limit of 96 seconds and a lower limit of 72 seconds will give a mean value of 84 seconds, which is totally different from another lot with this same mean value but a calculated lower limit of 56 seconds and an upper limit of 112 seconds. By only looking at the mean, this method does not detect shifts in the upper and lower limits, the critical values of an HTR. Although the mean of the HTR may be within the acceptable limits of this method, the therapeutic ranges may be clinically different from one another. Therefore, the mean value of the heparinized patients is not a reliable indicator for the HTR as a whole, since changes in the upper and lower limits are not taken into account.

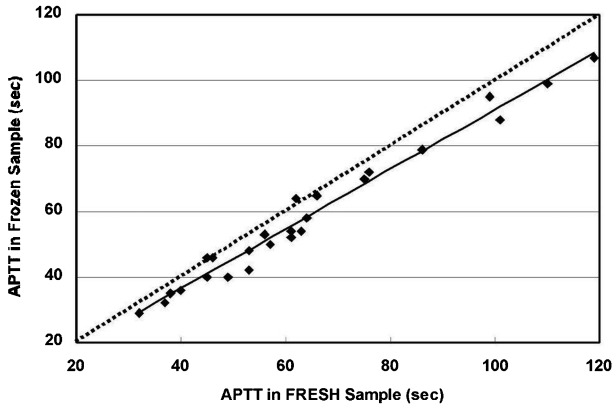

Fig. 6 Comparison of the APTT Values in properly prepared fresh and frozen plasma samples. APTT, activated partial thromboplastin time.

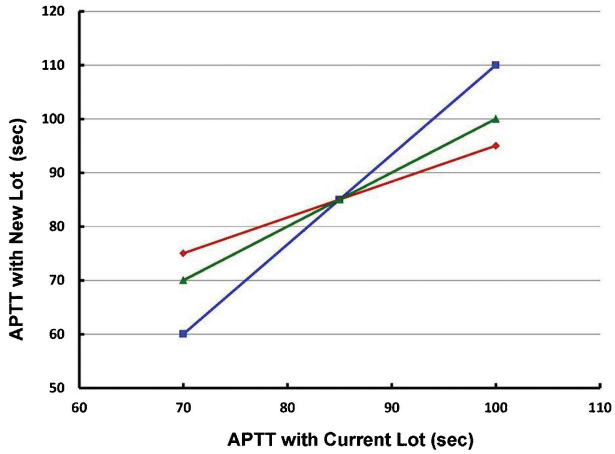

Fig. 7 Cumulative summary method. Hypothetical HRT with the same mean APTT value with the clinically significantly different lower and upper limits for the HTR. APTT, activated partial thromboplastin time; HTR, heparin therapeutic range.

Further, when the HTR is determined by the cumulative summary method in parallel with the ex vivo HTR method, the resulting HTR values can differ significantly (►**Table 3**). Although the mean HTR value remained within 5-second limit for 6 consecutive years using the cumulative summary method, the HTR as detected by the ex vivo method was somewhat different. These data indicate that the cumulative summary method is not a reliable technique to determine the HTR. It also calls into question the arbitrary 5-second difference limit to define the acceptability of the APTT reagent. There is no guideline as to how a laboratory should proceed if the mean values for multiple years are consistently above or below the mean. Drift is not taken into account by this method. There remain too many unanswered issues and concerns to make this method a viable means to determine the HTR.[10,19]

Recommendations and Conclusions

Although there is still no foolproof method to establish the APTT HTR, the following recommendations provide the most reliable protocols and methods for its determination (►**Table 4**).[10,19] If using the APTT to monitor UFH, the ex vivo method is the only valid method to determine the APTT-based HTR.[19]

A minimum of 20 samples are required for an accurate APTT HTR. If < 20 samples are used, there is the potential for clinically significant differences in the HTR. The HTR will not be affected if < 10% of the samples are from the same patient. The INR should be < 1.3, but if < 10% of the samples have an INR between 1.3 and 1.5, then no clinical difference in the HTR is found. Samples with an INR > 1.5 should not be used.[23,31]

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Table 3 Comparison of the cumulative summary method with the ex vivo method with the same instrument and reagent with successive years of different reagent lots

	Cum–sum	Cumulative drift	Determined ex vivo HTR
Reagent 1			
Year 1	64–91	0	64–91
Year 2	−2.2	−2.2	56–82
Year 3	−0.4	−2.6	63–89
Year 4	+3.1	+0.5	58–97
Reagent 2			
Year 1	48–91	0	48–91
Year 2	+4.2	+4.2	51–95
Year 3	+2.1	+6.3	57–101
Year 4	+1.6	+7.9	52–98
Year 5	+3.1	+11.0	55–98
Year 6	+0.4	+11.4	58–100

Abbreviations: Cum–sum, cumulative summary method; HTR, heparin therapeutic range.

Table 4 Acceptable and unacceptable parameters for determining the HTR

Parameters	
Acceptable	**Advantages**
> 20 heparinized plasma samples	20 samples and analysis usually provides acceptable outcomes However, preferably better to use 30–50 samples
< 10% of the same patient in HTR calculation	Individual patient samples does not unduly influence HTR values
Use sample with INR < 1.3	Warfarin does not unduly influence HTR values
Use frozen samples if comparison is made between fresh and frozen value	Allow for storage of heparin-containing samples if fresh samples difficult to obtain Remove significant outlier samples
Use samples with < 10,000 platelets/μL	No substantial effect of platelets (either fresh or frozen) if platelets are < 10,000/μL
Determine on main and back-up instrument	Determine average HTR range between both instruments, if substantial difference, repeat
Freezing samples for heparin assay	Platelet count must be < 10,000/μL
Unacceptable	**Disadvantages**
< 20 data points for HTR determination	Statistically significant difference and great variation in HTR
> 10% of the same patient in calculation	May cause shifting of HTR especially if only using 20 patient samples
Using samples with INR > 1.5	May shift the HTR to higher set of values
Use frozen samples without comparison with fresh values	May shift HTR to incorrect level
Sample (fresh or frozen) with > 10,000 platelets/μL for APTT or heparin level	May cause the HTR to be clinically significantly decreased
Determine in different hospital with same lot and instrument	Based on sample and laboratory differences, significant variation of HTR

Abbreviations: APTT, activated partial thromboplastin time; HTR, heparin therapeutic range; INR, international normalized ratio.
Note: The acceptable and unacceptable pre-analytical and analytical characteristics are listed in with comments on the advantages and disadvantages.

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Table 5 Options for determining HTR for small and moderate hospitals

APTT-based methods
Ex vivo comparison of heparin level with APTT
Use fresh samples from larger hospital for ex vivo method
Freeze samples for APTT and heparin levels (platelet count in plasma is critical) and should be $< 10{,}000/\mu L$
At multihospital networks, perform at > 2 facilities and if agree within 10%, accept for all hospitals in network
Non-APTT–based method
Direct assay of anti-FXa activity

Abbreviations: APTT, activated partial thromboplastin time; FXa, factor Xa; HTR, heparin therapeutic range.

Frozen samples may be used to determine the HTR if the APTT values are similar between the fresh and frozen samples. Frozen samples whose APTT values do not correlate with the fresh sample values must be removed from the calculation, otherwise a shift in the HTR may be seen. The use of frozen samples will allow small- or moderate-sized hospitals to determine an HTR by storing heparin-containing samples from previously heparinized patients. When freezing samples for APTT and heparin assays, platelet poor plasma ($< 10{,}000$ platelets/μL) must be used to prevent heparin neutralization.

Due to differences in laboratory procedures and sample collection, HTR ranges should not be shared among hospitals, even if the same reagent lot and instrument model are used.[23] They should be determined by each laboratory. However, in multihospital networks using the same APTT reagent lot and same instrument models may perform ex vivo HTR at more than two hospitals and if the HTR obtained at each evaluation laboratory does not vary by more than 10% then it might be adapted across the hospitals. The same HTR may be used on the same model of instrument in the same laboratory. When using two different instrument models (primary and backup) with the same detection method, the HTR should be determined on both instruments and HTR averaged for the two instrument ranges so the laboratory has a single range.[19,23] If they differ by $> 10\%$, another 20 samples (minimum) should be evaluated and if still different then the instruments should be checked.

A range provided by a manufacturer or range extracted from the literature is also unacceptable.[19,23] Differences among APTT reagents eliminate the use of a ratio of 1.5:2.5× control as a valid HTR.[19,23,32] In addition, an arbitrarily determined range, based on tradition, is also not valid as it has no statistical proof of accuracy. The "spiked curve" method is not an accurate method for determining the HTR.[19,23,32] It does not correlate with the ex vivo method and yields a clinically significantly higher HTR.[23]

The cumulative summary method is not recommended to validate the HTR as there is little evidence to support the accuracy of this method. There are countless unanswered questions for this protocol. Since published data on the cumulative summary method is minimal, this method has not been "evidence-based" evaluated, so its true utility to determine an accurate HTR is not known.

The laboratory has two choices for UFH monitoring (►**Table 5**). First, the ex vivo method compares the APTT value to a theoretical "average" heparin concentration based on statistical calculations.[10,19] In small- or moderate sized-hospitals with few heparinized patients, the ex vivo method can be used by obtaining fresh samples from a larger hospital to perform their own ex vivo method or they can over time freeze samples for APTT and heparin values and performs the ex vivo method for a new lot.[23] The second option is using a direct heparin assay (antifactor Xa activity), which does not rely on the APTT method. This method is gaining momentum as a more accurate and overall cost-effective method. The UFH concentration in the plasma should be between 0.3 and 0.7 IU/mL for full anticoagulation.[1,10,22,33]

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