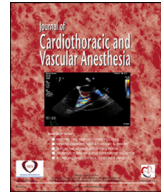


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Original Article

Anticoagulation Monitoring Strategies During Cardiopulmonary Bypass in Patients With Antiphospholipid Syndrome: A Systematic Review

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Objectives: Antiphospholipid syndrome (APS) is an autoimmune prothrombotic disorder that complicates anticoagulation during cardiovascular surgery requiring cardiopulmonary bypass (CPB). This systematic review aimed to characterize the anticoagulation monitoring strategies reported during CPB in patients with APS and to identify recurring limitations and clinical patterns rather than to assess comparative efficacy between management approaches.

Design: Systematic review of published clinical studies.

Setting: Hospital-based cardiovascular surgery and perioperative care settings, including single- and multi-institutional reports.

Participants: Patients with a confirmed diagnosis of APS who underwent cardiac or cardiovascular surgery using CPB with heparin anticoagulation.

Interventions: Intraoperative anticoagulation strategies during CPB, including activated clotting time (ACT)–based monitoring and adjunctive strategies such as heparin concentration monitoring (Hepcon), anti–factor Xa assays, and viscoelastic testing.

Measurements and Main Results: A Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020–compliant search of PubMed, Scopus, and the Cochrane Library identified 66 studies, of which 17 met the inclusion criteria. ACT monitoring was reported in 25 patients, Hepcon-guided heparin concentration monitoring in 25, and heparin-ACT titration in 1; most studies used multimodal monitoring approaches. Among 62 patients, 15 perioperative complications were reported, predominantly from a single cohort study that contributed the majority of quantitative outcome data. The aggregated data illustrated the heterogeneous use of monitoring strategies and recurrent concerns regarding the reliability of ACT alone.

Conclusions: Anticoagulation monitoring during CPB in patients with APS remains heterogeneous and insufficiently standardized. The available evidence does not permit conclusions regarding comparative efficacy among monitoring strategies. Instead, this review highlights recurrent limitations of ACT-based monitoring and the heterogeneous use of adjunctive modalities in reported cases, providing a conceptual framework to inform future prospective investigations.

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Key Words: antiphospholipid syndrome; cardiopulmonary bypass; anticoagulation management; activated clotting time; heparin concentration monitoring; anti–factor Xa activity

ANTIPHOSPHOLIPID SYNDROME (APS) IS an autoimmune disorder characterized by the persistent presence of antiphospholipid antibodies and is clinically associated with arterial or venous thrombosis or pregnancy loss.¹ The underlying pathophysiology reflects a hypercoagulable state driven by

endothelial dysfunction, complement activation, and platelet activation.^{1,2} In addition to the 2006 Sydney classification criteria,³ the 2023 American College of Rheumatology (ACR)–European Alliance of Associations for Rheumatology (EULAR) classification criteria were introduced as a

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refinement of the existing framework.⁴ While retaining anti-cardiolipin (aCL) antibodies, anti- β 2-glycoprotein I (anti- β 2GPI) antibodies, and lupus anticoagulant (LAC) as core laboratory components, the 2023 criteria incorporate entry criteria and weighted clinical and laboratory domains within a structured point-based system. Vitamin K antagonists, particularly warfarin, remain the standard of care for patients with APS. Heparin is used in the perioperative setting and in patients with contraindications to oral anticoagulants. In contrast, the efficacy and safety of direct oral anticoagulants in APS remain uncertain, and current consensus guidelines discourage their use in high-risk patients.^{1,5}

Cardiovascular involvement frequently occurs in patients with APS, particularly those with concomitant systemic lupus erythematosus. Valvular abnormalities, including leaflet thickening and vegetations, are frequently observed along with coronary artery disease and aortic pathology.⁶ Moreover, antiphospholipid antibodies are associated with an increased risk of valvular disease in systemic lupus erythematosus.⁷ These lesions often necessitate surgical intervention; therefore, cardiac surgery in APS patients is not a rare scenario.⁸ However, these patients face significant risks of both thrombosis and bleeding during the perioperative period, and morbidity and mortality rates are reported to be higher than those of patients without APS.⁹ Although APS is primarily recognized as a prothrombotic disorder, perioperative hemorrhagic complications also have been described in cardiac surgery patients, particularly in the context of anticoagulation management and cardiopulmonary bypass (CPB).⁸

Anticoagulation during CPB generally involves the administration of heparin, followed by protamine reversal. In routine practice, the anticoagulant effect of heparin is assessed by activated clotting time (ACT), typically targeted to be ≥ 480 seconds.¹⁰ In patients with APS, the presence of LAC can cause marked prolongation or instability of conventional monitoring indices such as ACT. This occurs because LAC inhibits the *in vitro* assembly of the prothrombinase complex on phospholipids, leading to prolonged ACT and activated partial thromboplastin time.^{5,11} Consequently, alternative monitoring strategies—including heparin concentration measurement (Hepcon HMS; Medtronic),¹² anti-Xa assay,⁵ and point-of-care viscoelastic testing (thromboelastography [TEG], rotational thromboelastometry [ROTEM])¹³—have been adopted in clinical practice. Current professional society guidelines on anticoagulation during CPB do not specify an optimal monitoring approach for patients with APS.¹⁰ A meta-analysis of heparin and protamine dosing strategies in CPB demonstrated that blood concentration-based management may reduce bleeding compared with weight-based dosing,¹⁴ suggesting that monitoring strategies can directly influence clinical outcomes. However, robust APS-specific data are lacking, and no consensus has been reached regarding the most reliable monitoring modality.

The existing literature underscores this gap. Classic case series and early reviews have emphasized the high perioperative risk in patients undergoing cardiac surgery.^{15,16} Recent studies have noted that the current evidence remains limited,

consisting mainly of small case series and isolated reports.^{17,18} This persistent lack of evidence highlights the need for a systematic synthesis of the available literature to provide a strong foundation for consistent clinical decision making. Accordingly, this systematic review aimed to characterize the anticoagulation monitoring strategies reported during CPB in patients with APS undergoing cardiac surgery and to descriptively synthesize their practical limitations and clinical patterns rather than to determine comparative management efficacy.

Methods

Search Strategy

The authors systematically searched PubMed, Scopus, and the Cochrane Library from inception through September 2025. The search strategy combined terms related to APS and CPB with those related to anticoagulation monitoring methods, including ACT, Hepcon, anti-Xa assay, TEG, and ROTEM. The complete search strategies for all databases are presented in [Supplementary Table S1](#). This systematic review was not prospectively registered in Prospero. Given the exploratory nature of the topic and the predominance of case-based literature, the review was conducted as a descriptive systematic synthesis.

Eligibility Criteria

The authors predefined eligibility criteria based on patient population, surgical exposure, anticoagulation monitoring method, outcomes, and study design. Eligible studies included adult patients (≥ 18 years) with a clearly stated diagnosis of APS, irrespective of the classification criteria applied. An APS diagnosis was accepted as reported by the original authors, even when insufficient information was available to verify adherence to classification criteria. Surgical exposure was defined as cardiovascular surgery performed with CPB, without restrictions on procedure type, including valve surgery, coronary artery bypass grafting, aortic surgery, or combined surgical procedures. Intraoperative anticoagulation during CPB was required to be performed with heparin. Eligible studies had to provide detailed descriptions of intraoperative anticoagulation monitoring methods, including but not limited to ACT, heparin-ACT titration, Hepcon system, anti-Xa assay, or viscoelastic testing methods such as TEG or ROTEM. Studies also needed to report at least one perioperative clinical outcome, including thrombotic events (eg, CPB circuit clotting, myocardial infarction, stroke, or graft occlusion), bleeding events (eg, blood loss, transfusion requirement, or re-exploration for hemostasis), other thrombosis- or bleeding-related complications, or perioperative mortality. When detailed information on complications was unavailable, studies were still included if they clearly reported survival status and hospital discharge data. Eligible study designs included case reports, case series, observational studies (prospective or retrospective), and randomized controlled trials. Exclusion criteria included studies in which the APS diagnosis was not explicitly

stated or was insufficiently described, procedures performed without CPB, procedures performed with anticoagulants other than heparin during CPB, absence of intraoperative anticoagulation monitoring, or absence of relevant clinical outcomes. Basic science studies (in vitro or animal models) and non-original publications, including reviews, editorials, and conference abstracts, were excluded.

Study Selection

Two reviewers independently screened titles, abstracts, and full texts, followed by a detailed assessment of potentially eligible articles. Discrepancies were resolved through consensus.

Data Extraction

The authors extracted the following information from each included study: (1) study design, year, and country; (2) patient demographic characteristics and APS diagnostic certainty; (3) antiphospholipid antibody profile, including LAC status (positive, negative, or unknown), triple positivity (positive for LAC, aCL antibodies, and anti- β 2GPI antibodies), and the presence or absence of catastrophic APS; (4) type of surgery and CPB duration; (5) monitoring devices and methods used; (6) observed ACT; and (7) outcomes including intraoperative anticoagulation results, thrombotic and bleeding complications, transfusion requirements, reoperation, and mortality. Diagnostic certainty of APS was classified into three categories: (1) definite (studies that explicitly reported that the cases met the established APS diagnostic criteria); (2) prior/history (studies that only mentioned a history or prior diagnosis of APS); and (3) unspecified (studies that lacked sufficient information to confirm APS but described the cases as APS in the title, abstract, or discussion). Monitoring methods were grouped a priori into the following categories for analysis: (1) ACT, including point-of-care ACT devices; (2) Hepcon system; (3) heparin-ACT titration; (4) anti-Xa assay; and (5) viscoelastic testing (including TEG, ROTEM, and Sonoclot [Sienco]). For data extraction, the number of patients monitored exclusively with each device as a standalone strategy was recorded. When multiple monitoring devices were used concurrently, each specific combination was extracted separately and summarized in a dedicated table. This approach enabled the evaluation of both the independent use of each modality and the patterns of multimodal monitoring strategies. Baseline ACT values were extracted as reported. When an activator type (eg, celite or kaolin) was specified, values were recorded separately and were not pooled across activators because of known inter-assay variability. In cases in which the Hepcon system was used and ACT values were reported without device specifications, the authors assumed that the ACT was measured using Hepcon. These patients were not included in the overall ACT group. Heparin-ACT titration data, reported without the use of the Hepcon system, were analyzed separately from the overall ACT data because of their distinct methodologic bases. Although viscoelastic testing modalities were extracted separately, they were combined into a single

“viscoelastic” category because of the limited number of reports for each device.

Results

Search Results

The initial search identified 66 unique records. After title and abstract screening, 30 studies were selected for full-text review. Finally, 17 articles met the eligibility criteria (Fig 1).

Study Characteristics

The characteristics of the included studies are summarized in Table 1. A total of 17 studies were included,^{19–35} consisting of 14 case reports, 2 case series comprising 5 patients in total, and 1 retrospective cohort study involving 43 patients. Among the 62 patients, 25 (40%) were male and 37 (60%) were female. Among patients included in the case reports and case series (n = 17), the mean age was 48.6 years (range, 25–80 years). One case series (n = 2) included patients in their 50s, whereas the retrospective cohort study (n = 43) did not report age data. Regarding the diagnosis of APS, 45 patients had a confirmed diagnosis, 15 had a history of APS, and 2 had an unspecified diagnosis. LAC positivity was frequently reported. However, triple positivity and detailed antibody profiles were inconsistently documented, and several studies did not specify antibody status beyond historical diagnosis. Catastrophic APS was rarely represented among the included cases. Monitoring methods were reported for all included cases (Table 2). ACT was performed in 25 patients, Hepcon in 25, and heparin-ACT titration in 1. Most studies combined multiple monitoring methods. The reported combinations were as follows: ACT and Hepcon (n = 2); ACT and viscoelastic (n = 2); heparin-ACT titration and viscoelastic (n = 3); ACT and anti-Xa (n = 1); Hepcon and viscoelastic (n = 1); ACT, Hepcon, and anti-Xa (n = 1); and ACT, viscoelastic, and anti-Xa (n = 1). The distribution of studies using each monitoring method is shown in Figures 2 and 3. Baseline ACT had a median value of approximately 155 seconds (range, 101–235 seconds).

Fifteen perioperative complications were reported across 62 patients. Among these, 12 occurred in the retrospective cohort study and 3 occurred in case reports or case series. Overall, thrombotic events occurred in 4 of 57 patients (7.0%), bleeding events occurred in 8 of 58 patients (13.8%), and cerebrovascular accidents (CVAs) (ischemic v hemorrhagic, unspecified) occurred in 3 of 43 patients (7.0%). One perioperative death was reported. Additional details, including surgical details, anticoagulation management, specific clinical outcomes, and conclusions, are provided in Supplementary Tables S2 to S4.

In the cohort study, among patients monitored with ACT alone (n = 23), thrombotic events occurred in 2 (8.7%), bleeding events in 3 (13.0%), and CVAs in 2 (8.7%). In the Hepcon group (n = 20), thrombotic events occurred in 2 (10%), bleeding events in 2 (10%), and CVAs in 1 (5%).

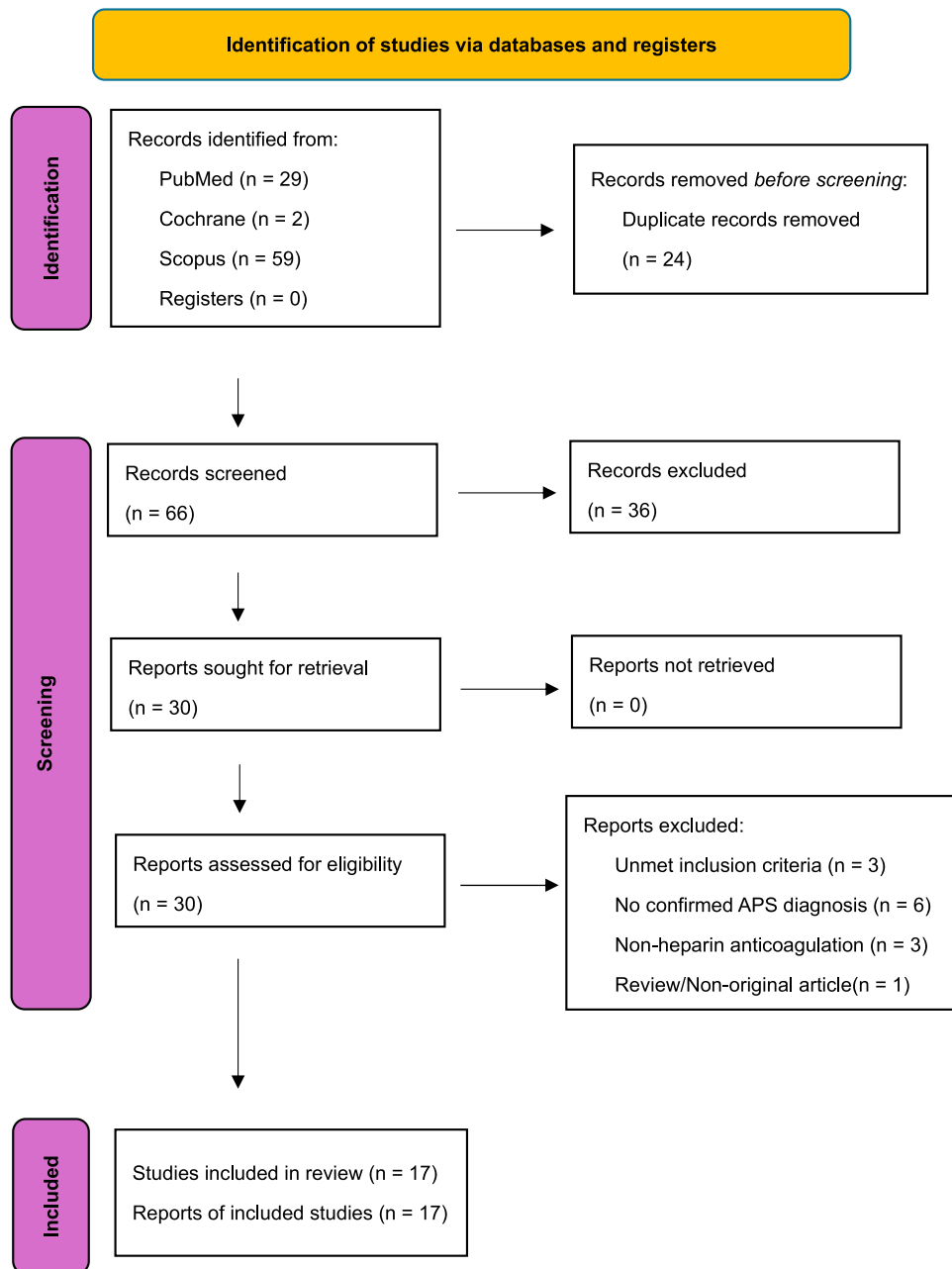


Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram. APS, antiphospholipid syndrome.

Reported event counts reflect heterogeneous denominators derived from individual case reports and small case series and should not be interpreted as incidence rates or comparative outcomes.

Risk-of-Bias Assessment

All included studies—case reports, case series, and observational studies—were appraised using the Joanna Briggs Institute critical appraisal checklist. Each study type (case reports, case series, and cohort studies) was evaluated using a 7-item checklist. The results of the risk-of-bias assessment are presented in [Supplementary Figures S1](#) and [S2](#). The assessment

reflected the predominantly case-based nature of the included literature. Most reports were single case reports or small case series, limiting the assessment of selection methods and outcome ascertainment. While reporting of clinical details was generally adequate (Q2–Q4), several studies had unclear risk regarding case selection processes and completeness of outcome reporting. Only one retrospective cohort study provided structured comparative data, but even this study was subject to potential selection bias and limited generalizability. Overall, the evidence base was characterized by small sample sizes, retrospective designs, and heterogeneity in reporting, which restrict the strength of inference that can be drawn from the available data.

Table 1
Characteristics of Included Studies

Authors	Year	Country	Study Design	N	Age, y	Sex	Diagnostic Certainty of APS	LAC Status	Triple Positivity*	Catastrophic APS	Monitoring Methods	Baseline ACT (s)	Outcome†
Lennon et al. ¹⁹	2003	Australia	Case report	1	33	F	Unspecified	Unknown	Unknown	No	ACT, anti-Xa	147	NR
Lango et al. ²⁰	2004	Poland	Case report	1	42	F	Prior/history	Yes	Unknown	No	Hepcon, ACT, anti-Xa	147 (celite), 193 (kaolin)	NR
Ishida et al. ²	2015	Japan	Case report	1	38	M	Prior/history	Yes	Yes	No	Hepcon	144 (celite), 235 (kaolin)	1
Lee et al. ²²	2015	Singapore	Case report	1	59	F	Prior/history	Yes	Yes	Yes	ROTEM, ACT	158	0
Mishra et al. ²³	2016	United Kingdom	Case series	3	34	M	Prior/history	Yes	Unknown	No	Hepcon	NR	1
					25	M	Prior/history	Yes	Unknown	No	Hepcon	NR	0
					52	F	Prior/history	Unknown	Unknown	No	Hepcon	NR	1
Nakajima et al. ²⁴	2017	Japan	Case report	1	43	F	Prior/history	Yes	Unknown	No	Heparin-ACT titration, Sonoclot	NR	0
Samejima et al. ²⁵	2017	Japan	Case report	1	72	F	Prior/history	Yes	Unknown	No	Hepcon, ROTEM	NR	0
Seki et al. ²⁶	2018	Japan	Case series	2	50s	F	Prior/history	Yes	No	No	ACT	202	0
					50s	F	Prior/history	Yes	No	No	ACT	152	0
Nakajima et al. ²⁷	2020	Japan	Case report	1	45	F	Prior/history	Yes	Unknown	No	Heparin-ACT titration, TEG	NR	0
Ural and Edelson ²⁸	2021	United States	Case report	1	80	M	Prior/history	Yes	Unknown	No	Hepcon	180	0
Yoshinaga et al. ²⁹	2021	Japan	Case report	1	71	F	Prior/history	Yes	No	No	Hepcon, ACT	101	0
Malviya et al. ³⁰	2022	United States	Case report	1	30	F	Unspecified	Yes	Yes	No	ACT, TEG	183	0
Katunarcic and Boettcher ³¹	2024	United States	Case report	1	40	F	Definite (2023 ACR/EULAR)	Yes	Yes	No	Hepcon, ACT	158	0
Kimishima et al. ³²	2024	Japan	Case report	1	63	F	Definite (2006 Sydney)	Yes	Yes	No	Heparin-ACT titration	165	0
Michael et al. ³³	2024	United States	Retrospective Cohort	20 23	NR NR	8 M, 12 F 12 M, 11 F	Definite (2006 Sydney)	100% 78%	55% 9%	No	Hepcon ACT	153 (median) 140 (median)	5 7
Park et al. ³⁴	2024	United States	Case report	1	32	F	Prior/history	Unknown	Unknown	Yes	TEG, ACT, anti-Xa	103	NR
Sasaki et al. ³⁵	2025	Japan	Case report	1	68	M	Prior/history	Yes	Unknown	No	TEG, heparin-ACT titration	135	NR

NOTE. Diagnostic certainty of APS was classified into three categories: (1) definite (criteria) (studies that explicitly reported that the cases met the established APS diagnostic criteria); (2) prior/history (studies that only mentioned a history or prior diagnosis of APS); and (3) unspecified (studies that lacked sufficient information to confirm an APS diagnosis but nonetheless described the cases as having APS in the title, abstract, or discussion).

Abbreviations: ACR, American College of Rheumatology; ACT(s), activated clotting time (seconds); APS, antiphospholipid syndrome; EULAR, European Alliance of Associations for Rheumatology; F, female; LAC, lupus anticoagulant; M, male; NR, not reported; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

* Positivity for anticardiolipin antibody, anti- β 2-glycoprotein I antibody, and LAC.

† Thrombotic or bleeding events.

Table 2
Outcomes Stratified by Monitoring Method

Monitoring	Studies	Patients	Thrombotic Event	Bleeding Event	CVA	Mortality
ACT	2	25	2 of 25 (8.0%)	3 of 25 (12%)	2 of 23 (8.7%)	0 of 2
Heparin-ACT titration	1	1	0 of 1 (0%)	0 of 1 (0%)	0 of 0	0 of 1
Hepcon	4	25	2 of 24 (8.3%)	5 of 25 (20%)	1 of 20 (5%)	0 of 5
ACT + Hepcon	2	2	0 of 2 (0%)	0 of 2 (0%)	0 of 0	0 of 2
ACT + viscoelastic	2	2	0 of 2 (0%)	0 of 2 (0%)	0 of 0	1 of 2
Heparin-ACT titration + viscoelastic	3	3	0 of 2 (0%)	0 of 2 (0%)	0 of 0	0 of 3
ACT + anti-Xa	1	1	0 of 0	0 of 0	0 of 0	0 of 1
Hepcon + viscoelastic	1	1	0 of 1 (0%)	0 of 1 (0%)	0 of 0	0 of 1
ACT + Hepcon + anti-Xa	1	1	0 of 0	0 of 0	0 of 0	0 of 1
ACT + viscoelastic + anti-Xa	1	1	0 of 0	0 of 0	0 of 0	0 of 1
Total	18	62	4 of 57 (7.0%)	8 of 58 (13.8%)	3 of 43 (7.0%)	1 of 19 (5.3%)

NOTE. Outcomes are shown as n of N (events/reports). CVAs have been reported only in cohort studies. In cases in which the Hepcon system was used and ACT values were reported without the specifications of the device, the authors assumed that ACT was measured by Hepcon and not included in the ACT count. Heparin-ACT titration data collected without the use of the Hepcon system were not included in the ACT count. Event counts are based on heterogeneous denominators derived from individual case reports and small case series. These values do not represent incidence rates and should not be interpreted as comparative outcomes. Abbreviation: ACT, activated clotting time; CVA, cerebrovascular accident.

Discussion

This review systematically identified and summarized intraoperative anticoagulation monitoring strategies and clinical outcomes in patients with APS who underwent cardiac surgery using CPB and heparin for anticoagulation. The key findings are as follows: First, most published reports were limited to case reports and small case series. Second, diverse monitoring modalities, including ACT, Hepcon, anti-Xa, and viscoelastic testing, have been described; however, standardized protocols, target values, and usage criteria remain lacking. Third, systematic evaluation of clinical outcomes was limited. Case reports and series rarely detail postoperative outcomes, raising

concerns about publication bias, particularly the selective reporting of uncomplicated cases. The only study reporting quantitative outcomes was a retrospective cohort analysis that found no significant differences between ACT alone and Hepcon monitoring; however, the single-center and retrospective design limited its external validity.

A narrative review embedded within a case report by Katunaric and Boettcher (2024)¹⁹ previously summarized anticoagulation management during CPB in patients with APS; however, methodologic inconsistencies—such as the inclusion of cases lacking a definitive APS diagnosis—limited its methodologic rigor. In contrast, this review applied predefined inclusion criteria and incorporated newly

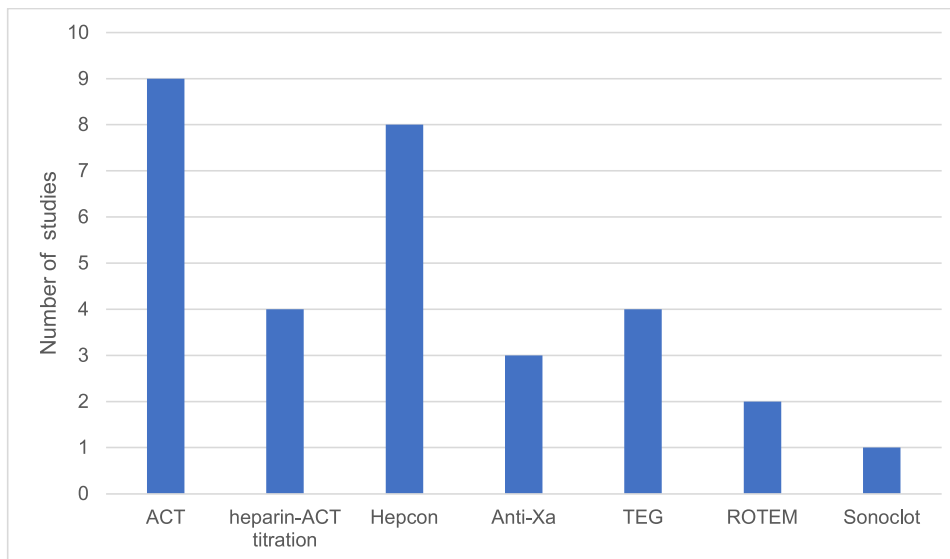


Fig 2. Monitoring methods distribution: any use. ACT, activated clotting time; TEG, thromboelastography; ROTEM, rotational thromboelastometry.

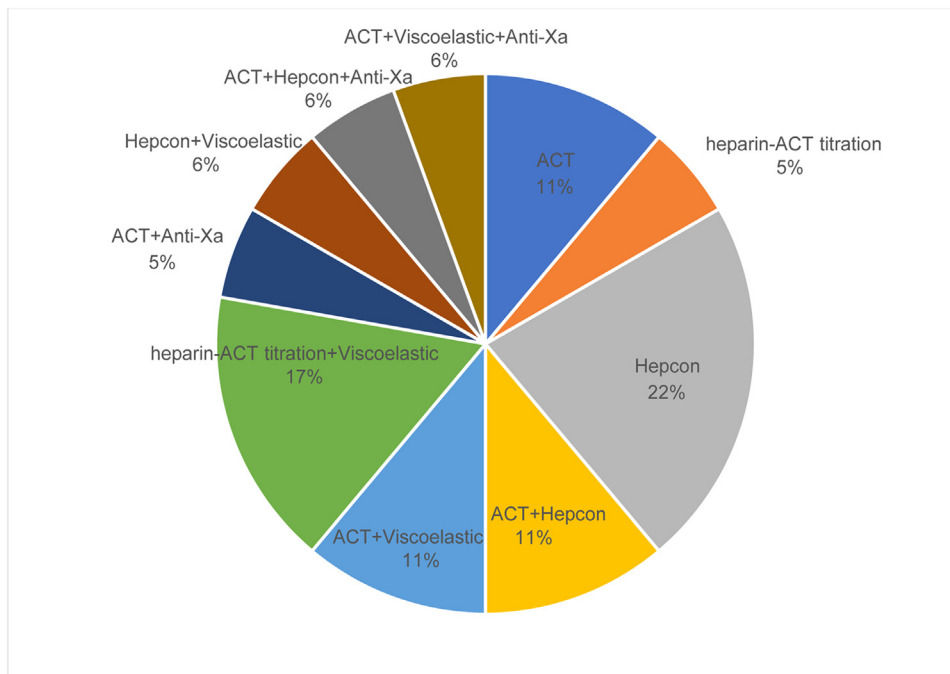


Fig 3. Monitoring methods distribution: standalone or combined strategies. ACT, activated clotting time; TEG, thromboelastography; ROTEM, rotational thromboelastometry.

published reports, including a recent retrospective cohort study ($n = 43$).²⁰ Compared with prior reviews, this study provides a more systematic and up-to-date synthesis of the currently available evidence.

The normal range of ACT is approximately 80 to 120 seconds, although it depends on the activator (celite, kaolin, etc) and the device used.³⁶ In the current cohort of patients with APS, median baseline ACT was approximately 155 seconds, which may be considered modestly prolonged relative to the conventional reference range. Moreover, even when baseline ACT values fall within the reference range, the presence of LAC may limit the reliability of ACT measurements, emphasizing the need for alternative or adjunctive monitoring modalities. It is important to note that such interference is not unique to ACT and also may affect other assay-dependent strategies, including heparin concentration–based systems, thereby complicating interpretation across monitoring modalities.

The limited reliability of ACT in patients with APS cannot be attributed solely to the interference of LAC in phospholipid-dependent coagulation reactions. In practice, factors such as prior heparin exposure or consumptive states may reduce antithrombin activity, potentially attenuating the anticoagulant effect of heparin and limiting adequate ACT prolongation.^{37,38} Moreover, the degree of coagulopathy may vary according to the type and profile of the antiphospholipid antibodies.³ Notably, triple-positive patients—those positive for aCL antibodies, anti- β 2GPI antibodies, and LAC—are reported to have the highest thrombotic risk, further complicating intraoperative anticoagulation management.³⁹ Therefore, in patients with APS, background factors such as antithrombin activity and

antibody profile should be considered when interpreting monitoring results and planning anticoagulation strategies.

Because most of the published evidence comprised single case reports or small series and only a few structured comparative studies were available, formal statistical assessment of differences between monitoring devices was not feasible. Nevertheless, the authors descriptively analyzed the available data to identify potential patterns relevant to clinical practice. However, outcome reporting was largely confined to a single retrospective cohort study of ACT versus Hepcon, whereas case reports and small series rarely included detailed descriptions of postoperative complications. This imbalance in the evidence base, combined with reporting bias, has resulted in disproportionate representation of outcome data derived from ACT and Hepcon, thereby precluding meaningful comparisons across the full range of monitoring modalities. Nevertheless, the available evidence highlights the heterogeneous use of alternative or adjunctive monitoring modalities in reported cases, especially when ACT measurements were considered unreliable. The single cohort study did not demonstrate significant reported outcome differences between ACT and Hepcon, whereas case reports highlighted a wide variety of strategies, emphasizing that surgery can be performed safely with careful anticoagulation management. Monitoring methods can be briefly summarized as follows: ACT (Hemochron and related devices) measures the coagulation time of whole blood mixed with an activator, such as celite or kaolin. ACT remains the most widely available, rapid, simple, and inexpensive test; however, its accuracy may be affected by LAC, hypothermia, hemodilution, and other factors.¹⁰ Heparin-ACT titration

Table 3
Characteristics of Monitoring Methods

	Principle	Advantages	Limitations
ACT	Clotting time after activation	Rapid; inexpensive; widely available	Affected by lupus anticoagulant; poor reliability
Heparin-ACT titration	Heparin dose-response curve	Inexpensive; widely available; more quantitative management than ACT only	Requires more time than Hepcon system; inability to optimize protamine reversal
Hepcon system	Direct heparin concentration via protamine titration	Rapid; less affected by lupus anticoagulant; enables optimized protamine reversal	Requires specific device; expensive
Anti-Xa	Plasma heparin activity against factor Xa	Not affected by lupus anticoagulant; high-reliability laboratory gold standard for measuring heparin activity	Delayed turnaround (tens of minutes)
Viscoelastic	Dynamics during clot formation	Rapid; provides global coagulation profile	Not specified in heparin monitoring

enables estimation of the heparin dose-response relationship and provides more quantitative management than ACT alone; however, it is manual, less standardized, and slower than Hepcon.²⁵⁻²⁷ Furthermore, when ACT measurements are affected by LAC, determining the protamine dose based solely on ACT is unreliable. The Hepcon device integrates ACT measurement with heparin/protamine titration and provides a rapid estimation of blood heparin concentration and an optimized protamine dose with less susceptibility to LAC.^{40,41} Despite these advantages, it remains equipment dependent and expensive. The anti-Xa assay is considered the gold standard for measuring heparin activity independent of LAC^{5,10}; however, it is time-consuming, equipment dependent, and labor intensive. Viscoelastic testing (TEG and ROTEM) provides an assessment of coagulation, including fibrinogen, platelets, and fibrinolysis, but it is not specific for heparin management.¹³ Park et al.³⁰ combined ACT, anti-Xa, and TEG in their monitoring approach. ACT and anti-Xa levels were measured before and after heparin and protamine administration, whereas TEG was used when coagulopathy was detected during chest wall closure because anti-Xa results required 35 minutes. This illustrates the importance of tailoring monitoring strategies according to the characteristics and limitations of each modality. Table 3 summarizes the advantages, limitations, and practical considerations of each monitoring device in patients with APS undergoing CPB. Building on these considerations, the authors propose a pragmatic anticoagulation monitoring algorithm for APS patients undergoing CPB (Fig 4). Rather than advocating the superiority of any single monitoring modality, this algorithm is intended to integrate the complementary strengths of available tools while acknowledging their inherent limitations. Accordingly, the proposed algorithm should be interpreted as a conceptual, hypothesis-generating framework derived from recurrent patterns in the literature rather than as a recommendation or evidence-based protocol. Its purpose is to provide a structured approach to decision making in a high-risk population in which standardized guidance remains unavailable. Future efforts should therefore focus on refining anticoagulation protocols tailored to the unique characteristics

of patients with APS and the intraoperative CPB environment. The establishment of such strategies will require prospective registry-based studies and larger systematic evaluations that can better account for heterogeneity in patient profiles, monitoring approaches, and perioperative management.

Limitations

This study has some limitations. First, the available evidence consisted predominantly of case reports and small case series, resulting in potential publication bias and methodologic heterogeneity. Outcome reporting was inconsistent, and denominators varied across studies, limiting interpretability and precluding reliable estimation of event rates or formal statistical comparisons between monitoring strategies. Second, diagnostic certainty of APS was variably documented in some cases, and the phenotypic characterization of APS was inconsistently reported. While LAC positivity was frequently documented, triple positivity and detailed antibody profiles were often not specified, and catastrophic APS was rarely represented. This incomplete and heterogeneous reporting limits the ability to explore whether specific APS subtypes influence anticoagulation monitoring reliability or perioperative outcomes. Third, substantial heterogeneity in the monitoring protocols, devices, and reporting standards precluded direct comparisons across studies. Finally, despite a comprehensive search, the possibility of missed or unpublished cases cannot be excluded.

A key strength of this review was that it systematically aggregated scattered case reports and series, providing a clearer overview of the diversity of anticoagulation monitoring approaches used in patients with APS undergoing CPB. By identifying structural gaps in the evidence base, including the absence of prospective comparative studies, inconsistent phenotypic characterization, heterogeneous outcome reporting, and variability in monitoring protocols, this review may help inform more standardized reporting and future prospective investigations in this high-risk population.

Conceptual framework for anticoagulation monitoring during CPB in APS

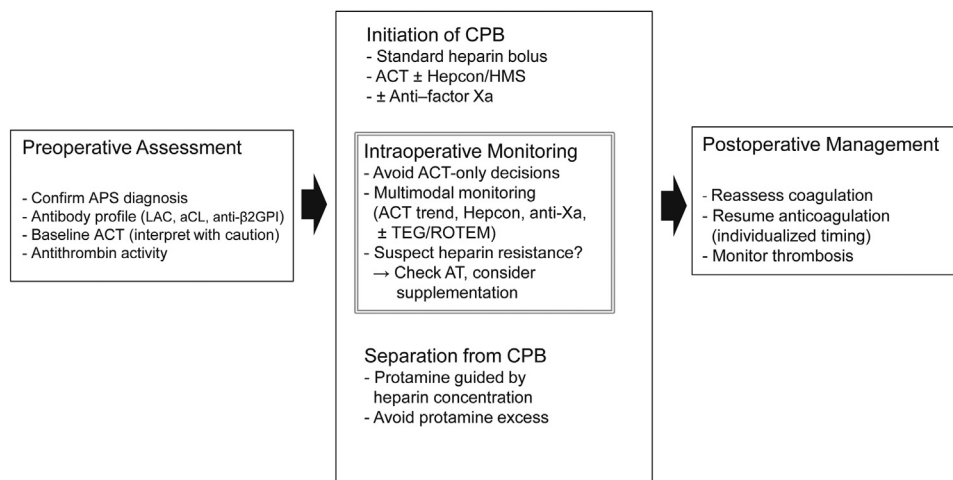


Fig 4. Conceptual framework for anticoagulation monitoring during cardiopulmonary bypass (CPB) in antiphospholipid syndrome (APS), derived from patterns observed in published case-based literature. During CPB in patients with APS, interpretation of monitoring results may be complicated by lupus anticoagulant (LAC)-related assay interference and heterogeneous patient characteristics. The framework summarizes clinical scenarios in which adjunctive monitoring modalities were considered, including unexplained activated clotting time (ACT) prolongation, discordance between ACT values and the intraoperative clinical context, known LAC positivity, or suspected heparin resistance. In such situations, alternative assessments—such as heparin concentration-based systems, anti-factor Xa measurement, or viscoelastic testing—were described to aid interpretation of anticoagulation status. In terms of operational reference targets (pragmatic CPB ranges), when heparin concentration-based monitoring is used (eg, Hepcon), commonly reported CPB practice targets whole-blood heparin concentrations of approximately 3 to 4 IU/mL.⁴² When anti-factor Xa monitoring is used, targets for full CPB anticoagulation are not standardized and typically require assay dilution and institution-specific calibration for the CPB range. As an example from the cardiac surgery literature, an anti-factor Xa activity around approximately 1.1 IU/mL has been reported to correspond to ACT > 400 seconds during extracorporeal circulation.⁴³ These numeric values are provided as pragmatic reference ranges from general CPB practice and should be applied in conjunction with institutional protocols and clinical context given that APS-specific optimal targets remain undefined. This framework is intended as a conceptual and hypothesis-generating synthesis rather than a prescriptive protocol. It does not imply comparative superiority among modalities but aims to support providing structured clinical reasoning in a setting in which standardized evidence remains limited. aCL, anticardiolipin; anti-β2GPI, anti-β2-glycoprotein I; AT, antithrombin; HMS, Hemostasis Management System; TEG, thromboelastography; ROTEM, rotational thromboelastometry.

Conclusions

This review systematically identified and synthesized the existing literature on anticoagulation monitoring during CPB in patients with APS undergoing cardiac surgery. Current evidence remains predominantly based on case reports, and no standardized monitoring approach has been established. Although a wide range of monitoring modalities and combination strategies have been reported, substantial heterogeneity precludes meaningful comparisons or conclusions regarding comparative efficacy. These findings highlight the complexity of anticoagulation monitoring in this population and provide a descriptive, hypothesis-generating framework to guide future prospective investigations.

Declaration of competing interest

The authors declare that they have no competing interests.

CRediT authorship contribution statement

Shotaro Yoshida: Writing – original draft, Investigation, Formal analysis, Data curation. **Osamu Ishida:** Writing –

review & editing, Methodology, Conceptualization. **Koji Tsutsumi:** Supervision.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT (GPT-5.2; OpenAI) in order to improve the English language and readability of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1053/j.jvca.2026.03.026](https://doi.org/10.1053/j.jvca.2026.03.026).

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