UFH Monitoring in ECMO and Cardiac Surgery: The Search for a Valid Reference Standard

Summary of a Perspective article | Frontiers in Medicine 2026;13:1818646 | Weber CF, Zacharowski K, Calatzis A, Lindner ML

Why this paper matters to Haemoview

This Perspective article — co-authored by Andreas Calatzis, inventor of ClotPro® — delivers a landmark challenge to conventional UFH monitoring in the two clinical settings where ClotPro® and Multiclot® are most commonly deployed: cardiac surgery with cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO). The authors argue that no universally validated reference assay exists for UFH in these settings, that anti-Xa assays are being used as if validated when they are not, and that the entire field requires conceptual re-evaluation. Published in Frontiers in Medicine in May 2026, it also directly cites a 2026 prospective study comparing ClotPro® IN/HI-test against aPTT and anti-Xa in critically ill patients.

Study at a glance

Item	Detail
Article type	Perspective (expert opinion/analysis), open access CC BY
Authors	Weber CF, Zacharowski K, Calatzis A*, Lindner ML (*ClotPro inventor, LMU Munich)
Journal	Frontiers in Medicine 2026;13:1818646. DOI: 10.3389/fmed.2026.1818646
Clinical scope	Cardiac surgery with CPB, ECMO, ICU heparin therapy
Core argument	Anti-Xa assays have never been formally validated as a reference standard in CPB or ECMO. Using an unvalidated assay to calibrate other tests creates a methodological paradox that undermines the entire evidence base for current UFH monitoring targets.
ClotPro link	ClotPro IN-test is explicitly named in the paper as a VET assay used for UFH monitoring; a 2026 ClotPro prospective ICU study (Mirus et al., BMC Anaesthesiology) is cited as key evidence.

The methodological paradox — the core finding

The paper's central argument: the assay clinicians treat as the 'gold standard' for UFH monitoring in CPB and ECMO (anti-Xa) has never been validated for those specific settings. Yet it is used to calibrate and benchmark all other tests — including point-of-care tools and VET. The authors call this a conceptual circularity that cannot be resolved until context-specific validation studies are done.

Key message: Sixty years after the introduction of the ACT, reliable UFH monitoring in extracorporeal circulation remains, in the authors' own words, 'an unresolved challenge'.

Key findings in detail

1 | The dextran sulphate problem — assays over- or underestimate heparin

- Anti-Xa assays differ fundamentally on whether they contain dextran sulphate (DS). DS was added to prevent ex vivo heparin neutralisation by platelet factor 4 (PF4) during sample handling. Assays with DS: HemosIL Liquid Anti-Xa (Werfen), INNOVANCE Heparin (Siemens), BIOPHEN Heparin LRT (Hyphen). Assays without DS: STA Liquid Anti-Xa (Stago), Technochrom Anti-Xa (Technoclone).
- In CPB and ECMO, in vivo PF4 release is substantial. DS-containing assays may liberate heparin already neutralised in vivo by PF4 or by protamine, generating falsely elevated anti-Xa values that do not reflect biologically active heparin.
- Conversely, assays without DS may allow ex vivo PF4 to neutralise heparin during transport and centrifugation, producing falsely low anti-Xa values.
- After protamine in cardiac surgery, DS-containing assays may show residual anti-Xa activity that does not exist biologically — leading to unnecessary additional protamine dosing.

2 | Four clinical scenarios demand different monitoring approaches

Clinical scenario	Key issue for monitoring
Standard-dose UFH (e.g., DVT/ICU)	DS may be appropriate — ex vivo PF4 is the dominant problem here. Anti-Xa with DS performs best.
High-dose UFH during CPB	Very high concentrations dominate — DS effect proportionally small. ACT is established POC standard.
Low-moderate UFH during ECMO	Lower concentrations magnify DS distortion. Anti-Xa results may be meaningfully misleading. Most problematic scenario.
Post-protamine residual heparin	DS liberation of protamine-bound heparin creates falsely elevated readings — clinically dangerous for protamine dosing.

3 | VET (including ClotPro) — named, cited, and positioned for validation

- The paper explicitly names ClotPro IN-test (alongside ROTEM in-tem and TEG CK) as VET assays proposed for UFH monitoring in ECMO and cardiac surgery.
- A 2026 prospective study (Mirus et al., BMC Anaesthesiology) comparing ClotPro® IN/HI-test against aPTT and anti-Xa in critically ill patients is cited as key supporting evidence.
- Using clotting time ratios (IN-test vs HI-test — with vs without heparinase) may improve assay performance in quantifying residual heparin.
- The paper also honestly acknowledges that VET assays share some confounders with aPTT/ACT — underscoring why prospective validation studies in CPB/ECMO are urgently needed.

4 | A research agenda — and where ClotPro belongs

- Authors call for three steps per indication: (1) define an appropriate reference method, (2) establish clinically meaningful acceptance criteria, and (3) validate candidate monitoring tools — explicitly including point-of-care assays.
- This positions VET-based heparin monitoring, including ClotPro®, as a legitimate candidate for formal validation — not an outlier.

Relevance to ClotPro® and Multiclot® users

This paper directly strengthens the Haemoview clinical narrative across the most common settings for ClotPro® and Multiclot® use.

Paper finding	Relevance to ClotPro/Multiclot users
No validated reference assay for UFH in CPB/ECMO	When clinicians claim anti-Xa is their gold standard, this paper — from leading authorities including the ClotPro inventor — explains why that is a flawed assumption in cardiac surgery and ECMO.
DS anti-Xa may overestimate post-protamine heparin	A whole-blood VET approach (IN-test vs HI-test ratio) circumvents the plasma-based dextran sulphate problem — directly measuring the clotting response including all in vivo interactions.
ECMO: most problematic scenario for current assays	ECMO teams face the greatest uncertainty in UFH monitoring. The 2026 Mirus et al. ClotPro study provides prospective data supporting the IN/HI-test approach in exactly this population.
ClotPro IN-test named for UFH monitoring	Direct third-party endorsement by co-author Calatzis (ClotPro inventor) and independent experts Weber, Zacharowski, and Lindner — in peer-reviewed Frontiers in Medicine.
Validation studies called for urgently	Positions Haemoview — through ClotPro/Multiclot and the growing VET evidence base — at the frontier of what the field needs next.

Suggested customer conversation points

- When you measure anti-Xa in your ECMO patients — do you know whether your reagent contains dextran sulphate? This paper explains why it matters significantly.
- After protamine, do you trust your anti-Xa result? The authors — including the inventor of ClotPro — argue that DS-based assays may be overestimating residual heparin.
- A whole-blood VET approach using heparinase — comparing the IN-test and HI-test — reflects what is actually happening in the patient's blood, not just in platelet-poor plasma.

Source

Weber CF, Zacharowski K, Calatzis A, Lindner ML. Monitoring unfractionated heparin in ECMO and cardiac surgery: the search for a valid reference standard. Front. Med. 2026;13:1818646.

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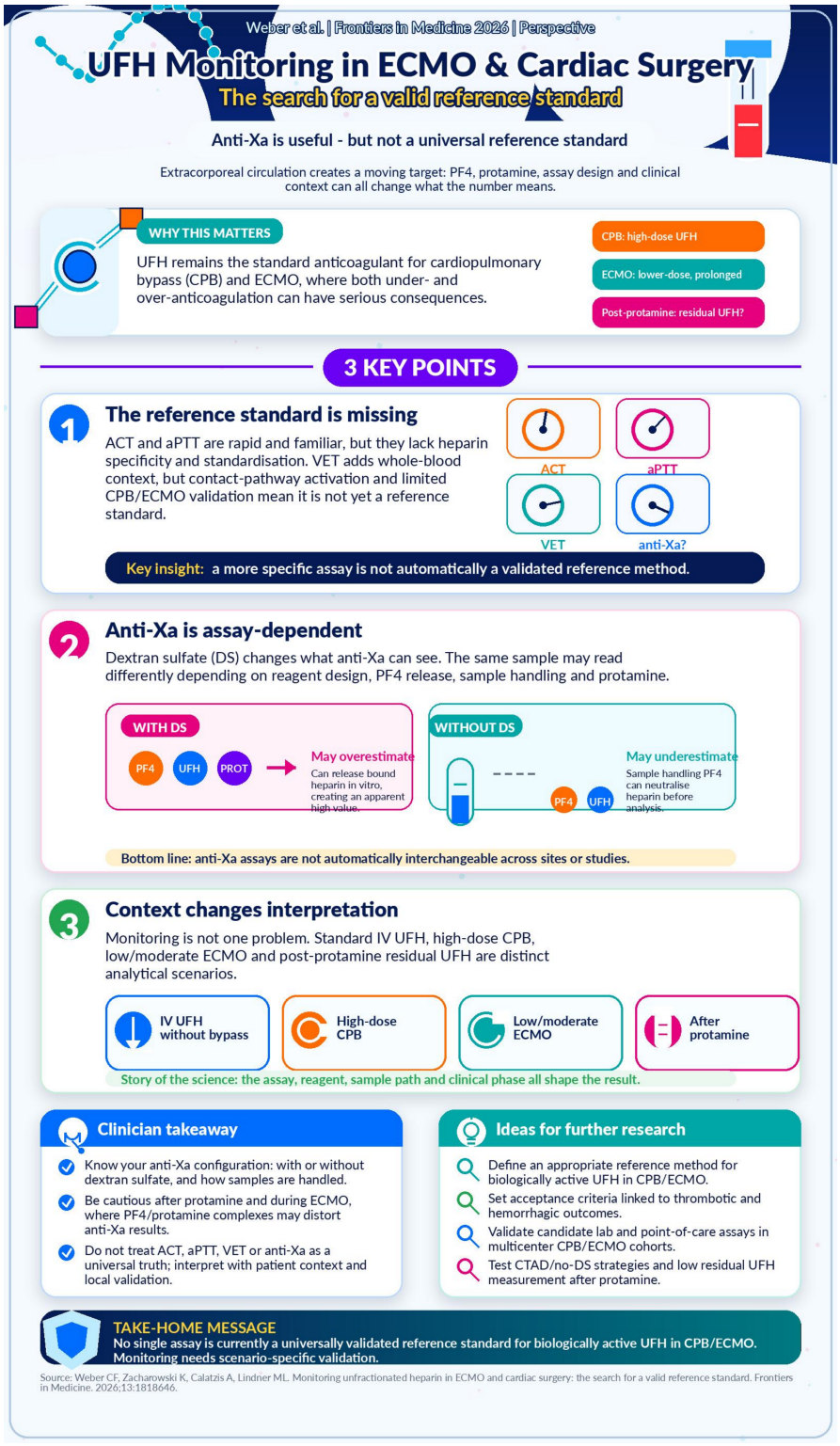
Related: Mirus M et al. ClotPro® IN/HI-test vs aPTT and anti-Xa in critically ill patients. BMC Anaesthesiology 2026;26:222.

Visual Summary — Infographic

The following infographic provides a visual overview of the key points from Weber et al. 2026, suitable for sharing with clinical colleagues.



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