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REVIEW ARTICLE

Heparin – Messias or Verschlimmbesserung?

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Abstract

A heightened risk of thrombosis noted early on with the severe acute respiratory syndrome coronavirus 2 infection led to the widespread use of heparin anticoagulation in the coronavirus disease 2019 (COVID-19) pandemic. However, reports soon started appearing in the literature where an apparent failure of heparin to prevent thrombotic events was observed in hospitalized patients with this viral infection. In this review, we explore the likely mechanisms for heparin failure with particular relevance to COVID-19. We also explore the role of anti-Xa assays and global hemostatic tests in this context. The current controversy of dosing heparin in this disease is detailed with some possible mechanistic reasons for anticoagulant failure. We hope that lessons learnt from the use of heparin in COVID-19 could assist us in the appropriate use of this anticoagulant in the future.

KEYWORDS

COVID-19, heparin, heparin-resistance, LMWH, Sars CoV-2, thrombosis

1 | INTRODUCTION

Since its discovery in the early part of the 20th century, heparins have remained the backbone of anticoagulant management. Despite the advent of very effective oral anticoagulants, heparins remain in the anticoagulation armamentarium and are likely to continue to do so in circumstances where oral anticoagulants may be impractical. However, despite a great track record of efficacy, there are instances where heparin is ineffective. Early recognition of thrombosis as a frequent complication in coronavirus disease 2019 (COVID-19) urged clinicians to consider heparin anticoagulation as a “Messias” (German for Messiah) in the management of this pandemic. Huge debate followed with uncertainty regarding the dose of heparin required, with one publication citing 75 randomized controlled trials in this setting.¹ Along with this widespread interest have come reports of increased bleeding and ineffectiveness of therapeutic doses of heparin in critically ill patients with COVID-19 making this anticoagulant a “verschlimmbesserung” (German for an attempted

improvement that only makes things worse).^{2–5} At the time of publication, heparin is recommended at prophylactic or intermediate doses in COVID-19 infection, although guidelines may shortly change to therapeutic dosing in noncritically ill patients based on recent results from the ATTACC, REMAP-CAP, and ACTIV-4a trial platforms.⁶ In this context, it is worthwhile examining how this “to and froing” regarding heparin happened to remind ourselves when, how and why this anticoagulant should be used.

2 | HOW DOES HEPARIN WORK AS AN ANTICOAGULANT?

Heparin is a heterogenous preparation of linear, highly sulphated heparan sulfate glycosaminoglycans, purified usually from porcine intestines.⁷ It exerts the majority of its anticoagulant effect by potentiating the action of antithrombin (AT). Binding of heparin to AT induces conformational changes leading to expulsion of the reactive

center loop that promotes interaction with proteases, such as thrombin or activated FX (FXa), upon which the loop is cleaved, and the substrate is trapped and inactivated.⁸ Unlike FXa, for inactivation of thrombin, it must also bind to the heparin molecule bound to AT. The heparin molecule must therefore be long enough to reach both proteins, necessitating a chain of 13 monosaccharide units or more and a weight of 5400 kDa. Consequently, low molecular weight heparins (LMWH) predominantly inhibit FXa whereas larger unfractionated heparin (UFH) inhibits both FXa and thrombin.⁹⁻¹¹

3 | HEPARIN RESISTANCE: MECHANISMS

"Heparin resistance" in venous thromboembolism (VTE) is defined as the need for more than 35 000 units of UFH per 24 h to prolong the APTT into the therapeutic range.¹² This differs from "heparin failure," which indicates a failure of heparin to prevent thrombosis. It also differs from biochemical heparin failure, in which heparin insufficiently downregulates coagulation *ex vivo*. Although there is obvious overlap between heparin resistance, clinical heparin failure, and biochemical heparin failure, there may be instances in which heparin resistance and/or biochemical heparin failure coincides with adequate thrombosis protection or vice versa. One cause of heparin resistance relates to heparin's ability to bind nonspecifically to many proteins other than AT, such as fibrinogen, factor VIII, and platelet factor 4¹³⁻¹⁶ (Table 1). Because many of these proteins are acute phase reactants, and heparin resistance is commonly seen in acutely unwell patients, those with cancer, or associated with pregnancy, its finding in the setting of COVID-19 is not surprising.¹⁷ Heparin "pseudo-resistance" refers specifically to elevated FVIII or fibrinogen levels shortening the APTT despite adequate plasma heparin concentrations, and elevated FVIII may also cause genuine heparin resistance.¹⁸ Heparin also binds to and is metabolized by endothelial cells and macrophages, which are activated in COVID-19 infection.¹⁹ Additionally, thrombocytosis, more commonly seen in severe disease²⁰ and possibly related to enhanced production of thrombopoietin by the liver may cause heparin resistance, possibly by excess release of platelet factor 4 from platelets.²¹ Because heparin acts by potentiating AT, decreased AT levels can play a role in heparin

TABLE 1 Causes of heparin resistance

Decreased antithrombin levels
Nonspecific binding of heparin to acute phase proteins such as fibrinogen, and to platelet factor 4
Heparin binding to and being metabolized by endothelial cells and macrophages
Thrombocytosis
"Pseudo" resistance: elevated factor VIII or fibrinogen levels shortening the APTT despite adequate plasma heparin concentrations.
"Functional" resistance: elevated baseline coagulation potential (e.g., marked inflammatory states), which could mean the standard doses of heparin may be insufficient to prevent thrombosis.

resistance. The majority of COVID-19 cases have low-normal AT levels, but there is some suggestion that patients with more severe disease have lower levels, and a possible association of decreased AT with obesity has been raised.²²⁻²⁴

4 | DIFFERENTIATING HEPARIN RESISTANCE FROM HEPARIN FAILURE

The accepted definition of heparin resistance does not necessarily mean a failure of anticoagulation. This is best explained by the example of the anti-Xa test that is designed to provide a measure of heparin concentration in the plasma. Because the anti-Xa test may underestimate the plasma heparin concentration when AT levels are low or when FVIII levels are elevated, but not affect its anticoagulant potential, heparin resistance *per se* may not translate into failure of anticoagulation.²⁵ Importantly, patients with adequate heparin plasma levels may also be heparin resistant when baseline coagulation potential is substantially elevated from the marked inflammation in COVID-19 (thromboinflammation principle). In this scenario, although heparin is effective in inhibiting coagulation as usual, the extreme basal hypercoagulability may mean the doses of heparin required are insufficient (see Figure 1).

5 | HEPARIN RESISTANCE IN COVID-19: CLINICAL ASPECTS

The finding that *in vivo* markers of activation of coagulation are substantially elevated even in patients with adequate heparinization suggests a failure of heparin to adequately anticoagulate in COVID-19.²⁶ In a group of 15 intensive care unit (ICU) patients receiving therapeutic anticoagulation, 80% of the 10 patients being managed with UFH infusions had heparin resistance, and peak anti-Xa levels were suboptimal in the five patients receiving therapeutic LMWH. There was no association between subtherapeutic heparin, FVIII, fibrinogen or AT levels, and anti-Xa levels correlated with activated partial thromboplastin ratio excluding heparin pseudo-resistance.²⁷ Another study by the same group showed reduced *in vitro* recovery of anti-Xa levels with LMWH compared with the direct oral anticoagulants rivaroxaban and apixaban in ICU patients. Again, no correlation with AT deficiency was observed.²⁸ A comparison of anti-FXa activity in patients with COVID-19 administered prophylactic LMWHs identified significantly lower mean anti-FXa levels in ICU patients compared with ward-level patients, with 95% of ICU patients failing to achieve an anti-FXa level of 0.2–0.4 IU/ml versus 27% of ward patients.²⁹ Another ICU group achieved targeted anti-Xa levels using four-fold the usual dose of the LMWH nadroparin, with uncertain clinical benefit.³⁰

It is currently not known whether the anticoagulation failure seen in COVID-19 (i.e., occurrence of thrombotic events on-heparin treatment) relates to (1) an absolute failure of anticoagulant activity, (2) a relative failure i.e. a failure to adequately decrease elevated

FIGURE 1 Heparin resistance in coronavirus disease 2019 and inflammatory diseases. In those with marked underlying inflammation, weight-based prophylactic doses of heparin may be inadequate to prevent thrombosis. This may be due to various reasons leading to heparin resistance discussed in the text. On the other hand, if the inflammation is controlled or not marked, the doses of heparin may be sufficient to prevent thrombosis. No easily available tests are currently available to determine the “adequacy” of heparin as an antithrombotic in these situations

anticoagulant potential, or (3) an inability to reach desired heparin plasma concentrations without or despite the administration of unusually large doses of heparin (i.e., heparin resistance). Resistance affects both UFH and LMWHs and appears more marked with worsening disease. Although high levels of circulating acute phase reactants likely contribute to anticoagulation failure by binding heparin, a true measure of heparin resistance (i.e., how much the drug has successfully inhibited excess thrombin generated) is still lacking.

6 | CAN ANTI-XA BE HELPFUL TO “DETECTING” HEPARIN RESISTANCE?

Hematologists are besotted with laboratory measurements of anti-coagulant activity. When LMWHs came into the market, there was unease despite evidence from several studies that monitoring was not required.³¹ Unlike UFH, which binds variably and nonspecifically to numerous proteins, LMWHs do not bind to the endothelium or plasma proteins, and thus have a very high bioavailability, and formulaic pharmacokinetics.³² The currently accepted indications for monitoring LMWHs with anti-Xa assays are those with significant

TABLE 2 Issues with anti-Xa assays for heparin monitoring

Variability in relative anti-Xa and antithrombin activities between different low molecular weight heparins
Poor comparability between commercially available anti-Xa chromogenic assays
Not yet shown to be accurate predictors of bleeding or antithrombotic efficacy
Interpretation depends on correct timing of the assays
May significantly underestimate levels in patients with inherited or acquired AT deficiency
Little information on heparins' collateral antithrombotic effects (e.g., tissue factor pathway inhibitor release)
No information on heparins' effects on platelet function

renal impairment, pregnancy, pediatric patients, and those at extremes of body weight.³³

Despite being widely accepted as the ideal heparin monitoring test, anti-Xa measurements have some flaws (Table 2).³⁴ Problems include (1) variability in relative anti-Xa and antithrombin activities between preparations, for example, tinzaparin increases APTT more than enoxaparin at any given level of anti-Xa activity,³⁵⁻³⁷ (2) poor

comparability between commercially available anti-Xa chromogenic assays,^{38,39} and crucially that (3) anti-Xa levels are not good predictors of bleeding or antithrombotic efficacy in patients treated with LMWHs.^{40,41} Anti-Xa levels must be taken at set time points for levels to be interpretable, and anti-Xa monitoring also significantly underestimates LMWH levels in patients with AT deficiency including in chronic liver disease.⁴² Additionally, anti-Xa activity provides no information on other LMWH effects such as on tissue factor pathway inhibitor release, or platelet function.³²

Despite the potential for heparin resistance, none of the recent guidelines has recommended routine LMWH monitoring in COVID-19, reflecting the uncertain benefit this information provides.⁴³⁻⁴⁸ Conversely, use of anti-Xa monitoring in addition to APTT may be beneficial in COVID-19 patients in whom heparin resistance is suspected. APTT readings may be falsely shortened in patients receiving UFH with an elevated C-reactive protein, dependent upon the chosen assay or high FVIII levels.⁴⁹ Anti-Xa monitoring may therefore be preferable in these patients, which is of relevance to a significant proportion of COVID-19 patients.⁵⁰ A pre-COVID study of 539 hospitalized patients receiving UFH found that patients with disproportionately prolonged APTT readings compared with anti-Xa values had worse clinical outcomes. The authors suggested that concurrent measurement of both readings could be useful in stratifying bleeding risk and determining dose.⁵¹ This may reflect the fact that, although anti-Xa may be a direct measure of heparin concentration, it does not always correlate with global hemostatic state.⁵² One group that encountered biochemical heparin resistance amongst patients requiring veno-venous extracorporeal membrane oxygenation also reported discrepancies between matched APTT and anti-Xa readings, adapting anticoagulation doses based on a combination of results.⁵³ The APTT range that correlates with a specific anti-Xa range is affected by both the APTT and anti-Xa reagents, and one cannot simply compare results using differing reagents.⁵⁴

7 | CAN VISCOELASTIC AND THROMBIN GENERATION TESTS BE HELPFUL IN PLACE OF ANTI-XA?

Neither APTT nor anti-Xa can measure the overall hemostatic potential. Viscoelastic tests such as thromboelastography and rotational thromboelastometry provide global measures of hemostasis, which may be of value in COVID-19. Several studies have found evidence of increased clot strength, although clinical correlation with thrombotic outcomes has not been demonstrated.^{24,55,56} One study, using thromboelastography, reported that lack of clot lysis at 30 min, suggestive of impaired fibrinolysis was associated with increased risk of VTE. Forty-four patients were included in the analysis. VTE occurred in 50% of patients with no evidence of clot lysis at 30 min and an elevated D-dimer (>2600 ng/ml), compared with 0% of patients without either risk factor.⁵⁷ Hypofibrinolysis was also shown in study using rotational thromboelastometry.⁵⁸ Viscoelastic tests are not standardized, are affected by numerous preanalytic factors, and

inter-laboratory variability is high. They seem to show a hypercoagulable state in COVID-19 patients, but how they can best be used to decide on, and monitor anticoagulation has not been defined.

Tests of thrombin generation (TG) are sensitive to the effects of both pro- and anticoagulant proteins, but are not routinely performed in clinical practice. In 89 patients with COVID-19, of whom 24 received no anticoagulation, 45 received standard heparin thromboprophylaxis and 20 received intermediate-dose anticoagulation, TG was significantly increased in patients without thromboprophylaxis compared with those receiving heparin.⁵⁸ Patients receiving thromboprophylaxis had similar TG profiles to controls, and in severe COVID-19 infection, intermediate-dose anticoagulation had a greater effect on TG than prophylaxis. Addition of thrombomodulin (TM) to TG tests allows concomitant measuring of both pro- and anticoagulant factors. TM is expressed on the endothelium, binds to thrombin, and the resulting thrombin-TM complex activates protein C, inhibiting coagulation.⁵⁹ TM-modified TG was significantly increased in COVID-19 patients not receiving anticoagulation compared with those on thromboprophylaxis and controls, suggesting a putative role for protein C deficiency, or a defect in the TM-mediated anticoagulation pathway.⁶⁰ Other studies also showed normal TG profiles in patients receiving heparin thromboprophylaxis.^{58,61,62} One study of 38 ICU patients with COVID-19 receiving standard heparin prophylaxis reported increased TG in patients with VTE versus those without. However, TM-modified TG was not associated with decreased protein C levels.⁶³ In Campello *et al.*'s study, 24% of patients developed VTE; however, whether TG profiles differed in these patients is not stated.⁶⁰ In particular, whether heparin failure could be predicted by persistent abnormal TG has not been shown. At the time of writing, TG remains an interesting but largely research-based tool with limited general availability.

8 | COULD INADEQUATE DOSING EXPLAIN ANTICOAGULATION FAILURE OF HEPARIN IN COVID-19?

Increased thrombosis was recognized early in patients from Wuhan wherein prophylactic anticoagulation (not a widespread practice in China for hospitalized inpatients) reduced mortality in patients with severe disease only.⁶⁴ A large retrospective study of more than 4000 patients has recently confirmed the mortality benefit of LMWH prophylaxis in all comers with COVID-19 requiring hospital admission.⁶⁵ However, soon after the publication of Tang *et al.*'s initial data, a plethora of European studies, mostly of critically ill patients showed failure of prophylactic anticoagulation,⁶⁶ persuading clinicians to start trials with higher doses of heparin. These augmented doses were even trialed in patients without documented venous or arterial thrombosis, a practice that would never normally be considered.

Preliminary non-peer-reviewed results from a large multiplatform randomized controlled trials provide somewhat conflicting data. The ATTACC, REMAP-CAP, and ACTIV-4a trial platforms combined their forces to compare therapeutic LMWH or UFH versus

local VTE prophylaxis for 14 days, or until discharge (or independence from oxygen in the ATTACC platform) in COVID-19. Data from more than 2000 patients have been analyzed. Patients were stratified into severe, requiring organ support or ICU, or moderate, requiring hospitalization but not ICU, disease states. In severe patients, heparin dose did not lead to a significant difference in organ support-free days or mortality. Hospital survival was 64.3% for therapeutic anticoagulation versus 65.3% for prophylactic (OR 0.88; 95% CI 0.67–1.16).⁶⁷

Conversely, in the moderate group, the probability that therapeutic anticoagulation increased organ support-free days was 99% (OR 1.29; 95% CI 1.04–1.61), and mortality was reduced by 4.6% (95% CI 0.7–8.1%). Baseline D-dimer did not predict outcomes.^{67–69} Across the groups, mortality was not significantly affected by heparin dose (OR 1.21; 95% CI 0.87–1.68).⁶

The INSPIRATION randomized clinical trial of intermediate (1 mg/kg enoxaparin) versus prophylactic (40 mg enoxaparin) LMWH also recently published their initial findings. In this study of 562 patients with COVID-19 requiring ICU level care, the primary composite end point (venous or arterial thrombosis, death within 30 days, or the need for extracorporeal membrane oxygenation for severe respiratory failure) occurred in 45.7% of the intermediate-dose LMWH group and 44.1% of the prophylactic LMWH group, showing no benefit from the higher dose.⁷⁰

The ACTION study compared prophylactic LMWH with rivaroxaban, or initial heparin followed by rivaroxaban in the small proportion (6%) of patients requiring ICU-level care. The primary outcome was a composite of time to death, duration of hospitalization, and duration of supplemental oxygen use, analyzed using the win ratio method (a ratio >1 favors therapeutic anticoagulation). The win ratio was 0.86 (95% CI 0.59–1.22) showing no benefit from therapeutic anticoagulation in this largely moderate cohort.⁷¹ These results are somewhat at odds with those of the ATTACC, REMAP-CAP, and ACTIV-4a group. Heparin may be superior to rivaroxaban in the context of COVID-19, for reasons we will elaborate in the following section; however, a direct comparison with therapeutic heparin is required to determine this.

Available data regarding heparin dose thus show benefit from prophylactic heparin compared with no heparin, but only a possible role for higher doses in certain subsets. Certainly, therapeutic anticoagulation in severely ill patients without proven VTE has not been shown to improve outcomes. The impact of other causes of thrombosis in COVID-19, which are not affected by heparin, may underpin this observation.

9 | CAN DIFFERENT MECHANISMS FOR THROMBOSIS EXPLAIN THE ANTICOAGULATION FAILURE IN COVID-19?

Non-anticoagulant properties of heparin can have antithrombotic functions. For example, it can have an impact on platelets and inhibit their function in a von Willebrand factor (VWF)-dependent fashion.⁷²

Platelet activation by protease activated receptor-1, a downstream target of thrombin, is also reduced by heparin, impairing activation.⁷³ Another interesting non-anticoagulant function is its antiviral role. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein interacts directly and strongly with heparan sulfate, meaning that exogenous heparin could competitively inhibit viral entry into cells. This may not be applicable to LMWHs, which do not show this capability.⁷⁴ Heparin also has numerous anti-inflammatory properties. It inhibits complement activation through binding the complement factors C1 complex, C3 convertase, and the membrane attack complex responsible for terminal cell lysis.⁷⁵ It can restore impaired glycocalyx functionality by performing the function of syndecan-1 and by mobilizing an intercellular pool of syndecan-1.^{76,77}

Many of the forementioned noncoagulant properties of heparin demonstrated in the research setting have not been replicated clinically in patients. This may reflect the complex pathophysiology occurring in COVID-19, such that “blocking” only one of these pathways may not translate to improved outcomes. Nor do we know how much heparin is needed to mediate these effects and how this might vary in those with marked inflammation or very high viral loads. Additionally, some facets of COVID-19 coagulopathy may be less susceptible to the effects of heparin, contributing to anticoagulation failure.

9.1 | Inflammation

The inflammatory milieu generated by COVID-19 infection is highly prothrombotic. Interleukin-1 (IL-1) is produced following detection of COVID-19 by the innate immune system. IL-1 promotes production of IL-6,⁷⁸ which enhances production of plasminogen activator inhibitor-1, a key inhibitor of fibrinolysis.⁵⁷ Under the influence of cytokines, tissue factor (TF) is upregulated on endothelial cells and monocytes.^{79,80} TF is a crucial cofactor for factor VII (FVII), which once bound can convert FIX and FX to their active forms, leading to thrombin generation and fibrin formation.⁸¹ The cytokine storm induces platelet activation with P-selectin expression, TF production and release of proinflammatory microparticles seen.⁸² Stimulation of endothelial cells by cytokines and direct viral-mediated cellular damage, enables release of VWF from Weibel-Palade bodies,⁸³ thromboxane, which induces platelet aggregation, and plasminogen activator inhibitor-1, which inhibits tissue-type plasminogen activator and urokinase plasminogen activator, usually present at the endothelial cell surface.⁸⁴ Increased VWF may lead to platelet aggregation and thrombosis, with higher VWF levels seen with worsening disease severity.^{85–87} Proinflammatory cytokines and chemokines also bind to heparin, enabling exogenous heparin to compete with endogenous heparins for binding.⁸⁸

9.2 | Neutrophil extracellular traps

NETosis is the process by which neutrophil extracellular traps (NETs) are formed. These extracellular webs of DNA, histones, proteins, and

enzymes released by neutrophils in response to infection can have a proinflammatory and thrombotic effect when inadequately regulated.^{89,90} COVID-19 patient serum and sputum contains raised levels of specific markers of NETs, correlating with disease severity.⁹¹ Busch *et al.*⁹² showed that treatment of normal donor neutrophils with COVID-19 patient serum induced NETosis, only when serum from critically ill patients was used. The complement system may promote this process specifically in COVID-19 infection, by binding to the SARS-CoV-2 N-protein, leading to generation of C5a. C5a activates neutrophils, stimulating NETosis and further complement activation within an amplification loop.⁹³ Histones released from NETs enhance thrombin generation in a platelet-dependent manner,⁹⁴ by activating platelets, causing aggregation, thrombocytopenia and thrombosis.⁹⁵ Heparin neutralizes the cytotoxicity of extracellular histones and prevents pulmonary histone accumulation in rabbits after intravenous histone administration.^{96,97}

9.3 | Contact activation

The contact system forms part of the innate immune system, designed to produce an inflammatory immune response against pathogens, foreign materials, and aberrant or cancerous cells or proteins.⁹⁸ The key proteins of the contact system are factor XII, prekallikrein and high molecular weight kininogen (HMWK). Busch *et al.* assessed activation of coagulation in COVID-19 by measuring activated coagulation factors in complex with their natural inhibitors. They found increased levels of kallikrein:C1 esterase inhibitor in nearly 90% of patients with severe infection, and FXIa:α1-antitrypsin in 95%. Levels were related to disease-severity and remained elevated despite LMWHs, in keeping with the fact that heparin only has a mild effect on contact activation.⁹² Another group demonstrated activation of the contact system in COVID-19 patients in the ICU by high consumption of FXII, prekallikrein, and HMWK. Complement activation was also increased, with C3a/C3 levels and prekallikrein and HMWK consumption predictive of mortality.⁹⁹ Given these results, and the evidence of increased NETosis with worsening disease, one can hypothesize that SARS-CoV-2 has a specific procoagulant effect through complement-stimulated NETosis and recruitment of the contact system, that is not mitigated by current COVID-19 treatments including LMWH.

10 | WHAT ABOUT BLEEDING WITH HEPARIN THERAPY?

To confound matters further, bleeding is common in the critically ill,¹⁰⁰ and performing clinical trials in critical care is fraught with challenges.¹⁰¹ Balancing treatments affecting hemostasis in such unwell patients is often extremely difficult, and harder still to conduct in a rigorous, randomized manner enabling firm conclusions to be drawn. The ATTACC, REMAP-CAP, and ACTIV-4a trial platforms reported that major bleeding was approximately doubled by therapeutic

anticoagulation: moderate disease 1.9% with therapeutic anticoagulation versus 0.9% with prophylaxis, and severe disease 3.7% versus 1.8%.⁶⁷⁻⁶⁹ In the INSPIRATION study, major bleeding was also increased in the intermediate-dose LMWH group at 2.5% versus 1.4%.⁷⁰ A study of 56 COVID-19 patients requiring ICU level care reported major bleeding in 18% and thrombosis in 29%. Bleeding occurred significantly later than thrombosis after ICU admission and was associated with a preceding fall in fibrinogen levels and D-dimers. All patients who bled were anticoagulated, with nine of 10 receiving treatment-dose heparin. Supratherapeutic anticoagulation (anti-Xa > 0.7 IU/ml for UFH and >1 IU/ml for LMWHs) was present in 60% of cases either on the day of bleeding or the day prior. The authors hypothesized that falling fibrinogen and D-dimers may herald an increased risk of bleeding after the initial prothrombotic hyperinflammatory phase, and that monitoring of anticoagulation and possible dose de-escalation is required to reduce bleeding risk.¹⁰²

Although robust data are limited, heparin is likely to confer a hemorrhagic risk in COVID-19, particularly at higher doses. Caution should be exerted, especially in patients with severe thrombocytopenia or hypofibrinogenemia¹⁰³; however, better predictive tools for bleeding in patients with mild thrombocytopenia and reduced fibrinogen levels are also required. D-dimers were identified in two recent publications to be predictive of bleeding risk with heparin in COVID-19.^{103,104} In a retrospective, multicenter study of 400 COVID-19 patients, of which approximately 140 were critically ill, elevated D-dimers at hospital admission predicted bleeding complications in addition to thrombotic risk.¹⁰³ The two predictive markers for bleeding in this analysis were a platelet count <150 × 10⁹/L and D-dimer > 2500 ng/ml (OR 2.90; 95% CI 1.05–7.99; and 3.56; 95% CI 1.01–12.66, respectively).¹⁰³ In a large analysis involving almost 2000 patients, of which two-thirds received intermediate and the rest therapeutic-dose anticoagulation, 5.7% of patients developed major and 6.7%, nonmajor bleeding.¹⁰⁴ Multivariate analysis showed the risk of bleeding correlated with D-dimer levels >10 times the upper normal range (hazard ratio 2.23; 95% CI 1.38–3.59), alongside raised ferritin, being critically ill and therapeutic-dose anticoagulation.¹⁰⁴ This could imply that D-dimer, which is also an inflammatory marker, could be a surrogate indicator of bleeding risk.¹⁰⁵ Inflammation is well-known to be associated with widening of endothelial gap junctions, which can exacerbate bleeding with high-intensity anticoagulation (see Figure 2). This hypothesis clearly needs confirmation in prospective trials but is indeed an intriguing research idea.

11 | CONCLUSIONS

The rise and fall of heparin in COVID-19 represents a cautionary tale. Clear data exist that LMWH prophylaxis reduces VTE in hospital inpatients.¹⁰⁶⁻¹⁰⁸ Early reports of reduced mortality in patients receiving heparin, alongside opposing reports of heparin failure, led to widespread adoption of increasing doses of anticoagulation, in the absence of clear evidence of benefit. As data from larger, randomized trials become available, it seems more apparent that the

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FIGURE 2 Bleeding with heparin anticoagulation. In the absence of overdosing, bleeding with heparin anticoagulation is extremely rare. However, in patients with diseases associated with severe inflammation, the latter process can open up the endothelial gap junctions and cause leakage of the intravascular components (bleeding). This extravasation can also happen with severe thrombocytopenia, since platelets play a crucial role in maintaining the endothelial integrity. In the situations of widened endothelial gap junctions, high doses of heparin can cause bleeding (most often noted in critically ill patients)

initial enthusiasm was not well founded. Currently, no convincing evidence exists that increasing heparin doses above prophylactic benefits critically ill COVID-19 patients, although there may be a role in moderate disease. Alternate anticoagulants such as the direct oral anticoagulants (in noncritically ill patients) and intravenous direct thrombin inhibitors (in critically ill patients) also warrant exploration in trial settings, as may interventions affecting other components of COVID-19 coagulopathy, such as antiplatelet agents and complement cascade inhibitors. As treatment of COVID-19 is evolving, the management of coagulopathy may also change. Dexamethasone is now standard of care in many centers for patients requiring supplemental oxygen.¹⁰⁹ Up-front use of systemic corticosteroids will impact the inflammatory picture seen in COVID-19 with likely downstream effects on thrombogenicity. We await further peer-reviewed results with interest, but for the present time, clinicians are advised to consider the available contemporary guidelines, enrol patients into clinical trials, and treat each patient on a case-to-case basis.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Dawn Swan wrote the manuscript, Jecko Thachil conceived and reviewed the manuscript, and Ton Lisman and Marc Carrier provided critical appraisal.

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