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Anticoagulation as a therapeutic strategy for hospitalised patients with COVID-19

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A B S T R A C T

The COVID-19 pandemic has devastated the global community and continues to cause significant morbidity and mortality worldwide. The development of effective vaccines has represented a major step towards reducing transmission and illness severity but significant challenges remain, particularly in regions where vaccine access has been limited. COVID-19 is associated with hypercoagulability and increased risk of thrombosis, with greatest risk among the critically ill. Interestingly, early observational data suggested that anticoagulant therapy might improve clinical outcomes, aside from thrombotic events, in patients with COVID-19. In this review we summarise data generated from three published randomised clinical trials which have sought to determine the effect of therapeutic heparin anticoagulation on efficacy and safety outcomes in hospitalised patients with COVID-19: the multiplatform REMAP-CAP, ACTIV-4a and ATTACC randomised controlled trials and the RAPID trial. In the multiplatform REMAP-CAP, ACTIV-4a and ATTACC randomised controlled trials, therapeutic heparin was not associated with benefit in critically ill patients with COVID-19 compared with usual care (adjusted proportional odds ratio (OR) for increased organ-support free days up to day 21: 0.83; 95% credible interval, 0.67–1.03, posterior probability of futility 99.9%). Conversely, among hospitalised patients without critical illness, therapeutic heparin was associated with an increased probability of organ support-free days alive (adjusted OR, 1.27; 95% credible interval, 1.03–1.58). The RAPID trial also evaluated the effect of therapeutic heparin compared with prophylactic heparin in non-critically ill patients. In this study, therapeutic heparin did not significantly reduce the odds of the primary composite outcome (death, mechanical ventilation or intensive care unit admission) (OR 0.69; 95% confidence interval [CI], 0.43 to 1.10; p = 0.12) but was associated with a significant reduction in all-cause mortality [OR, 0.22 (95%-CI, 0.07 to 0.65)]. Collectively these studies suggest that therapeutic anticoagulation with heparin may reduce the severity of illness and potentially even confer a survival benefit in hospitalised, non-critically ill patients with COVID-19. No benefit for therapeutic anticoagulation with heparin was evident in critically ill patients with COVID-19. Therefore, while the results of additional studies in this evolving field are pending, it is important to approach decisions regarding therapeutic heparin in moderately ill hospitalised patients with COVID-19 in a measured and individualised manner.

1. Introduction

Over 200 million individuals have been infected with the SARS-CoV-2 virus since the emergence of the pandemic in late 2019 and the global death toll now stands at almost 5 million people [1]. Worryingly, in recent months, chronic morbidity has also become increasingly recognised among survivors [2–4]. The development of effective vaccines has represented a major step towards infection containment but vaccine supply remains challenging for many countries, particularly in lower to middle income countries [5–7]. Sub-optimal uptake of vaccination is also impacting ability to achieve herd-immunity in some regions [8–10]. Until these obstacles can be addressed, it is likely that the global community will continue to face outbreaks of infection and the emergence of novel variants [11]. Reducing the risk of progression to severe COVID-19 among infected individuals is vital, not only in order to reduce the mortality rate but also in order to mitigate against the risk of healthcare system collapse [12,13]. Efforts to improve COVID-19 treatment strategies must therefore continue to be prioritised.

COVID-19 is associated with hypercoagulability and an increased risk of thrombosis. Importantly, elevated D-dimer levels have been identified as being predictive of poor clinical outcomes including critical illness and death [14–16]. The risk of thrombosis appears to be

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increased in all hospitalised patients with COVID-19 but the risk is greatest among patients with critical illness requiring organ support [15,17,18]. In situ pulmonary artery thrombosis and microvascular thrombosis appear to be prominent features of severe COVID-19 and may contribute to the development of the acute respiratory distress syndrome (ARDS) [19–21]. Furthermore, there is evolving evidence that sustained endotheliopathy and hypercoagulability may be implicated in long COVID syndrome pathogenesis [4,22]. The observed relationship between inflammatory coagulation activation and COVID-19 severity have prompted a tremendous response from the global scientific community to define the pathobiology of this hypercoagulability [21,23].

At an early stage of the pandemic observational data emerged suggesting that anticoagulant therapy might confer a survival benefit in COVID-19 [24]. Consequently, the role of anticoagulation as a therapeutic strategy for COVID-19 has become an area of immense research interest [25]. Heparin anticoagulation has been of particular interest, due to its known additional anti-inflammatory and possible anti-viral properties [26]. Heparin was discovered over a century ago and was the first anticoagulant used medically. It is a naturally occurring glycosaminoglycan that is produced by mast cells and basophils and exerts its anticoagulant activity through antithrombin [26]. Heparins are widely available and therefore are an excellent candidate class of drugs to feasibly mitigate thrombo-inflammation associated with COVID-19 on a global scale.

To date, 28 clinical studies have sought to explore the role of heparin-based regimens in improving outcomes in hospitalised non-ICU patients and a further 19 have sought to do so in the critical care setting [25]. These studies address pertinent clinical questions regarding the efficacy and safety of differing doses, routes of administration and timing of various heparin regimens with respect to disease course. In this review we summarise data generated from the recently published multiplatform REMAP-CAP, ACTIV-4a and ATTACC randomised controlled trials and the RAPID trial which have sought to determine the effect of therapeutic heparin anticoagulation in hospitalised patients with COVID-19 [27–29].

2. Therapeutic heparin in hospitalised patients with moderate or severe COVID-19

The following trials have recently evaluated the effect of therapeutic heparin as a potential treatment adjunct in hospitalised patients with COVID-19 (Table 1). These international, multicentre trials evaluated patients with different levels of disease severity as they hypothesized differential heparin effect.

2.1. The REMAP-CAP, ACTIV-4a and ATTACC multiplatform trials

Two publications reporting outcomes from a pragmatic, adaptive open-label randomized controlled trial involving three platforms were recently published, describing the effects of heparin in two strata: the non-critically ill and the critically ill[27 28]. These platform trials consisted of the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia), ACTIV-4a (Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 Antithrombotics Inpatient Platform Trial) and ATTACC (Antithrombotic Therapy to Ameliorate Complications of COVID-19) [27,28]. These trials recruited hospitalised patients with COVID-19 and compared therapeutic heparin to usual care pharmacologic thromboprophylaxis. Options for heparin therapy included both subcutaneous low molecular weight heparin (LMWH) or intravenous unfractionated heparin (UFH). Low-dose and intermediate-dose heparin were permitted in the usual care arm, with treatment choice determined by individual investigators based on local practice.

Patients were stratified as being critically ill and non-critically ill based on baseline organ support needs. Critical illness was defined by need for high flow oxygen, non-invasive ventilation (NIV), invasive

Table 1
The REMAP-CAP, ACTIV-4a & ATTACC Multiplatform RCTs and RAPID RCT: Evaluating the role of therapeutic heparin in hospitalised patients with COVID-19.

	REMAP-CAP, ACTIV-4a and ATTACC Trials [27] (Critically ill)	REMAP-CAP, ACTIV-4a and ATTACC Trials [28] (Non-critically ill)	RAPID trial [29] (Non-critically ill)
Study design	Adaptive open label RCT	Adaptive open label RCT	Adaptive open label RCT
Enrolment period	April 2020–Dec 2020	April 2020–Jan 2021	May 2020–April 2021
Sites	393 sites, 10 countries	121 sites, 9 countries	28 sites, 6 countries
Population (number)	1103	2219	465
D-Dimer at inclusion	Not required for inclusion	**Stratified by d-dimer post randomization:** 1. High: ≥2 ULN 2. Low: > 2 ULN 3. Unknown	**Elevated D-Dimer required for inclusion:** 1. ≥2 ULN or 2. Any elevated D-dimer + SPO2 ≤93% (FiO2 0.21)
Study period	21 days	21 days	28 days
Experimental arm: • Drug & Dose • Number assigned • Adherence (%)	Therapeutic heparin 536 85.9%	Therapeutic heparin 1171 88.3%	Therapeutic heparin 228 97.4%
Control arm: • Drug & Dose • Number assigned • Adherence (%)	Usual care* 567 92.1%	Usual care* 1048 98.3%	Low dose heparin 237 97.9%
Primary Outcome	**Organ support free days up to day 21 [median (IQR)]** Treatment arm: 1(-1 to 16) Usual Care arm: 4 (−1 to 16) (aOR 0.67–1.03); Probability of futility of therapeutic heparin: 99.9%	**Proportion of patients surviving until hospital discharge without requiring critical care support (%)** Treatment arm: 80.2% Usual care arm: 76.4% (Adjusted OR, 1.27; 95% CrI, 1.03 to 1.58); Probability of superiority of therapeutic heparin: 98.6%	**Death, invasive/non-invasive mechanical ventilation or ICU admission** Treatment arm: 16.2% Low dose heparin arm: 21.9% (OR 0.69, 95% confidence interval 0.43 to 1.10, p = 0.12)
Death	**Death in hospital:** Treatment arm: 37.3% Usual care arm: 35.5%	**Death in hospital:** Treatment arm: 7.3% Usual care arm: 8.2%	**Death from any cause:** Treatment arm: 1.8% Low dose heparin arm: 7.8% (OR 0.22, 95% confidence interval 0.07 to 0.65, p = 0.006)
Major bleeding	Treatment arm: 3.8% Usual care arm: 2.3% (Adjusted OR, 1.48; 95% CrI, 0.75 to 3.04)	Treatment arm: 1.9% Usual care arm: 0.9% (Adjusted OR, 1.80; 95% CrI, 0.90 to 3.74)	Treatment arm: 0.9% Usual care arm: 1.7% (OR 0.52, 95% confidence interval 0.09 to 2.85; P = 0.69)

*Usual care: Consisted of prophylactic or intermediate dose heparin in the multiplatform studies.

(RCT: randomised controlled trial; ULN: Upper limit of normal; Spo2: Peripheral oxygen saturations; OR: Odds radio; CrI: Credible interval).

mechanical ventilation, vasopressors, inotropes, or extracorporeal membrane oxygenation (ECMO). Moderate (non-critical) illness was defined as the absence of these requirements. Only patients with confirmed COVID-19 infection were included in this multiplatform trial. Randomization occurred in a 1:1 fashion in ACTIV-4a and in a response-adaptive manner in REMAP-CAP and ATTACC. Patients with clear anticoagulation indication or contraindication were excluded. Furthermore, those on baseline dual antiplatelet therapy (DAPT) or at high risk of imminent death were excluded. Treatment continued for 14 days or until recovery, which was defined as hospital discharge or discontinuation of supplemental oxygen therapy for at least 24 h. The primary endpoint of organ support-free days at day 21 was calculated using a numerical scale between zero and 21, and an inpatient death was allocated a value of −1. Secondary endpoints included all-cause mortality and thrombotic and bleeding events. Monthly interim analyses were performed to assess for superiority or inferiority.

In the study of therapeutic heparin in the critically ill patient stratum, recruitment was ceased following nine months of recruitment when an interim analysis demonstrated that the statistical criterion for futility had been met [27]. 1207 patients with severe COVID-19 from 393 sites and 10 countries had been randomised at this point (534 patients to therapeutic heparin and 564 to usual care and these were included in the primary analysis). Baseline characteristics were similar between treatment arms and demonstrated a male preponderance. Patients were predominantly white and mostly derived from a UK population. Over 80% of recruited patients were receiving concomitant glucocorticoid prescription therapy. The median value for organ support-free days was 1 in the therapeutic arm and 4 in the usual care arm. The median adjusted proportional odds ratio (OR) for the effect of therapeutic heparin on organ-support free days was 0.83 (95% credible interval, 0.67–1.03), with a posterior probability of futility of 99.9%. Fewer patients had major thrombotic events in the therapeutic arms (6.4% vs. 10.4%) but there were more episodes of major bleeding (3.8% vs 2.3%). Overall, in this trial of patients with severe COVID-19 therapeutic-dose heparin did not increase the number of days free of organ support nor the probability of survival to discharge.

In the stratum with moderate COVID-19, the investigators also explored the effect of therapeutic heparin [28]. Hospitalised patients with moderate COVID-19 were eligible for inclusion to the ACTIV-4a and ATTACC trials if they were within 72 h of admission; and to the REMAP-CAP study if they were within 14 days of admission. Recruited patients were stratified by baseline d-dimer values into high (≥2ULN), low (<2 ULN) or unknown groups. The trial was stopped when the prespecified criteria for superiority of therapeutic heparin were met. Among the 2219 patients (1171 therapeutic and 1048 usual care) who were included in the primary analysis, the posterior probability was 98.6% (adjusted OR 1.27, credible interval 1.03–1.58) that therapeutic heparin increased organ support-free days when compared to usual care thrombotic prophylaxis, irrespective of baseline d-dimer level. Of note, 79.6% of patients in the intervention arm received therapeutic anticoagulation, while the remaining 8.7% received subtherapeutic, 5.8% received intermediate dosing and 5.8% received low dose heparin. This was reported as 88.3% protocol adherence (including therapeutic and subtherapeutic doses) in the treatment arm. Protocol adherence was 98.3% in the usual care arm (71.7% low dose and 26.5% intermediate dose heparin). Major thrombotic events occurred in 8.0% in the therapeutic arm versus 9.9% in the usual care group (adjusted OR 0.72, 95% credible interval 0.53–0.98), and major bleeding occurred in 1.9% and 0.9% (adjusted OR 1.80, 95% credible interval 0.90–3.74), respectively.

2.2. The RAPID trial

The RAPID (The Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 Pandemic) trial evaluated the effect of therapeutic heparin compared with prophylactic heparin in hospitalised patients with moderate COVID-19 and elevated d-dimer levels [29]. This was a pragmatic adaptive multicentre, open-label randomized controlled trial, conducted in 28 sites, in 6 countries. Patients admitted for less than 5 days to hospital wards, with laboratory confirmed COVID-19 were eligible for inclusion. D-dimer levels ≥2 times the upper limit of normal (ULN) were required. Alternatively, any d-dimer level above the ULN were eligible if accompanied by oxygen saturation ≤93% on room air. The primary outcome was a composite of all-cause death, mechanical ventilation (invasive or non-invasive) or intensive care unit admission, evaluated at 28 days. Meeting any component of the primary outcome at baseline, absolute indication or contraindication to anticoagulation (e.g. elevated bleeding risk) were among the exclusion criteria. Patients were randomly assigned therapeutic or dose-capped prophylactic heparin in a 1:1 fashion, stratified by site and age threshold of 65 years. The primary analysis was based on the intention-to-treat (ITT) principle.

465 inpatients with moderate COVID-19 were randomised in the RAPID trial, of whom 228 were assigned therapeutic heparin and 237 prophylactic heparin. 97.4% (n = 222) and 97.9% (n = 232) received the allocated treatment within 48 h of randomization. At 28 days 16.2% (n = 37) of the therapeutic cohort and 21.9% (n = 52) of the prophylactic group met the primary composite outcome (OR, 0.69; 95% confidence interval [CI], 0.43 to 1.10; p = 0.12). Only 1.8% (n = 4) of patients receiving therapeutic heparin died during the study follow up period in contrast to 7.6% (n = 18) in the prophylactic heparin group (OR, 0.22; 95%-CI, 0.07 to 0.65). The number of venous thromboembolic events was 0.9% (n = 2) and 2.5% (n = 6) in the therapeutic and prophylactic heparin groups, respectively (OR, 0.34, 95%-CI, 0.07 to 1.71). Major bleeding occurred in 0.9% (n = 2) of those prescribed therapeutic heparin and 1.7% (n = 4) of the prophylactic heparin group (OR, 0.52; 95%-CI, 0.09 to 2.85).

Collectively, the results of the RAPID and the multiplatform trials suggest that therapeutic heparin is of benefit in hospitalised patients with moderate illness but not in those with critical illness. It seems plausible therefore that therapeutic-dose heparin modulates the negative effects of thrombo-inflammation when applied earlier in the course of disease requiring hospitalization.

3. Anticoagulant therapy as a treatment MODALITY for COVID-19: unanswered questions

The results of the multiplatform trial by the ATTACC, ACTIV-4a, and REMAP-CAP investigators and the RAPID trial are compelling and potentially practice changing, as they suggest that therapeutic heparin is safe and efficacious for patients with moderate COVID-19. A number of key differences exist between these trials however, which warrant discussion. An increase in organ support-free days and increased probability of survival without the requirement for organ-support, irrespective of baseline d-dimer level, was demonstrated in the multiplatform trial. Adherence to protocol-assigned anticoagulation dosing regimens differed between trials. Protocol adherence to therapeutic anticoagulation was 88.3% in the multiplatform trial and 97.4% in the RAPID trial, and may have attenuated the results in the former. Adherence to prophylactic anticoagulation was similar, at 98.3% and 97.9% respectively. In the multiplatform study, the number of major bleeding events was numerically higher in the therapeutic heparin arm in both the critical care and non-critical care populations, although this observation did not achieve statistical significance. An increased incidence of major bleeding with therapeutic heparin was not observed in the RAPID Study, which focused exclusively on non-critically ill patients. The low incidence of major bleeding overall in these studies is reassuring. As both studies excluded patients at high risk of bleeding, these results may not be generalisable to hospitalised patients with higher bleeding risks.

Individualised, patient-centred treatment decisions regarding the role of therapeutic anticoagulation is vital in ensuring that the potential benefits of such a treatment approach can be appropriately harnessed without exposing patients to unnecessary risks. These data suggest that therapeutic heparin anticoagulation is not appropriate to initiate in the critical care setting for the purposes of attenuating disease severity. Whether it is efficacious and safe to continue therapeutic heparin in moderately ill hospitalised patients who subsequently develop critical illness necessitating organ support was not the focus of either of these trials and therefore remains an important unanswered question.

Differing doses of heparin therapy and alternative anticoagulants have also been explored as potential therapeutic strategies for COVID-19. A study comparing intermediate-dose heparin in comparison to fixed-dose standard thromboprophylaxis has also failed to demonstrate a benefit in severe COVID-19, although additional studies are ongoing [30]. Studies evaluating the role of the direct oral anticoagulants have also not shown any evidence of a survival benefit to date or of a disease-modifying effect [31]. Initial observational data suggested that anti-platelet therapy might be beneficial in COVID-19 although no survival advantage or reduction in disease severity was detected in a recent randomised controlled trial. The outcomes from additional studies are also awaited [32,33].

The negative results of the multiplatform study in critically ill patients with COVID-19 and positive results of the multiplatform and RAPID trials in the moderately ill suggest that earlier treatment in the course of hospitalization is preferable. It is biologically plausible that early initiation of heparin therapy may modulate dysregulated thrombo-inflammation and mitigate associated pulmonary endothelialitis and alveolar destruction. Later initiation of therapeutic heparin may alter the safety profile, augmenting the risk of major haemorrhage and attenuating the potential for benefit. Furthermore, the ideal treatment duration is unclear. Patients in the multiplatform study were treated for up to 14 days, while patients in the RAPID trial were treated for a maximum of 28 days, with a mean duration of 6.5 days. Patients in these studies received either intravenous or subcutaneous heparin preparations but LMWH was the most frequently used agent. The inhaled route of administration was not examined in these trials and this is the focus of additional studies including the INHALE-HEP (Inhaled Nebulised Unfractionated Heparin for the Treatment of Hospitalised Patients With COVID-19) [34], NEBUHEPA (Nebulised Heparin in Severe Acute Respiratory Syndrome COVID-19) and PACTR202007606032743 [25]. This is on a backdrop of prior research of nebulised heparin in other respiratory conditions including asthma [35], chronic obstructive pulmonary disease [36] and acute respiratory distress syndrome [37,38]. A prospective meta-analysis would be invaluable to facilitate the interpretation of the findings from these clinical trials where clinical characteristics and trial methodology have differed.

4. Conclusion

Therapeutic anticoagulation with heparin appears to be associated with favourable outcomes among moderately-ill patients admitted to hospital with COVID-19. These potential benefits are not evident in critically ill hospitalised patients with COVID-19. Globally, as the number of people infected with SARS-CoV-2 continues to rise and novel, highly-infectious variants emerge, the search for efficacious, affordable therapeutic interventions persists. The studies described in this review suggest that therapeutic heparin may confer benefit in select hospitalised patients with moderate COVID-19, following careful individualised risk assessment. Additional research is required to guide routine clinical practice in this dynamically evolving field.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Relevant conflicts of interest: These authors were study investigators for The RAPID (The Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 Pandemic) trial

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