Should anticoagulation be used in the treatment of severe COVID-19?

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KEY FINDINGS

Based on low-quality data, there is benefit from the use of anticoagulants for severe COVID-19. This effect needs to be confirmed through randomized controlled trials.

- A proportion of patients with severe COVID-19 develop a hypercoagulable state on the 7th-14th day of illness.(1)
- Some experts believe that anticoagulation, most commonly with low-molecular weight heparin (LMWH), may be of benefit to prevent disease progression and reduce mortality in COVID-19.(2,3)
- Evidence from two retrospective cohort studies show that the use of LMWH in COVID-19 is associated with:(4,5)
    - Improved surrogate markers for disease progression (increase in lymphocyte & platelet counts and decrease in D-dimer, fibrinogen degradation products, and IL-6)
    - Reduced 28-day mortality in high risk patients
- There are four ongoing registered clinical trials on the use of anticoagulants for COVID-19.
- The dose, duration, and timing of anticoagulation are not well established.
- Indirect evidence from studies on disseminated intravascular coagulation (DIC) showed no significant increase in bleeding complications with anticoagulation, but as there is risk of bleeding especially in the presence of thrombocytopenia, caution in such cases is advised.
- The International Society of Thrombosis and Hemostasis and the Philippine Society of Vascular Medicine recommend that initiation of anticoagulation using LMWH be considered in certain subsets of patients with COVID-19.(6,7)

RESULTS

As of April 23, 2020, there is no randomized controlled trial that answers the question posted. Four clinical trials aiming to evaluate the effect of anticoagulation on the prognosis of COVID-19 patients are ongoing. ***(See Appendix 1, Characteristics of Ongoing Clinical Trials)*** Nonetheless, we identified two retrospective cohorts that studied the association between use of anticoagulants in COVID-19 and disease progression and/or mortality, and a retrospective cohort and a network meta-analysis that address the issue of safety. Selection bias, lack of control of confounders, and indirectness were methodological flaws identified. ***(See Appendix 2, Characteristics of Included Studies)***

The use of LMWH in patients with severe COVID-19 was associated with significant decreases in D-dimer levels and IL-6 levels, and reduced risk of 28-day mortality among those who met the sepsis-induced coagulopathy (SIC) criteria ≥4 (OR 0.37 [95% CI 0.15-0.90], p=0.029 or those with D-dimer levels >6 times elevated (OR 0.44 [95% CI 0.22-0.87], p=0.017).(4,5) There seemed to be no significant difference in bleeding complications between anticoagulants and placebo, but there was a consistent tendency towards an increase in bleeding-related transfusions as the clinical condition becomes more severe among patients with bacterial sepsis-induced disseminated intravascular coagulation.(8,9)

CONCLUSION

Based on low-quality evidence, there seems to be benefit, seen as reduction in 28-day mortality and improvement in inflammatory and coagulation markers, from the use of anticoagulants in severe COVID-19. This effect needs to be confirmed through randomized controlled trials.

Declaration of Conflict of Interest

No conflict of interest

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Appendix 1. Characteristics of Ongoing Clinical Trials

No	Clinical Trial ID/Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	Trial Evaluating Efficacy and Safety of Anticoagulation in Patients with COVID-19 Infection, Nested in the Corimmuno-19 Cohort (CORIMMUNO-COAG) (NCT04344756)	Not yet recruiting	20 April to 31 July 2020	RCT Open-label (Phase 2)	France	Adult patients (≥18 years old) with COVID-19 pneumonia hospitalized in conventional or intensive care units divided into 2 groups: Group 1 - patients not requiring ICU at admission with mild disease to severe pneumopathy according to the WHO criteria of severity of COVID pneumopathy, and with symptom onset before 14 days, with need for oxygen but no non-invasive ventilation (NIV) or high flow Group 2 - Respiratory failure AND requiring mechanical ventilation; WHO progression scale ≥6; no do-not-resuscitate (DNR) order	Tinzaparin (INNOHEP®) IU/kg/24h for 14 days if creatinine clearance (Cockcroft) ≥ 20mL/min, otherwise unfractionated heparin (Calciparine®, Héparine Sodique Choay®) subcutaneously or intravenous with an anti-Xa target between 0.5 and 0.7 IU/mL for 14 days	Standard of Care for COVID-19 and a subcutaneous preventive anticoagulation for at least 14 days with enoxaparin 4000 IU/24h, tinzaparin 3500 IU/24h or dalteparin 5000 IU/24h if creatinine clearance (Cockcroft) ≥ 30mL/min or unfractionated heparin 5000 IU/12h if creatinine clearance < 30mL/min	Primary outcomes; 1) Survival without ventilation (VNI or mechanical ventilation) [Time Frame: day 14] (Group 1) 2) Ventilator free survival [Time Frame: day 28] (Group 2)

2	Preventing COVID-19 Complications With Low- and High-dose Anticoagulation (COVID-HEP) (NCT04345848)	Not yet recruiting	14 April to 30 November 2020	RCT Single-blind (Phase 3)	Switzerland	Adult patients with COVID-19 infections admitted to an acute non-critical medical ward with admission D-dimer levels >1000 ng/mL or an acute critical ward (ICU or intermediate care unit)	Therapeutic doses of subcutaneous enoxaparin or intravenous unfractionated heparin from admission until end of hospital stay or clinical recovery using 2 different doses of anticoagulation.	Prophylactic doses of subcutaneous enoxaparin or intravenous unfractionated heparin from admission until end of hospital stay or clinical recovery using 2 different doses of anticoagulation. If hospitalized in the ICU, an augmented thromboprophylaxis regimen as standard of care.	Primary outcomes; 1) Composite outcome arterial or venous thrombosis, disseminated intravascular coagulation and all-cause mortality [Time Frame: 30 days] 2) Risk of arterial or venous thrombosis, disseminated intravascular coagulation and all-cause mortality

3	Austrian CoronaVirus Adaptive Clinical Trial (ACOVACT) (NCT04351724)	Recruiting	16 April to 01 December 2020	RCT Open-label (Phase 2 and Phase 3)	Austria	Adult patients (≥18 years old) with confirmed COVID-19 who are hospitalized, with O2 saturation <94% on room air or >3% drop if with COPD. eGFR >20 mL/min required for patients in the rivaroxaban substudy	Rivaroxaban 2.5 mg 2-0-2 or 10 mg ½-0-1/2, as applicable	Thromboprophylaxis according to local standard, most likely to be low molecular weight heparin	Time to clinical improvement (defined as time from randomization to a sustained improvement (>48 hours) of ≥1 category on 2 consecutive days (compared to the status at randomization) measured on a proposed 7-category WHO ordinal scale, as follows: 1. Not hospitalized, no limitations on activities 2. Not hospitalized, limitation on activities 3. Hospitalized, not requiring supplemental oxygen 4. Hospitalized, requiring supplemental oxygen 5. Hospitalized, on non-invasive ventilation or high flow oxygen devices 6. Hospitalized, on invasive ventilation or ECMO 7. Death
4	Effects of different VTE prevention methods on the prognosis of hospitalized patients with novel coronavirus pneumonia (COVID-19) (ChiCTR2000030946)	Recruiting	10 Feb to 10 April 2020	Nonrandomized controlled trial	China	Adult patients aged (18-80 years) diagnosed with confirmed new coronavirus pneumonia and in need of hospitalization and with VTE score ≥4	Low molecular weight heparin therapy	Mechanical preventive antiocagulation	Effects of low molecular weight heparin and mechanical preventive anticoagulation on the prognosis of hospitalized patients with novel coronavirus pneumonia (effects not specified)

Appendix 2. Characteristics of Included Studies

No	Title/Author	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes	Key findings
1	SHI C et al.	Retrospective Cohort	China	42 Severe COVID-19 patients. Critically ill patients were excluded	LMWH in addition to other treatments The dose, timing, and duration of LMWH were not controlled	No heparin in addition to other treatments	D-dimer CRP Lymphocytes IL-6 Timing of labs and LMWH dosing schedule were not controlled	* LMWH group had significant decreases in D-dimer levels, fibrinogen degradation products (FDP), and IL-6 levels (Note: Baseline D-dimer levels were higher in the heparin group vs the control group, suggesting a more hypercoagulable state at baseline) * LMWH group had significant increases in lymphocytes & platelets vs the control group * No significant difference in change of CRP
2	TANG N et al.	Retrospective Cohort	China	449 patients with severe COVID-19 (stratified into subgroups based on sepsis induced coagulopathy [SIC] and D-dimer) 99 patients (22%) received heparin for ≥7 days (94 on LMWH [enoxaparin] and 5 on unfractionated heparin) *The SIC score is composed of platelet count, prothrombin time (PT), and SOFA score. A SIC ≥4 is considered high risk	LMWH with duration ≥7 days; some used unfractionated heparin	No heparin	28-day mortality and laboratory parameters	* No difference in 28-day mortality between groups * On multivariate analysis: - D-dimer, PT, and age positively correlated with 28-day mortality - Platelet count negatively correlated with 28-day mortality * Use of heparin associated with reduction in mortality with (univariate analysis) in those with: SIC ≥4 and D-dimer >3.0 ug/mL (6x the upper limit of normal)

3	YATABE T et al.	Network meta-analysis	Japan	Nine RCTs including patients with septic DIC, eligible for bleeding complications 1340 patients (1237 for studies looking at bleeding complications)	Anticoagulant	Placebo	Incidence of bleeding	* No significant differences in bleeding complications * Studies included made use of different durations and doses of anticoagulants * Antithrombin had 40% probability of being the best treatment in terms of bleeding complications. * Heparin had a 95.2% probability of being the worst treatment. * The number of patients included in the study was too limited to evaluate the incidence of bleeding complications accurately.
4	YAMAKAWA K et al.	Retrospective cohort	Japan	2663 consecutive patients with bacterial sepsis, stratified according to DIC and SOFA scores 1247 received anticoagulants (144 heparin/danaparoid) 1416 no anticoagulant	Anticoagulant	Placebo	Bleeding	* Although the differences were not statistically significant, there was a consistent tendency towards an increase in bleeding-related transfusions in all SOFA score subsets in the anticoagulant group, as seen below: SOFA score ≤7; OR 1.414 (0.817, 2.447) p=0.216 SOFA score 8–12; OR 1.306 (0.836, 2.041) p=0.241 SOFA score13–17;OR 1.739 (0.886, 3.412) p=0.108 SOFA score ≥18;OR 9.516 (0.861, 105.193) p=0.066