Thromboembolic event of covid

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NRITLD
Patients who are admitted to the hospital with coronavirus disease 2019 (Covid-19) are at high risk for thrombosis, particularly venous thromboembolism (VTE).

In a meta-analysis of 66 studies, the overall prevalence of VTE among patients with Covid-19 was 14.1%, with the highest incidence (22.7%) among those admitted to intensive care units (ICUs).
• Systemic hypercoagulability is a feature of Covid-19, and early studies have shown an association between plasma d-dimer levels and survival.

• These data have prompted a search for better thrombosis prevention, considering that the high frequencies of VTE occurred in patients who were already receiving standard thromboprophylaxis, mostly with low-molecular-weight heparin
Potential for increased risk of VTE and adverse outcomes:
- Age
- Bedridden, stasis
- Inflammatory response, endothelial injury
- Hemostatic abnormalities, DIC

VTE Prophylaxis, if not contraindicated

COVID-19 Death

Moderate / Severe COVID-19

Mild COVID-19

Asymptomatic, tested, SARS-CoV-2+ Infection

Asymptomatic, Untested, and SARS-CoV-2 + [vector]

SARS-CoV-2 - [uninfected population]
A. Risk Factors
- Acute illness
- Bedridden, stasis
- Genetics
- Fever
- Diarrhea
- Sepsis
- Liver injury
- CKD
- COPD
- HF
- Malignancy

B. Hemostatic Abnormalities
- Pulmonary microthrombi
- Intravascular coagulopathy
- Myocardial injury
- ↑ Cardiac biomarkers
- ↑ D-Dimer, FDPs, PT
- ↓ Platelets

C. Clinical Outcomes
- Venous Thromboembolism
- Myocardial Infarction
- Disseminated Intravascular Coagulation

Inflammatory Response
Endothelial Dysfunction
Superimposed Infection
- Lymphopenia
- Inflammatory cytokines
  - ↑ IL-6, CRP
### Summary of findings

1. Coagulopathy is manifest as elevated fibrinogen, elevated D-dimers, and minimal change in PT, aPTT, and platelet count in early stages of infection.

2. Increasing IL-6 levels are correlated with increasing fibrinogen levels.

3. Coagulopathy appears to be related to severity of illness and resultant thromboinflammation and not intrinsic viral activity.

4. Elevated D-dimer at admission is associated with increased mortality.

5. Rising D-dimer after admission precedes multiorgan failure and overt DIC:
   - Noted to start at 4 d after admission in nonsurvivors
   - Longer duration of hospital stay associated with increasing D-dimer and development of sepsis physiology

6. Bleeding manifestations are not common despite coagulopathy.
<table>
<thead>
<tr>
<th>Laboratory variable</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard coagulation and platelet panel</strong></td>
<td></td>
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</tbody>
</table>
| D-dimer | ↑↑↑ | Markedly elevated  
3- to 4-fold elevation associated with high mortality |
| FDPs | ↑↑ | Elevated |
| Fibrinogen | ↑↑ | Elevated  
Decreasing trend if patient’s condition progresses towards consumptive coagulopathy phenotype (e.g., DIC) |
| aPTT | ←→ (↑) | In normal range OR slightly prolonged |
| PT | ←→ (↑) | In normal range OR slightly prolonged |
| Platelet count | ←→ (↓) (↑) | Near normal OR mildly decreased  
Ranging from 100–150 × 10^9 cells/L in 70–95% patients with severe COVID-19, platelet count < 100 × 10^9 cell/L was detected in about 5% of severe COVID-19 patients. Could be slightly increased based on limited data from small cohorts |
<p>| <strong>Advanced rheological parameters</strong> | |
| Plasma viscosity | ↑↑ | Increased 2-fold, on average |
| Factor VIII activity | ↑ | Increased |
| von Willebrand factor | ↑ | Increased |
| Antithrombin activity | (↓) | Modestly decreased |
| Free protein S | (↓) | Modestly decreased |
| Protein C | (↑) | Modestly increased |</p>
<table>
<thead>
<tr>
<th>Blood test</th>
<th>Direction of change</th>
<th>Comparator (case vs control)</th>
<th>Reference(s)</th>
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</thead>
<tbody>
<tr>
<td>D-dimer</td>
<td>↑</td>
<td>Severe versus non-severe</td>
<td>17</td>
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<tr>
<td>Fibrinogen</td>
<td>↑</td>
<td>ICU versus ref range</td>
<td>16</td>
</tr>
<tr>
<td>Platelets</td>
<td>→ / ↓</td>
<td>Severe versus non-severe</td>
<td>17 100</td>
</tr>
<tr>
<td>aPTT</td>
<td>→</td>
<td>Severe versus non-severe</td>
<td>17 90</td>
</tr>
<tr>
<td>PT</td>
<td>→ / ↑</td>
<td>Severe versus non-severe</td>
<td>17 102</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>→ / ↑</td>
<td>COVID-19 versus healthy control</td>
<td>103</td>
</tr>
<tr>
<td>PAI-1</td>
<td>↑</td>
<td>Autopsy versus ref range</td>
<td>43</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>↑</td>
<td>Severe versus non-severe</td>
<td>17</td>
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<tr>
<td>Lymphocytes</td>
<td>↓</td>
<td>Severe versus non-severe</td>
<td>17</td>
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<tr>
<td>Neutrophils</td>
<td>↑</td>
<td>Severe versus non-severe</td>
<td>17</td>
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<tr>
<td>Factor VIII</td>
<td>↑</td>
<td>ICU versus non-ICU</td>
<td>39</td>
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<tr>
<td>VWF</td>
<td>↑</td>
<td>ICU versus non-ICU</td>
<td>39</td>
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<tr>
<td>Soluble P-selectin</td>
<td>↑</td>
<td>ICU versus non-ICU</td>
<td>39</td>
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<tr>
<td>CRP</td>
<td>↑</td>
<td>Severe versus non-severe</td>
<td>17</td>
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<tr>
<td>Procalcitonin</td>
<td>↑</td>
<td>Severe versus non-severe</td>
<td>17 90</td>
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<tr>
<td>Ferritin</td>
<td>↑</td>
<td>Severe versus non-severe</td>
<td>90</td>
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<tr>
<td>Complement</td>
<td>↑</td>
<td>Autopsy versus ref range</td>
<td>64</td>
</tr>
<tr>
<td>COVID-19+</td>
<td>Coagulation tests</td>
<td>Standard-dose VTE PPX</td>
<td>Escalated-dose* VTE PPX</td>
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<tr>
<td><strong>Outpatient</strong></td>
<td></td>
<td>Consider†</td>
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<td><strong>Inpatient</strong></td>
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<tr>
<td>Ward</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>ICU</td>
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<tr>
<td>Confirmed VTE</td>
<td>X</td>
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<tr>
<td>Presumed PE‡</td>
<td>X</td>
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<tr>
<td>ARDS</td>
<td>X</td>
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<tr>
<td>Society/Document (PubMed ID number)</td>
<td>Antithrombotic agent and dosage</td>
<td>Population</td>
<td>Duration of treatment</td>
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<tr>
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<tr>
<td>COVID-19 patients WITHOUT diagnosis of VTE</td>
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<tr>
<td><strong>International Society of Thrombosis and Haemostasis (ISTH) (PMID: 32338827)</strong></td>
<td>LMWH (in standard VTE prophylactic dose, in the absence of contraindications* OR UFH (twice or thrice daily) OR DOACs (least preferred, due to interference w/ immunosuppressant and antiviral drugs), in the absence of relevant contraindications* All in standard VTE prophylactic doses* Intermediate-dose LMWH in-hospital may be considered in severe patients LMWH (preferred agent, once daily) OR UFH (twice or thrice daily) All in standard VTE prophylactic doses* Intermediate-dose LMWH in-hospital can be considered in high-risk patients Full-dose heparin treatment is not recommended</td>
<td>All COVID-19 patients who require hospitalization (including non-critically ill patients) All non-ICU hospitalized COVID-19 patients</td>
<td>During the whole duration of hospital stay Extended duration thromboprophylaxis with LMWH or DOAC for 2–6 weeks (14 days at least, up to 30 days) post-discharge in selected patients with low risk for bleeding and key VTE risk factors could be used***</td>
</tr>
<tr>
<td><strong>STH – Subcommittee of Perioperative and Critical Thrombosis and Haemostasis of the Scientific and Standardization Committee (PMID: 32459046)</strong></td>
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<tr>
<td><strong>Italian Society on Thrombosis and Haemostasis (SISET) (PMID: 32281926)</strong></td>
<td>LMWH OR UFH OR fondaparinux All in standard VTE prophylactic dose, in the absence of contraindications* Intermediate-dose LMWH in-hospital (enoxaparin 4000 IU subcutaneously, twice daily) could be considered on an individual basis in patients with multiple risk factors for VTE Full-dose heparin treatment is not recommended</td>
<td>All hospitalized COVID-19 patients</td>
<td>During the whole duration of the hospital stay Maintained at home for 7–14 days post-discharge in case of pre-existing or persisting VTE risk factors</td>
</tr>
</tbody>
</table>
LMWH, once daily, preferred agent OR UFH, twice daily
Both in standard VTE prophylactic dose, in the absence of contraindications*
Mechanical VTE prophylaxis in patients with contraindications in immobilized patients
Prophylactic anticoagulation is the only fully recommended modality
Intermediate-dose LMWH in-hospital could be an option in select patients (minority of the panel support this option)
Full-dose heparin treatment is not recommended

Hospitalized patients with COVID-19 who have: respiratory failure or comorbidities such as active malignancy or heart failure, are bedridden or requiring intensive care

During the whole duration of hospital stay
Extended duration thromboprophylaxis with LMWH or DOAC for up to 45 days among patients with high VTE risk and low risk of bleeding****

COVID-19 patients WITH confirmed diagnosis of VTE
International Society of Thrombosis and Haemostasis (ISTH) (PMID: 32338827) Not discussed N/A N/A

ISTH – Subcommittee of Perioperative and Critical Thrombosis and Haemostasis of the Scientific and Standardization Committee (PMID: 32459046)
LMWH
(inpatient setting; a change from treatment-dose DOACs or VKAs to in-hospital LMWH should be considered in critical care patients with relevant coexistent medications, based on renal function and thrombocyte count)

All hospitalized COVID-19 patients with established VTE
Duration of anticoagulation treatment should be at least 3 months
<table>
<thead>
<tr>
<th>LMWH</th>
<th>OR</th>
<th>UFH</th>
<th>OR</th>
<th>DOACs</th>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Standard VTE therapeutic doses in the absence of contraindications(^a)</td>
</tr>
</tbody>
</table>

**Duration of treatment in this scenario should be according to established classic guidelines for therapeutic anticoagulation of established VTE**

In patients requiring therapeutic doses of LMWH or DOACs, a careful monitoring of renal function with anti-factor Xa or plasma DOAC levels assays should be instituted.

VKAs and DOACS significantly interfere with concomitant antiviral treatment and individualized risk/benefit approach should be applied for every patient.

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<table>
<thead>
<tr>
<th>UFH, parenteral (preferred in critical patients that might undergo procedures)</th>
<th>OR</th>
<th>LMWH, subcutaneous (preferred in patients unlikely to undergo procedures)</th>
<th>DOACs OR LMWH (preferred as post-discharge therapy due to reduced need for contact with healthcare workers required for INR monitoring of VKAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All in standard VTE therapeutic doses, in the absence of contraindications(^a)</td>
<td></td>
<td>Mechanical VTE prophylaxis in patients with contraindications in immobilized patients</td>
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</tbody>
</table>

**Hospitalized patients with COVID-19 with established VTE**

**Duration of treatment in this scenario should be according to established classic guidelines for therapeutic anticoagulation of established VTE**
• For patients who are already on an anticoagulant for another condition, continue the patient’s current therapeutic dose unless contraindicated by a change in clinical circumstances.

  Consider switching to low molecular weight heparin if the patient’s clinical condition is deteriorating and the patient is not currently on low molecular weight heparin
COVID-19 outpatients receiving warfarin who are in isolation and thus unable to have international normalized ratio monitoring may be candidates for switching to direct oral anticoagulant therapy.

Patients receiving warfarin who have a mechanical heart valve, ventricular assist device, valvular atrial fibrillation, or antiphospholipid antibody syndrome or who are lactating should continue treatment with warfarin.

Hospitalized patients with COVID-19 who are taking anticoagulant or antiplatelet therapy for underlying medical conditions should continue this treatment unless significant bleeding develops, or other contraindications are present.
High risk factors

- advanced age
- stay in the ICU
- cancer
- a prior history of VTE
- thrombophilia
- severe immobility
- elevated D-dimer levels (> 2 times of upper normal range)
- an IMPROVE VTE score of 4 or more
• The Food and Drug Administration approved the use of rivaroxaban 10 mg daily for 31 to 39 days in these patients
• Among 75 registered clinical trials of different antithrombotic strategies with different agents in patients with Covid-19, a majority have involved the use of heparin or LMWH.

• The INSPIRATION trial, which compared intermediate doses of LMWH with standard-dose prophylaxis in 562 patients who were being treated in an ICU, showed no between-group difference in the primary outcome (a composite of adjudicated acute VTE, arterial thrombosis, treatment with extracorporeal membrane oxygenation, or death) but more bleeding in the intermediate-dose group.
In a preprint article, the authors reported the findings of the RAPID trial, which evaluated therapeutic heparin as compared with prophylactic heparin or LMWH in 465 patients who were not critically ill.

In that trial, there was also no difference between groups in the primary outcome (a composite of ICU admission, noninvasive or invasive mechanical ventilation, or death), but the therapeutic anticoagulation group had a lower incidence of death at 28 days.
Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

ABSTRACT

BACKGROUND
Thrombosis and inflammation may contribute to the risk of death and complications among patients with coronavirus disease 2019 (Covid-19). We hypothesized that therapeutic-dose anticoagulation may improve outcomes in noncritically ill patients who are hospitalized with Covid-19.

METHODS
In this open-label, adaptive, multiplatform, controlled trial, we randomly assigned patients who were hospitalized with Covid-19 and who were not critically ill (which was defined as an absence of critical care–level organ support at enrollment) to receive pragmatically defined regimens of either therapeutic-dose anticoagulation with heparin or usual-care pharmacologic thromboprophylaxis. The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death (assigned a value of −1) and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge. This outcome was evaluated with the use of a Bayesian statistical model for all patients and according to the baseline D-dimer level.
RESULTS
The trial was stopped when prespecified criteria for the superiority of therapeutic-dose anticoagulation were met. Among 2219 patients in the final analysis, the probability that therapeutic-dose anticoagulation increased organ support–free days as compared with usual-care thromboprophylaxis was 98.6% (adjusted odds ratio, 1.27; 95% credible interval, 1.03 to 1.58). The adjusted absolute between-group difference in survival until hospital discharge without organ support favoring therapeutic-dose anticoagulation was 4.0 percentage points (95% credible interval, 0.5 to 7.2). The final probability of the superiority of therapeutic-dose anticoagulation over usual-care thromboprophylaxis was 97.3% in the high D-dimer cohort, 92.9% in the low D-dimer cohort, and 97.3% in the unknown D-dimer cohort. Major bleeding occurred in 1.9% of the patients receiving therapeutic-dose anticoagulation and in 0.9% of those receiving thromboprophylaxis.

CONCLUSIONS
In noncritically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis. (ATTACC, ACTIV-4a, and REMAP-CAP ClinicalTrials.gov numbers, NCT04372589, NCT04505774, NCT04359277, and NCT02735707.)
Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

ABSTRACT

BACKGROUND
Thrombosis and inflammation may contribute to morbidity and mortality among patients with coronavirus disease 2019 (Covid-19). We hypothesized that therapeutic-dose anticoagulation would improve outcomes in critically ill patients with Covid-19.

METHODS
In an open-label, adaptive, multiplatform, randomized clinical trial, critically ill patients with severe Covid-19 were randomly assigned to a pragmatically defined regimen of either therapeutic-dose anticoagulation with heparin or pharmacologic thromboprophylaxis in accordance with local usual care. The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death (assigned a value of –1) and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge.

The members of the executive writing committee and the block writing committee assume responsibility for the overall content and integrity of this article. The full names, academic degrees, and affiliations of the members of the executive writing committee and the block writing committee are listed in the Appendix. Address reprint requests to Dr. Zarychanski at the Sections of Hematology/Oncology and Critical Care, University of Manitoba, Winnipeg, MB, Canada R3E 0V9, or at rzarychanski@cancercare.mb.ca.

*The full list of investigators and collaborators is provided in the Supplementary Appendix, available at NEJM.org.
RESULTS
The trial was stopped when the prespecified criterion for futility was met for therapeutic-dose anticoagulation. Data on the primary outcome were available for 1098 patients (534 assigned to therapeutic-dose anticoagulation and 564 assigned to usual-care thromboprophylaxis). The median value for organ support–free days was 1 (interquartile range, −1 to 16) among the patients assigned to therapeutic-dose anticoagulation and was 4 (interquartile range, −1 to 16) among the patients assigned to usual-care thromboprophylaxis (adjusted proportional odds ratio, 0.83; 95% credible interval, 0.67 to 1.03; posterior probability of futility [defined as an odds ratio <1.2], 99.9%). The percentage of patients who survived to hospital discharge was similar in the two groups (62.7% and 64.5%, respectively; adjusted odds ratio, 0.84; 95% credible interval, 0.64 to 1.11). Major bleeding occurred in 3.8% of the patients assigned to therapeutic-dose anticoagulation and in 2.3% of those assigned to usual-care pharmacologic thromboprophylaxis.

CONCLUSIONS
In critically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin did not result in a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than did usual-care pharmacologic thromboprophylaxis. (REMAP-CAP, ACTIV-4a, and ATTACC ClinicalTrials.gov numbers, NCT02735707, NCT04505774, NCT04359277, and NCT04372589.)
One factor may be that in the critically ill patients, the underlying thrombotic and inflammatory damage may have been too advanced to have been influenced by higher doses of heparins.

In severe Covid-19, thrombus formation is driven by an orchestra of cytokines, activated complement, platelets, endothelial and inflammatory cells, and microvesicles that provide an efficient catalytic surface for clotting reaction.

These surface-bound complexes and fibrin-bound thrombin are quite resistant to inhibition by antithrombin, the key cofactor in heparin and LMWH.
• The available evidence does not support use of therapeutic-dose heparin or LMWH for thrombosis prevention in critically ill patients.
• Other antithrombotic or even profibrinolytic strategies may be warranted.
• Whether intermediate or therapeutic doses of thromboprophylactic drugs are effective and safe in moderately ill patients with Covid-19 remains an important question.