Clinical Trials for Vascular Complications of COVID-19: An Overview

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CPC Clinical Research
Disclosures

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Overview

• Background
• Clinical Trial Framework
  – Trial setting
  – Study population
  – Therapeutic intervention
  – Outcomes
  – Operational challenges
• Example trials
• Conclusions
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Thrombosis plays a major role in COVID-19

Incidence of Thrombotic Events in Hospitalized Patients with COVID-19 in a NYC Health System

<table>
<thead>
<tr>
<th></th>
<th>PE (Events, No. (%))</th>
<th>DVT (Events, No. (%))</th>
<th>Stroke (Events, No. (%))</th>
<th>MI (Events, No. (%))</th>
<th>Other thromboembolism (Events, No. (%))</th>
<th>Any thrombotic event (Events, No. (%))</th>
<th>No thrombotic event (Events, No. (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hospitalized patients (ICU and non-ICU) (n = 3334)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, No. (%)</td>
<td>106 (3.2)</td>
<td>129 (3.9)</td>
<td>54 (1.6)</td>
<td>298 (8.9)</td>
<td>32 (1.0)</td>
<td>533 (16.0)</td>
<td>2801 (84.0)</td>
</tr>
<tr>
<td>All-cause mortality, No. (%)</td>
<td>40 (37.7)</td>
<td>36 (27.9)</td>
<td>20 (37)</td>
<td>153 (51.3)</td>
<td>11 (34.4)</td>
<td>230 (43.2)</td>
<td>587 (21.0)</td>
</tr>
</tbody>
</table>

Thrombotic events detected in 31% of 184 Dutch COVID-19 ICU patients

Subsegmental pulmonary embolism

Pulmonary microthrombus

Renal vein organizing thrombus
Role of Tissue Factor in COVID-19

- A major activator of the coagulation cascade during viral infection
- Incorporation into viral envelope may lead to dysregulation of coagulation cascade
- Plays a central role in inflammatory signaling and dysregulated immunity related to viral infections
- Enhances viral dissemination
Heparin associated with reduced mortality in severe COVID-19

Retrospective analysis of 449 patients

## Society Thromboprophylaxis Recommendations* for Hospitalized COVID-19 Patients

<table>
<thead>
<tr>
<th>Patient population</th>
<th>ISTH</th>
<th>Anticoagulation Forum</th>
<th>ACC</th>
<th>ASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ICU hospitalized COVID-19</td>
<td>• Prophylaxis recommended (LMWH&gt;UFH)</td>
<td>• Prophylaxis recommended</td>
<td>• Prophylaxis recommended</td>
<td>• Prophylaxis recommended (LMWH&gt;UFH)</td>
</tr>
<tr>
<td></td>
<td>• Intermediate dose “can be considered”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Therapeutic AC not recommended</td>
<td>• Therapeutic AC not recommended</td>
<td>• Therapeutic AC not recommended</td>
<td>• Therapeutic AC not recommended</td>
</tr>
</tbody>
</table>

| ICU hospitalized COVID-19 | • Prophylaxis recommended (LMWH>UFH) | • Intermediate dose VTE prophylaxis |
| | | o Enoxaparin 40 mg SC bid or 0.5 mg/kg SC bid |
| | | o Heparin 7500 U SC TID |
| | | o Low-intensity heparin gtt |
| | • Therapeutic AC not recommended | • Therapeutic AC not recommended | • Therapeutic AC not recommended | • Therapeutic AC not recommended |

### Additional considerations
- Recommend against using biomarker thresholds (e.g. d-dimer) to trigger escalations in anticoagulation
- Recommend anti-Xa assay over aPTT
- Reasonable to increase intensity of anticoagulation or to switch anticoagulants in setting of recurrent clotting of access devices despite prophylactic anticoagulation

* Recommendations based on expert survey

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More than 30 trials of thromboprophylaxis in COVID-19 ongoing or planned
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Trial Setting

PRE-HOSPITAL
COVID+
Outpatient

HEP COVID
ASPEN
PARTISAN
COVID-HEP
IMPROVE
COVID-PACT
COVAC-TP
COVI-DOSE
RAPID-BRAZIL
FREEDOM COVID
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INHIXACOV19
ACOVACT
CORIMMUNO-COAG

NCT04508439

CONVALESCENT
COVID+
Discharged

ACTIV-4
COVID-PREVENT
NCT04508439
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Predictors of Mortality in COVID-19

191 patients in Wuhan, China

**IL-6**

**D-dimer**

**Troponin**

D-dimer predicts mortality in critically ill COVID-19

**Graph:**
- **Title:** 639 ICU COVID-19 patients in Europe
- **Y-axis:** Cumulative ICU Survival
- **X-axis:** Overall Survival (days)
- **Legend:**
  - D-dimer (µg/ml)
  - <1560
  - ≥1560

**Graph Details:**
- **HR 2.71 (95% CI 1.56 - 4.73)**
### Thrombosis Risk Scores in Hospitalized Patients

#### Padua

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Cancer</td>
<td>+3</td>
</tr>
<tr>
<td>Previous VTE (excluding superficial vein thrombosis)</td>
<td>+3</td>
</tr>
<tr>
<td>Reduced Mobility</td>
<td>+3</td>
</tr>
<tr>
<td>Already known thrombophilic condition</td>
<td>+3</td>
</tr>
<tr>
<td>Recent (≤1 month) trauma and/or surgery</td>
<td>+2</td>
</tr>
<tr>
<td>Elderly Age (≥70 years)</td>
<td>+1</td>
</tr>
<tr>
<td>Heart and/or respiratory failure</td>
<td>+1</td>
</tr>
<tr>
<td>Acute MI and/or Ischemic Stroke</td>
<td>+1</td>
</tr>
<tr>
<td>Acute infection and/or rheumatologic disorder</td>
<td>+1</td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>+1</td>
</tr>
<tr>
<td>Ongoing hormonal treatment</td>
<td>+1</td>
</tr>
</tbody>
</table>

#### IMPROVE

#### SIC

### Table 6—Adjusted Cox Associative Model for 3-Month VTE and Points Assigned to Each Patient Characteristic

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>HR (95% CI)</th>
<th>χ²</th>
<th>P Value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>4.7 (3.0-7.2)</td>
<td>48</td>
<td>&lt;.001</td>
<td>3</td>
</tr>
<tr>
<td>Known thrombophilia</td>
<td>3.5 (1.1-11)</td>
<td>5.2</td>
<td>.04</td>
<td>2</td>
</tr>
<tr>
<td>Current lower-limb paralysis</td>
<td>3.0 (1.6-5.7)</td>
<td>11</td>
<td>.001</td>
<td>2</td>
</tr>
<tr>
<td>Current cancer</td>
<td>2.8 (1.9-4.2)</td>
<td>27</td>
<td>&lt;.001</td>
<td>2</td>
</tr>
<tr>
<td>Immobilized ≥7 d</td>
<td>1.9 (1.3-2.7)</td>
<td>11</td>
<td>.001</td>
<td>2</td>
</tr>
<tr>
<td>ICU/CCU stay</td>
<td>1.8 (1.1-2.9)</td>
<td>6.1</td>
<td>.01</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥60 y</td>
<td>1.7 (1.1-2.6)</td>
<td>6.3</td>
<td>.01</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 3—Scoring for the diagnosis of sepsis-induced coagulopathy

<table>
<thead>
<tr>
<th>Category</th>
<th>Parameter</th>
<th>0 point</th>
<th>1 point</th>
<th>2 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time</td>
<td>PT-INR</td>
<td>≤1.2</td>
<td>&gt;1.2</td>
<td>&gt;1.4</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Platelet count (×10⁹/L)</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Total SOFA</td>
<td>SOFA four items</td>
<td>0</td>
<td>1</td>
<td>≥2</td>
</tr>
</tbody>
</table>

SOFA, Sequential Organ Failure Assessment
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COVID-19 Disease Progression

Stage I
(Early Infection)

Viral response phase

Stage II
(Pulmonary Phase)

IIA

IIIB

Stage III
(Hyperinflammation Phase)

Host inflammatory response phase

Immunothrombosis

Siddiqui HK and Mehra MR. J Heart and Lung Transplant 2020
Thromboprophylaxis in COVID-19

Bikdeli B et al. Thromb Haemost. 2020
Study Intervention: Target vs. Intensity

Most trials focused on varying intensity of existing therapies rather than on varying targets.
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Outcomes

• Efficacy
  – Clinical endpoints
  – Novel endpoints

• Safety

Adaptive COVID-19 Treatment Trial (ACTT) Scale

1. Death
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7. Not hospitalized, limitation on activities and/or requiring home oxygen
8. Not hospitalized, no limitations on activities

Post-COVID-19 Functional Status (PCFS)

Beigel JH et al. NEJM 2020
Klok FA et al. Eur Respir J 2020
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Operational Challenges for COVID-19 Trials

- Informed consent
- Drug manufacturing and delivery
- Monitoring
- Endpoint identification and adjudication
- Timelines
- Competing studies
Overview

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PREVENT-HD
A Study of Rivaroxaban to Reduce the Risk of Major Venous and Arterial Thrombotic Events, Hospitalization and Death in Medically Ill Outpatients With Acute, Symptomatic COVID-19 Infection

Patients with Positive COVID-19 Test for Infection (e.g., PCR)

Screening Period
Up to 14 days

Screening Visit
Day -14 to Day -1

Rivaroxaban 10 mg OD (+ standard of care)

Placebo OD (+ standard of care)

N = \sim 4000
(1:1)

Day 1

Day 35

At least one risk factor:
- Age \geq 60
- Any history of VTE
- History of CAD, PAD, Cerebrovascular
- History of thrombophilia
- History of cancer
- History of diabetes
- History of heart failure
- Body Mass Index \geq 35 kg/m2
- D-dimer > ULN

Primary efficacy endpoint: Composite symptomatic VTE, MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolism, all-cause hospitalization, or all-cause mortality up to Day 35

Primary safety: ISTH critical site and fatal bleeding
**Trial Setting**

**PRE-HOSPITAL**
- COVID+ Outpatient
  - PREVENT-HD
  - ETHIC
  - ACTIV-4
  - NCT04498273
  - NCT04400799

**HOSPITALIZED**
- COVID+ Inpatient
  - HEP COVID
    - ASPEN
    - PARTISAN
    - COVID-HEP
    - IMPROVE
    - COVID-PACT
    - COVAC-TP
    - COVI-DOSE
    - RAPID-BRAZIL
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**CONVALESCENT**
- COVID+ Discharged
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  - NCT04508439

An Affiliate of:
HEP-COVID Trial
Systemic Anticoagulation With Full Dose Low Molecular Weight Heparin (LMWH) vs. Prophylactic or Intermediate Dose LMWH in High Risk COVID-19 Patients

**Inclusion criteria:**
1. Age ≥ 18 yrs
2. COVID-19 positive
3. Hospitalized with RR >20 or resting O2 sat < 92%
4. DD > 6 X ULN OR SIC score ≥ 4

**Randomization**

- **Stratum 1** Subjects in ICU
  - Enoxaparin 1mg/kg SQ BID
  - SOC Px or intermediate dose heparin

- **Stratum 2** Subjects not in ICU
  - Enoxaparin 1mg/kg SQ BID
  - SOC Px or intermediate dose heparin

**Primary Efficacy Endpoint:** Composite of total venous thromboembolism, arterial thromboembolism, all-cause mortality on Day 30 ± 2

**Key Secondary Efficacy Endpoint:** Primary efficacy endpoint at Day 10 + 4

**Other Secondary Efficacy Endpoints:** Progression to ARDS, need for intubation, rehospitalization on Day 30 ± 2

**Principal Safety Endpoint:** Major Bleeding (ISTH Definition) on Day 30 ± 2

**Sample size:** 308 with event rate in control of 42%, RRR of 40%, power of 80% and 2-sided alpha 5%
Trial Setting

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- ACOVACT

**CONVALESCENT**

COVID+
Discharged

- ACTIV-4
- COVID-PREVENT
- NCT04508439

An Affiliate of:

NCT04505774

Trial Setting
Recombinant Nematode Anticoagulant Protein c2 (rNAPc2)

• Small recombinant protein cloned from hookworm
• Potent, long-acting inhibitor of tissue factor
• Anticoagulant activity, safety, and PK established from clinical trials in 700+ patients
rNAPc2 Targets More Than Coagulation

rNAPc2 lowers D-dimer and inflammation and improves survival in Ebola-infected non-human primates

D-dimer

IL-6

MCP-1

Survival

rNAPc2 reduces viral load in mice inoculated with HSV1

Virus

Heart

Lung

Hirudin
NAPc2
Apixaban

Days

Days

Days post infection

Days post infection

Lancet 2003;362:1953
J Thromb Haemost 2019;17:482
rNAPc2

Anti-inflammatory and anti-viral properties
**ASPEN-COVID-19**
Assessing Safety and Efficacy of rNAPc2 in COVID-19

**Phase 2b**

**Screening up to 7d**

**Inclusion**
- SARS-CoV-2 positive
- D-dimer > ULN

**Endpoints**
1° efficacy: ΔD-dimer (baseline to day 8)
2° efficacy: coagulation and inflammatory biomarkers
Other exploratory EPs
1° safety: clinically relevant bleeding

- rNAPc2 lower dose, n=25
- rNAPc2 higher dose, n=25
- Heparin SOC, n=50

30d follow up
Trial Setting

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COVID+ Outpatient

HOSPITALIZED
COVID+ Inpatient

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COVID+ Discharged

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An Affiliate of:
ACTIV-4 Antithrombotics
Accelerating COVID-19 Therapeutic Interventions and Vaccines

<table>
<thead>
<tr>
<th>Setting/Population</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRE-HOSPITAL</strong></td>
<td>Elevated D-dimer and CRP</td>
<td>Hospitalization for CV/pulmonary events, arterial or venous thrombosis, all-cause mortality up to 45 days</td>
</tr>
<tr>
<td><strong>INTERVENTION</strong></td>
<td>Apixaban 5 mg, Apixaban 2.5 mg, Aspirin 81 mg, Placebo</td>
<td><strong>HOSPITALIZED</strong></td>
</tr>
<tr>
<td></td>
<td>Therapeutic heparin, Prophylactic heparin</td>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td><strong>CONVALESCENT</strong></td>
<td>Discharged after COVID-19 hospitalization</td>
<td><strong>ANTITHROMBOTIC THERAPY</strong></td>
</tr>
</tbody>
</table>
Conclusions

• Thrombosis is a significant vascular complication in COVID-19

• Many COVID-19 thromboprophylaxis trials ongoing or planned
  – Varying intensities of existing therapies
  – Novel therapeutic targets

• Operational considerations remain a challenge

• Collaborative and innovative efforts to expedite scientific discovery and improve treatment for COVID-19 patients