Therapeutic Anticoagulation with Heparin in Covid-19:

Final results of the multiplatform trial
BACKGROUND
mpRCT of Therapeutic Anticoagulation in Covid-19

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University Health Network
University of Toronto
Thrombosis and Organ Failure in Covid-19


Ackermann et al. NEJM 2020
Current practice/guidelines: Wide variability

Heparin:
1. Antithrombotic
2. Direct anti-viral (e.g., Clausen *Cell* 2020)
3. Direct anti-inflammatory (e.g., ↓ IL6)

Variable treatment effect?
- Treatment effect may vary by stage (e.g., TNM)
- D-dimer may be predictive of treatment effect
Hypothesis

An initial strategy of therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin improves survival to hospital discharge with reduced use of ICU-level organ support in hospitalized patients.
Hypothesis

An initial strategy of therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin improves survival to hospital discharge with reduced use of ICU-level organ support in hospitalized patients.

A hypothesis shared by 3 platforms...
Multiplatform randomized controlled trial (mpRCT)

Goal:
• Accelerate evidence generation in a rapidly evolving pandemic
• Maximize external generalizability

Approach:
• Protocols of 3 adaptive RCTs evaluating therapeutic heparin in patients hospitalized for Covid-19 were integrated into a single prospective mpRCT
  • Detailed alignment of eligibility criteria, interventions, outcome measures, and data collection
  • Joint analysis plan for the mpRCT population.
• Independent DSMBs oversaw the platforms using a coordinated oversight model
• Central end point adjudication committee with consensus definitions.
Participants

- Patients hospitalized for Covid-19, stratified on the basis of illness severity at enrollment:
  - Severe disease (ICU-level care; critically ill)
  - Moderate disease (hospitalized; non-critically ill) severity states, further stratified on the basis of baseline D-dimer:
    - high D-dimer group (D-dimer ≥2 times local ULN)
    - low D-dimer group (D-dimer <2 times local ULN)
    - unknown D-dimer group
Participants

• **Severe disease** (ICU-level care) defined by use of respiratory or cardiovascular organ support (oxygen via high-flow nasal cannula, non-invasive or invasive mechanical ventilation, vasopressors, or inotropes) in an ICU
  – In ACTIV-4a, receipt of ICU-level organ support, irrespective of hospital setting, defined ICU-level care

• **Moderate disease** was defined as hospitalization for Covid-19 without requirement for ICU-level care
  – Participants admitted to an ICU but without receipt of such organ support were considered moderately ill
Participants

• Patients were ineligible for enrollment in the ATTACC and ACTIV-4a platforms after 72 hours following hospital admission for Covid-19 or in-hospital SARS-CoV-2 confirmation, and in the REMAP-CAP platform after 14 days following admission

• Patients were also excluded if discharge was expected within 72 hours, or if they had a clinical indication for therapeutic anticoagulation, high risk for bleeding, requirement for dual antiplatelet therapy, or known heparin allergy including HIT
Primary outcome

- Organ support-free days
  - An ordinal outcome composed of survival to hospital discharge and, among survivors, the number of days free of ICU-level organ support through day 21.
  - Patients dying during the index hospitalization through day 90 are assigned -1 (the worse possible outcome).
  - Patients surviving to hospital discharge without receipt of organ support are assigned 22 (the best possible outcome).
Primary outcome

- Organ support-free days

  - Reflects both utilization of critical care therapies and survival
  - Higher values indicating better outcomes
  - The outcome was selected to function across a spectrum of illness severity, and to minimize ascertainment bias
Secondary outcomes

• Components of the primary outcome
• Thrombotic events and death
  – Arterial thrombosis
  – Venous thrombosis
• ISTH major bleeding
• Heparin induced thrombocytopenia
Statistical Framework

mpRCT of Therapeutic Anticoagulation in Covid-19

Lindsay Berry, PhD

Berry Consultants
Statistical Innovation

ATTACC
REMAP-CAP

ACTIV-4
Acute Inpatient Anti-Thrombotic Study
mpRCT: ACTIV-4a, ATTACC, REMAP-CAP

- Together create a “multi-platform randomized clinical trial”
- One overarching primary analysis model
  - Monthly adaptive analyses
  - Unified set of pre-specified adaptive rules for each patient group
- Patient groups:
  - Severe
  - Moderate, high D-dimer
  - Moderate, low D-dimer
  - Moderate, unknown D-dimer
Bayesian primary analysis model

• Primary Endpoint: Organ support-free days (OSFD)
  – Ordinal outcome; ranging from --1 (worst) to 22 (best)

• Modeled with cumulative logistic model
  \[ \log\left(\frac{\pi_y}{1-\pi_y}\right) = [\text{State}]_y + [\text{Covariates}] + [\text{TAC}]_{\text{state;D–dimer}} \]

• Estimate posterior distribution of unknown model parameters
  • Synthesizes prior information + observed data
  • Neutral priors used for intercepts and covariate effects
Bayesian primary analysis model

• Primary Endpoint: Organ support-free days (OSFD)
  – Ordinal outcome; ranging from $-1$ (worst) to 22 (best)

• Modeled with cumulative logistic model

$$\log \left( \frac{\pi_y}{1-\pi_y} \right) = [\text{State}]_y + [\text{Covariates}] + [\text{TAC}]_{\text{state} \text{; D–dimer}}$$

• Covariates:
  • Site, age, sex, D-dimer group, and time period of enrollment
  • Important to explain variability in OSFD outcomes in evolving pandemic environment
Bayesian primary analysis model

• Primary Endpoint: Organ support-free days (OSFD)
  – Ordinal outcome; ranging from −1 (worst) to 22 (best)

• Modeled with cumulative logistic model

\[
\log \left( \frac{\pi_y}{1 - \pi_y} \right) = [\text{State}]_y + [\text{Covariates}] + [\text{TAC}]_{\text{state};\text{D–dimer}}
\]

• Treatment effect estimated for each patient group
  • Odds ratio >1 implies benefit = increased survival and days free of organ support
  • Bayesian hierarchical prior **dynamically borrows** information between groups

• Secondary model estimates “all moderate” effect
How does dynamic borrowing work?

A) Variability in treatment effect

- No pooling
- Complete pooling

B) Consistent treatment effect

- No pooling
- Complete pooling
How does dynamic borrowing work?

A) Variability in treatment effect

B) Consistent treatment effect

No pooling

Dynamic borrowing

Complete pooling

No pooling

Complete pooling

Group 1

Group 2

Group 3

Pooled
How does dynamic borrowing work?

A) Variability in treatment effect

B) Consistent treatment effect
Pre-specified adaptations

• Adaptations driven by Bayesian posterior probabilities
• At each adaptive analysis, the following are evaluated by patient group:
  – **Superiority:** > 99% posterior probability odds ratio >1
  – **Futility:** > 95% posterior probability odds ratio <1.2
  – **Response adaptive randomization (RAR)** based on the probability TAC is effective (ATTACC/REMAP-CAP only)
• Continue each patient group until a conclusion of superiority/futility is reached
  – No pre-specified conclusions/RAR for moderate patients with **unknown** D-dimer, but contribute to model estimates of covariates and dynamic borrowing
mpRCT designed to accelerate evidence generation

• Harmonization of analysis plan and data sharing between three large COVID-19 platform trials
• Treatment effect estimated in pre-specified patient groups
  – Dynamic borrowing most efficient use of information with possibility of treatment effect heterogeneity
• Bayesian framework driving adaptations, providing interpretable results in light of many uncertainties of pandemic
RESULTS

mpRCT of Therapeutic Anticoagulation in Covid-19

Ewan C. Goligher MD, PhD
University Health Network
University of Toronto

ATTACC
REMAP-CAP
ACTIV-4
Acute Inpatient Anti-Thrombotic Study
## Trial Course

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<tr>
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<tbody>
<tr>
<td>Moderate Unknown D-dimer</td>
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<tr>
<td>Moderate Low D-dimer</td>
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<tr>
<td>Moderate High D-dimer</td>
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<tr>
<td>Severe</td>
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### Trial Course

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<tr>
<td>Severe</td>
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</tbody>
</table>

- Response-adaptive randomization applied
Trial Course

- Moderate Unknown D-dimer
- Moderate Low D-dimer
- Moderate High D-dimer
- Severe

Futility Conclusion
Response-adaptive randomization applied
Trial Course

- Moderate Low D-dimer
- Moderate Unknown D-dimer
- Moderate High D-dimer
- Severe

**Response - adaptive randomization applied**

**Futility conclusion**

**Response-adaptive randomization applied**
Trial Course

- Moderate Unknown D-dimer
- Moderate Low D-dimer
- Moderate High D-dimer
- Severe

Futility conclusion
Response-adaptive randomization applied
Superiority conclusion
### mpRCT Recruitment

<table>
<thead>
<tr>
<th>Group</th>
<th>Therapeutic-Dose Anticoagulation (n with primary endpoint)</th>
<th>Usual-care thromboprophylaxis (n with primary endpoint)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Covid-19</td>
<td>534</td>
<td>564</td>
</tr>
<tr>
<td>Moderate Covid-19 (overall)</td>
<td>1171</td>
<td>1048</td>
</tr>
<tr>
<td>D-dimer ≥2x ULN</td>
<td>339</td>
<td>291</td>
</tr>
<tr>
<td>D-dimer &lt;2x ULN</td>
<td>570</td>
<td>505</td>
</tr>
<tr>
<td>D-dimer unknown</td>
<td>262</td>
<td>252</td>
</tr>
</tbody>
</table>
## mpRCT Populations

<table>
<thead>
<tr>
<th>Group</th>
<th>Moderate Covid-19 (n=2231)</th>
<th>Severe Covid-19 (n=1103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>59 years</td>
<td>61 years</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>59%</td>
<td>70%</td>
</tr>
<tr>
<td>Country of enrolment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>9%</td>
<td>71%</td>
</tr>
<tr>
<td>USA</td>
<td>48%</td>
<td>16%</td>
</tr>
<tr>
<td>Canada</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Brazil</td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>15%</td>
<td>2%</td>
</tr>
<tr>
<td>Platform of enrolment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTACC</td>
<td>52%</td>
<td>4%</td>
</tr>
<tr>
<td>ACTIV-4a</td>
<td>35%</td>
<td>12%</td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td>13%</td>
<td>84%</td>
</tr>
</tbody>
</table>
## mpRCT Populations

<table>
<thead>
<tr>
<th>Group</th>
<th>Moderate Covid-19 (n=2231)</th>
<th>Severe Covid-19 (n=1103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/low flow oxygen/unspecified</td>
<td>96%</td>
<td>1%</td>
</tr>
<tr>
<td>High flow oxygen</td>
<td>2%</td>
<td>33%</td>
</tr>
<tr>
<td>Non-invasive ventilation</td>
<td>2%</td>
<td>38%</td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>0%</td>
<td>28%</td>
</tr>
<tr>
<td>Co-interventions at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agent</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>36%</td>
<td>31%</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>62%</td>
<td>82%</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>0.5%</td>
<td>2%</td>
</tr>
</tbody>
</table>
Primary Endpoint: Organ Support-Free Days

Adjusted OR 0.83 (95% CrI 0.67-1.03)

**Futility**: Prob(OR<1.2) = 99.9%

**Inferiority**: Prob(OR<1) = 95.0%
Primary Endpoint: Organ Support-Free Days

Severe Covid-19

- Adjusted OR 0.83 (95% CrI 0.67-1.03)
- **Futility**: Prob(OR<1.2) = 99.9%
- **Inferiority**: Prob(OR<1) = 95.0%

Moderate Covid-19

- Adjusted OR 1.27 (95% CrI 1.03-1.58)
- **Superiority**: Prob(OR>1) = 98.6%
- 4% adjusted difference in risk of requiring organ support or dying (20% vs. 24%)
### Primary Endpoint by D-dimer in Moderate Covid-19

#### Table 2. Primary Outcome of Organ Support–Free Days.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Therapeutic-Dose Anticoagulation</th>
<th>Usual-Care Thromboprophylaxis</th>
<th>Adjusted Difference in Risk (95% Credible Interval)†</th>
<th>Adjusted Odds Ratio (95% Credible Interval)‡</th>
<th>Probability of Superiority of Therapeutic-Dose Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients/total no. (%)</td>
<td>percentage points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with moderate disease</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Overall group§</td>
<td>939/1171 (80.2)</td>
<td>801/1048 (76.4)</td>
<td>4.0 (0.5 to 7.2)</td>
<td>1.27 (1.03–1.58)</td>
<td>98.6</td>
</tr>
<tr>
<td>D-dimer cohort¶</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>High level</td>
<td>264/339 (77.9)</td>
<td>210/291 (72.2)</td>
<td>5.1 (0.0 to 9.9)</td>
<td>1.31 (1.00–1.76)</td>
<td>97.3</td>
</tr>
<tr>
<td>Low level</td>
<td>463/570 (81.2)</td>
<td>403/505 (79.8)</td>
<td>3.0 (−1.2 to 6.3)</td>
<td>1.22 (0.93–1.57)</td>
<td>92.9</td>
</tr>
<tr>
<td>Unknown level</td>
<td>212/262 (80.9)</td>
<td>188/252 (74.6)</td>
<td>4.9 (0.00 to 9.9)</td>
<td>1.32 (1.00–1.86)</td>
<td>97.3</td>
</tr>
</tbody>
</table>
## Secondary Endpoints: Severe Covid-19

### Table 2. Primary and Secondary Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Therapeutic-Dose Anticoagulation (N=536)</th>
<th>Usual-Care Thromboprophylaxis (N=567)</th>
<th>Adjusted Difference in Risk (95% Credible Interval)</th>
<th>Adjusted Odds Ratio (95% Credible Interval)</th>
<th>Probability of Superiority %</th>
<th>Probability of Futility %</th>
<th>Probability of Inferiority %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ support–free days up to day 21†‡</td>
<td>median no. (IQR)</td>
<td>percentage points</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival to hospital discharge‡</td>
<td>335/534 (62.7)</td>
<td>364/564 (64.5)</td>
<td>–4.1 (−10.7 to 2.4)</td>
<td>0.84 (0.64 to 1.11)</td>
<td>10.8</td>
<td>99.6</td>
<td>89.2</td>
</tr>
<tr>
<td>Major thrombotic events or death§</td>
<td>213/531 (40.1)</td>
<td>230/560 (41.1)</td>
<td>1.0 (−5.6 to 7.4)</td>
<td>1.04 (0.79 to 1.35)</td>
<td>40.3</td>
<td>—</td>
<td>59.7</td>
</tr>
<tr>
<td>Major thrombotic events¶</td>
<td>34/530 (6.4)</td>
<td>58/559 (10.4)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Death in hospital</td>
<td>199/534 (37.3)</td>
<td>200/564 (35.5)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Any thrombotic events or death§</td>
<td>217/531 (40.9)</td>
<td>232/560 (41.4)</td>
<td>1.5 (−4.9 to 8.0)</td>
<td>1.06 (0.81 to 1.38)</td>
<td>33.4</td>
<td>—</td>
<td>66.6</td>
</tr>
<tr>
<td>Any thrombotic events¶</td>
<td>38/530 (7.2)</td>
<td>62/559 (11.1)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Death in hospital</td>
<td>199/534 (37.3)</td>
<td>200/564 (35.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding§</td>
<td>20/529 (3.8)</td>
<td>13/562 (2.3)</td>
<td>1.1 (−0.6 to 4.4)</td>
<td>1.48 (0.75 to 3.04)</td>
<td>12.8</td>
<td>—</td>
<td>87.2</td>
</tr>
</tbody>
</table>
Secondary Endpoints: Moderate Covid-19

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Therapeutic-Dose Anticoagulation</th>
<th>Usual-Care Thromboprophylaxis</th>
<th>Adjusted Difference in Risk (95% Credible Interval)</th>
<th>Adjusted Odds Ratio (95% Credible Interval)</th>
<th>Probability of Effect of Therapeutic-Dose Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival until hospital discharge</td>
<td>1085/1171 (92.7)</td>
<td>962/1048 (91.8)</td>
<td>1.3 (−1.1 to 3.2)</td>
<td>1.21 (0.87 to 1.68)§</td>
<td>87.1¶</td>
</tr>
<tr>
<td>Survival without organ support at 28 days</td>
<td>932/1175 (79.3)</td>
<td>789/1046 (75.4)</td>
<td>4.5 (0.9 to 7.7)</td>
<td>1.30 (1.05 to 1.61)</td>
<td>99.1¶</td>
</tr>
<tr>
<td>Progression to intubation or death**</td>
<td>129/1181 (10.9)</td>
<td>127/1050 (12.1)</td>
<td>−1.9 (−4.1 to 0.7)</td>
<td>0.82 (0.63 to 1.07)</td>
<td>92.2¶</td>
</tr>
<tr>
<td>Major thrombotic event or death</td>
<td>94/1180 (8.0)</td>
<td>104/1046 (9.9)</td>
<td>−2.6 (−4.4 to −0.2)</td>
<td>0.72 (0.53 to 0.98)</td>
<td>98.0¶</td>
</tr>
<tr>
<td>Major thrombotic event</td>
<td>13/1180 (1.1)</td>
<td>22/1046 (2.1)</td>
<td></td>
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</tr>
<tr>
<td>Death in hospital</td>
<td>86/1180 (7.3)</td>
<td>86/1046 (8.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>22/1180 (1.9)</td>
<td>9/1047 (0.9)</td>
<td>0.7 (−0.1 to 2.3)</td>
<td>1.80 (0.90 to 3.74)</td>
<td>95.5††</td>
</tr>
</tbody>
</table>
Summary: Therapeutic-Dose Anticoagulation in Covid-19

• Critically ill patients with Covid-19 (on ICU organ support)
  – High probability of **harm** on organ support-free days and survival (95%)

• Non-critically ill patients with Covid-19 (not on ICU organ support)
  – High probability of **benefit**
    • ↑ organ support-free days to day 21 (98.6%)
    • ↓ progression to intubation or death (92.2%)
    • ↓ major thrombotic event or death (98.0%)
  – Low rate of major bleeding (~1% absolute risk increase)
Reply & Recap

mpRCT of Therapeutic Anticoagulation in Covid-19

Ryan Zarychanski MD, MSc
University of Manitoba, Winnipeg, Canada
CancerCare Manitoba, Winnipeg, Canada
What goes down relatively easy

• The Summary
  – High probability of **harm** in critically ill patients (95%)
  – High probability of **benefit** in non critically patients (99%)
    – ↑ organ support-free days to day 21 (98.6%)
    – ↓ progression to intubation or death (92.2%)
    – ↓ major thrombotic event or death (98.0%)
    – Low rate of major bleeding (~1% absolute risk increase)
What may require time to digest, but are strengths

- Bayesian framework
- Organ-support free days
- Responsive-adaptive randomization
- Heterogeneity of treatment effects
What could be cause for confusion?

• The mpRCT did not employ the use of non-concurrent controls

• Fitting in the result of the mpRCT into the current literature:
  – Results appear to be consistent with:
  – INSPIRATION (critically ill patients) - augmented anticoagulation with heparin was of no benefit
  – RAPID-COAG (non-critically ill patients) – therapeutic dose anticoagulation with heparin improved survival and reduced the need for ICU-level organ support
What we hope will be enduring contributions of the mpRCT

• Utility of adaptive platform trials
  – Re-affirming our ability to both learn and do in the face of multiple unknowns

• Model of global collaboration
  – Autonomous platforms contributing within a single trial
  – Data federation
  – DSMB harmonization
  – Inclusive authorship
Practice Implications: Therapeutic-Dose Anticoagulation in Covid-19

• Critically ill patients with Covid-19 (on ICU organ support)
  – High probability of **harm** on organ support-free days and survival (95%)
• Non-critically ill patients with Covid-19 (not on ICU organ support)
  – High probability of **benefit**
    • ↑ organ support-free days to day 21 (98.6%)
    • ↓ progression to intubation or death (92.2%)
    • ↓ major thrombotic event or death (98.0%)
  – Low rate of major bleeding (~1% absolute risk increase)
THANK YOU!!!