ATTACC, ACTIV-4a & REMAP-CAP
multiplatform RCT

Results of interim analysis

Release date: January 28, 2021
Results are pre-publication, not from locked databases and not peer reviewed
Thrombosis and COVID-19

• Thrombosis is a prominent feature—5-30% will develop thrombosis\(^1,2\)
• Venous and arterial events have been reported
• Microthrombosis may be a key mediator of COVID-19-related organ dysfunction, morbidity, and mortality

D-dimer

• Elevated D-dimer is associated with increased mortality and thrombosis
• ISTH recommends measuring D-dimer in hospitalized patients¹
• It is unknown how the D-dimer value should impact clinical decision making – intensity of care or anticoagulation strategies

Observational data:

- Retrospective cohort in New York City (n=2773)
  - Therapeutic anticoagulation associated with increased survival
  - Longer duration of anticoagulation associated with lower mortality in mechanically ventilated patients
  - Major bleeding 3% (therapeutic dose) vs 2% (standard dose)
- Limitations included survivor bias and confounding by indication
- Similar benefits of anticoagulants in other (weak) observational studies

Paranjpe I et al. J Am Coll Cardiol 2020;76:122-4
Hypothesis

• In hospitalized patients with confirmed COVID-19, therapeutic anticoagulation safely improves clinical outcomes
Multiplatform RCT (mpRCT)
A collaboration between three trial platforms

- **ATTACC**: Antithrombotic therapy to ameliorate complications of COVID-19
  - 58 sites in Canada, USA, Brazil, Mexico
- **REMAP-CAP**: Randomized embedded multi-factorial, adaptive platform trial
  - 290 sites in Canada, USA, UK, Ireland, EU, Saudi Arabia, Australia, New Zealand, Nepal, India, Pakistan
- **ACTIV-4a**: Accelerating COVID-19 therapeutic interventions and vaccines
  - 60 activated sites in USA and Spain

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Multiplatform RCT
A collaboration between three trial platforms

• Three independent international trial platforms
• Harmonized protocols
• Common primary / key secondary / safety outcomes
• Common combined prospective superiority and futility rules

• Goal: To answer a pressing question in COVID-19 management as effectively and as quickly as possible by combining trial enrolment across platforms
Multiplatform RCT

**Design:** Randomized, Open-Label, Adaptive Bayesian Trial

**Patients:** Adults hospitalized patients for COVID-19
- Signs and symptoms consistent with COVID-19
- Randomized within 72 hours of admission
  - 48 hours in REMAP-CAP for severe state (ICU) patients
Multiplatform RCT

**Intervention:**
- Therapeutic low molecular weight heparin (LMWH) or unfractionated heparin (UFH)
- therapeutic-dose as per hospital policy for treatment of venous thrombotic events (VTE)

**Control:**
- Usual care pharmacologic VTE prophylaxis
  - Usual care defined according to hospital policy or prescriber practice

**Duration of therapy:**
- 14 days or hospital discharge (or liberation from supplemental oxygen; ATTACC), whichever occurred first
Multiplatform RCT

Primary outcome: Organ support-free days (OSFDs to day 21)

• Ordinal scale combination of in-hospital mortality and organ support-free days
  – Days free of organ support through 21 days for survivors (0,1,2, ..., 21); Mortality assigned a value of −1 (worst score).
• A composite measuring clinically relevant morbidity and mortality

*Organ support = ICU level of care and receipt of mechanical ventilation, vasopressors, ECMO or high flow nasal oxygen
Multiplatform RCT

Key Secondary outcomes:

- **Safety**: Major hemorrhage (ISTH criteria) and HIT
- **Efficacy**: Mortality, intubation, major thrombosis, PE, VTE, stroke, MI, length of stay in ICU and hospital
Multiplatform RCT

• A priori, the mpRCT main analysis population was stratified by:
  – Severe state/critically ill patients (receiving organ support/ICU level care)
  – Moderate state patients (hospitalized but not initially requiring ICU therapies/level of care)
• Moderate patients further stratified according baseline D-dimer:
  – High D-dimer (baseline D-dimer ≥2x local upper limit of normal)
  – Low D-dimer (baseline D-dimer <2x local upper limit of normal)
  – Unknown (baseline D-dimer unknown)
ATTACC/REMAP-CAP/ACTIV-4a mpRCT

Adaptive Design Decision Rules

• Decision Rules
  • Declare Superiority: >99% posterior probability of superiority on primary outcome (proportional odds ratio > 1)
  • Declare Futility: <5% posterior probability of at least a 20% improvement for primary outcome (proportional odds ratio > 1.2)

• Decisions are evaluated separately for each stratum of D-dimer:
  • Severe and moderate (‘high’ or ‘low’ D-dimer) – stopping triggers enabled any stratum to stop as soon as results are available, speeding evidence generation
ATTACC, REMAP-CAP, and ACTIV-4a mpRCT

<table>
<thead>
<tr>
<th></th>
<th>ATTACC</th>
<th>ACTIV-4a/PROTECT</th>
<th>REMAP-CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platform/Domain leads</td>
<td>Ryan Zarychanski, Patrick Lawler, Ewan Goligher</td>
<td>Judy Hochman, Matthew Neal, Jeff Berger</td>
<td>Ryan Zarychanski, Ewan Goligher (Domain leads)</td>
</tr>
<tr>
<td>Primary funders</td>
<td>CIHR, LifeArc, Thistledown Foundation, Research Manitoba, Peter Munk Cardiac Centre, Ontario Together</td>
<td>NIH/NHLBI</td>
<td>NIHR (UK), NHMRC (AUS), PREPARE/RECOVER (EU), CIHR (CDN), UPMC (USA), HRC (NZ), Minderoo Foundation</td>
</tr>
<tr>
<td>Countries</td>
<td>4</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Sites</td>
<td>58</td>
<td>~60 activated of 190</td>
<td>290</td>
</tr>
<tr>
<td>Data Management Center</td>
<td>Socar (Switzerland)</td>
<td>Socar (Switzerland)</td>
<td>Spiral (Australia), UPMC (USA)</td>
</tr>
<tr>
<td>Platform Coordinating Center</td>
<td>Ozmosis Research / University of Manitoba</td>
<td>University of Pittsburgh and NYU</td>
<td>Monash University</td>
</tr>
<tr>
<td>Statistical Analysis Committee</td>
<td>Berry Consultants (Texas, USA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DSMB recommendation (accepted by all 3 platforms)

Moderate state (January 21, 2021)

All three platform DSMBs met and reviewed data from each of the platforms and each recommended

Discontinue enrolling patients as the pre-specified superiority stopping boundary has been achieved in both D-dimer strata. The safety profile supports the benefit of therapeutic anticoagulation in this patient population.
DSMB recommendation (accepted by all 3 platforms)

Severe state (December 19, 2020)

All three platform DSMBs met and reviewed data from each of the platforms and each recommended
(Severe state patients defined as admitted to an ICU AND receiving organ support (i.e. high flow nasal oxygen, receiving non-invasive or invasive mechanical ventilation, or are requiring vasopressor/inotrope)

• Discontinue enrolling patients as the pre-specified futility stopping boundary for therapeutic anticoagulation has been achieved

• Protocolized anticoagulation interventions in critically ill already randomized patients requiring organ support should cease, but follow-up should continue according to protocol
Platform Enrollment at Interim analysis

January 21, 2021

<table>
<thead>
<tr>
<th>Platform</th>
<th>Randomized (N)</th>
<th></th>
<th>Known OSFD (n)**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate</td>
<td>Severe</td>
<td>Total</td>
</tr>
<tr>
<td>ATTACC</td>
<td>1036</td>
<td>35</td>
<td>1071</td>
</tr>
<tr>
<td>ACTIV-4A</td>
<td>468</td>
<td>110</td>
<td>578</td>
</tr>
<tr>
<td>PROTECT*</td>
<td>52</td>
<td>19</td>
<td>71</td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td>216</td>
<td>959</td>
<td>1175</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1772</td>
<td>1123</td>
<td>2895</td>
</tr>
</tbody>
</table>

*PROTECT patients represent the vanguard/pilot phase of ACTIV4a

**Followed for 21-days and have a known outcome at the time of interim analysis
Baseline Age and Sex (Randomized as of January 4, 2021)

Dark shaded portion of bars represents those who have reached 21 days with known OSFD outcome

Pre-publication interim data, not from a locked database and not peer reviewed
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Primary outcome

<table>
<thead>
<tr>
<th>State &amp; D-dimer Strata</th>
<th>Proportional Odds Ratio Median (95% CrI)</th>
<th>Trial Statistical Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate state, low D-dimer</td>
<td>1.57 (1.14 - 2.19)</td>
<td><strong>Superiority</strong> [Probability of OR&gt;1 = 0.997]</td>
</tr>
<tr>
<td>Moderate state, high D-dimer</td>
<td>1.53 (1.09 - 2.17)</td>
<td><strong>Superiority</strong> [Probability of OR&gt;1 = 0.991]</td>
</tr>
<tr>
<td>Moderate state, missing D-dimer</td>
<td>1.51 (1.06 – 2.15)</td>
<td>n/a</td>
</tr>
<tr>
<td>Severe state</td>
<td>0.76 (0.60 – 0.97)</td>
<td><strong>Futility</strong> * [Probability of OR&gt;1.2 &lt; 0.001]</td>
</tr>
</tbody>
</table>

* Posterior probability of **in inferiority** [Probability of OR<1 = 0.985]

⚠️ Not evaluated for stopping at interim

OR >1 represents benefit. A higher OR occurs when either mortality is improved and/or if those who survive have reduced requirement for organ support.
Organ support-free days

Overall moderate state:
Requirement for organ support
Prophylactic anticoagulation – ~23%
Therapeutic anticoagulation – ~16%

Proportion requiring organ support represents a post-hoc analysis and is included to enhance clinical interpretation

Approx. proportion requiring organ support
~25%
~18%
~19%
~13%
~27%
~20%

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**Mortality** – not primary outcome (part of OSFDs)

<table>
<thead>
<tr>
<th>INTERIM</th>
<th>Moderate State</th>
<th>Severe State</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Therapeutic anticoagulation N = 699</td>
<td>Usual Care venous thromboprophylaxis N = 699</td>
</tr>
<tr>
<td>Mortality</td>
<td>40 (5.7%)</td>
<td>54 (7.7%)</td>
</tr>
<tr>
<td></td>
<td>Therapeutic anticoagulation N = 453</td>
<td>Usual Care venous thromboprophylaxis N = 442</td>
</tr>
<tr>
<td></td>
<td>160 (35.3%)</td>
<td>144 (32.6%)</td>
</tr>
</tbody>
</table>

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Major Bleeding

<table>
<thead>
<tr>
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<th>Moderate State</th>
<th>Severe State</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERIM</td>
<td><img src="image.png" alt="Image" /></td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>Therapeutic anticoagulation (N = 853)</td>
<td>Usual Care venous thromboprophylaxis (N = 742)</td>
<td>Therapeutic anticoagulation (N = 460)</td>
</tr>
<tr>
<td>Major Bleeding$^\phi$</td>
<td>14 (1.6%)</td>
<td>7 (0.9%)</td>
</tr>
</tbody>
</table>

$^\phi$Events reported are preliminary, unadjudicated, and potentially subject to reporting bias

Small differences in denominators when compared to mortality/OSFD exist due to variation in the days efficacy and safety outcome were forwarded by each platform to individual DSMBs and to the Statistical Analysis Committee.
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Thrombotic events

<table>
<thead>
<tr>
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<th>Severe State</th>
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</thead>
<tbody>
<tr>
<td><strong>INTERIM</strong></td>
<td>Therapeutic anticoagulation N = 853</td>
<td>Therapeutic anticoagulation N = 460</td>
</tr>
<tr>
<td></td>
<td>Usual Care venous thromboprophylaxis N = 742</td>
<td>Usual Care venous thromboprophylaxis N = 448</td>
</tr>
<tr>
<td>Thrombotic events*Φ</td>
<td>16 (1.9%)</td>
<td>24 (3.2%)</td>
</tr>
<tr>
<td></td>
<td>31 (6.7%)</td>
<td>53 (11.8%)</td>
</tr>
</tbody>
</table>

*Defined as Deep Vein Thrombosis, Pulmonary Embolism, Myocardial infarction, Ischemic Stroke, Other thrombotic event
ΦEvents reported are preliminary, unadjudicated, and potentially subject to reporting bias

Small differences in denominators when compared to mortality/OSFD exist due to variation in the days efficacy and safety outcome were forwarded by each platform to individual DSMBs and to the Statistical Analysis Committee.
Interim conclusion

• **In Moderate State:** Hospitalized, not on ICU Organ-Support
  – Therapeutic dose superior to usual care venous thromboprophylaxis with regard to organ support-free days in each d-dimer subgroup
  – Positive effect across morbidity and mortality components of primary endpoint
  – Major bleeding rate <2% on therapeutic anticoagulation
Interim conclusion

- **In Severe State** (Patients on ICU-level organ support at baseline)
  - Therapeutic heparin does not improve OSFDs to day 21
  - Probability that therapeutic heparin is inferior (harmful) compared to thromboprophylaxis is 98.5%
  - Numeric increase in major bleeding events and mortality, but rate of major bleeding was in the predicted range for critically ill patients on therapeutic anticoagulation (3.7%)
Interim discussion point:
Transition from ward to ICU (moderate to severe)

• Given divergent results in the severe (futile with high probability of inferiority/harm) vs moderate (superiority) states, how should we manage therapeutic anticoagulation (TAC) for moderate patients who become critically ill?
  – The trial protocol specified TAC to continue when patients became critically ill
    • This protocol arm was overall superior to usual care
  – Unknown whether TAC would have had greater overall benefit in moderate state if it had been discontinued in patients who became critically ill
  – Research ongoing to answer this question