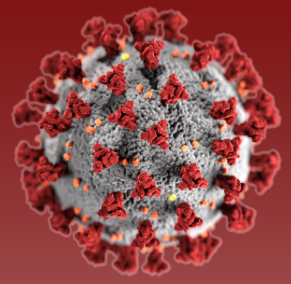


ATTACC, ACTIV-4a & REMAP-CAP

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Results are pre-publication, not from locked databases and not peer reviewed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

1. Tang N et al. J Thomb Haemost. 2020;18:844-7
2. Klok FA et al. Thromb Res. 2020;191:145-7

Release date: January 28, 2021

D-dimer

- Elevated D-dimer is associated with increased mortality and thrombosis
- ISTH recommends measuring D-dimer in hospitalized patients[1]
- It is unknown how the D-dimer value should impact clinical decision making – intensity of care or anticoagulation strategies

1. Thachil J et al. J Thromb Haemost. 2020;18:1023-6

Release date: January 28, 2021

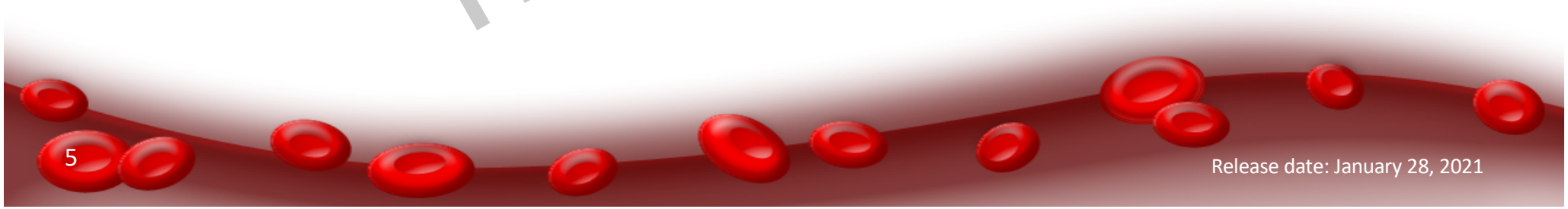
Observational data:

- 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

Release date: January 28, 2021

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

Release date: January 28, 2021

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

Release date: January 28, 2021

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)

Release date: January 28, 2021

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

Pre-publication interim data, not from a locked database and not peer reviewed

INTERIM

ATTACC, REMAP-CAP, and ACTIV-4a mpRCT

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

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

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

Platform Enrollment at Interim analysis

January 21, 2021

INTERIM

Platform	Randomized (N)			Known OSFD (n)**		
	Moderate	Severe	Total	Moderate	Severe	Total
ATTACC	1036	35	1071	906	35	941
ACTIV-4A	468	110	578	278	91	369
PROTECT*	52	19	71	52	19	71
REMAP-CAP	216	959	1175	162	750	912
Total	1772	1123	2895	1398	895	2293

*PROTECT patients represent the vanguard/pilot phase of ACTIV4a

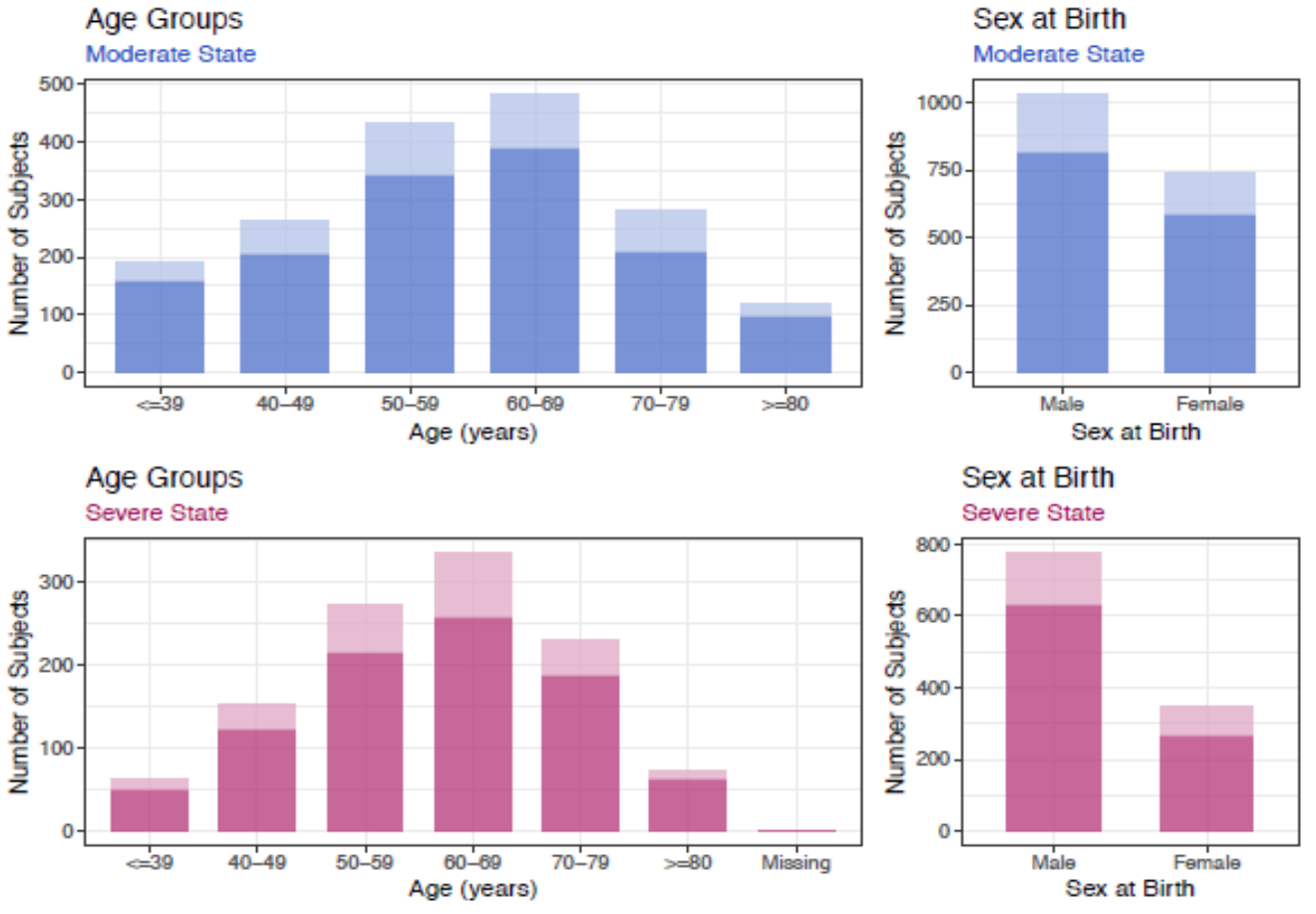
**Followed for 21-days and have a known outcome at the time of interim analysis

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

Baseline Age and Sex (Randomized as of January 4, 2021)

INTERIM

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



Release date: January 28, 2021

ATTACC, REMAP-CAP, and ACTIV IV-4a mpRCT

Primary outcome

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

* Posterior probability of **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

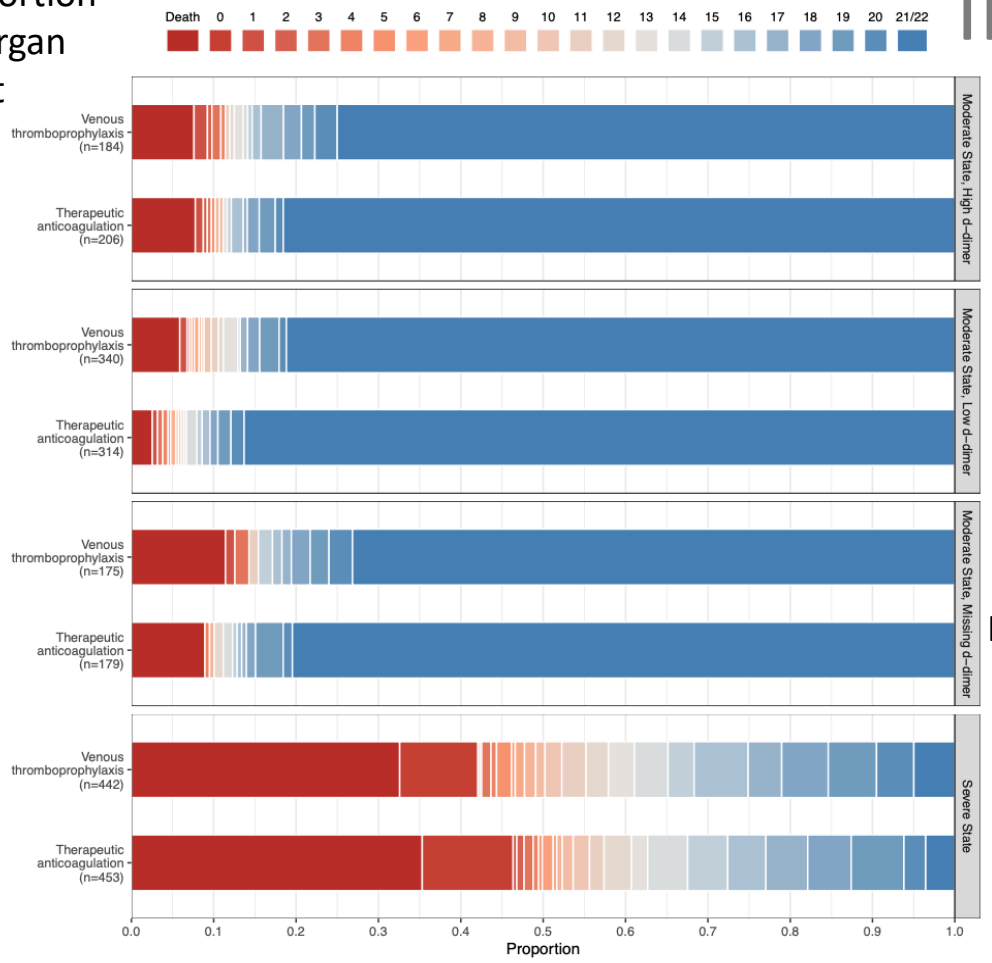
Release date: January 28, 2021

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

Organ support-free days

INTERIM

Approx. proportion requiring organ support



~25%
~18%

Moderate state; HIGH D-dimer

~19%
~13%

Moderate state; LOW D-dimer

~27%
~20%

Moderate state; MISSING D-dimer

Severe state

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

Release date: January 28, 2021

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

ATTACC, REMAP-CAP, and ACTIV-4a mpRCT

Mortality – not primary outcome (part of OSFDs)

	Moderate State		Severe State	
INTERIM	Therapeutic anticoagulation N = 699	Usual Care venous thromboprophylaxis N = 699	Therapeutic anticoagulation N = 453	Usual Care venous thromboprophylaxis N = 442
Mortality	40 (5.7%)	54 (7.7%)	160 (35.3%)	144 (32.6%)

Release date: January 28, 2021

ATTACC, REMAP-CAP, and ACTIV-4a mpRCT

Major Bleeding

	Moderate State		Severe State	
INTERIM	Therapeutic anticoagulation N = 853	Usual Care venous thromboprophylaxis N = 742	Therapeutic anticoagulation N = 460	Usual Care venous thromboprophylaxis N = 448
Major Bleeding[Φ]	14 (1.6%)	7 (0.9%)	17 (3.7%)	8 (1.8%)

[Φ]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.

ATTACC, REMAP-CAP, and ACTIV-4a mpRCT

Thrombotic events

	Moderate State		Severe State	
INTERIM	Therapeutic anticoagulation N = 853	Usual Care venous thromboprophylaxis N = 742	Therapeutic anticoagulation N = 460	Usual Care venous thromboprophylaxis N = 448
Thrombotic events*Φ	16 (1.9%)	24 (3.2%)	31 (6.7%)	53 (11.8%)

*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.

Release date: January 28, 2021

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