CancerCare Manitoba
ActionCancerManitoba

Blood Disorders Day 2021

FOR Health Professionals

Thrombosis and anticoagulation in COVID-19

Ryan Zarychanski, MD, MSc, FRCPC, Hematologist

Associate Professor Departments of Internal Medicine, Pharmacy and Community Health Sciences, Rady Faculty of Health Sciences, University of Manitoba

Clinician-Scientist, CancerCare Manitoba, Research Institute of Oncology & Hematology

Lyonel G. Israels Research Chair in Hematology, University of Manitoba

University of Manitoba

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Presenter Disclosure

Faculty : Ryan Zarychanski

Relationships with commercial interests:

- **Grants/Research Support:** No
- **Speakers Bureau/Honoraria:** No
- **Consulting Fees:** No
- **Patents and Liscencing Fees:** No

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Mitigating Potential Bias

- I will be making off-label recommendations based on high quality RCT data

Learning Objectives

1. Discuss thrombosis risk in COVID-19
2. Present evidence-informed strategies to inform up-front anticoagulation strategies
   - Hospitalized non-critically ill (ward-like) patients
   - Critically ill (ICU-like) patients
3. Provide treatment recommendations

Clinical case

- 55 yo male admitted to hospital with dyspnea
  - Diagnosed with COVID-19 by PCR
  - 87% on room air. Placed on 10 L NP
  - Treated with dexamethasone, tocilizumab
  - Standard-dose VTE prophylaxis (dalteparin 5000 U S/Q OD)

  - Is there a role for higher-dose anticoagulants to reduce thrombosis and improve clinical outcomes?

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

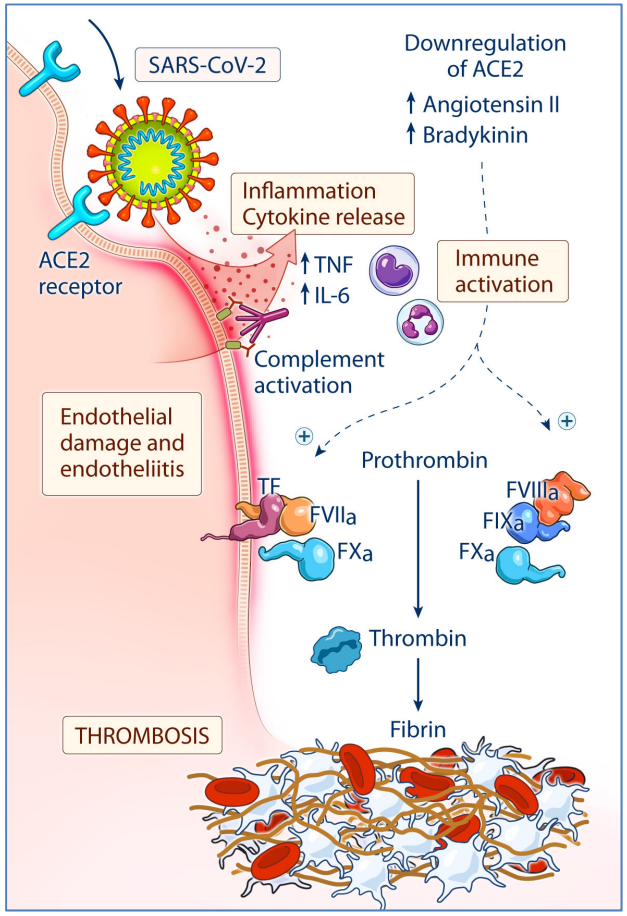
Thrombosis and COVID-19

- 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

Mechanisms of Thrombosis in COVID-19

- Endothelial injury / tissue factor expression
- Inflammation and immune activation
- ACE-2 down regulation
- NETs/NETosis
- Platelet and macrophage activation
- Complement activation
- Increased fibrinogen; reduced fibrinolysis
- Reduced natural anticoagulants
- ? antiphospholipid antibodies



Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

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

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

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Clinical Question

- In hospitalized patients with confirmed COVID-19, do enhanced anticoagulation doses (therapeutic- or ‘intermediate-dose’ safely improve clinical outcomes

Multi-platform RCT (mpRCT)

- **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

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

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

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Exclusion Criteria

ATTACC	ACTIV-4a/PROTECT	REMAP-CAP
• **Active bleeding** • **Risk factors for bleeding** • **Indication for therapeutic anticoagulation** • Platelet count <50 x109/L, INR >2.0, or baseline aPTT >50 (if available per SOC testing) • Hemoglobin <80 g/L • Bacterial endocarditis • **History of HIT** • **Dual anti-platelet therapy** • Imminent demise anticipated • Enrollment in other trials related to anticoagulation	• Contraindication to anticoagulation • Indication for therapeutic anticoagulation in the case that it cannot be stopped • Platelet count < 50x 10^9/L • Hemoglobin < 8 g/dL • Pregnancy • Patient on dual anti-platelet therapy, when the P2Y12 agent cannot be stopped safely	• Contraindication to therapeutic anticoagulation • Requirement for therapeutic anticoagulation • Dual anti-platelet therapy • Enrolment in another anticoagulation trial • Known or suspected previous adverse reaction to UFH or LMWH • Treating clinician believes that participation in the domain would not be in the best interests of the patient

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

mpRCT – Primary Outcome

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. ie. Burden of disease at a patient and systems level

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

mpRCT – Secondary outcomes

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

mpRCT – Analysis population

- **Main analysis population was stratified by:**
  - **Critically ill** patients (receiving ICU-level organ support)
  - **Moderately ill** patients (hospitalized but not initially requiring ICU therapies/level of care)
    - Moderately ill 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)

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

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, CCMBF, VGH Foundation.	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 Committee	Berry Consultants (Texas, USA)		

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Primary Outcome

State & D-dimer Strata	Proportional Odds Ratio Median (95% CrI)	Trial Statistical Conclusion
ALL MODERATE	1.29 (1.04 – 1.61)	**Superiority** [Probability of OR>1 = 99%]
Moderate state, low D-dimer	1.22 (0.93 – 1.57)	**Superiority** [Probability of OR>1 = 93%]
Moderate state, high D-dimer	1.31 (1.00 – 1.76)	**Superiority** [Probability of OR>1 = 97%]
Moderate state, missing D-dimer	1.32 (1.00 – 1.86)	n/a[⍋]
SEVERE	0.83 (0.67 – 1.03)	**Inferiority**[Probability of OR<1 = 95%]

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

In hospital survival

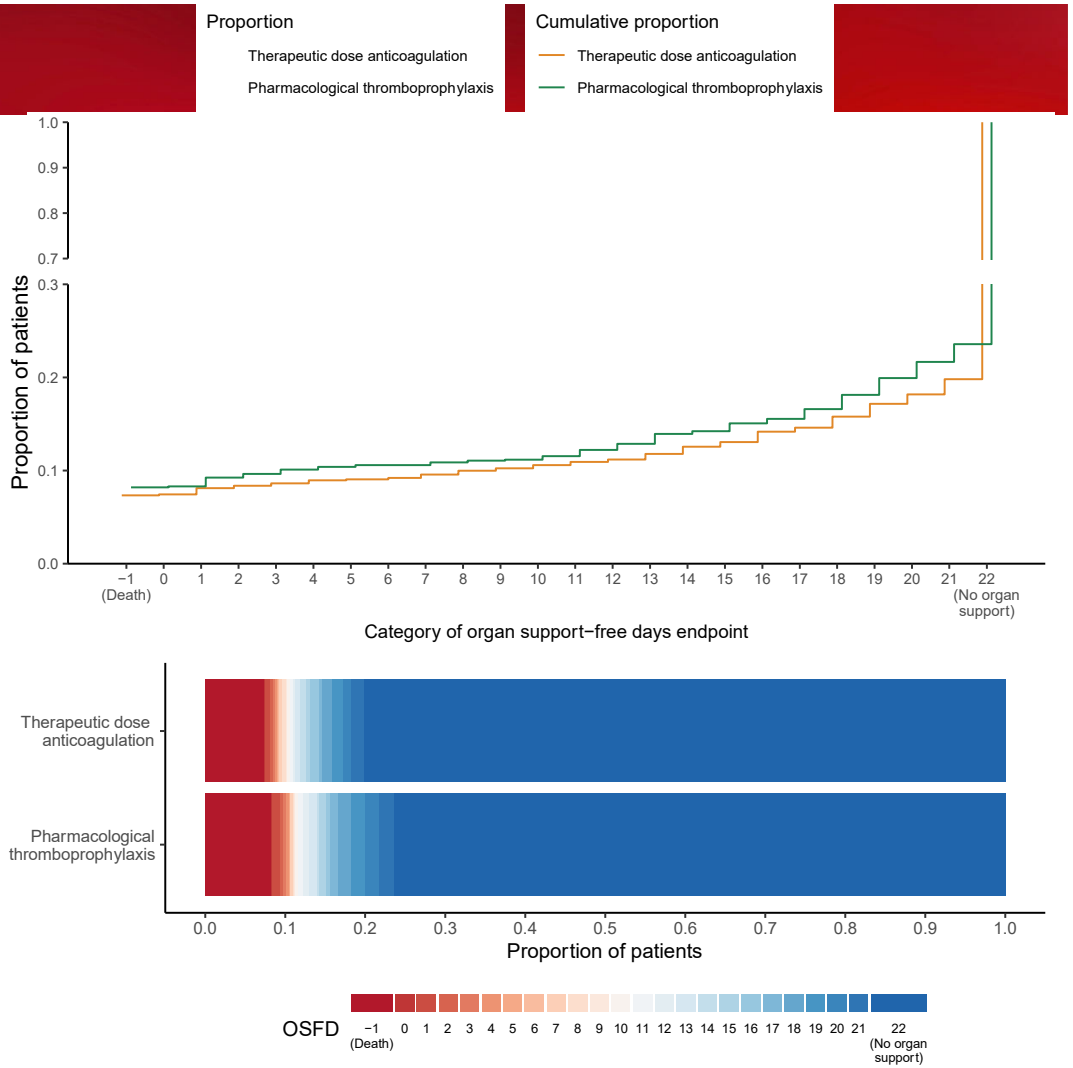
State & D-dimer Strata	Proportional Odds Ratio Median (95% CrI)	Trial Statistical Conclusion
ALL MODERATE	1.20 (0.86 – 1.63)	**Superiority** [Probability of OR>1 = 84%]
Moderate state, low D-dimer	1.21 (0.81 – 1.74)	**Superiority** [Probability of OR>1 = 82%]
Moderate state, high D-dimer	1.16 (0.79 – 1.71)	**Superiority** [Probability of OR>1 = 79%]
Moderate state, missing D-dimer	1.20 (0.81 – 1.83)	n/a[Δ]
SEVERE	0.85 (0.64 – 1.10)	**Inferiority**[Probability of OR<1 = 89%]

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Primary outcome:

Non-critically ill patients (not on organ support at baseline)

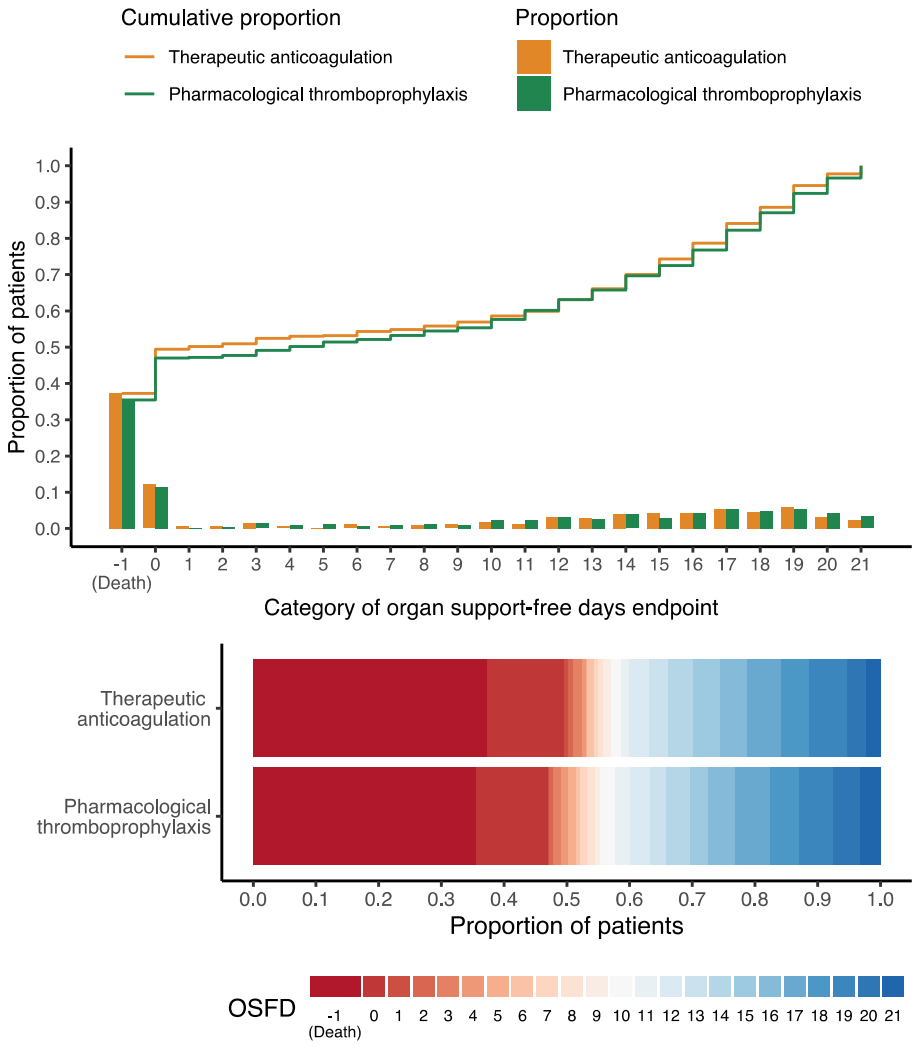


Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Primary outcome:

Critically ill patients (not on organ support at baseline)

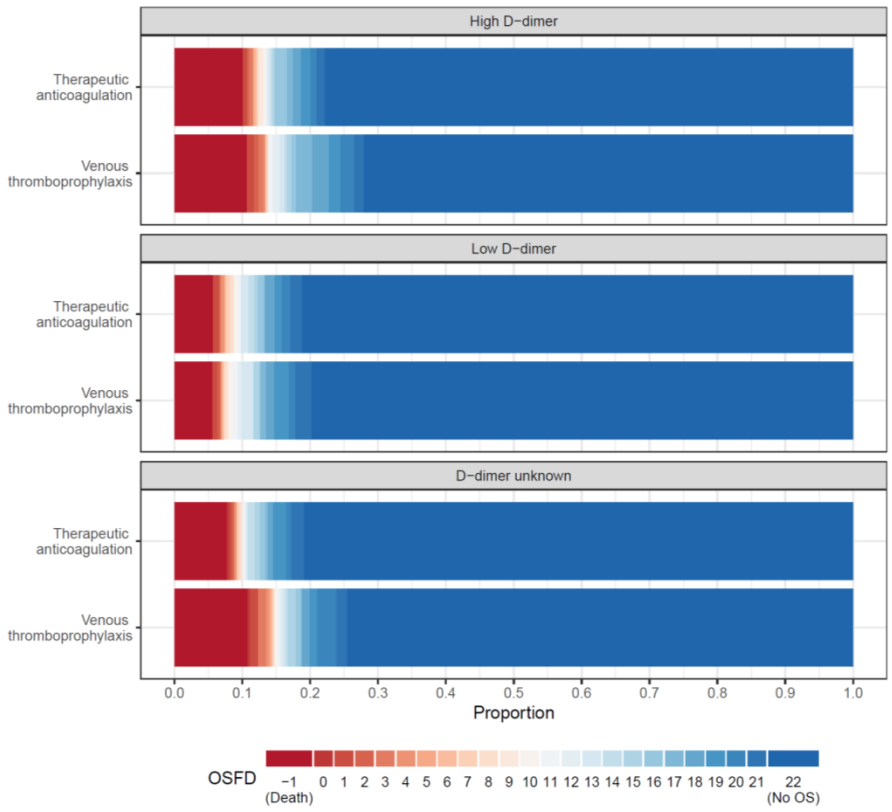


Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Primary outcome:

Non-critically ill patients (not on organ support at baseline)



HIGH D-dimer

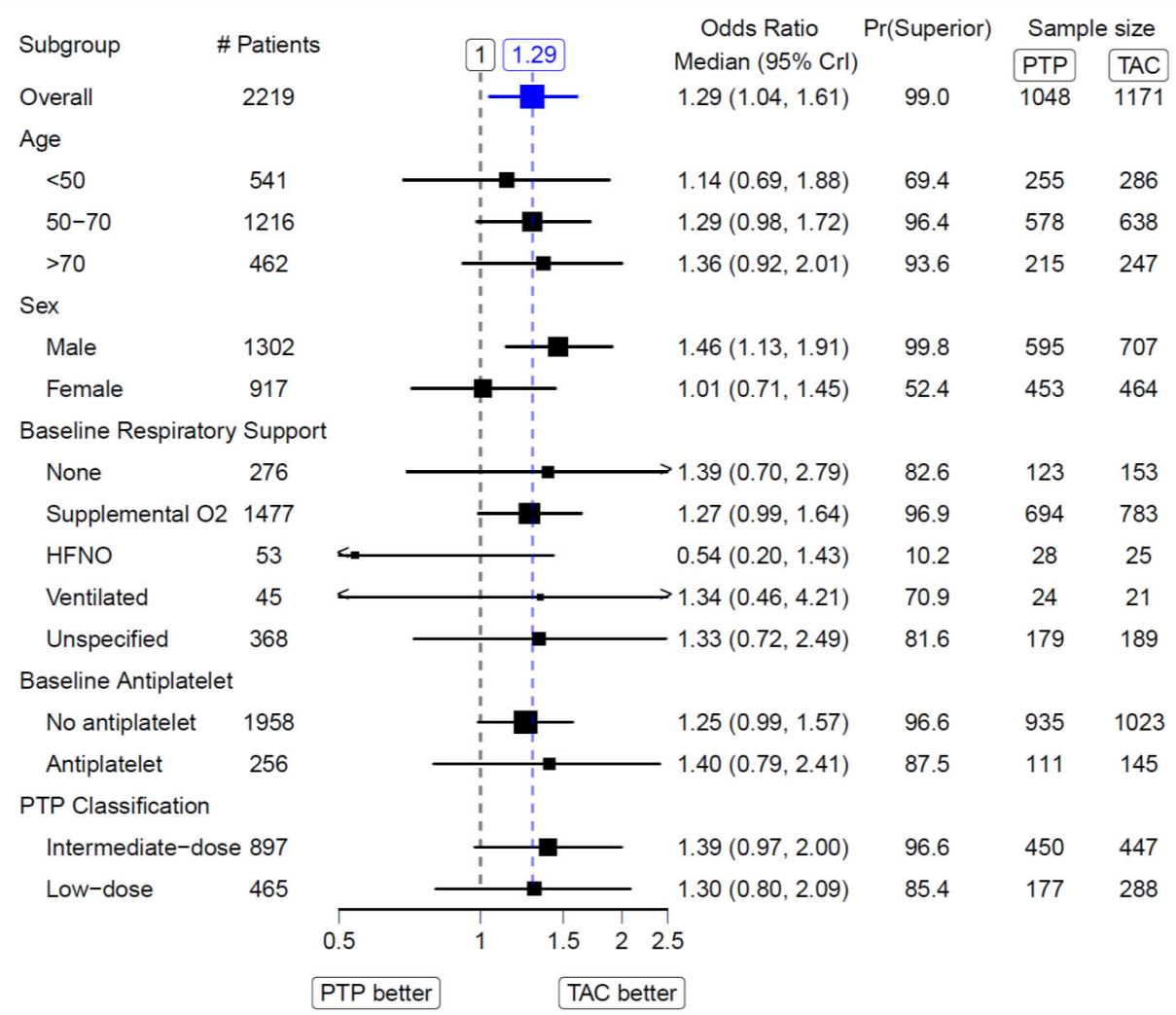
LOW D-dimer

Unknown D-dimer

Blood Disorders Day 2021

Primary outcome:

Non-critically ill patients (not on organ support at baseline)

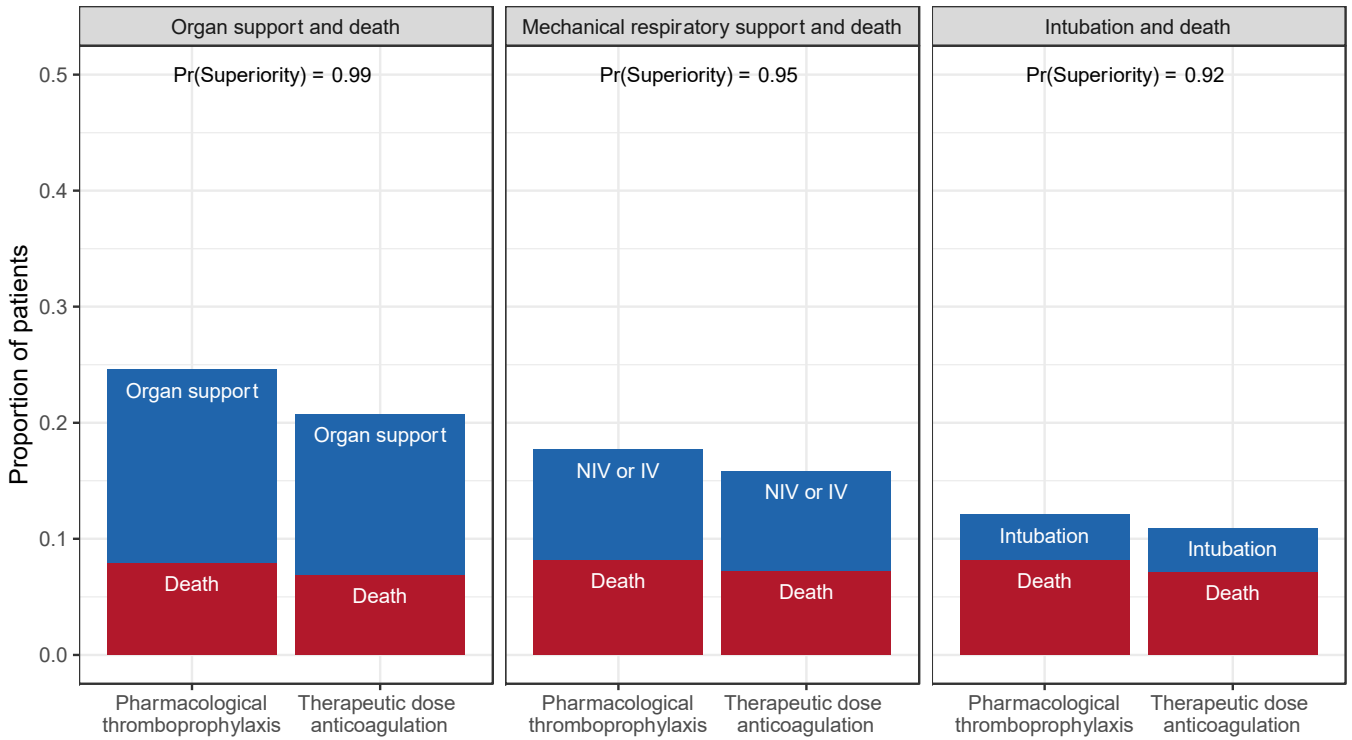


Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Adjusted absolute reduction of death/organ support = 4.5%

Non-critically ill patients (not on organ support at baseline)



Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Major thrombotic events and death

	Moderately ill (not on organ support at baseline)		**Critically ill patients** (Organ support at baseline)	
	Therapeutic anticoagulation	Usual Care venous thromboprophylaxis	Therapeutic anticoagulation	Usual Care venous thromboprophylaxis
Major thrombotic events*	8.6%	10.2%	40.1%	41.1%

*Defined as Pulmonary Embolism, Myocardial infarction, Ischemic Stroke, systemic arterial embolism

Summary – non critically ill patients

- Therapeutic dose heparin improves:
  - Survival to hospital discharge without need for organ support
  - Survival without intubation
  - Survival without thrombosis
  - Survival to hospital discharge

Conclusion

- **In Moderately ill patients:** Hospitalized, not on ICU Organ-Support
  - Therapeutic-dose anticoagulation increases the probability of survival to hospital discharge with reduced need for ICU level organ support
    - 14 days or until hospital discharge or liberation from supplemental O2
  - Positive effect across morbidity and mortality components of primary endpoint
  - Major bleeding rate <2% on therapeutic anticoagulation
  - Absolute benefit is higher in patients with elevated d-dimer and increased comorbidities

Conclusion

- **In Critically ill patients:** Hospitalized, on ICU Organ-Support
  - Therapeutic heparin does not improve survival or result in improvements in organ free support
  - Probability that therapeutic heparin is inferior (harmful) compared to thromboprophylaxis is **high**

Clinical case revisited

- 55 yo male admitted to hospital with dyspnea
  - Diagnosed with COVID-19 by PCR
  - 87% on room air. Placed on 10 L NP
  - Treated with dexamethasone, tocilizumab
  - Standard-dose VTE prophylaxis (dalteparin 5000 U S/Q OD)

  - Is there a role for higher-dose anticoagulants to reduce thrombosis and improve clinical outcomes?

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Yes – Consider therapeutic anticoagulation with heparin

- **If:** no contraindications to heparinization
- **For:** up to 14 days or until hospital discharge or liberation from supplemental O2
- **With:** low molecular weight heparin or unfractionated heparin

Transition from ward to ICU (moderate to severe)

- **Given divergent how should we manage therapeutic anticoagulation (TAC) for moderately-ill 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
  - It is 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

Blood Disorders Day 2021

CancerCare Manitoba
ActionCancerManitoba

Unanswered questions

- **Do these data apply to patients at home or in LTC facilities on oxygen? - Perhaps**
- **Can DOACs be used instead of LMWH/UFH? – Perhaps not**
- **Should patients receive extended duration anticoagulation post discharge? – Not sure**
- **What about ‘intermediate dose? – To be determined**

Thank you

Ryan Zarychanski MD MSc
rzarychanski@cancercare.mb.ca
@RZarychanski