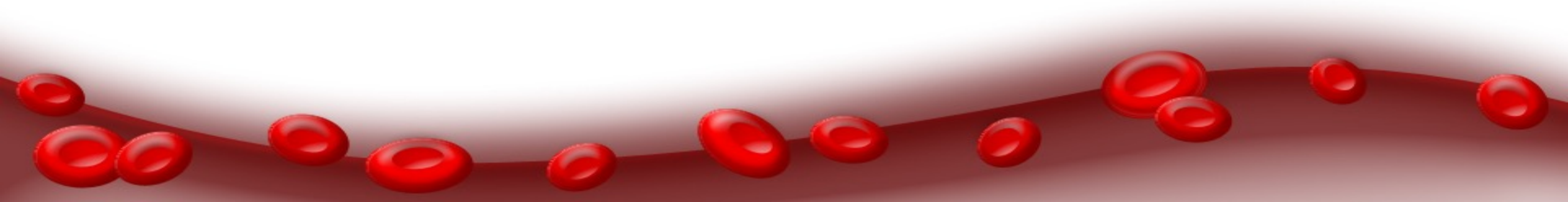
Therapeutic Anticoagulation with Heparin in Covid-19:

Final results of the multiplatform trial



BACKGROUND

mpRCT of Therapeutic Anticoagulation in Covid-19

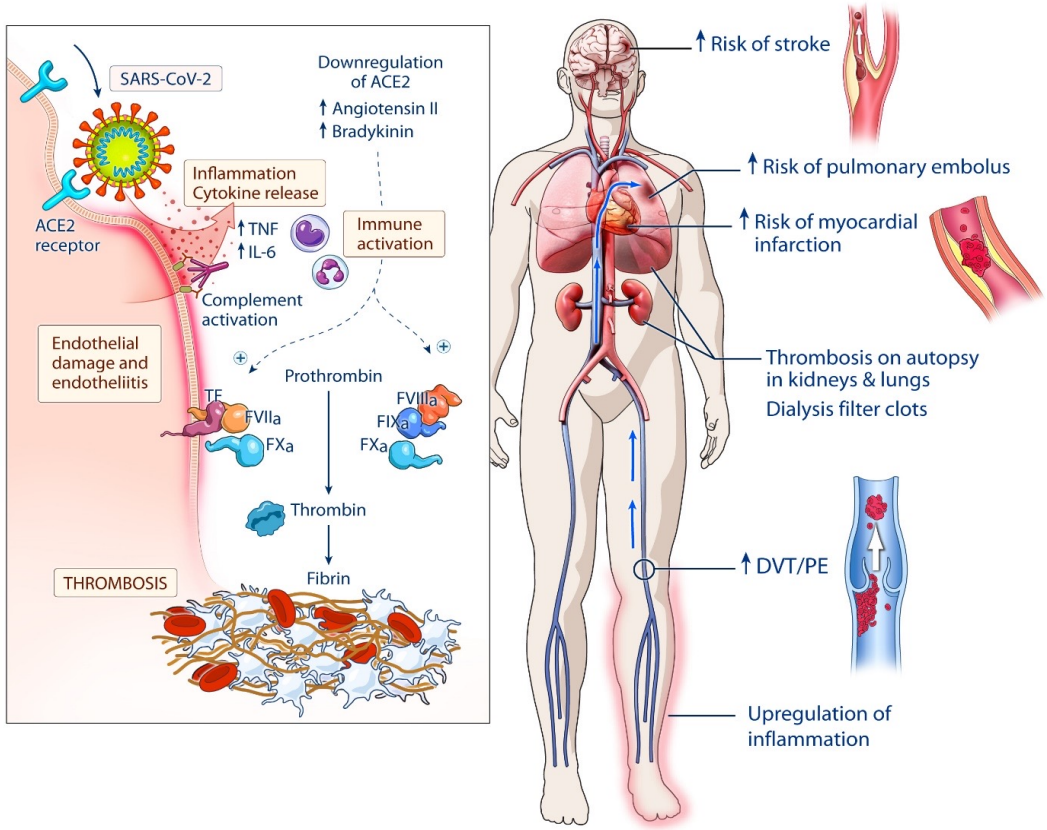
Patrick R. Lawler MD, MPH
Peter Munk Cardiac Centre
University Health Network
University of Toronto

ATTACC

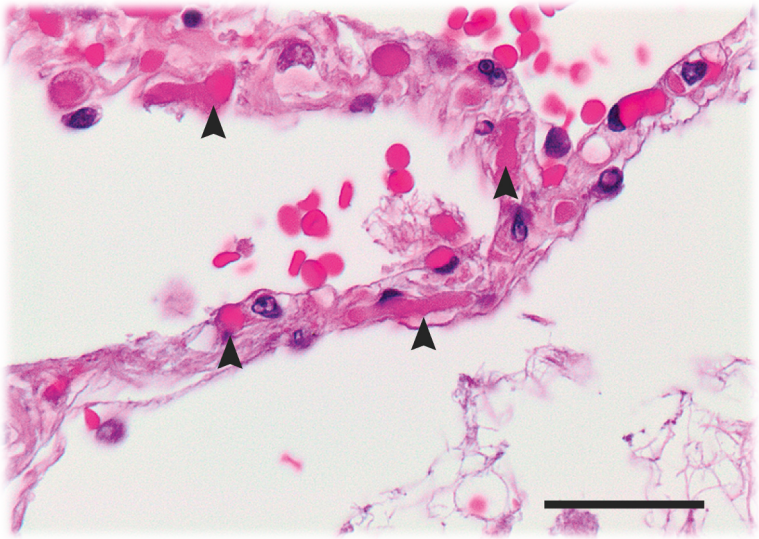
REMAP-CAP

ACTIV-4
Acute Inpatient Anti-Thrombotic Study

Thrombosis and Organ Failure in Covid-19



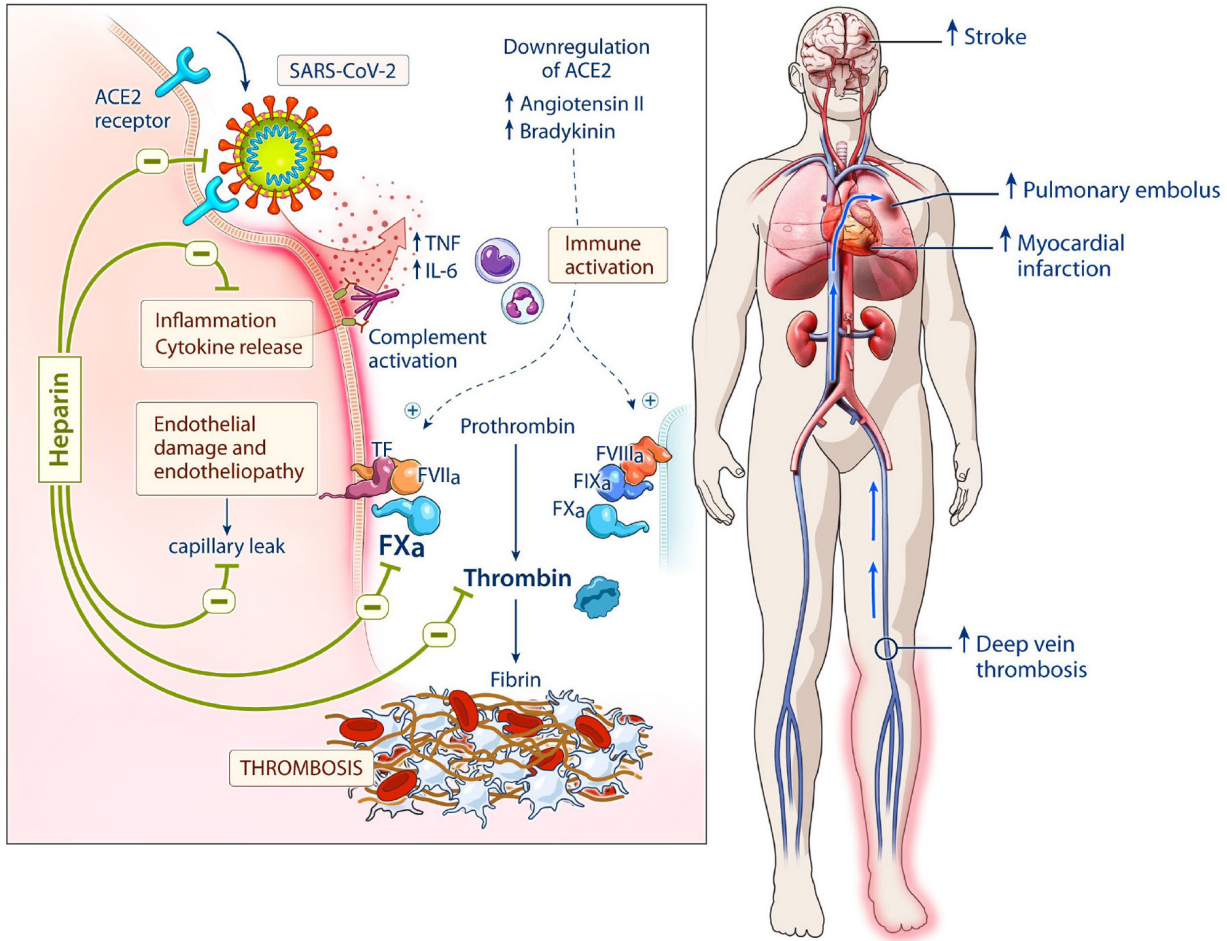
Godoy *et al. CMAJ* 2020



Microthrombi in the interalveolar septa of a lung from a patient who died from Covid-19.

Ackermann *et al. NEJM* 2020

Possible Role for Heparin in Covid-19



Houston *et al. Clinical Trials* 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.

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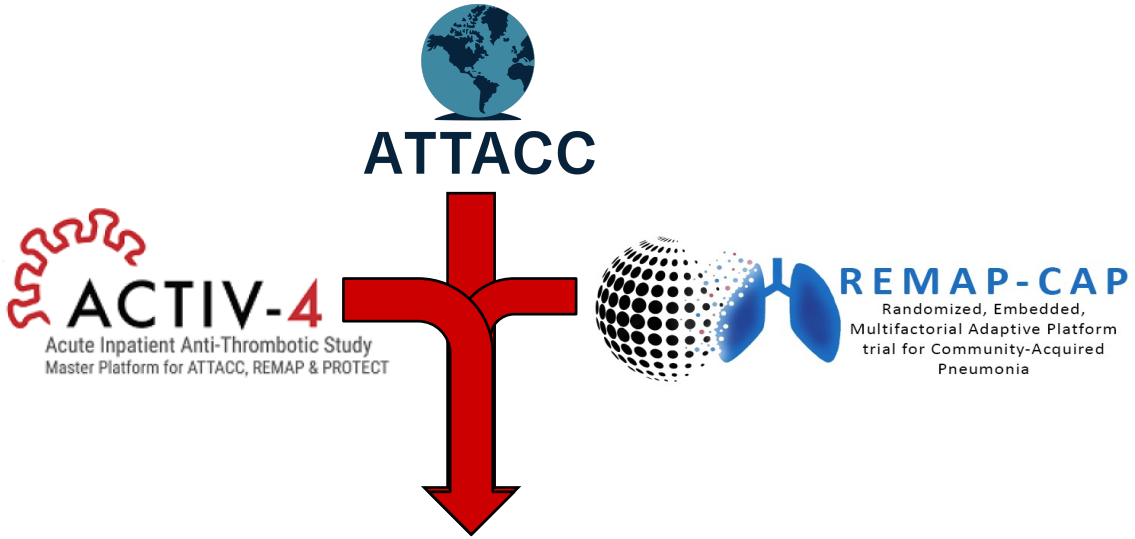
A hypothesis shared by 3 platforms…

ACTIV-4
Acute Inpatient Anti-Thrombotic Study
Master Platform for ATTACC, REMAP & PROTECT

ATTACC

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Multiplatform randomized controlled trial (mpRCT)



Multiplatform RCT

Goal:

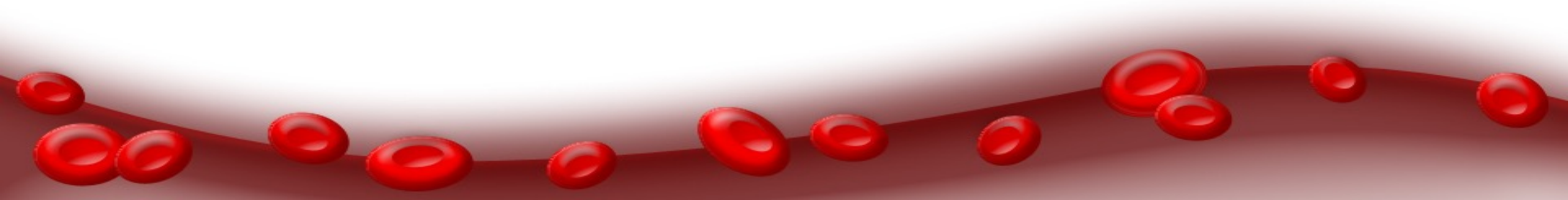
- Accelerate evidence generation in a rapidly evolving pandemic
- Maximize external generalizability

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

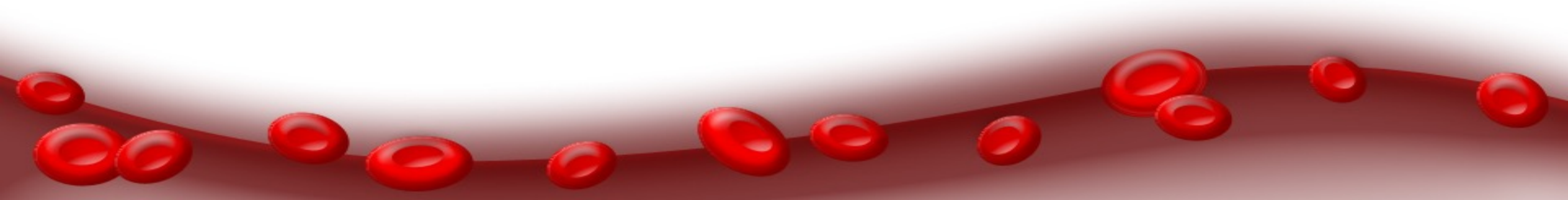
- Patients hospitalized for Covid-19, stratified on the basis of illness severity at enrollment:
  - Severe disease (ICU-level care; critically ill)
  - Moderate disease (hospitalized; non-critically ill) severity states, further stratified on the basis of baseline D-dimer:
    - high D-dimer group (D-dimer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

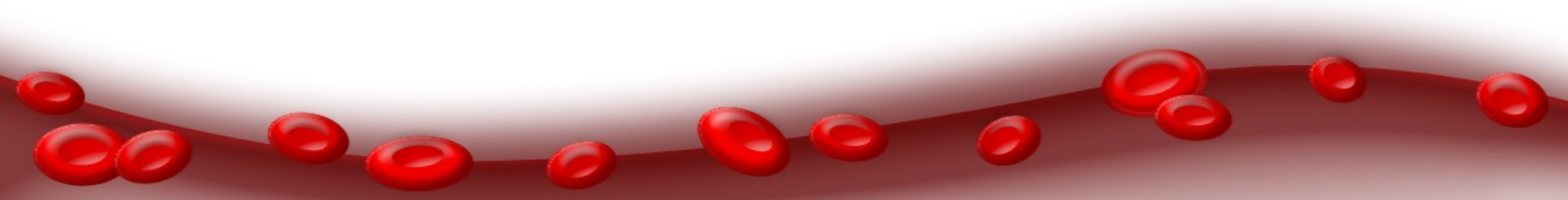
- Moderate disease was defined as hospitalization for Covid-19 without requirement for ICU-level care
  - Participants admitted to an ICU but without receipt of such organ support were considered moderately ill



Participants

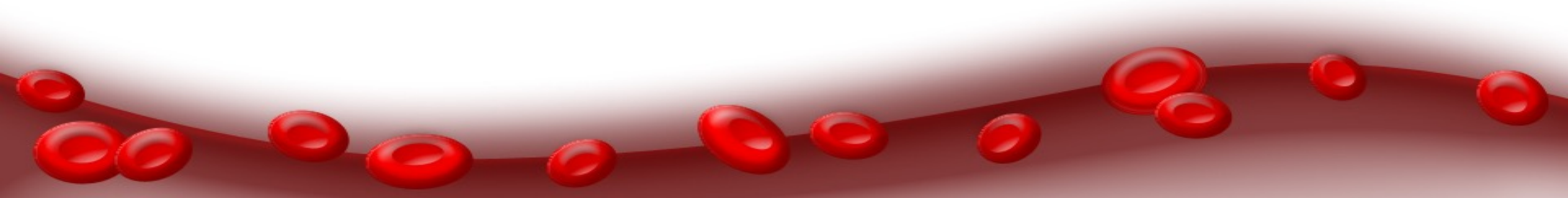
- Patients were ineligible for enrollment in the ATTACC and ACTIV-4a platforms after 72 hours following hospital admission for Covid-19 or in-hospital SARS-CoV-2 confirmation, and in the REMAP-CAP platform after 14 days following admission

- 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



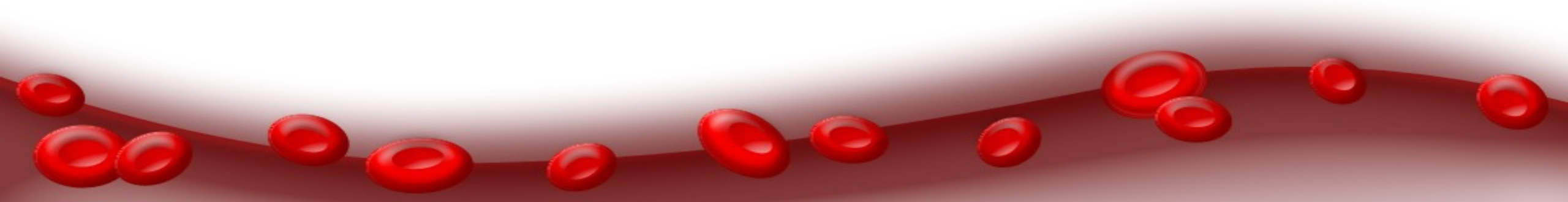
Primary outcome

- **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).



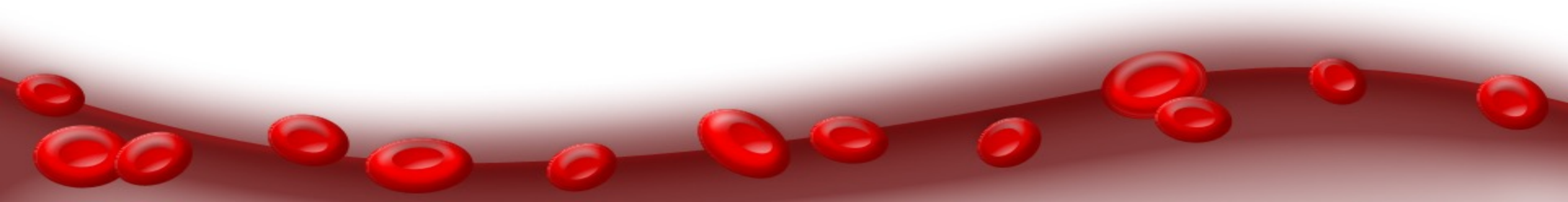
Primary outcome

- **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

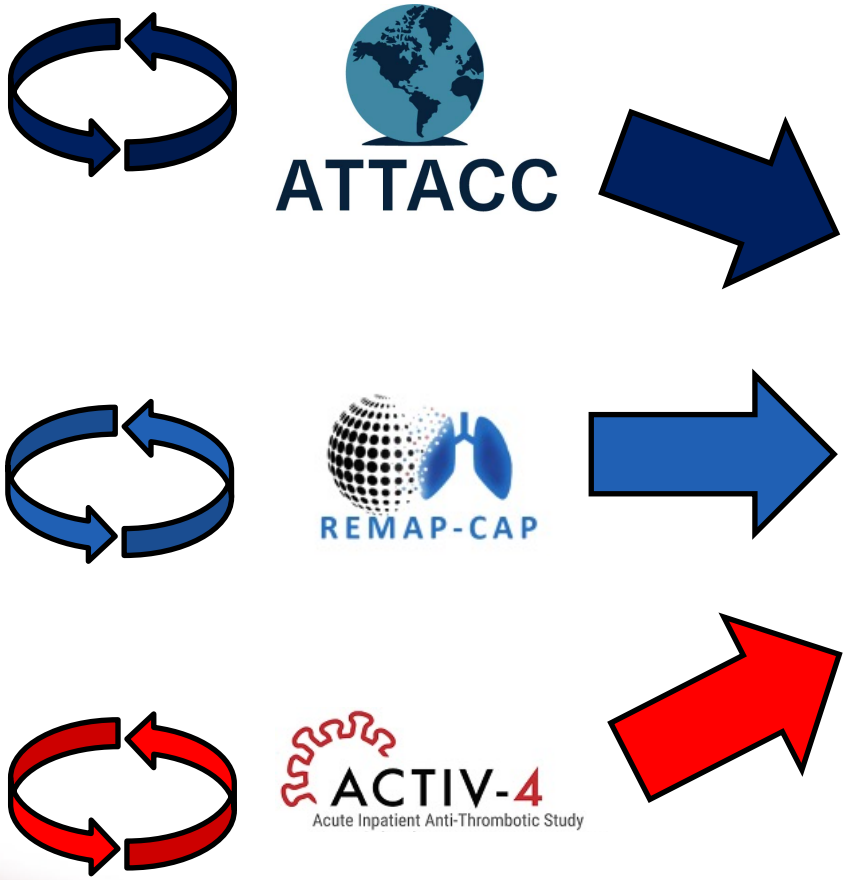
Lindsay Berry, PhD
Berry Consultants
Statistical Innovation

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

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

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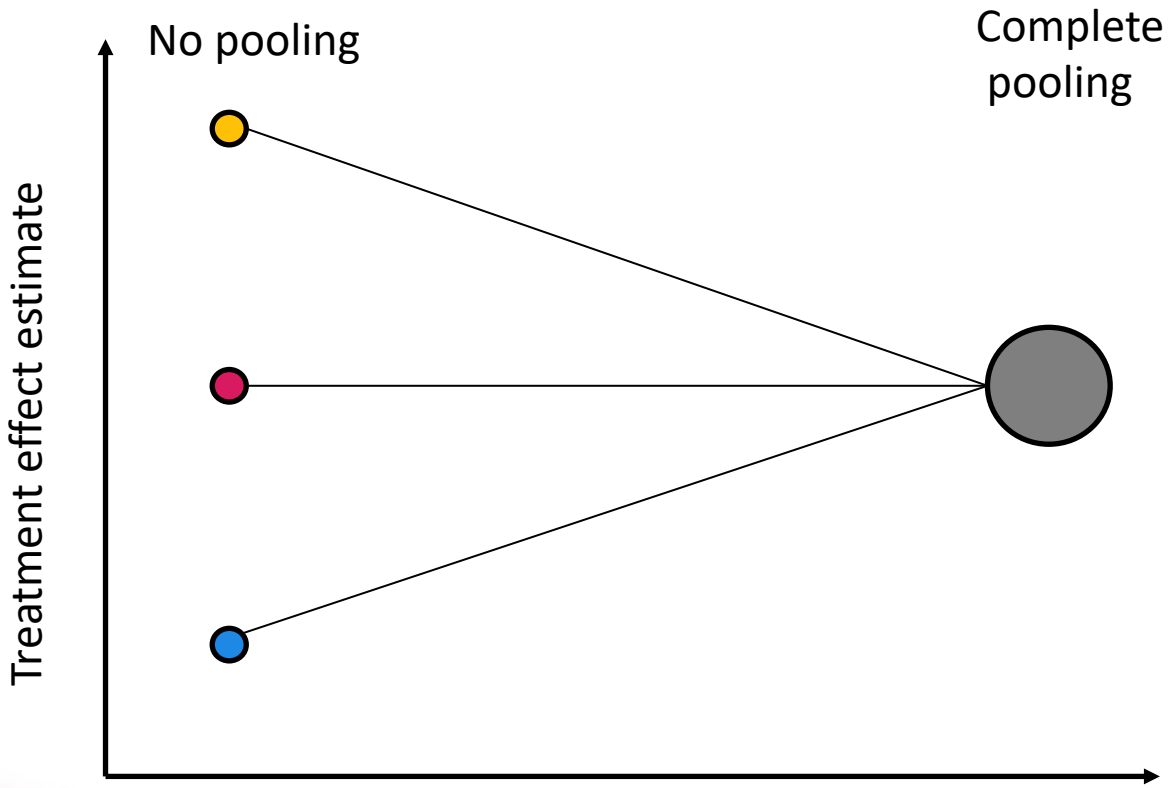
$$\log\left(\frac{\pi_y}{1-\pi_y}\right) = [\text{State}]_y + [\text{Covariates}] + [\text{TAC}]_{\text{state;D-dimer}}$$

- 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

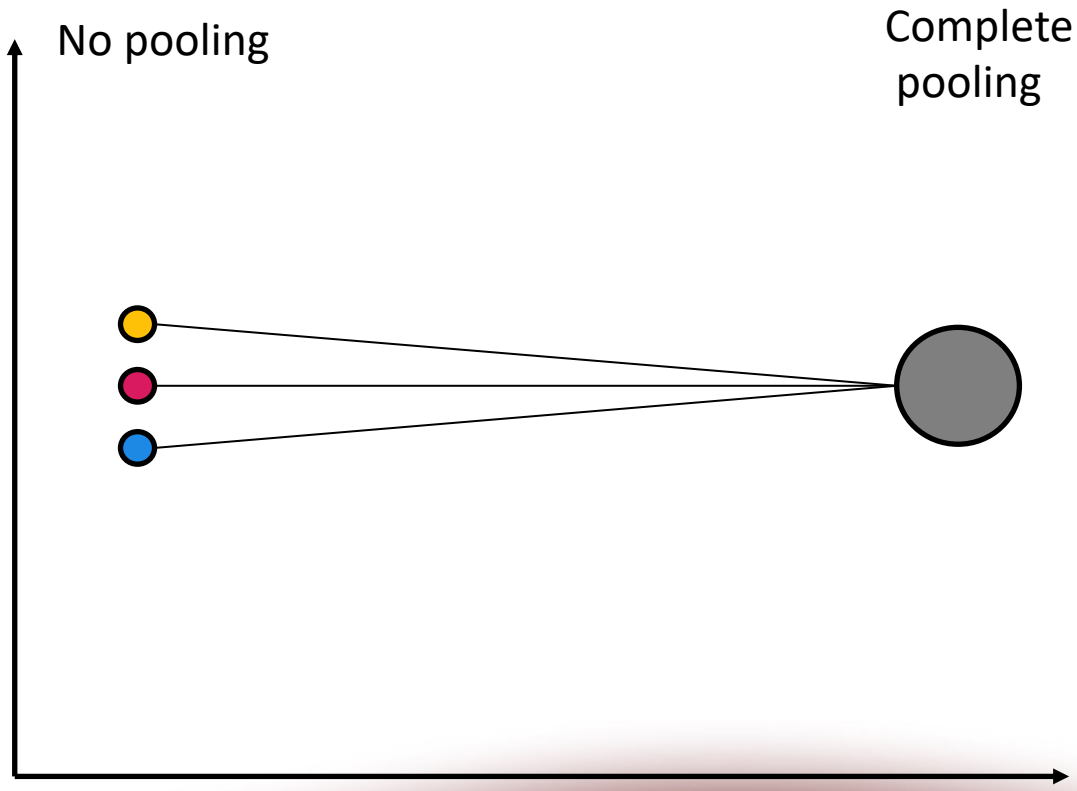
How does dynamic borrowing work?

Group 1
Group 2
Group 3
Pooled

A) Variability in treatment effect



B) Consistent treatment effect



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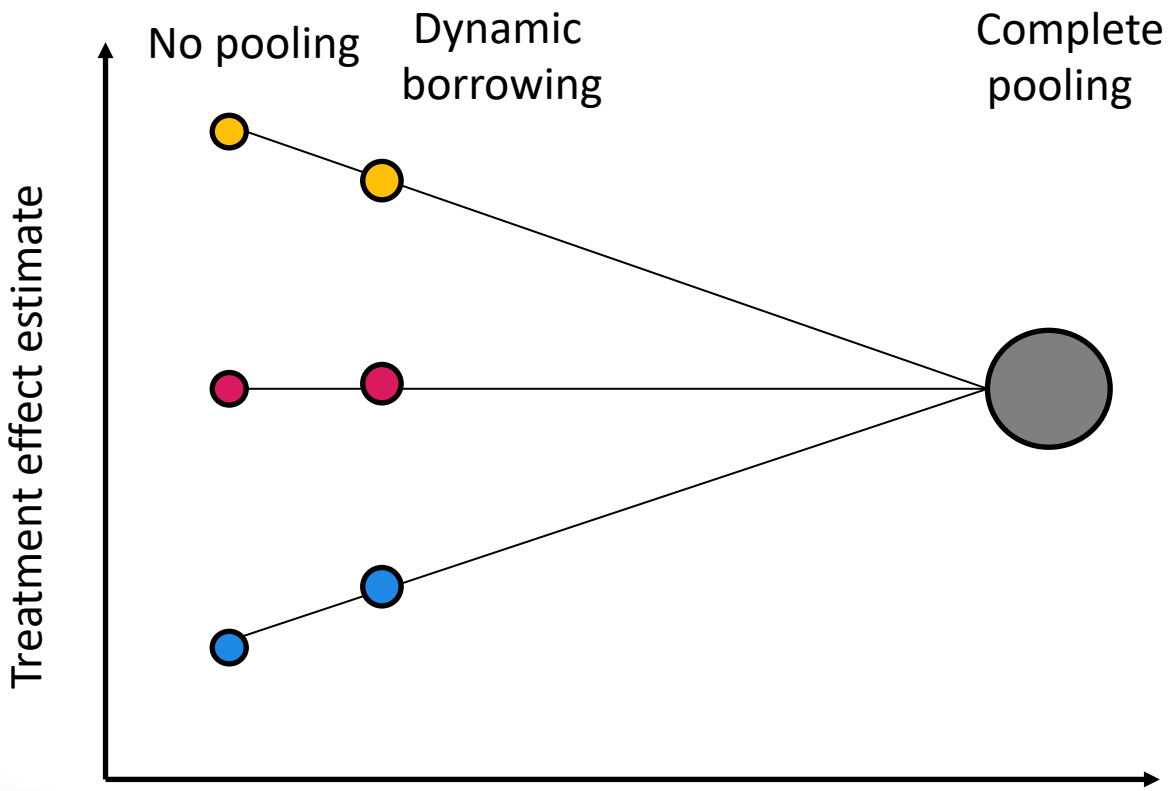

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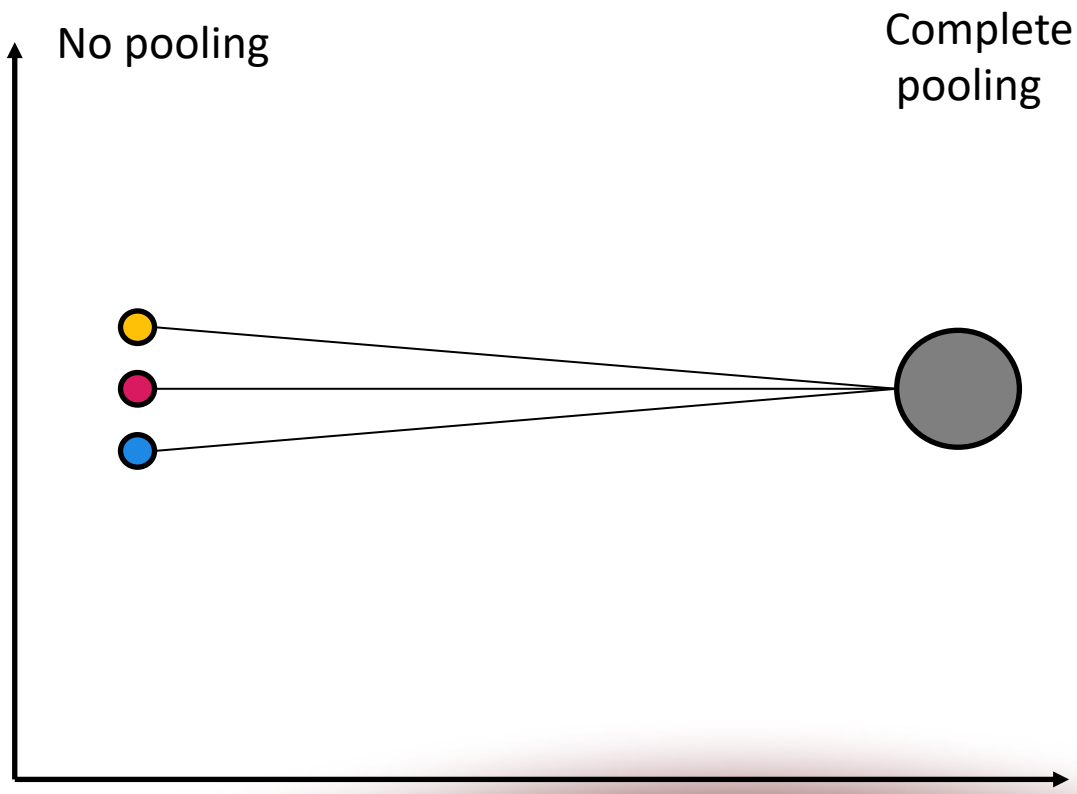

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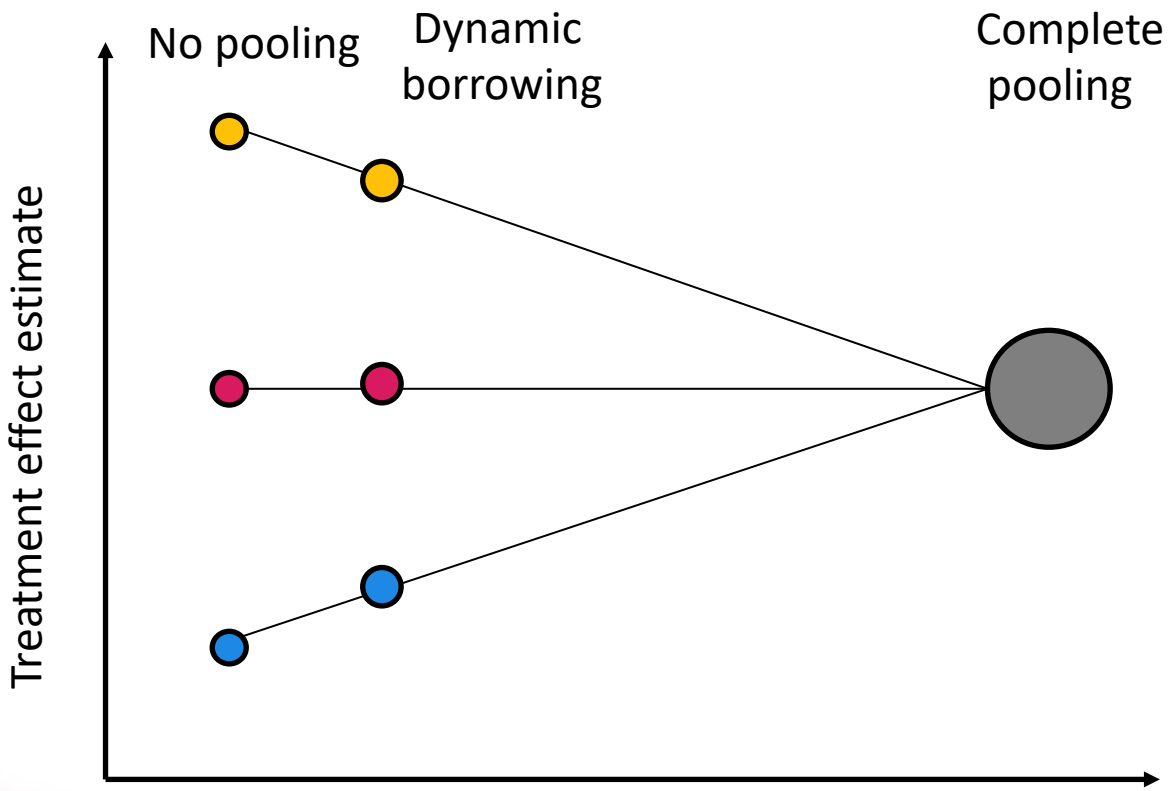

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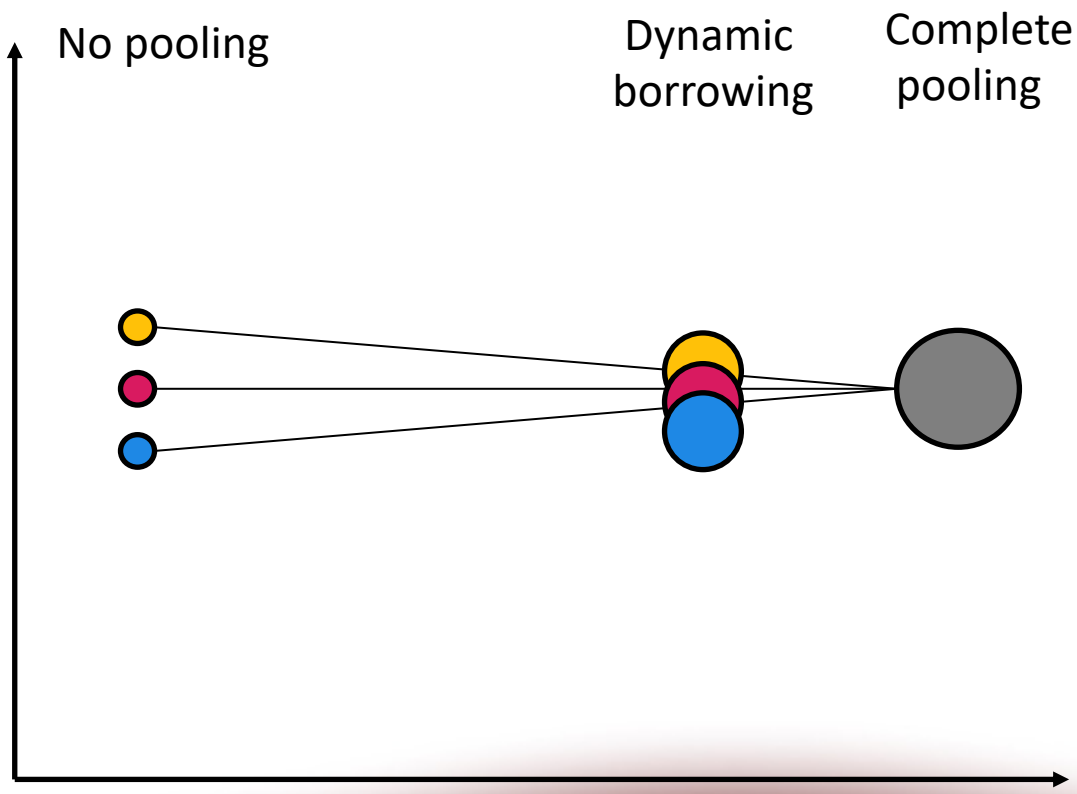
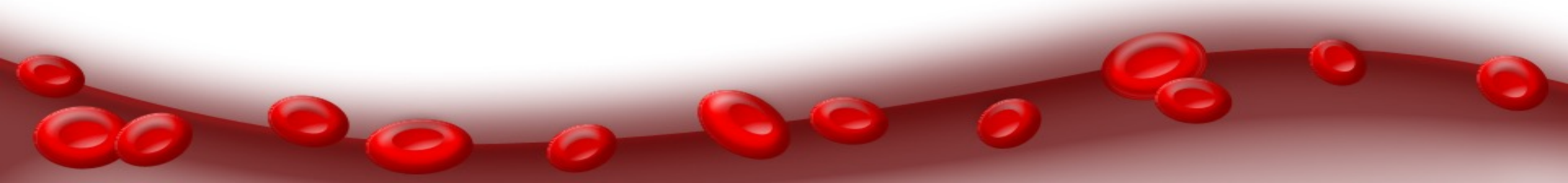


Pre-specified adaptations

- 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

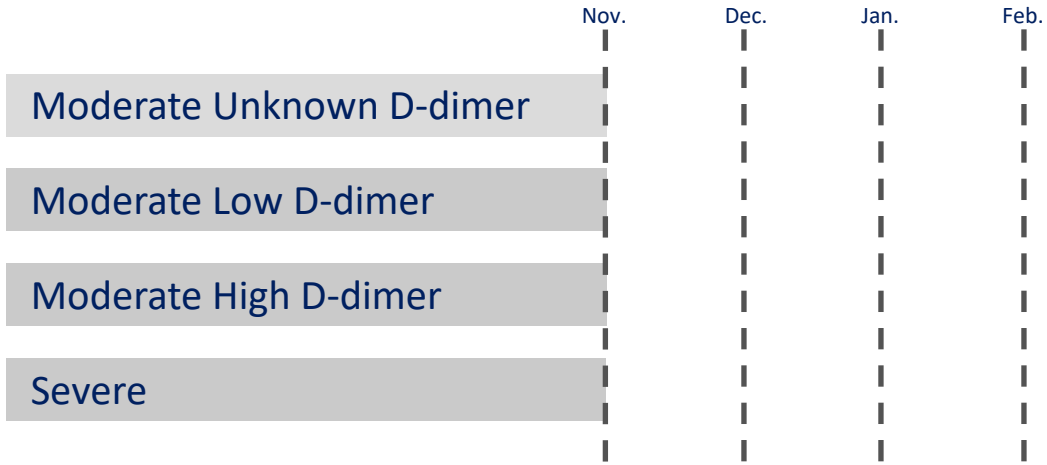
Ewan C. Goligher MD, PhD
University Health Network
University of Toronto

ATTACC

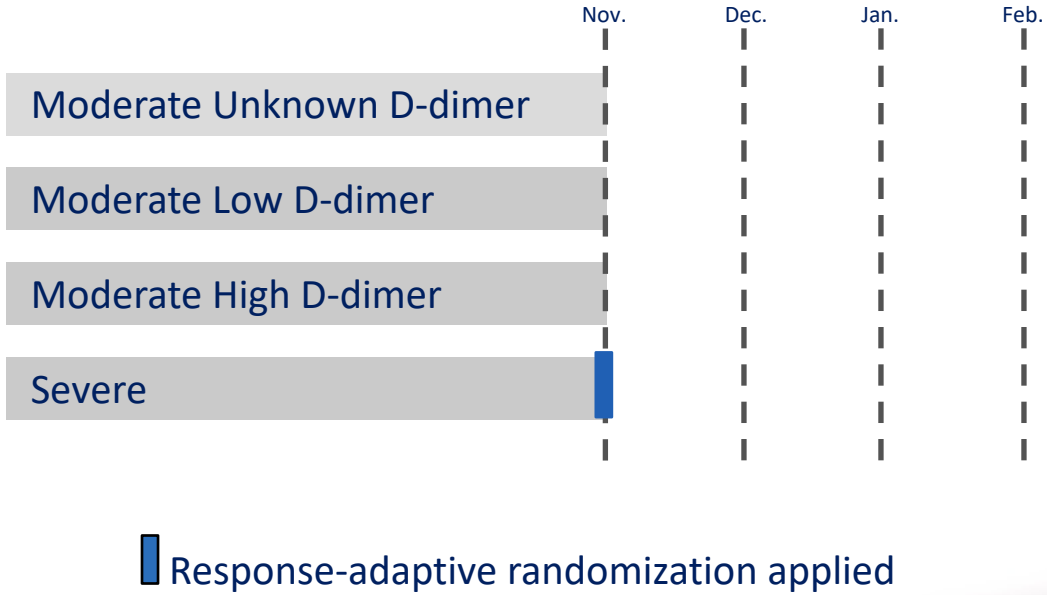
REMAP-CAP

ACTIV-4
Acute Inpatient Anti-Thrombotic Study

Trial Course



Trial Course



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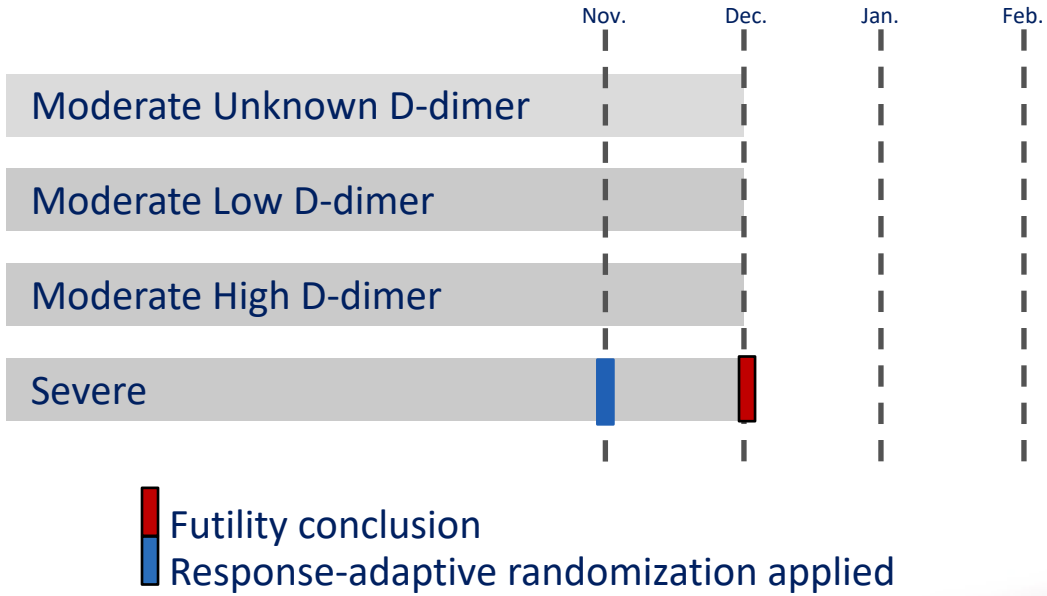

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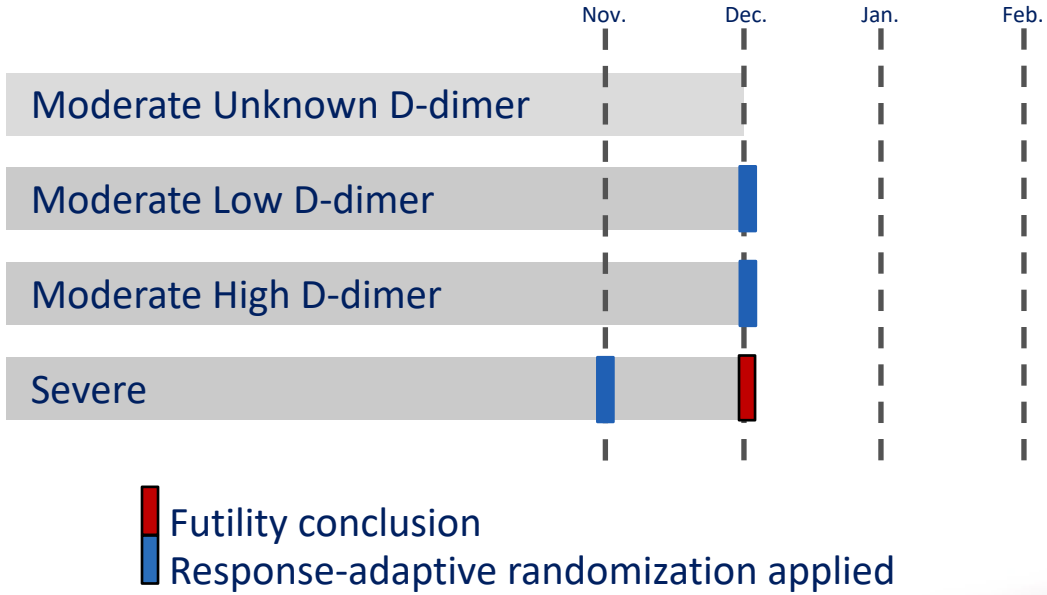
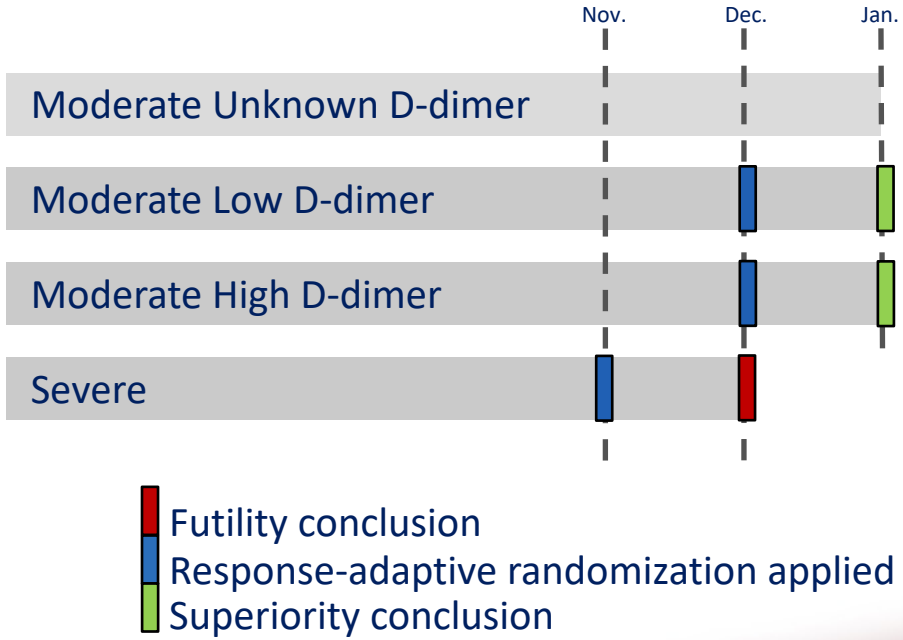
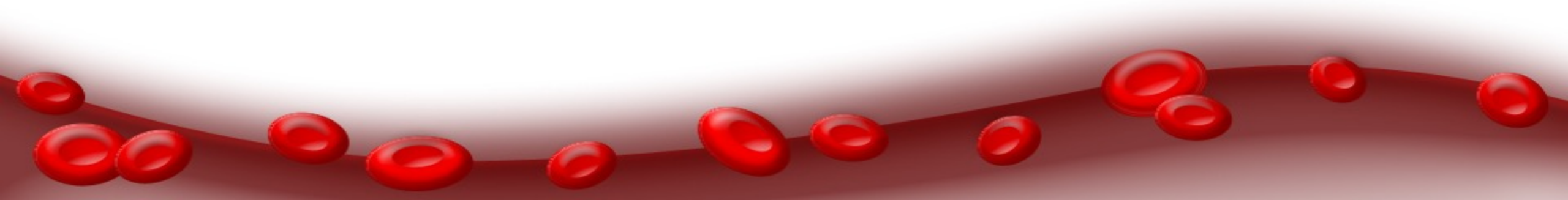


Trial Course



mpRCT Recruitment

Group	Therapeutic-Dose Anticoagulation (n with primary endpoint)	Usual-care thromboprophylaxis (n with primary endpoint)
Severe Covid-19	**534**	**564**
Moderate Covid-19 (overall)	**1171**	**1048**
D-dimer ≥2x ULN	339	291
D-dimer <2x ULN	570	505
D-dimer unknown	262	252



mpRCT Populations

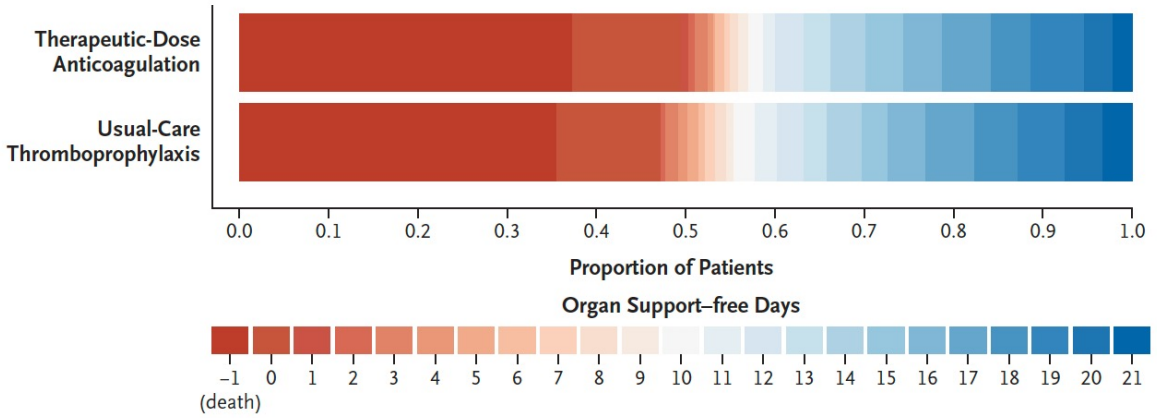
Group	Moderate Covid-19 (n=2231)	Severe Covid-19 (n=1103)
Age (mean)	59 years	61 years
Sex (% male)	59%	70%
Country of enrolment		
UK	9%	**71%**
USA	**48%**	16%
Canada	8%	9%
Brazil	**20%**	2%
Other	15%	2%
Platform of enrolment		
ATTACC	**52%**	4%
ACTIV-4a	**35%**	12%
REMAP-CAP	13%	**84%**

mpRCT Populations

Group	Moderate Covid-19 (n=2231)	Severe Covid-19 (n=1103)
Respiratory support		
None/low flow oxygen/unspecified	96%	1%
High flow oxygen	2%	33%
Non-invasive ventilation	2%	38%
Invasive ventilation	0%	28%
Co-interventions at baseline		
Antiplatelet agent	12%	8%
Remdesivir	36%	31%
Glucocorticoid	62%	82%
Tocilizumab	0.5%	2%

Primary Endpoint: Organ Support-Free Days

Severe Covid-19



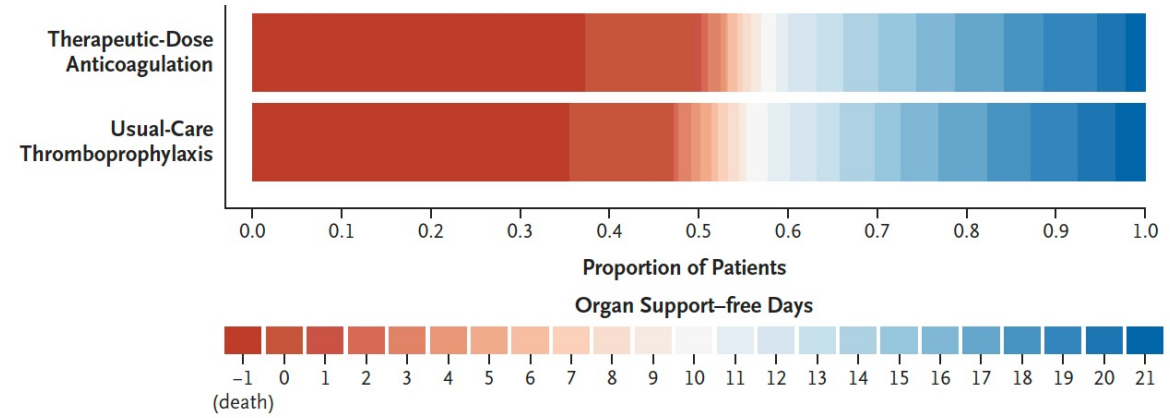
Adjusted OR 0.83 (95% CrI 0.67-1.03)

Futility: Prob(OR<1.2) = 99.9%

Inferiority: Prob(OR<1) = 95.0%

Primary Endpoint: Organ Support-Free Days

Severe Covid-19



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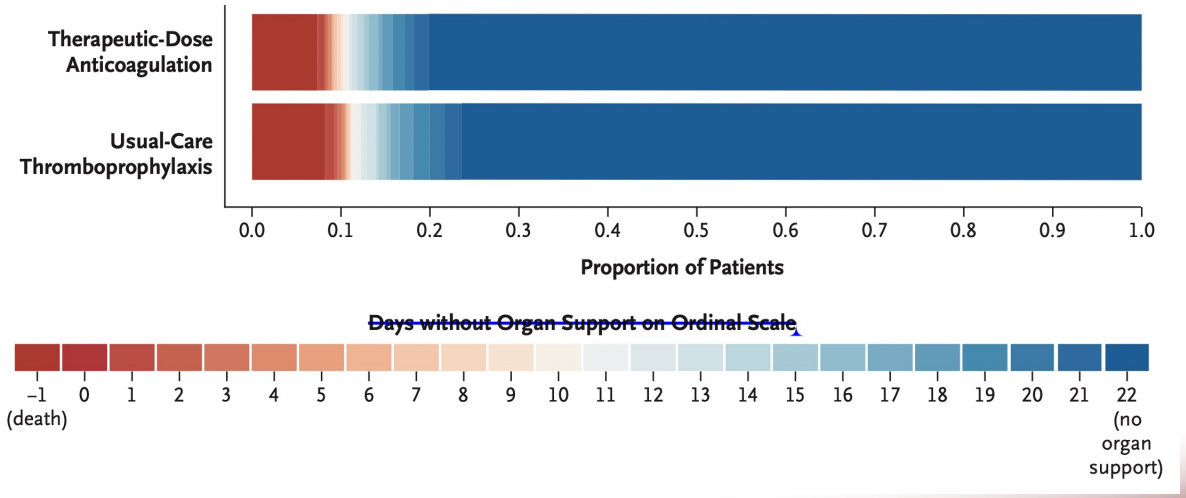
Moderate Covid-19



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.*

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

Secondary Endpoints: Severe Covid-19

Table 2. Primary and Secondary Outcomes.

Outcome	Therapeutic-Dose Anticoagulation (N=536)	Usual-Care Thromboprophylaxis (N=567)	Adjusted Difference in Risk (95% Credible Interval)	Adjusted Odds Ratio (95% Credible Interval)*	Probability of Superiority	Probability of Futility	Probability of Inferiority
	median no. (IQR)		*percentage points*		%	%	%
Organ support–free days up to day 21†‡	1 (–1 to 16)	4 (–1 to 16)	—	0.83 (0.67 to 1.03)	5.0	99.9	95.0
	no. of patients/total no. (%)						
Survival to hospital discharge‡	335/534 (62.7)	364/564 (64.5)	–4.1 (–10.7 to 2.4)	0.84 (0.64 to 1.11)	10.8	99.6	89.2
Major thrombotic events or death§	213/531 (40.1)	230/560 (41.1)	1.0 (–5.6 to 7.4)	1.04 (0.79 to 1.35)	40.3	—	59.7
Major thrombotic events¶	34/530 (6.4)	58/559 (10.4)	—	—	—	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—	—	—	—
Any thrombotic events or death§	217/531 (40.9)	232/560 (41.4)	1.5 (–4.9 to 8.0)	1.06 (0.81 to 1.38)	33.4	—	66.6
Any thrombotic events‖	38/530 (7.2)	62/559 (11.1)	—	—	—	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—	—	—	—
Major bleeding§	20/529 (3.8)	13/562 (2.3)	1.1 (–0.6 to 4.4)	1.48 (0.75 to 3.04)	12.8	—	87.2

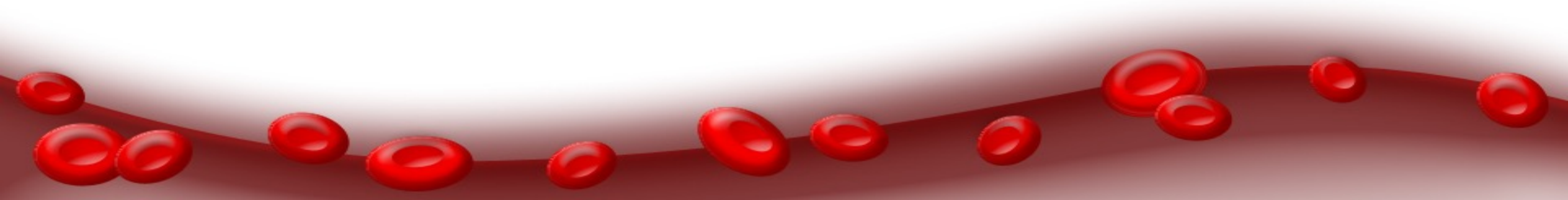
Secondary Endpoints: Moderate Covid-19

Table 3. Secondary Outcomes among All Patients with Moderate Disease.*

Outcome	Therapeutic-Dose Anticoagulation	Usual-Care Thromboprophylaxis	Adjusted Difference in Risk (95% Credible Interval)†	Adjusted Odds Ratio (95% Credible Interval)‡	Probability of Effect of Therapeutic-Dose Anticoagulation
	no. of patients/total no. (%)		*percentage points*		%
Survival until hospital discharge	1085/1171 (92.7)	962/1048 (91.8)	1.3 (–1.1 to 3.2)	1.21 (0.87 to 1.68)§	87.1¶
Survival without organ support at 28 days‖	932/1175 (79.3)	789/1046 (75.4)	4.5 (0.9 to 7.7)	1.30 (1.05 to 1.61)	99.1¶
Progression to intubation or death**	129/1181 (10.9)	127/1050 (12.1)	–1.9 (–4.1 to 0.7)	0.82 (0.63 to 1.07)	92.2¶
Major thrombotic event or death	94/1180 (8.0)	104/1046 (9.9)	–2.6 (–4.4 to –0.2)	0.72 (0.53 to 0.98)	98.0¶
Major thrombotic event	13/1180 (1.1)	22/1046 (2.1)			
Death in hospital	86/1180 (7.3)	86/1046 (8.2)			
Major bleeding	22/1180 (1.9)	9/1047 (0.9)	0.7 (–0.1 to 2.3)	1.80 (0.90 to 3.74)	95.5††

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

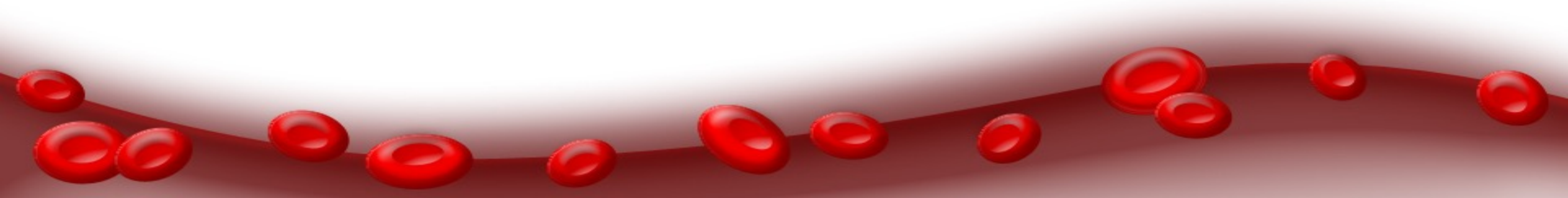
ATTACC

REMAP-CAP

ACTIV-4
Acute Inpatient Anti-Thrombotic Study

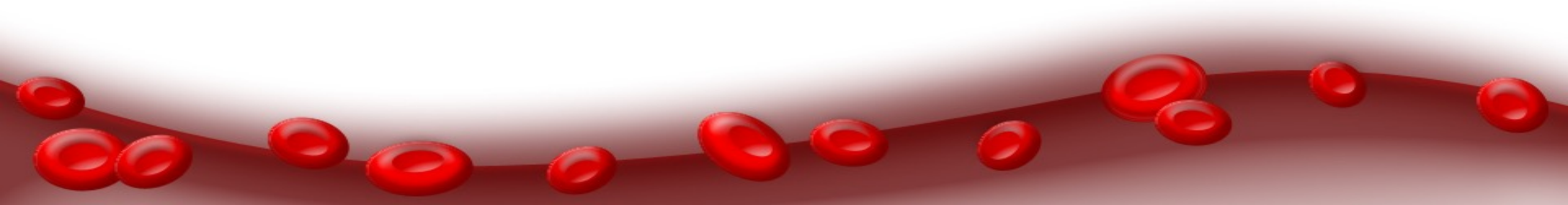
What goes down relatively easy

- 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

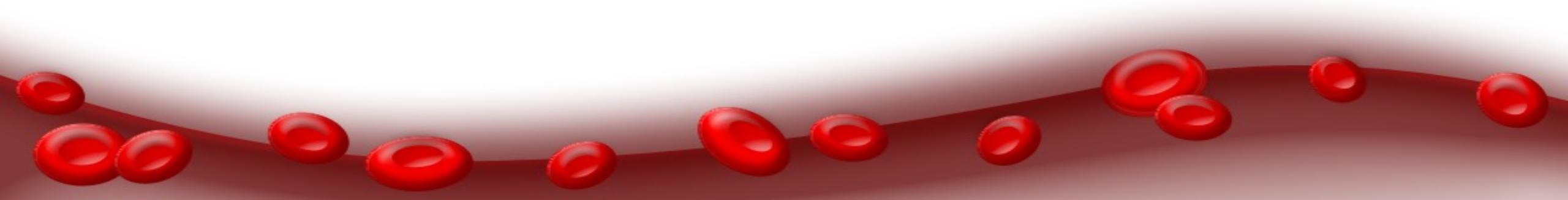
- Bayesian framework
- Organ-support free days
- Responsive-adaptive randomization
- Heterogeneity of treatment effects



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)
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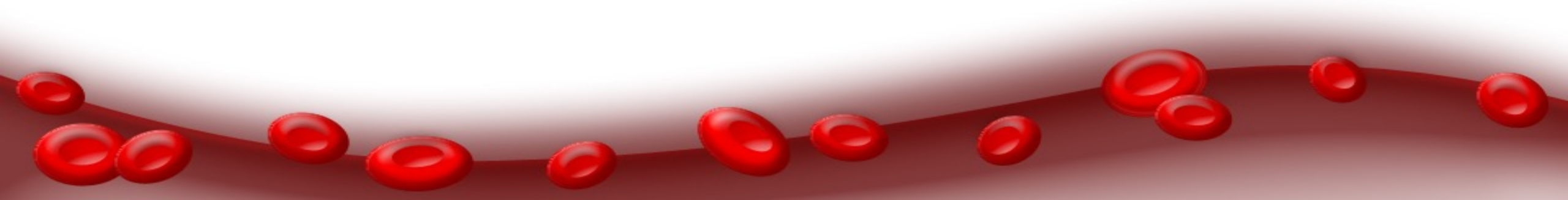


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