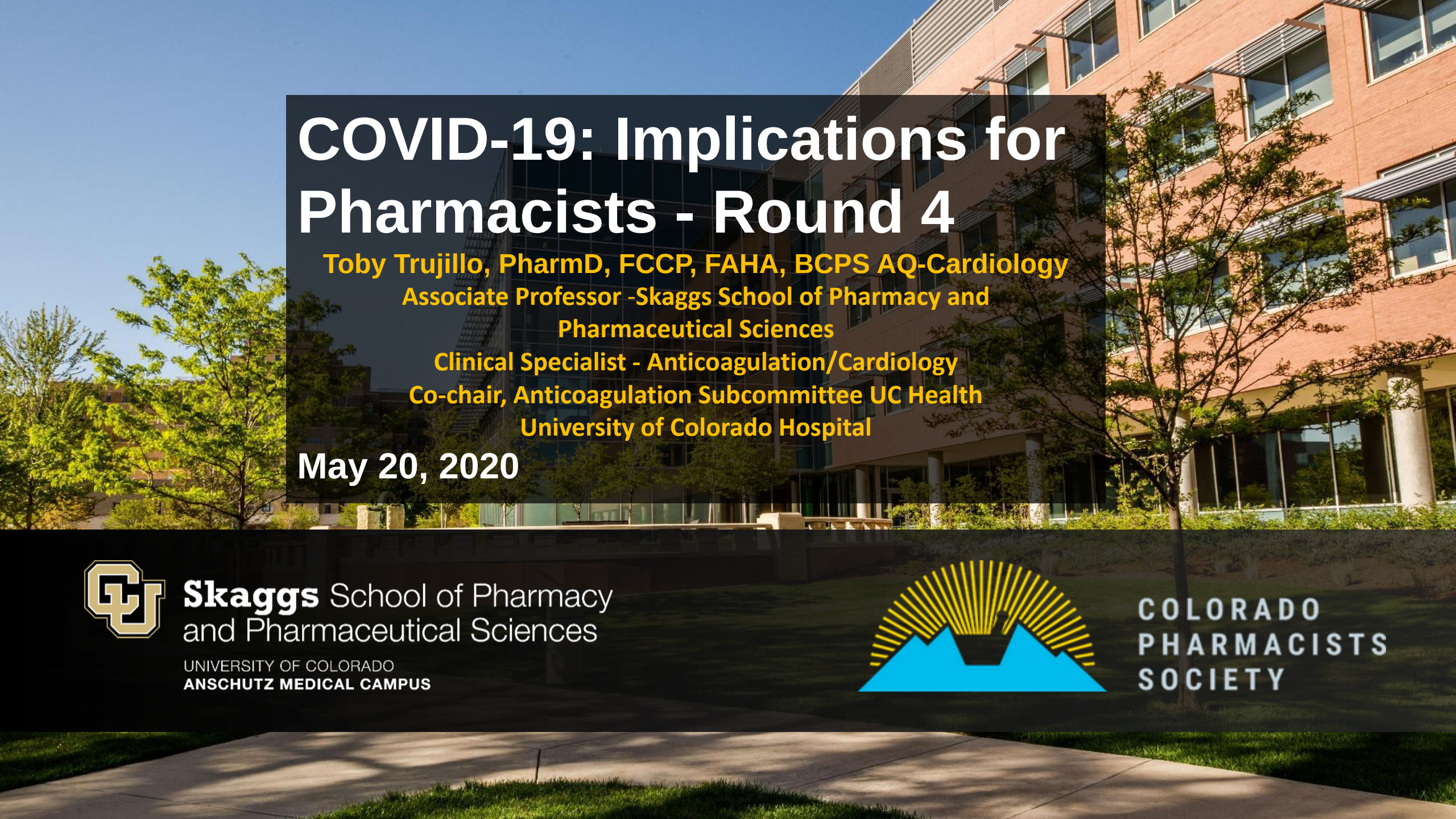

COVID-19: Implications for Pharmacists - Round 4

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May 20, 2020

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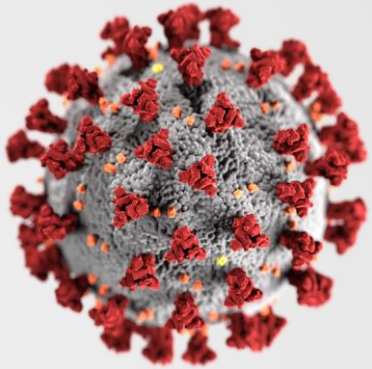
COLORADO PHARMACISTS SOCIETY

Disclosure Statement – No Financial Relationships to Disclose

Toby Trujillo

I have no relevant financial relationships with commercial interests pertaining to the content presented in this program.

Objectives



- Describe the risk of thromboembolic disease during active COVID-19 infection and the impact on morbidity and mortality.
- Appraise current available evidence on the role of anticoagulation in preventing thromboembolism and improving outcomes in hospitalized COVID-19 patients.
- Explain the potential benefit of extended VTE prophylaxis post discharge in patients recently hospitalized for COVID-19.

SARS-CoV-2
(Severe Acute Respiratory Syndrome Coronavirus 2)

- Coronavirus Disease 2019 (COVID-19)
  - Binds to ACE-2 receptor (alveolar cells, cardiac myocytes, vascular endothelium
  - Common Presenting Symptoms
    - Fever (98%), Cough (76%), Dyspnea (55%), mylagias/fatigue (44%)
  - Respiratory tract infection – viral pneumonia
  - Other findings
    - Acute kidney Injury (30%)
    - Liver dysfunction (29%)
    - Cardiac Complications (23%)
      - Acute cardiac injury, arrhythmia, acute stroke
      - ***Coagulation Abnormalities/Hypercoaguability***

Classification	Criteria	Estimated Percentage of COVID-19 Positive Patients
Mild	No pneumonia; uncomplicated upper respiratory infection	80%
Moderate	Mild pneumonia	
Severe	Severe pneumonia with respiratory rate > 30 bpm, severe respiratory distress or SpO_2 < 90% on room air	13.8%
Critical	ARDS[a]; severe cardiac complications[b]; sepsis or septic shock	6.1%

Pharmacotherapy 2020;40(5):382–386) doi: 10.1002/phar
Circulation doi:10.xxxx/jah3.5217

Hypercoagulability in COVID-19

- Most consistent hemostatic abnormalities
  - Mild thrombocytopenia
  - Increased D-dimer
    - Associated with higher risk mechanical ventilation, ICU admission, death
  - More severe disease – higher mortality (progression during hospitalization)
    - Prolongation of the prothrombin time (PT)
    - Prolongation of the thrombin time (TT)
    - Prolongation of activated partial thromboplastin time (aPTT)
    - More likely to meet criteria by ISTH for disseminated intravascular coagulation (DIC)
- *Unclear if these are specific effects of SARS-CoV-2 or cytokine storm that precipitates onset of Systemic Inflammatory Response Syndrome (SIRs) that are observed in other viral diseases*

JACC 2020. doi.org/10.1016/j.jacc/.2020.04.031

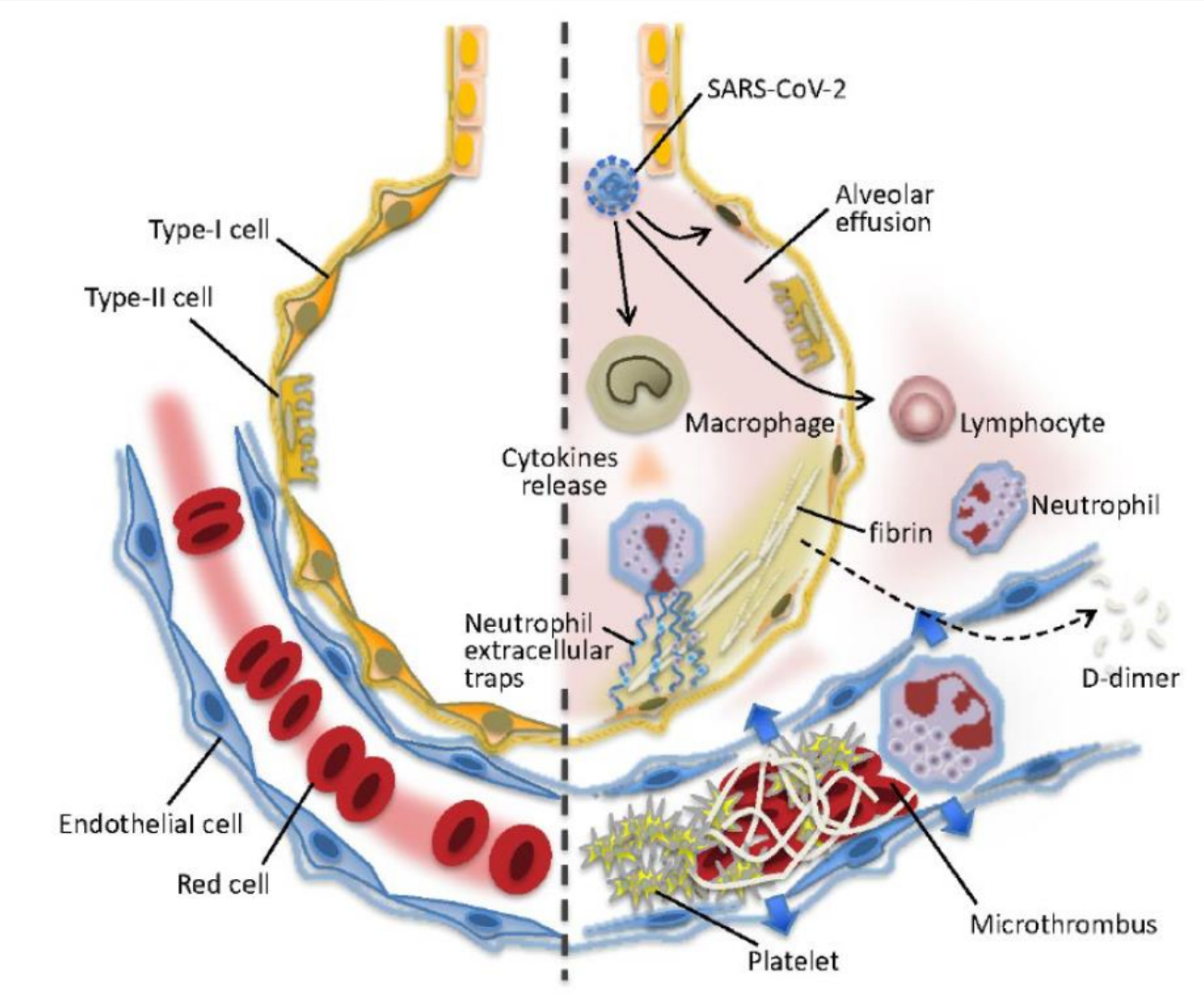
Hypercoagulability in COVID-19

- Exact etiology of this phenomenon is unclear
  - Some suggest thrombo-inflammation
    - Microvascular thrombosis in the setting of significant inflammatory changes on post-mortem pathology reports

- Increased incidence of VTE in COVID-19 pts with severe disease who are admitted to the ICU
  - Some groups are reporting VTE incidence as high as 27% in pts who are placed on standard VTE prophylaxis with LMWH
    - Standard failure rate of VTE prophylaxis in the ICU setting is 7-8%

Connors and Levy. *J Thromb and Haemost*. 2020; DOI: https://doi.org/10.1111/jth.14849
Fox, et al. *MedRxiv*2020; DOI: https://doi.org/10.1101/2020.04.06.20050575[not peer reviewed]
Lim, et al. *CritCare Med*. 2015;43:401-410.

Pulmonary Micro-thrombosis in Covid-19



Iba T, et al. *J Thromb Haemost* 2020 Mar 28; 395 (10229): 1054-1062. Epub 2020 Mar 11.

Annals of Internal Medicine®

ORIGINAL RESEARCH | 6 MAY 2020

Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study FREE

*Dominic Wichmann, MD *; Jan-Peter Sperhake, MD *; Marc Lütgehetmann, MD; Stefan Steurer, MD; Carolin Edler, MD; Axel Heinemann, MD; Fabian Heinrich; Herbert Mushumba, MD; Inga Kniep, MD; Ann Sophie Schröder, MD; Christoph Burdelski, MD; Geraldine de Heer, MD; Axel Nierhaus, MD; Daniel Frings, MD; Susanne Pfefferle, MD; Heinrich Becker, MD; Hanns Bredereke-Wiedling, MD; Andreas de Weerth, MD; Hans-Richard Paschen, MD; Sara Sheikhzadeh-Eggers, MD; Axel Stang, MD; Stefan Schmiedel, MD; Carsten Bokemeyer, MD; Marylyn M. Addo, MD, PhD; Martin Aepfelbacher, MD; Klaus Püschel, MD†; Stefan Kluge, MD†*

Academic hospital in Hamburg, Germany (n=12)

- Consecutive autopsies with fatal COVID-19 infection (mandated by state)
- DVT in 7/12 patients; fatal PE in 4
- VTE had not been suspected antemortem

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Incidence of thrombotic complications in critically ill ICU patients with COVID-19

F.A. Klok[a,*], M.J.H.A. Kruip[b], N.J.M. van der Meer[c], M.S. Arbous[d], D.A.M.P.J. Gommers[e], K.M. Kant[f], F.H.J. Kaptein[a], J. van Paassen[d], M.A.M. Stals[a], M.V. Huisman[a,1], H. Endeman[e,1]

3 Dutch ICUs (n=184)

- All given LMWH proph.
- 31% thrombosis by d15
- 25 PE (28% subseg'l)
- 3 DVT, 3 ATE
- ↑PT(>3s) ↑PTT(>5s)

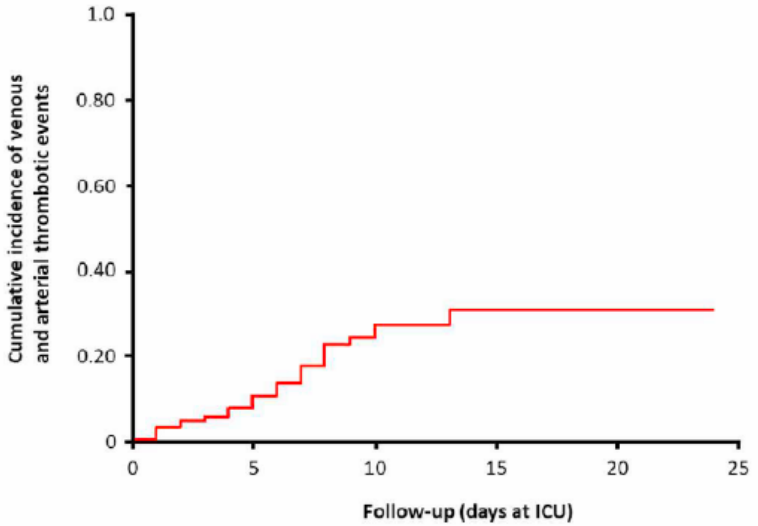


Fig. 1. Cumulative incidence of venous and arterial thrombotic complications during the course of intensive care unit admission of patients with proven COVID-19 pneumonia.

Klok et al. *Thromb Res* 2020 Apr 10 [Epub ahead of print]

Contents lists available at ScienceDirect

Thrombosis Research

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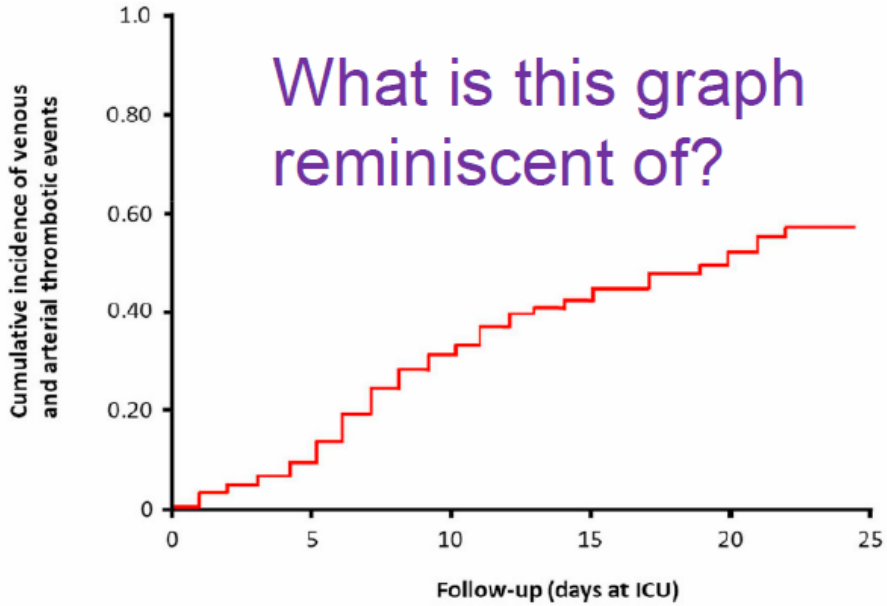
Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis

F.A. Klok[a,*], M.J.H.A. Kruip[b], N.J.M. van der Meer[c,d], M.S. Arbous[e], D. Gommers[f], K.M. Kant[g], F.H.J. Kaptein[a], J. van Paassen[e], M.A.M. Stals[a], M.V. Huisman[a,1], H. Endeman[f,1]

3 Dutch ICUs (n=184)

- Updated data (7→14d)
- 57% thrombosis by d25
- 65 PE (29% subseg'l)
- 3 DVT, 7 ATE (5 CVA's)
- HR 0.29 if adm. AC



Klok et al. *Thromb Res* 2020 Apr 30 [Epub ahead of print]

Anticoagulation Considerations for COVID-19

- Should all patients receive “standard” doses of VTE prophylaxis with anticoagulation?
  - Risk for under-dosing due to body weight as well as pro-inflammatory proteins
- Should all patients receive “intensified” or “escalated” doses of VTE prophylaxis?
- Should some or all patients be empirically treated with therapeutic anticoagulation?
  - IV UFH to therapeutic aPTT of Xa
  - Therapeutic LMWH
- Is there a role for tPA in severely ill patients?
- ***Drinking from a firehose – daily multiple articles published***

Clinical Evidence for Anticoagulation in COVID-19

- Retrospective case series in 449 consecutive pts with severe COVID-19 at 1 hospital from Jan 1 –Feb 13, 2020
- Exclusion criteria:
  - Bleeding diathesis
  - Hospital stay < 7 days
  - Lack of data regarding coagulation parameters or anticoagulation medications
  - Age < 18 yo
- 1786 pts were screened
  - 261 pts did not meet the definition of severe COVID-19 disease
  - 76 pts met exclusion criteria

Tang, et al. *J Thromband Haemost.* 2020;18:1094-1099

Clinical Evidence for Anticoagulation in COVID-19

- Patients:
  - 286 M (67.3%); 181 F (36.3%)
  - Average age: 65.1 yo
    - 272 pts (60.6%) had a comorbidity
      - HTN: 177 (39.4%)
      - Diabetes: 93 (20.7%)
      - Heart diseases: 41 (9.1%)
  - 99 pts (22%) received heparin (also included LMWHs) for at least 7 days
    - 94 pts received enoxaparin 40-60mg/day
    - 5 pts received unfractionated heparin 10,000 –15,000 units/day
    - No other anticoagulants were used
  - 97 pts (21.6%) met SIC (sepsis-induced coagulopathy) criteria (SIC score ≥ 4)
    - SIC scores based on: Platelet counts, PT-INR, and SOFA score

Tang, et al. *J Thromband Haemost.* 2020;18:1094-1099

Clinical Evidence for Anticoagulation in COVID-19

- Results
  - 134 pts (29.8%) had died at the end of the study period
    - There was no difference in 28-day mortality between pts that received heparin/LMWH and those who didn't:
      - 30.3% vs 29.7% (p=0.910)
  - In pts with a SIC score ≥ 4, heparin/LMWH treatment was associated with a lower 28-day mortality rate compared to those who did not receive heparin/LMWH:
    - 40% vs 64.2% (p=0.029)
  - In pts with D-dimer > 3.0 µg/mL (6x ULN), heparin/LMWH treatment was associated with a lower 28-day mortality compared to those who did not receive heparin/LMWH:
    - 32.8% vs 52.4% (p=0.017)

Tang, et al. *J Thromband Haemost.* 2020;18:1094-1099

Clinical Evidence for Anticoagulation in COVID-19

Limitations:

- Retrospective case series (observational study)
  - Endpoints not predefined
  - Cutoffs for SIC score and D-dimer levels were identified retrospectively, based on when they reached statistical significance
- Hypothesis generating only
  - Relatively small N
    - Those who received heparin/LMWH
    - Those who met SIC/D-Dimer cutoff criteria
- No discussion of bleeding rates
- No discussion of COVID-19 directed therapies

Tang, et al. *J Thromband Haemost.* 2020;18:1094-1099

Clinical Evidence for Anticoagulation in COVID-19

- Observational cohort study in 2,773 hospitalized pts with COVID-19 within a single health-system between March 14th and April 11th, 2020
- No inclusion/exclusion criteria set
- Cox proportional hazards model used to evaluate the effect of treatment-dose anticoagulation on in-hospital mortality
  - Anticoagulation included any form of anticoagulation (oral, subq, IV)
  - Statistical adjustments made for:
    - Age
    - Sex
    - Ethnicity
    - BMI
    - HTN
    - Heart failure
    - Atrial fibrillation
    - Type 2 diabetes
    - Anticoagulation use prior to hospital admission

Paranjpe, et al. *Journal of the American College of Cardiology.* 2020; DOI: https://doi.org/10.1016/j.jacc.2020.05.001

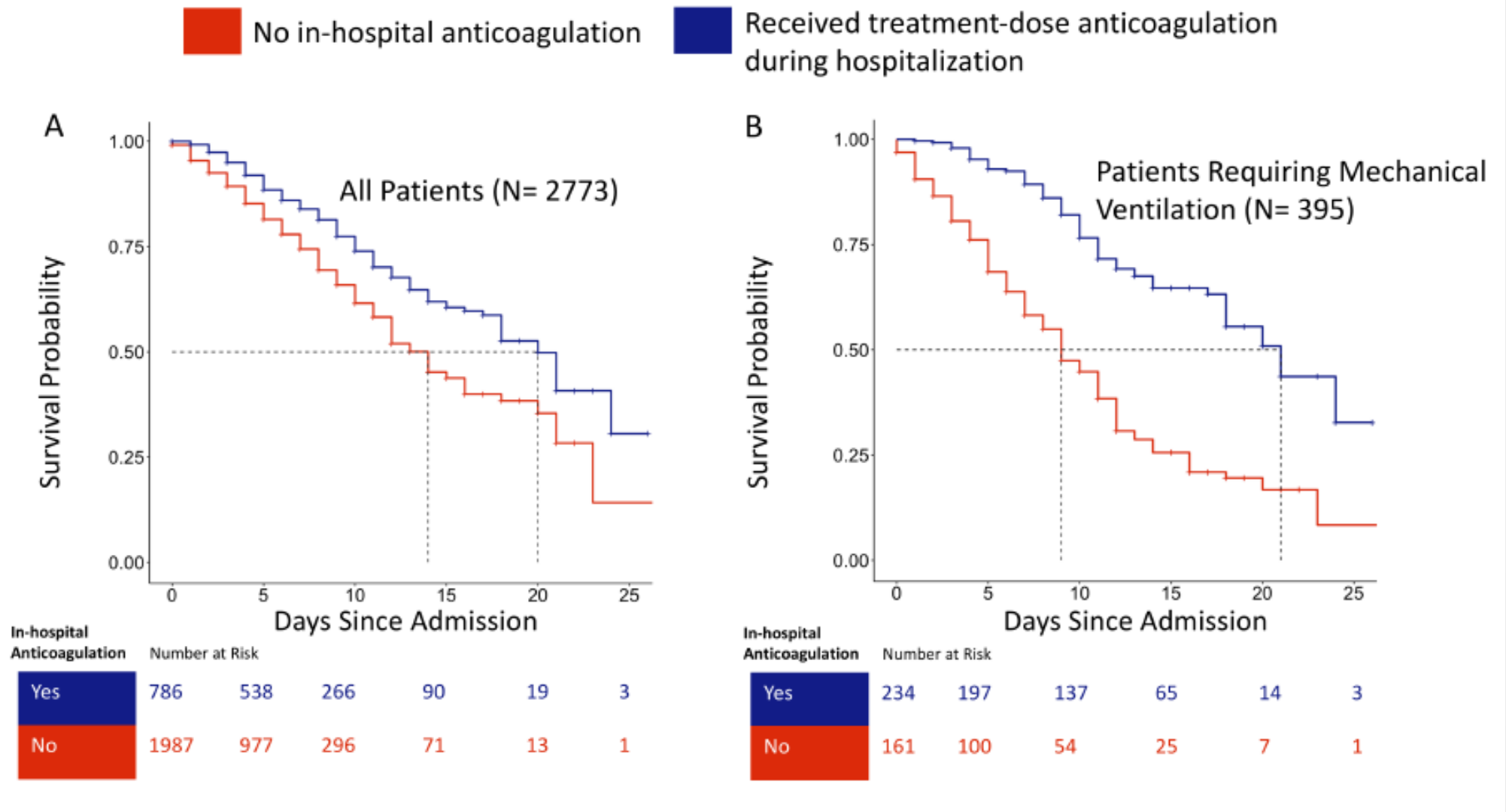
Clinical Evidence for Anticoagulation in COVID-19

Results

- 786 (28%) received anticoagulation during hospital admission
- Median hospital length of stay: 5 days (Interquartile range: 3-8 days)
- Median time from hospitalization to initiation of anticoagulation: 2 days (IQR: 0-5 days)
- Median duration of anticoagulation therapy: 3 days (IQR: 2-7 days)
- In hospital mortality rate
  - 22.5% with a median survival of 21 days in pts on anticoagulation vs 22.8% with a median survival of 14 days in pts who did not receive anticoagulation
- In pts who required mechanical ventilation
  - In hospital mortality was 29.1% with a median survival of 21 days in those who received anticoagulation vs 62.7% with a median survival of 9 days in those who did not

Paranjpe, et al. *Journal of the American College of Cardiology.* 2020; DOI: https://doi.org/10.1016/j.jacc.2020.05.001

Clinical Evidence for Anticoagulation in COVID-19



Paranjpe, et al. *Journal of the American College of Cardiology.* 2020; DOI: https://doi.org/10.1016/j.jacc.2020.05.001

Clinical Evidence for Anticoagulation in COVID-19

- Results
  - In a multivariate proportional hazards model, longer duration of anticoagulation was associated with a reduced risk of mortality
    - Adjusted HR: 0.86/day (95%CI: 0.82 –0.89; p < 0.001)
  - Bleeding
    - 3% (n=24) of pts who received anticoagulation had a bleeding event vs 1.9% (n=38) of those who did not receive anticoagulation
- Limitations
  - Observational study
    - Cohort population not well defined
    - Comorbidities (controlled for through statistical analysis)
    - COVID-19 disease status
    - Other COVID-19 directed therapies
  - Multiple anticoagulation therapies included
    - Doses unknown –described as “treatment”
  - Endpoints not predefined
  - Hypothesis generating only

Paranjpe, et al. *Journal of the American College of Cardiology.* 2020; DOI: https://doi.org/10.1016/j.jacc.2020.05.001

Resources for Thromboembolic Risk, Use of Anticoagulation in COVID-19

- Emergence of Institutional Antithrombotic Protocols for Coronovirus 2019. doi:10.1002/rth2.12358
- ISTH Interim Guidance on Recognition and Management of Coagulopathy in COVID-19. https://www.isth.org/page/covid19
- COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. https:doi.org/10.1016/j.jacc.2020.04.031
- COVID-19 and its implications for thrombosis and anticoagulation. DOI: 10.1182/blood.2020006582
- ***Thromboembolism and Anticoagulant Therapy During the Covid-19 Pandemic: Interim Clinical Guidance from the Anticoagulation Forum. https://acforum.org/web/***

Thromboembolism and Anticoagulant Therapy:
Interim Clinical Guidance from the Anticoagulation Forum

- Selected Recommendations
  - Pharmacologic VTE prophylaxis for all hospitalized non-pregnant patients with confirmed or highly suspected COVID-19, regardless of VTE risk assessment score (e.g. IMPROVE, Padua, Caprini) unless a contraindication exists
  - Non-critically ill hospitalized patients (i.e., ***not in an ICU***) with confirmed or highly suspected COVID-19
    - ***Standard dose VTE prophylaxis*** as per existing societal guidelines for medically ill and surgical hospitalized patients.
    - Dose adjustments for renal function or extremes of weight should follow product labeling and/or institutional protocols.

Thromboembolism and Anticoagulant Therapy-Interim Clinical Guidance from the Anticoagulation Forum

- Selected Recommendations
  - Critically ill patients (i.e., in an ICU) with confirmed or highly suspected COVID-19:
    - ***Increased doses of VTE prophylaxis***
      - Enoxaparin 40 mg subcutaneous twice daily
      - Enoxaparin 0.5 mg/kg subcutaneous twice daily
      - Heparin 7500 units subcutaneous three times daily
      - Or low-intensity heparin infusion (0.2 – 0.3 anti-Xa/ml)
    - This suggestion is based largely on expert opinion. Dose adjustments for renal function or extremes of weight should follow product labeling and/or institutional protocols.
  - We recommend ***against using biomarker thresholds***, such as elevated D-dimer, as the sole reason to trigger escalations in anticoagulant dosing outside the setting of a clinical trial.
  - For patients that are improving and transferring out of the ICU to the medical ward, ***it is reasonable to de-escalate*** to standard VTE prophylaxis dosing

Thromboembolism and Anticoagulant Therapy-Interim Clinical Guidance from the Anticoagulation Forum

- Selected Recommendations
  - We suggest that extended VTE prophylaxis is not necessary for all patients with COVID- 19 who are being discharged from the hospital.
    - Multidisciplinary discussion occur at or near the time of discharge to determine if a patient has ongoing VTE risk factors, may benefit from extended posthospital VTE prophylaxis, and has ensured access to VTE prophylactic medications.
  - If post-discharge prophylaxis is deemed reasonable:
    - Betrixaban
    - Rivaroxaban
    - Enoxaparin
- LMWH over UFH for the treatment of confirmed or suspected VTE whenever possible in patients with COVID-19.
  - Avoids additional laboratory monitoring, minimizes nursing and phlebotomy exposure, and limits use of personal protective equipment

Thromboembolism and Anticoagulant Therapy-Interim Clinical Guidance from the Anticoagulation Forum

- Selected Recommendations
  - We recommend using an anti-Xa assay rather than an aPTT to monitor therapeutic UFH in patients with COVID-19 whose aPTT is prolonged at baseline
  - We recommend against use of thrombolytics in patients with COVID-19 outside of a clinical trial setting unless there is another clinical indication for thrombolysis, such as ST elevation myocardial infarction, acute ischemic stroke, or high-risk (massive) PE with hemodynamic compromise

University of Colorado Hospital / University of Colorado Health Anticoagulation Subcommittee

ANTICOAGULATION RECOMMENDATIONS FOR HOSPITALIZED COVID-19 PATIENTS

Floor Patients	D-dimer <1500* AND TEG (MA) ≤ 70[&] (Only if available, see info below)	D-dimer > 1500* OR TEG (MA) > 70[&] (Only if available, see info below)
Weight <100 kg	Enoxaparin 40 mg QD	Enoxaparin 30 mg BID
Weight 100-150 kg	Enoxaparin 30 mg BID	Enoxaparin 40 mg BID
Weight > 150 kg	Enoxaparin 40 mg BID	Enoxaparin 0.5 mg/kg BID
AKI (GFR<30 ml/min)[#]	UFH 5000 U TID	UFH 7500 U TID

ICU Patients	D-dimer <1500* AND TEG (MA) ≤ 70[&] (Only if available, see info below)	D-dimer 1500* OR TEG (MA) > 70[&] (Only if available, see info below)
Weight <100 kg	Enoxaparin 40 mg QD	Enoxaparin 40 mg BID
Weight 100-150 kg	Enoxaparin 40 mg BID	Enoxaparin 0.5 mg/kg BID
Weight > 150 kg	Enoxaparin 60 mg BID	Enoxaparin 0.5 mg/kg BID
AKI (GFR<30 ml/min)[#]	UFH 5000 U TID	UFH 7500 U TID

University of Colorado Hospital / University of Colorado Health Anticoagulation Subcommittee

ANTICOAGULATION RECOMMENDATIONS FOR HOSPITALIZED COVID-19 PATIENTS

- COVID-19 patients with a ***history of thromboembolic disease and/or on chronic anticoagulation prior to admit*** should continue home anticoagulation regimen if clinically appropriate, or transition to alternative agent (most cases IV UFH) for therapeutic anticoagulation.

- COVID-19 patients who develop ***new arterial of venous thromboembolic events*** should be treated with therapeutic anticoagulation (UFH, LMWH) as standard of practice would dictate

- ***For high clinical suspicion of new thromboembolic events***, consider empiric therapeutic anticoagulation using heparin gtt and order a truncated, lower extremity DVT protocol (POCUS) as a confirmatory test.

University of Colorado Hospital / University of Colorado Health Anticoagulation Subcommittee

POST-ACUTE CARE ANTICOAGULATION CONSIDERATIONS FOR COVID-19 INPATIENTS

No Discharge Anticoagulation	Post-Acute Care Prophylactic Anticoagulation (Extended Prophylaxis) x 28 days: See below for options	Discharge on Therapeutic Anticoagulation
• Patients who received only regular-intensity prophylaxis throughout hospital stay (see blue highlights in table 2 and 3 below) • Patients who did not receive anticoagulation due to bleeding who have persistent risk factors for bleeding	*Any of the following indicates a patient should be considered for extended VTE prophylaxis. Patients should also have careful evaluation for the risk of bleeding:* • Patients who received "intensified" prophylaxis during hospitalization (see yellow highlights in table 2 and 3 below) • Patients who received therapeutic anticoagulation (typically UFH drip) for "hyperinflammatory state" without clinical suspicion of VTE or thrombosis • Patients with additional underlying risk factors for venous thrombosis, e.g. - active cancer - pregnancy (use LMWH; DOACs contraindicated) - comorbid chronic inflammatory or autoimmune condition (e.g. SLE) - Patients with an IMPROVE risk score ≥ 4 at discharge (2.9% or higher probability of VTE. https://www.outcomes-umassmed.org/IMPROVE/risk_score/index.html) *Assess patient for bleeding risk and weigh with potential benefit of extended prophylaxis.* • Patients with kidney or liver failure, anemia, major surgery in last 6 months, hx of GI or intracranial bleed are at increased risk of bleeding with anticoagulation	• Patients on chronic therapeutic anticoagulation prior to COVID-19 infection • Patients with new VTE, atrial fibrillation, arterial thrombosis or other standard indications for anticoagulation • Patient started on empiric therapeutic anticoagulation for clinically-suspected thrombosis (to complete a standard therapeutic course as for a person with proven thrombosis)

University of Colorado Hospital / University of Colorado Health Anticoagulation Subcommittee

POST-ACUTE CARE ANTICOAGULATION CONSIDERATIONS FOR COVID-19 INPATIENTS

Table 1 – Options for Consideration for Extended Prophylaxis of VTE in COVID + patients

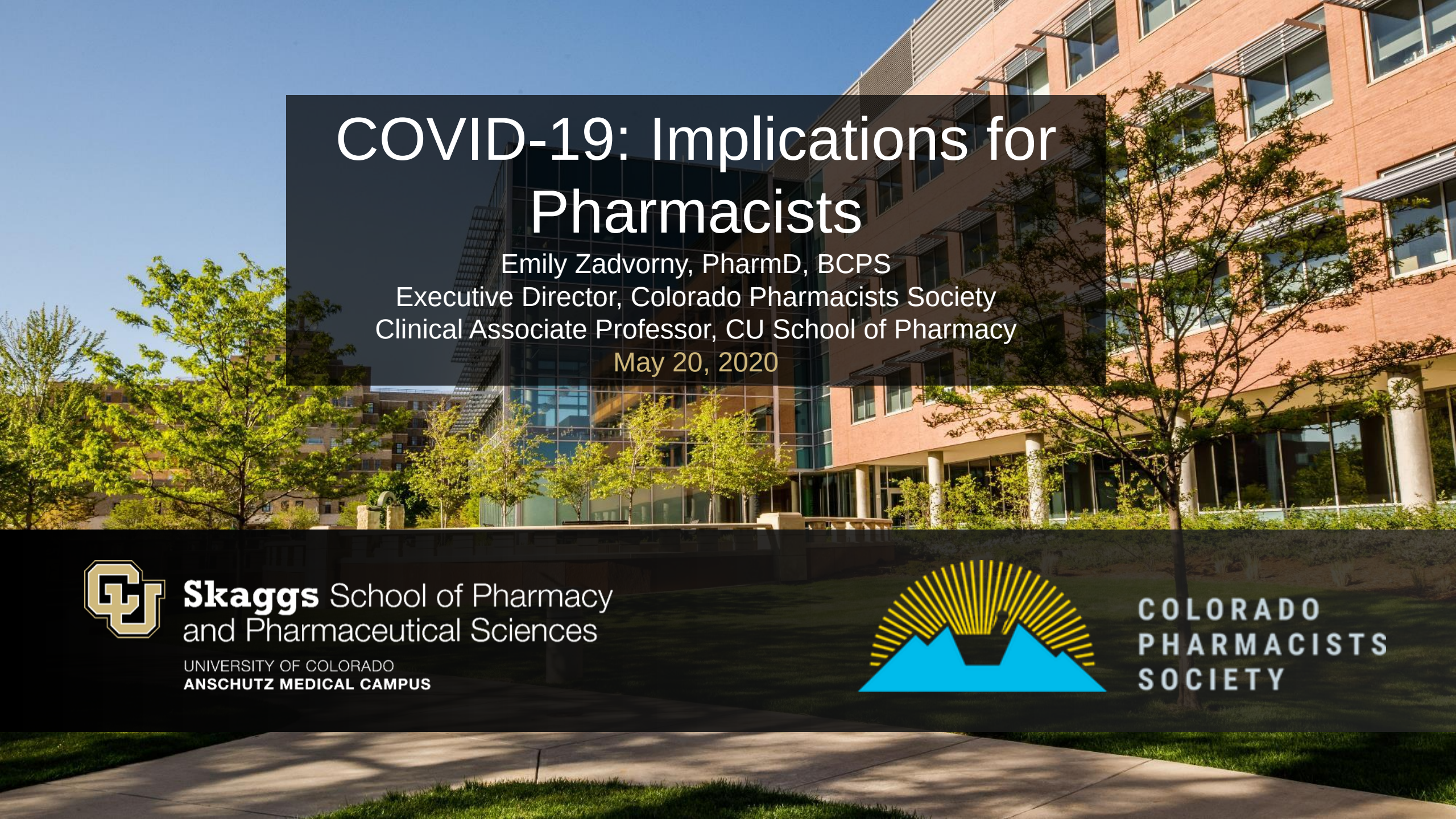
The following options should be considered on a patient by patient basis taking into consideration the strength of clinical data, likelihood of patient adherence, and availability of the agent as well as affordability

	Betrixaban 160 mg load, 80 mg once daily thereafter*	Enoxaparin 40 mg SQ once daily	Rivaroxaban 10 mg orally once daily*
Clinical trial notes	Agent with the best overall efficacy and safety data among listed options for extended prophylaxis in medically ill patients	Reduced the risk of VTE with a concomitant increased risk of bleeding when used for extended prophylaxis compared to placebo	Reduced the risk of VTE with a concomitant increased risk of bleeding when used for extended prophylaxis compared to placebo
Dose adjustment for organ dysfunction	If CrCL 15 to 29 mL/min: Betrixaban 80 mg load, 40mg once daily for 28 days If CrCL < 15 ml/min or AKI/ESRD, consult hematology or pharmacy for other options	If CrCL 15 to 29 mL/min: Enoxaparin 30mg subcut once daily for 28 days If CrCL < 15 ml/min or AKI/ESRD, consult hematology or pharmacy for other options	If CrCL < 30 ml/min, do not use, consider other options If CrCL < 15 ml/min or AKI/ESRD, consult hematology or pharmacy for other options

*FDA approved for prevention of VTE in patients hospitalized for medical illness up to 28 days after discharge

Wrap-up

- COVID-19 patients have significant hypercoaguability
- Observational studies indicate even standard doses of prophylaxis may not be adequate, especially in ICU patients
- Available observational studies indicates anticoagulation may improve outcomes. Still undetermined:
  - Prophylaxis versus treatment
  - Timing of initiation?
  - Extended prophylaxis for some or all patients?
- Role of antithrombotic therapy in ambulatory COVID-19 positive patients?
  - ASA
  - Prophylactic doses of anticoagulants



COVID-19: Implications for Pharmacists

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May 20, 2020

Skaggs School of Pharmacy and Pharmaceutical Sciences
UNIVERSITY OF COLORADO
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COLORADO PHARMACISTS SOCIETY

Colorado Pharmacists Society-Update Recent and Future Activities

- Working with Board of Pharmacy on emergency rules for COVID19.
- Ensuring ability of pharmacists in Colorado to TEST and VACCINATE beyond emergency period
- CDPHE collaboration – strategies on how pharmacists can help in state efforts
- Connecting hospital leadership with FDA leaders to gain insight and feedback regarding medication shortages and remdesivir distribution
- Telehealth expansion – pharmacist provision and payment
- Legislative session reconvening May 26th; advocacy for scope/payment
- Annual Meeting: VIRTUAL! June 4-5th; www.copharm.org to register!