5-2021

Review of Prophylactic Anticoagulation Strategies and Outcomes for COVID-19 Patients (Research in Progress)

Caleb Galindo
Providence Portland Medical Center, caleb.galindo@providence.org

Pamela Levine
Providence St. Vincent Medical Center, Pamela.Levine@providence.org

Melanie Geer
Providence, melanie.geer@providence.org

Review of Prophylactic Anticoagulation Strategies and Outcomes for COVID-19 Patients (Research in Progress)

Caleb Galindo, PharmD; Pamela Levine, PharmD; Melanie Geer, PharmD

PROVIDENCE Health & Services

Background

- In March of 2020, the World Health Organization (WHO) declared the spread of COVID-19 a global pandemic.
- Though largely considered a respiratory disease, research continues to demonstrate additional impacts of COVID-19 on other organ systems.[2, 3]
- A key characteristic of COVID-19 is marked inflammation leading to hypercoagulability.[2, 3, 6]
- Infected patients are at a higher risk of developing thromboembolic events (VTE and stroke) compared to healthy adults. [2, 3, 6]
- Some clinicians have trialed varying anticoagulation strategies for patients with COVID-19 based on coagulation parameters such as D-dimer.[4, 5, 6]
- Multiple expert groups have released preliminary guidance on anticoagulation strategies for patients with COVID-19; however, there is a lack of consensus.[1, 4, 5, 6, 7]
- Early reports suggested high rates of VTE in patients infected with COVID-19, despite standard prophylactic doses of anticoagulants.[3, 5]

Purpose

- Information from this study is intended to give insight into which anticoagulation strategy is optimal for patients diagnosed with COVID-19.

Definitions

- **Standard dosing** – administration of anticoagulant drugs for the primary prevention of VTE
- **Intermediate dosing** – off-label anticoagulant dose greater than standard dosing but lesser than treatment dosing, intended for primary prevention of VTE
- **Treatment dosing** – anticoagulation dosing strategy for the treatment of VTE(s) already present
- **Bleeding A** – overt bleeding requiring medical intervention and interruption/delayed dosing of anticoagulation
- **Bleeding B** – bleeding possibly requiring medical intervention but not requiring interruption or temporary interruption/delayed dosing of anticoagulation

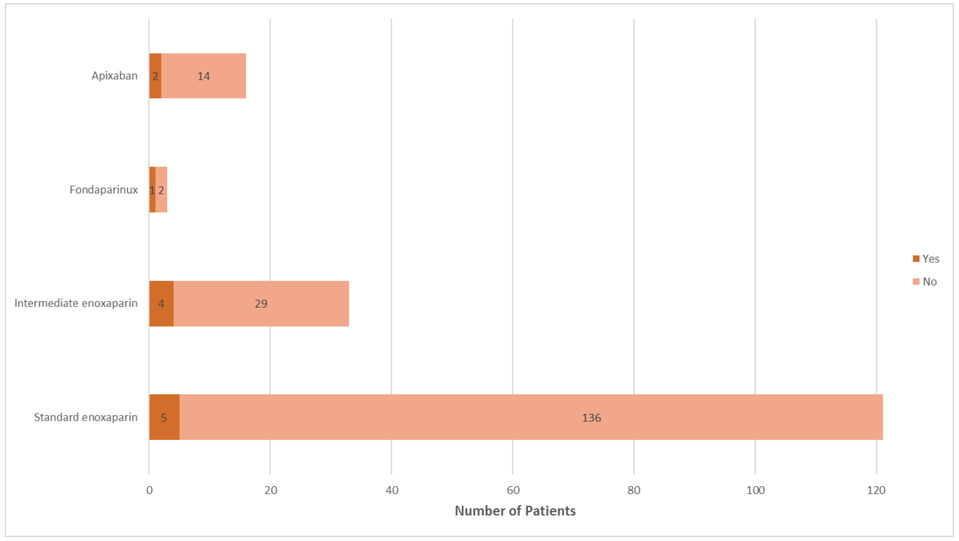
Methods

- Study design
  - Retrospective review of medical records
  - Data represented here is a homogenous sample (~50%) of a total of 473 patient records to be analyzed
- Inclusion criteria
  - Adults aged 18 years or older and active diagnosis of COVID-19, hospitalized in one of two institutional hospitals in Portland, OR between March 1, 2020 - October 1, 2020, and receiving anticoagulation
- Exclusion criteria
  - Heparin-induced thrombocytopenia in last 100 days, stroke within 30 days, history of hemorrhagic stroke, gastrointestinal bleed in last 60 days, platelet count < 25,000 platelets/microliter, active bleeding upon admission, patients on dual-antiplatelet therapy, patients with brain/spinal/ophthalmologic surgery in last 30 days
- Primary outcome
  - Evaluate inpatient prophylactic anticoagulation strategies and assess outcomes regarding efficacy in the prevention of thromboembolic events
- Secondary outcomes
  - Evaluate safety (presence of bleeding possibly requiring medical intervention) of varying dosing strategies and choice of prophylactic anticoagulation

Total Incidence of Thromboembolic Events and Bleeding

Agent	Thromboembolism	Bleeding A	Bleeding B
Apixaban (n=17)	2 (11.8%)	3 (17.6%)	
Dabigatran (n=1)			
Fondaparinux (n=3)	1 (33.3%)		
Heparin SQ (n=17)			1 (5.9%)
Intermediate enoxaparin (n=33)	4 (12.1%)	5 (15.1%)	4 (12.1%)
Standard enoxaparin (n=142)	5 (3.5%)	1 (0.7%)	10 (7%)
Rivaroxaban (n=1)			
Treatment enoxaparin (n=4)			1 (25%)
Warfarin (n=3)			1 (33.3%)
Total (n=229)	12 (5.2%)	9 (4.1%)	17 (7.4%)

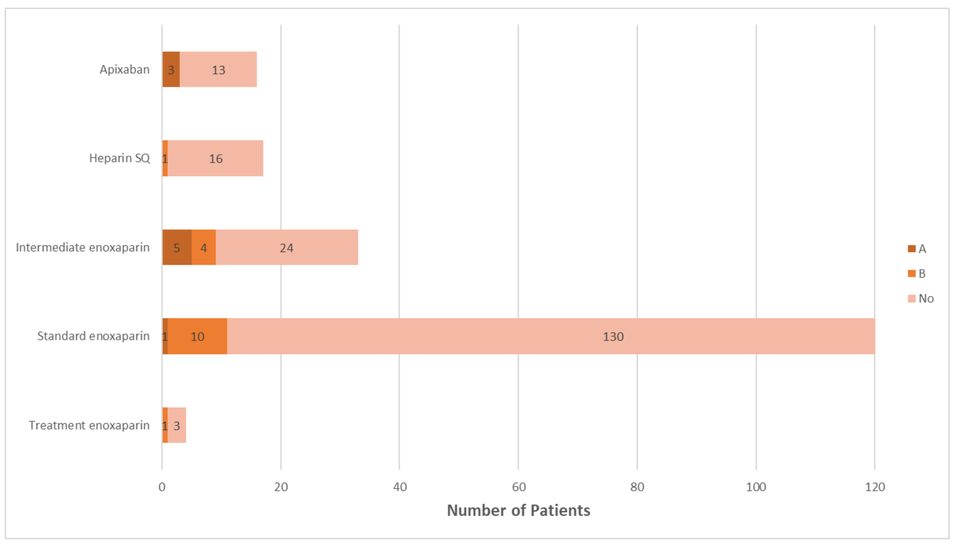
Incidence of Thromboembolic Events According to Medication and Dosing Strategy



Thromboembolic Events According to Medication and Dosing Strategy

Agent	Stroke	PE	DVT + PE	DVT	Total
Apixaban (n=17)	1			1	2
Fondaparinux (n=3)			1		1
Intermediate enoxaparin (n=33)			1	3	4
Standard enoxaparin (n=142)		2	1	2	5
Total (n=229)	**1**	**2**	**3**	**6**	**12**

Incidence of Bleeding According to Medication and Dosing Strategy



Discussion

Patient Population

- Total of 229 patients included in analysis
- Average age 62 years, range 18-96
- Exclusion data (18 patients)
  - Hx of hemorrhagic stroke, COVID-19 resolved before administration of anticoagulant, presenting with a bleed, on dual-antiplatelet therapy

Currently Available Data:

- Significant difference ($X^2 = 4.009$, $p = 0.0452$) between incidence of thromboembolism in standard enoxaparin vs intermediate enoxaparin, with greater incidence in intermediate group
- Currently no meaningful trends/differences among anticoagulants with limited samples (dabigatran, fondaparinux, rivaroxaban, warfarin).
- Among dosing strategies with outcomes of interest, there appears to be no evidence of increased risk of VTE with prophylaxis enoxaparin compared to other dosing strategies (though sample sizes for these are small).
- Among dosing strategies with outcomes of interest, there appears to be evidence of increased risk of bleeding with agents other than prophylaxis enoxaparin (apixaban, intermediate enoxaparin, treatment enoxaparin)

Limitations

- This is a snapshot of patients in the beginning of the pandemic when clinical guidance on optimal anticoagulation strategies was limited and evolving.
- Overall practice and treatment of patients diagnosed with COVID-19 has evolved over time and may present confounding factors in assessing outcomes.
- This data is limited in capturing overall incidence of VTE as it is limited to inpatient data. Incidence of VTE after hospitalization is not represented in this data and may exhibit differences based on anticoagulation strategy.
- Data collected included patients in all areas of the hospital; meaningful difference in acuity of COVID-19 and effect on VTE/bleeding may be underrepresented in this format.

Going Forward

- This data is in line with the 2021 ASH recommendation for standard enoxaparin over intermediate/therapeutic intensity anticoagulation in COVID-19 patients without DVT/PE[1]
- Further analysis into biomarkers, particularly D-dimer, may be insightful for patients receiving intermediate dosing enoxaparin.
- Analysis of demographic trends in patients with outcomes of interest may provide valuable insight.
- Statistical analysis pending larger sample is in progress.
- Additional research into current COVID-19 patients to account for changes in clinical practice and new strains of the virus is warranted.

References

1. Cuker A, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv*. 2021 Feb 9;5(3):872-888.
2. Dobesh PP, Trujillo TC. Coagulopathy, Venous Thromboembolism, and Anticoagulation in Patients with COVID-19. *Pharmacotherapy*. 2020 Nov;40(11):1130-1151.
3. Miesbach W, Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. *Clin Appl Thromb Hemost*. 2020 Jan-Dec;26:1076029620938149.
4. Mucha SR, et al. Coagulopathy in COVID-19: Manifestations and management. *Cleve Clin J Med*. 2020 Jul 31;87(8):461-468.
5. Paranjpe I, et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. *J Am Coll Cardiol*. 2020 Jul 7;76(1):122-124.
6. Tang N, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020 Apr;18(4):844-847.
7. Thachil J, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020 May;18(5):1023-1026.