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Brief Report

THROMBOSIS AND HEMOSTASIS

Postdischarge thrombosis and hemorrhage in patients with COVID-19

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KEY POINTS

- **Cumulative incidence of overall thrombosis was 2.5% and of bleeding was 3.7% at day 30 after discharge for hospitalization for COVID-19.**
- **These data highlight the importance of a data-driven risk-benefit ratio assessment for postdischarge extended thromboprophylaxis.**

Coronavirus disease 2019 (COVID-19) is associated with a prothrombotic state with a high incidence of thrombotic events during hospitalization; however, data examining rates of thrombosis after discharge are limited. We conducted a retrospective observational cohort study of discharged patients with confirmed COVID-19 not receiving anticoagulation. The cohort included 163 patients with median time from discharge to last recorded follow-up of 30 days (interquartile range [IQR], 17-46 days). The median duration of index hospitalization was 6 days (IQR, 3-12 days) and 26% required intensive care. The cumulative incidence of thrombosis (including arterial and venous events) at day 30 following discharge was 2.5% (95% confidence interval [CI], 0.8-7.6); the cumulative incidence of venous thromboembolism alone at day 30 postdischarge was 0.6% (95% CI, 0.1-4.6). The 30-day cumulative incidence of major hemorrhage was 0.7% (95% CI, 0.1-5.1) and of clinically relevant nonmajor bleeds was 2.9% (95% CI, 1.0-9.1). We conclude that the rates of thrombosis and hemorrhage appear to be similar following hospital discharge for COVID-19, emphasizing the need for randomized data to inform recommendations for universal postdischarge thromboprophylaxis. (*Blood*. 2020;136(11):1342-1346)

Introduction

Alteration in laboratory coagulation parameters and the occurrence of arterial and venous thrombosis are well recognized in patients with coronavirus disease 19 (COVID-19).[1,2] The immunothrombotic phenomenon is believed to be related to endothelial injury and subsequent activation of the coagulation cascade and thrombin generation.[3] In the absence of prospective data, professional societies and individual institutions have published interim recommendations to guide anticoagulation management in COVID-19, including consideration of extended thromboprophylaxis following discharge.[4-6]

In acutely ill medical populations, the risk of venous thromboembolism (VTE) extends beyond the duration of the hospitalization, with up to 80% of events occurring in the post–hospital-discharge period (30-45 days) following index hospitalization.[7] There is equipoise regarding the net clinical benefit conferred by extended thromboprophylaxis following hospitalization, and the American Society of Hematology (ASH) Guideline Panel recommended only inpatient prophylaxis with low-molecular-weight heparin.[8-13]

In the absence of randomized or prospective data for patients with COVID-19, guidelines suggest postdischarge thromboprophylaxis based on individual bleeding and thrombotic risk.[4-6,14,15] Considering the high rates of in-hospital thrombosis in COVID-19, aggressive thromboprophylaxis is recommended during hospitalization.[4,14,16] Whether the prothrombotic state of COVID-19 persists after hospital discharge is not known.

Study design

A retrospective analysis of consecutive patients hospitalized with a diagnosis of COVID-19 at the Beth Israel Deaconess Medical Center (BIDMC) from March to May 2020 was performed. Approval was obtained from the local institutional review board, and the study was conducted in accordance with the Declaration of Helsinki. Inclusion criteria included age of at least 18 years and a positive polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 from a nasopharyngeal swab (real-time severe acute respiratory syndrome coronavirus 2 assay). A total of 406 patients with COVID-19 were initially admitted during the time period. Patients were excluded if they: remained hospitalized at time of analysis (n = 17); died during hospitalization (n = 102); were discharged without any form of postdischarge contact in the BIDMC electronic medical record by 31 May 2020 (n = 93); or were discharged on therapeutic anticoagulation (n = 27; consort diagram in the supplemental Figure, available on the *Blood* Web site). Patients discharged on prophylactic-dose anticoagulation were also excluded from

Table 1. Thrombotic and bleeding events post–hospital discharge

Age, y	Sex	Length of hospital stay, d	ICU stay	Postdischarge day event occurred	Type	Event details	Anticoagulation received during index hospitalization
Thrombosis							
33	Female	14	Yes	3	PE	Presented with acute shortness of breath and diagnosed with bilateral segmental pulmonary emboli	Enoxaparin: 40 mg once daily
80	Female	3	No	21	Left ventricular thrombus, central retinal artery occlusion	Presented to emergency room with acute unilateral blindness; echocardiogram revealed a ventricular aneurysm with thrombus	Heparin: 5000 U twice daily
51	Female	8	No	25	Thrombosis of arteriovenous dialysis fistula	Chronic dialysis for end-stage renal disease developed thrombus of established brachial fistula used for access	Heparin: 5000 U twice daily
59	Female	11	Yes	40	Ischemic stroke	Presented with vision loss, headache, and neglect and diagnosed with left parieto-occipital infarct	Heparin: 5000 U twice daily/ Enoxaparin: 40 mg once daily
Hemorrhage							
78	Male	11	Yes	13	Major hemorrhage	Mechanical fall with femoral fracture, received transfusion due to hematoma	Enoxaparin: 40 mg once daily
60	Female	9	No	16	CRNMB	Large subcutaneous hematoma over lumbar sacral area following mechanical fall with referral to emergency room	Heparin: 5000 U twice daily
77	Female	4	No	24	CRNMB	Recurrent epistaxis prompted admission for embolization	Heparin: 5000 U twice daily
59	Male	14	No	30	CRNMB	Gross hematuria required catheter placement and urologic evaluation	None
73	Male	6	No	31	Major hemorrhage	Fall with head strike resulted in subarachnoid hemorrhage	Enoxaparin: 40 mg once daily
51	Male	13	No	31	CRNMB	Mechanical fall with scalp hematoma, required emergency management	Enoxaparin: 40 mg once daily

ICU, intensive care unit.

primary analysis with thrombosis and hemorrhages reported separately (n = 13). For patients with multiple admissions related to COVID-19, the first admission was considered the index admission.

The primary outcomes of interest were the cumulative incidence of thrombosis or hemorrhage at day 30 after discharge among patients who did not receive postdischarge thromboprophylaxis. Bleeding was assessed according to the International Society on Thrombosis and Haemostasis definitions and included major bleeding and clinically relevant nonmajor bleeding (CRNMB).[17] Baseline data included patient demographics, comorbidities, and use of anticoagulants during hospitalization. Thrombotic and hemorrhagic events were evaluated independently by 2 data abstractors (R.P. and T.B.); disagreements were adjudicated by a third investigator (J.I.Z.).

Estimates of the cumulative incidence of venous and thrombotic arterial events as well as hemorrhage were calculated by Kaplan-Meier methodology along with 95% confidence intervals (CIs). Competing risk analyses were not performed due to low 30-day postdischarge mortality.

Results and discussion

A total of 163 patients met eligibility criteria and were included in the primary analysis (characteristics of patients included are available in the supplemental Table). One patient, who was readmitted after the index hospitalization, died of progressive respiratory failure secondary to COVID pneumonia.

Four thrombotic events were recorded in the primary study cohort (4 of 163; 2.5%) including 1 segmental pulmonary embolism (PE), intracardiac thrombus, thrombosed arteriovenous fistula, and ischemic stroke (Table 1). Cumulative incidence of overall (venous and arterial) thrombosis was 2.5% (95% CI, 0.8% to 7.6%) at day 30 after discharge (Figure 1). Median duration to thrombotic event postdischarge was 23 days (interquartile range, 12-33). The cumulative incidence of VTE alone at day 30 postdischarge was 0.6% (95% CI, 0.1-4.6).

Six patients in the cohort experienced hemorrhagic events during the follow-up period (6 of 163; 3.7%). The cumulative incidence of hemorrhage at day 30 after discharge was 3.7% (95% CI, 1.4% to 9.8%) (Figure 1). Four of the hemorrhagic events were classified as CRNMB, and 2 patients developed major bleeds (Table 1). Both major bleeds followed mechanical falls: 1 patient developed a limb hematoma that required multiple transfusions and the other a head strike leading to a subarachnoid hemorrhage. There were no fatal bleeds. Median duration to a bleeding event was 27 days (interquartile range, 16-31 days). The cumulative incidence of major bleeds and CRNMB at day 30 postdischarge was 0.7% (95% CI, 0.1-5.1) and 2.9% (95% CI, 1.0-9.1), respectively.

Among the 13 patients discharged on thromboprophylaxis, there were no observed thrombotic or hemorrhagic complications. Ten patients were discharged on low-molecular-weight heparin, 2 on a direct oral anticoagulant, and 1 patient on unfractionated heparin (all at prophylactic dosages). Three patients were discharged to inpatient facilities where thromboprophylaxis was continued. Seven patients were pregnant when admitted and were discharged on anticoagulation that extended for an additional 2 weeks. Two patients underwent orthopedic procedures during hospitalization and continued thromboprophylaxis per standard of care. One patient was continued on rivaroxaban thromboprophylaxis after discharge due to concern regarding COVID-19 coagulopathy.

Epidemiologic data suggest that up to 80% of all hospitalization-associated VTEs occur after discharge.[7,18,19] Given the high reported rates of thrombosis in hospitalized patients with COVID-19, we anticipated that this increased risk would extend into the outpatient setting. The observed rate of symptomatic thrombotic events in our cohort (0.6%), only 1 of which was a deep vein thrombosis or PE, is low and comparable to those observed in control arms of randomized interventional studies (0.3% to 2.5%) at 28 to 35 days.[9,10,20,21] We believe that the observed rates of thrombosis are reflective of the true symptomatic incidence of thrombosis. For the primary analyses, we excluded 13 patients discharged on thromboprophylaxis. All but 1 of those patients had secondary indications for continued thromboprophylaxis beyond COVID-19 coagulopathy (ie, pregnancy, orthopedic surgery, or continued inpatient rehabilitation). The rate of thrombosis within 30 days postdischarge should be generalizable to the larger population of hospitalized

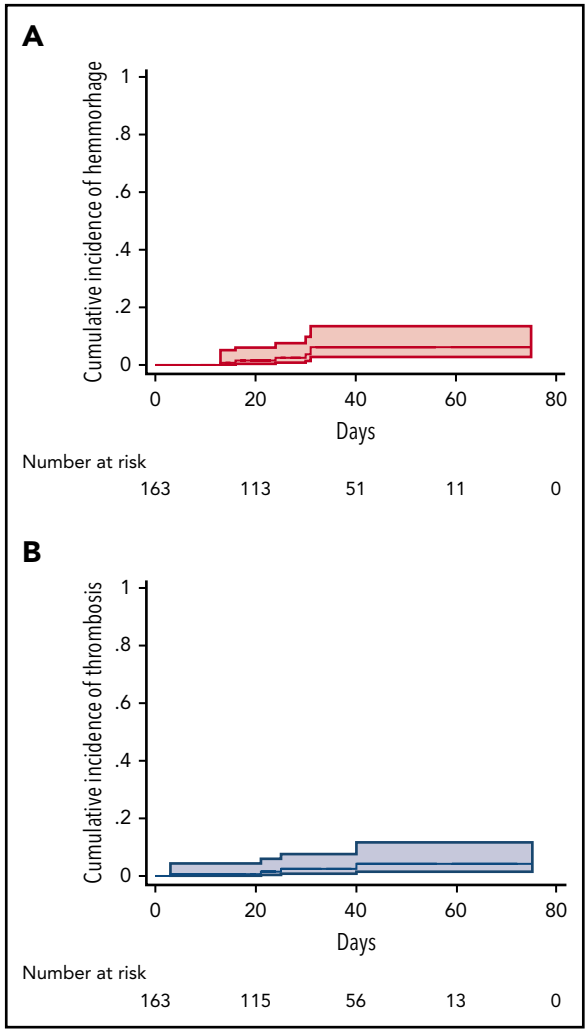

Figure 1. Patients discharged following acute hospitalization for COVID-19. (A) Cumulative incidence of overall hemorrhage and (B) arterial/venous thrombosis. Shaded areas represent 95% CIs.

patients with COVID-19 infection in the absence of secondary indications for continued thromboprophylaxis.

There is an emerging signal of increased bleeding during hospitalization for COVID-19 that needs to be balanced against the risk of thrombosis.[22] In randomized studies, the cumulative incidence rates of major and CRNMB at 4 to 5 weeks postdischarge in the placebo arms range between 0.7% and 2%.[9,10,12] In our cohort, the cumulative incidence of major hemorrhage was 0.7% and CRNMB was 2.9%. Given the retrospective study design, true bleeding rates may be lower as patients without follow-up were excluded; these patients may have been less acutely ill and less likely to have experienced bleeding. We also note that 4 bleeding events (including 2 major bleeds) occurred following mechanical falls in debilitated patients who were discharged after lengthy hospitalizations (Table 1), which is of particular relevance when considering the relative risks and benefits of extended prophylaxis following COVID-19 hospitalization.

To the best of our knowledge, this is the first study to systematically evaluate bleeding and thrombosis rates in patients discharged with COVID-19. Thrombosis and bleeding risk is likely

modulated by factors including age, coagulation profile, comorbidities, severity of index illness, and degree of immobility. Our study design and event rate did not allow meaningful multivariable analysis of variables predictive of thrombosis or hemorrhage. Inclusion into this analysis required the patients to have at least 1 postdischarge medical evaluation, as we did not want to assume that patients without contact did not experience a thrombotic event. We suspect that the low rate of VTE observed is actually an overestimation of the true event rate as healthier patients with fewer comorbidities are less likely to seek medical care postdischarge (and suffer a thrombotic or bleeding event). We also acknowledge that the relatively limited sample size warrants caution in interpretation of our results; prospective studies are required to definitively establish rates of hemorrhagic and thrombotic events.

Extended-duration pharmacological thromboprophylaxis is recommended for high-risk surgical patients,[23] but the net clinical benefit in acutely ill medical patients is less clear and is thus not universally recommended.[24] A meta-analysis of randomized controlled trials assessing in-hospital prophylaxis to "extended-duration" prophylaxis demonstrated that thromboprophylaxis can reduce the risk of VTE, but with an increased risk of hemorrhage.[25] Very few patients in our cohort received extended thromboprophylaxis; thus we cannot comment on the relative safety or efficacy of anticoagulation following discharge in COVID-19. However, based on an observed rate of hemorrhage in the nonanticoagulated cohort, we would be cautious in recommending extended-duration thromboprophylaxis without a clear indication (eg, major surgery) outside of a clinical trial.

Authorship

Contribution: R.P., W.C.A., K.A.B., and J.I.Z. designed the study; R.P., T.B., M.M., A.K., and P.B. collected and analyzed data; J.I.Z. and R.P. wrote the manuscript; and all authors reviewed the final manuscript and contributed to its preparation.

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Footnotes

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For original data, please contact jzwicker@bidmc.harvard.edu.

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REFERENCES

1. Cao W, Li T. COVID-19: towards understanding of pathogenesis. *Cell Res.* 2020; 30(5):367-369.
2. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood.* 2020;135(23):2033-2040.
3. Levi M, Thachil J. Coronavirus disease 2019 coagulopathy: disseminated intravascular coagulation and thrombotic microangiopathy-either, neither, or both [published online ahead of print 8 June 2020]. *Semin Thromb Hemost.* doi:10.1055/s-0040-1712156.
4. Bikdeli B, Madhavan MV, Jimenez D, et al; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020;75(23):2950-2973.
5. Cohoon KP, Mahé G, Tafur AJ, Spyropoulos AC. Emergence of institutional antithrombotic protocols for coronavirus 2019. *Res Pract Thromb Haemost.* 2020;4(4):510-517.
6. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost.* 2020;18(5):1023-1026.
7. Hull RD, Merali T, Mills A, Stevenson AL, Liang J. Venous thromboembolism in elderly high-risk medical patients: time course of events and influence of risk factors. *Clin Appl Thromb Hemost.* 2013;19(4):357-362.
8. Spyropoulos AC, Raskob GE. New paradigms in venous thromboprophylaxis of medically ill patients. *Thromb Haemost.* 2017;117(9): 1662-1670.
9. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al; ADOPT Trial Investigators. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med.* 2011;365(23): 2167-2177.
10. Gibson CM, Halaby R, Korjian S, et al; APEX Investigators. The safety and efficacy of full- versus reduced-dose betrixaban in the Acute Medically Ill VTE (Venous Thromboembolism) Prevention With Extended-Duration Betrixaban (APEX) trial. *Am Heart J.* 2017;185: 93-100.
11. Spyropoulos AC, Ageno W, Albers GW, et al; MARINER Investigators. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. *N Engl J Med.* 2018;379(12): 1118-1127.
12. Cohen AT, Spiro TE, Spyropoulos AC; MAGELLAN Steering Committee. Rivaroxaban for thromboprophylaxis in acutely ill medical patients [comment]. *N Engl J Med.* 2013;368(20):1945-1946.
13. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv.* 2018;2(22):3198-3225.
14. Lee AYY, Connors JM, Kreuziger LB, et al. COVID-19 and coagulopathy: frequently asked questions. American Society of Hematology. Available at: http://www.hematology.org/covid-19/covid-19-and-coagulopathy. Accessed 19 May 2020.
15. Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis.* 2020;50(1): 72-81.
16. Ciavarella A, Peyvandi F, Martinelli I. Where do we stand with antithrombotic prophylaxis in patients with COVID-19? [editorial]. *Thromb Res.* 2020;191:29.
17. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S; Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost.* 2015;13(11): 2119-2126.
18. Amin A, Neuman WR, Lingohr-Smith M, Menges B, Lin J. Venous thromboembolism prophylaxis and risk for acutely medically ill patients stratified by different ages and renal disease status. *Clin Appl Thromb Hemost.* 2019;25:1076029618823287.
19. Amin AN, Varker H, Princic N, Lin J, Thompson S, Johnston S. Duration of venous thromboembolism risk across a continuum in medically ill hospitalized patients. *J Hosp Med.* 2012; 7(3):231-238.

20. Cohen AT, Spiro TE, Büller HR, et al; MAGELLAN Investigators. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368(6):513-523.

21. Hull RD, Schellong SM, Tapson VF, et al; EXCLAIM (Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients With Prolonged Immobilization) study. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. *Ann Intern Med*. 2010; 153(1):8-18.

22. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. 2020;136(4):489-500.

23. Anderson DR, Morgano GP, Bennett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. *Blood Adv*. 2019;3(23):3898-3944.

24. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141(suppl 2):e195S-e226S.

25. Liew AY, Piran S, Eikelboom JW, Douketis JD. Extended-duration versus short-duration pharmacological thromboprophylaxis in acutely Ill hospitalized medical patients: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Thrombolysis*. 2017;43(3): 291-301.