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CASE REPORT

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Breakthrough venous thromboembolic events in five patients with COVID-19 on direct oral anticoagulants

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Abstract

What is known and objective: Coronavirus disease 2019 (COVID-19) is associated with increased risk of venous thromboembolism (VTE). Guidance for VTE prophylaxis continues to evolve, including addressing direct oral anticoagulants (DOACs) continued upon hospitalization.

Case summaries: We present 5 patients hospitalized for COVID-19 while on DOACs. Four patients had atrial fibrillation and had a previous VTE. Four patients developed acute VTE and one developed stroke-like symptoms. Monitoring D-dimer assisted with the detection of VTE. Three patients died, and two were discharged alive.

What is new and conclusion: Therapeutic failure with DOACs appears to be commonplace in COVID-19. Further research is needed to determine whether there is an underlying cause to this association.

KEYWORDS

factor Xa Inhibitors, heparin, low molecular weight, pulmonary embolism, SARS-CoV-2

1 | WHAT IS KNOWN AND OBJECTIVE

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has created unique challenges since its discovery in Wuhan, China.[1] Evidence demonstrates significant cardiovascular complications, particularly coagulopathy. A hypercoagulable state predisposes patients to venous thromboemboli (VTE) via endothelial dysfunction, inflammation, platelet activation and venous stasis.[2]

For hospitalized patients not previously on anticoagulation, the need for VTE prophylaxis is well-established.[3] Therapeutic options include unfractionated heparin (UHF), low-molecular-weight heparin (LMWH) or fondaparinux. The International Society on Thrombosis and Haemostasis (ISTH) gives preference to UHF or LMWH for VTE prophylaxis in both critically ill and non-critically ill patients.[4,5] Vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACS) are cautioned due to drug-drug interactions.[4] The American College of Chest Physicians recommends LMWH, UHF and fondaparinux over DOACs and LMWH and fondaparinux over UHF to limit healthcare worker exposure.[6] Caution with DOACs is again advised due to the possibility of hemodynamic instability, drug-drug interactions and risk of acute kidney injury altering pharmacokinetics and increasing bleeding risk.[6]

Despite the abundance of guidance for initiating VTE prophylaxis in patients not previously on anticoagulation, there is little direction for patients admitted on therapeutic DOACs for other indications (nonvalvular atrial fibrillation and previous VTE). Current evidence cautions against DOACs for increased bleeding rather than therapeutic failure. Guidance for anticoagulation in this scenario is not well-established, and thus directed to standard of care for hospitalized non-COVID patients.[3] Herein, we describe 5 cases of patients taking DOACs for other indications who developed breakthrough VTEs.

2 | CASE PRESENTATIONS

This case series occurred at a regional COVID care facility. As part of standard hospitalized care, all patients are evaluated for appropriate VTE prophylaxis or treatment therapy daily. Patients who are

TABLE 1 Patient details

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographics	77-year-old white male	70-year-old white male	76-year-old white male	80-year-old white male	92-year-old white male
Past medical history	Atrial fibrillation, dyslipidaemia	Atrial fibrillation CAD, CHF, COPD, diabetes type 2, dyslipidaemia, hypertension,	Atrial fibrillation, CHF, dyslipidaemia, hypertension, asthma, diabetes type 2	CAD, CHF, dyslipidaemia, hypertension, history of pulmonary embolus	Atrial fibrillation, CAD, CHF, dyslipidaemia, CLL, CAD s/p CABG, ischaemic cardiomyopathy, sick sinus syndrome s/p PPM, HLD, HLD, paroxysmal Afib, anaemia of chronic disease and chronic pleural effusion.
Home anticoagulant	Apixaban 5 mg twice daily	Apixaban 5 mg twice daily	Rivaroxaban 20 mg daily	Rivaroxaban 20 mg daily	Apixaban 2.5 mg twice daily
Other home medications	Metoprolol Atorvastatin	Aspirin, carvedilol, dulaglutide, furosemide, insulin glargine, lansoprazole, losartan, montelukast, simvastatin	Atorvastatin, bisoprolol, buspirone, digoxin, dulaglutide, escitalopram, esomeprazole, insulin lispro, levothyroxine, losartan, pregabalin, ropinirole, tamsulosin, trazodone	Amiodarone, aspirin, atorvastatin, furosemide, insulin aspart, insulin detemir, levothyroxine, mirtazapine, sertraline	Carvedilol, ferrous sulphate
COVID/ infection-related therapies	Convalescent plasma Dexamethasone Cefepime	Convalescent plasma Dexamethasone	Convalescent plasma Dexamethasone Cefepime, linezolid	Convalescent plasma Dexamethasone Cefepime, linezolid	Convalescent plasma Dexamethasone Remdesivir Cefepime, linezolid
Highest Oxygen requirement prior to VTE	Supplemental oxygen (15 L/min)	Supplemental oxygen (10 L/min)	High flow nasal cannula	Mechanical ventilation	High flow nasal cannula
Reason for VTE workup	D-dimer > 5000 ng/mL	D-dimer 2721 ng/mL	Shortness of breath, D-dimer > 5000 ng/mL	Increasing O2 requirement, unable to safely perform CT	Left-sided facial droop with aphasia, D-dimer 3160 ng/mL
VTE findings	Chest CT demonstrated bilateral upper lobe pulmonary emboli	Venous ultrasound demonstrating partially occluding and soft echogenic material in the lumen of the popliteal and femoral veins	Chest CT demonstrated small pulmonary embolism in distal segmental and subsegmental pulmonary artery branches of right lower lobe	Venous ultrasound demonstrated echogenic material in lumen of femoral vein, appears acute on chronic	Clinical diagnosis of a stroke. Care was withdrawn and no further imaging was performed
Treatment rendered	Change to enoxaparin 1 mg/kg every 12hr	Change to enoxaparin 1 mg/kg every 12 hr	Change to enoxaparin 1 mg/kg every 12 hr	Change to enoxaparin 1 mg/kg every 12 hr	Care withdrawn
Highest oxygen requirement after VTE	Mechanical ventilation	Supplemental oxygen (5 L/min)	Mechanical ventilation	Mechanical ventilation	Care withdrawn
Patient outcome	Deceased	Discharge to skilled nursing facility	Discharge to inpatient rehabilitation	Deceased	Deceased

on home anticoagulation are continued on that agent. There have been 14 patients in our cohort who were admitted on DOACs. Five patients (35.7%) either presented with DOAC failure or developed a VTE during their hospitalization. Full case details are presented in Table 1. D-dimers were trended in Frigure 1, often used to supplement the evaluation of VTE prophylaxis.

Patient 1 presented 4 days after diagnosis. He was continued on home apixaban 5 mg twice daily for chronic atrial fibrillation. Initial D-dimer was less than 200 ng/mL. On day 14, D-dimer rose to 2746 ng/mL and then greater than 5000 ng/mL, prompting a chest computed tomography (CT) for pulmonary embolism (PE) protocol. On day 15, the CT demonstrated bilateral upper lobe pulmonary emboli. Apixaban was discontinued, and enoxaparin 1 mg/kg every 12 h was initiated. The patient's respiratory status continued to worsen, requiring mechanical ventilation. He then developed multi-system organ failure and was transitioned to comfort care.

Patient 2 presented 2 days after COVID-19 symptom onset and was continued on home apixaban 5 mg twice daily for paroxysmal atrial fibrillation. Initial D-dimer was less than 200 ng/mL and increased to 2721 ng/mL, prompting further investigation. Venous Doppler ultrasound of the lower extremities demonstrated partially occluding and soft echogenic material in the lumen of the popliteal and femoral veins. Apixaban was discontinued, and enoxaparin 1 mg/kg every 12 h and warfarin were initiated. The patient was discharged to a skilled nursing facility.

Patient 3 initially presented 14 days after diagnosis of COVID-19 diagnosis with worsening shortness of breath. The patient was on rivaroxaban 20 mg daily for atrial fibrillation. Initial D-dimer was greater than 5000 ng/mL, leading to a chest CT for PE protocol, which demonstrated small pulmonary embolism in distal segmental and subsegmental pulmonary artery branches of right lower lobe. Rivaroxaban was discontinued, and enoxaparin 1 mg/kg every 12 h was initiated. The patient was eventually changed back to rivaroxaban and discharged to inpatient rehabilitation.

Patient 4 initially presented with increasing shortness of breath about a week after symptom onset. The patient was on rivaroxaban 20 mg daily for history of DVT. The patient was mechanically ventilated upon admission and changed to enoxaparin. Chest CT for PE protocol could not be performed due to patient acuity and poor prognosis. Venous Doppler ultrasound was arranged on day 3 in which demonstrated acute on chronic DVT of the femoral vein. Enoxaparin 1 mg/kg twice daily was continued until care was withdrawn.

Patient 5 presented with productive cough for the past 10 days. The patient was on apixaban 2.5 mg twice daily for atrial fibrillation, dose adjusted by his outpatient cardiologist. On admission, his dose was increased to 5 mg twice daily. Initially, the patient did not appear ill, only complaining of mild diarrhoea and a slight productive cough. He remained relatively stable until day 4 when his O2 requirement increased. Increased swelling and erythema were noted in the right lower extremity which was preliminarily read as a DVT. The patient was temporarily switched to enoxaparin 1 mg/kg twice daily and considered an apixaban failure. Venous Doppler ultrasound report stated findings were consistent with a chronic DVT, prompting conversion back to apixaban 5 mg twice daily. On day 8, D-dimer rose to over 3100 and the patient displayed significant left-sided facial droop and left-sided hemiplegia. The patient was somnolent and poorly communicating. He was clinically diagnosed with a stroke. Care was withdrawn, per his wishes.

3 | WHAT IS NEW AND CONCLUSION

This case series describes a relatively high percentage of DOAC failure in COVID-19–positive patients admitted to an inpatient facility. Concern of DOAC efficacy in COVID-19 has been previously described. Di Tano and colleagues described a breakthrough CT-diagnosed PE while on rivaroxaban for atrial fibrillation in a 79-year-old male. The patient was subsequently switched to enoxaparin.[7]

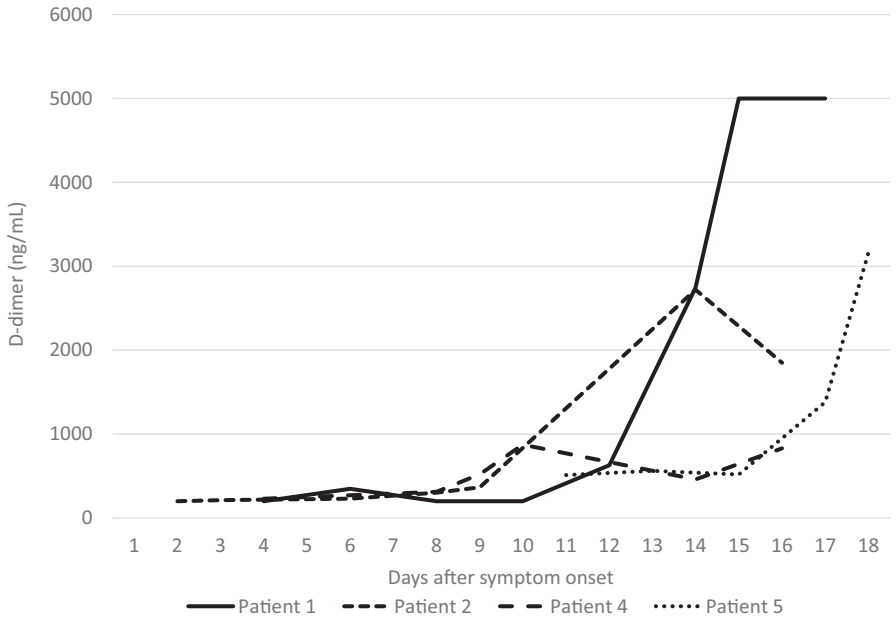

FIGURE 1 D-dimer trend. Note that patient 3 had a single D-dimer value on day 15 reported as >5000 ng/mL

While drug-drug interactions are a known cause of DOAC failure, our case series does not include patients with significant drug-drug interactions. Additionally, this case series involves predominantly non-critically ill patients on DOACs at the time of new thrombosis, which should lessen the theoretical risks of decreased oral absorption of medications in the absence of critical illness as a reason for DOAC failure. The exact mechanism for DOAC failure is unknown. Drug-drug interactions and medication compliance should always be considered in a therapeutic failure. In the absence of inadequate dosing, one possible mechanism that explains this phenomenon is that the SARS-CoV-2 infects the host cells using the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in several organs and the endothelial cells of the vasculature.[8] Direct viral infection of these endothelial cells leads diffuse endothelial inflammation or endotheliitis.[8] While the DOACs are exclusively anticoagulants, heparin and LMWH possess both anticoagulant and anti-inflammatory properties.[9]

Our understanding of the pleiotropic effects of heparin continues to evolve. A systematic review found that heparin can decrease the level of inflammatory biomarkers but ultimately concluded that further research is needed from larger studies.[9] Currently, proposed mechanisms include inhibition of neutrophil chemotaxis, neutralization of inflammatory cytokines and leucocyte migration, inhibition of the complement factor C5a and sequestration of acute-phase proteins.[10-15] These effects are better described in sepsis, a disease known for interacting effects of inflammation and coagulation.[11]

Treatment for VTE should target full anticoagulation, though choice of agent should balance patient factors such as concomitant organ dysfunctions with the need to try to minimize healthcare worker exposure with frequent laboratory draws. For those that are critically ill, parenteral anticoagulation with LMWH or fondaparinux is recommended over oral therapy.[6] For patients that clot while on home therapies, the chest guidelines provide a framework for management.[6] Specifically, if VTE occurs on a DOAC, a change to full dose LMWH or UHF is warranted. If VTE occurs on LMHW, dose increase of 25 to 30% should be considered.[6]

There are several limitations including this being an all-male, all-white, elderly population. Given our small cohort, it is unknown whether age, race and sex contributed to these findings. Data regarding prehospital outpatient management are unavailable, and we are unable to speculate on non-hospitalized rates. The timing of patient 4 is somewhat obscure. We debated not including this case. But ultimately the prescribers felt, in their professional judgement, that this was rivaroxaban failure and was therefore included. Additionally, association does not prove causality. Further research is needed from larger institutions to validate or refute our findings. In the interim, we are considering converting patients admitted with COVID-19 on DOACs to therapeutic UHF or LMWH, which is currently a circulating proposal.[16,17]

The United Kingdom National Health Service is closest to adopting the recommendation to convert DOACs to therapeutic UHF or LMWH.[18] They again highlight the possibility of drug-drug interactions with DOACs, elude to the additional anti-inflammatory properties of UHF and LMWH, and recommend that DOACs "could be switched" to a LMWH.[18] However, the United States National Institutes of Health make no recommendations outside of standard of care.[3] The American College of Cardiology does not mention DOACs and states that the optimal prophylactic strategy requires further investigation.[2]

Based on this case series, there appears to be the possibility that COVID-19 may lead to higher rates of DOAC failure. Although an exact mechanism is unknown, DOACs have no effect on endotheliitis while UHF and LMWH have pleiotropic anti-inflammatory properties. Further research is needed to evaluate these claims. In the interim, we suggest a low threshold for changing hospitalized patients with COVID-19 on DOACs to UHF or LMWH.

CONFLICT OF INTEREST

The authors report no funding and no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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