



When to opt for preemptive anticoagulation with SARS-CoV-2 infection in the long-term care facilities

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Introduction

Early reports of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection from Wuhan, China in late December 2019 presaged the global pandemic, infecting millions and causing substantial morbidity and mortality, especially among older adults. The USA accrued over 80 million cases and over a million deaths by the end of the 2nd year of the pandemic, the most among developed countries [1, 2]. Individuals of all ages are at increased risk for SARS-CoV-2 infection, and severe disease. However, the probability of serious COVID-19 is higher in persons > 60 years of age, those living in a nursing home or long-term care facility (LTCF), and those with chronic medical conditions. In the early months of the pandemic, COVID-19 deaths in LTCFs accounted for more than 40% of all COVID-19 deaths in the USA [3]. Known to predispose to thrombotic complications, Coronavirus disease 2019 (COVID-19), the illness that afflicts many with SARS-CoV-2 infection, places residents of LTCFs at exceptionally high risk of death. This article will review the available guidance to support initiating anticoagulation in SARS-CoV-2-positive patients residing in

LTCFs, and discuss our experience initiating anticoagulation in LTCF residents with COVID-19. Because of limited access to antiviral therapies in many places worldwide, anticoagulation in high-risk residents of LTCF remains a consideration for reducing COVID-19-related thrombotic outcomes.

SARS-CoV-2 and thrombotic complications

Vascular complications of SARS-CoV-2 are common and can lead to thrombogenesis with a variety of clinical manifestations, such as deep vein thrombosis, COVID toe, pulmonary embolism. In the USA, patients ill enough to require hospitalization now receive prophylactic dose anticoagulation as a standard of care for COVID-19. However, the role of post-discharge prophylactic dose anticoagulation is still unclear in LTCF residents.

The MICHELLE trial randomized 320 hospitalized patients with COVID-19 who were considered at high risk for venous thromboembolism (TE) into two groups who receive rivaroxaban 10 mg oral daily for 35 days after discharge or no anticoagulant. A total of 3% of the rivaroxaban-treated patients had venous TE, symptomatic arterial embolism, and fatal cardiovascular events, compared to 9% of the controls [4]. Although this makes a good argument for using thromboprophylaxis upon hospital discharge, it has yet to become routine practice.

Prophylactic dose anticoagulation now is the standard of care for COVID-19 patients during hospitalization in the USA, as is post-discharge anticoagulation for those at high risk and severe cases. However, the role of prophylactic dose anticoagulation in non-hospitalized remains still unclear in LTCF residents. Understanding the risk for thrombo-occlusive phenomena with SARS-CoV-2 infection and vaccination helps to formulate a strategy to prevent or

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treat thrombotic complications in individuals at risk, such as LTCF residents.

Considering thromboembolic prophylaxis for LTCF residents

In the USA, LTCF providers often manage COVID-19-infected patients in the LTCF setting with the goal of avoiding hospitalization, if possible, especially if their advance directives limit the escalation of care.

Increased age, multimorbidity, and immobility increases the direct risk of hypercoagulability from SARS-CoV-2 infection. Severe fatigue, respiratory failure, and isolation policies to mitigate SARS-CoV-2 transmissibility exacerbate immobility and increase the risk for thrombotic disease and residents' PADUA Prediction score for Thromboembolism (TE). TE risk further increases with comorbidities, such as cancer, history of TE, chronic kidney disease especially end stage renal disease on hemodialysis, BMI > 30, Type 1 and 2 Diabetes Mellitus, coronary artery disease and age greater than 70 years. Given the potential for severe consequences from coagulopathy driven by the SARS-CoV-2 virus or its spike protein, it is reasonable to consider the risks and benefits of responding to the event, versus anticipating the event and prophylactically intervening. The risk for these outcomes depends on each resident's individual risk factors.

In the absence of contraindications, these risks make it reasonable to consider treatment "in place," i.e., in the LTCF/nursing home, and includes prophylactic anticoagulation for those infected with SARS-CoV-2. However, the best guidance available to improve prognosis comes from hospital-based studies, which often have access to medications not available in the LTCF, thereby reducing the applicability to this highly vulnerable population. Because we often want to treat these individuals without subjecting them to hospital transfer, i.e., in place, we need to consider the role of anticoagulants in conjunction with other strategies available for the LTC setting. This consideration has a local resource context, including the availability of other remedies, such as effective antivirals or monoclonal antibodies, and the selection of anticoagulants.

Depending on the location, LTCF residents may have monoclonal antibodies and/or antivirals available. If there is no access to other effective therapies in the LTCF, then anticoagulants deserve consideration.

A study conducted by Tang et al. showed that anticoagulant therapy with low molecular weight heparin (LMWH) improved prognosis in patients with elevated D-dimer levels [5]. Although several professional societies like The American College of Cardiology (ACC), International Society of Thrombosis and Hemostasis (ISTH), World Health Organization, and a Shanghai expert consensus recommend anticoagulation with LMWH for

hospitalized patients [6], evidence for its use in the LTCF setting remains lacking. Because of LMWH's expense, its requirement for injection (and close contact), an oral anticoagulant may be preferred in the LTCF.

Absent availability for effective treatment with antivirals or monoclonal antibodies to modify the risk of SARS-CoV-2 infection, we still need to balance the risks and benefits of TE anticoagulation chemoprophylaxis. When considering prophylactic oral anticoagulation, genetic influences on the risk of VTE should be considered as well. Asian ethnicity is associated with a lower risk of TE, whereas Black Americans have almost a fivefold greater incidence of TE [7], but it remains unknown whether this is a genetic predisposition versus some other factor resulting from social determinants of health. Also consider the type of medication, dosage, and duration before treatment initiation.

Figure 1, "A Framework for Recommendations," describes a pathway to consider while treating LTCF residents in place. Immediately update goals of care for all LTCF residents and whenever clinical status changes to determine how aggressively to intervene, (e.g., treat in place or in the hospital). If treating in place, consider triaging SARS-CoV-2 infected residents to anticoagulation based on the assessment of risk and benefit.

As part of our LTCF standard of care, we discuss goals of care with residents and their families. At the prospect of COVID-19 entering our facility, we intentionally set aside time to renew these discussions in the context of both the poor outcomes associated with SARS-CoV-2 and of available therapies. These discussions also address treatment options, including decisions to treat in place with or without palliative care, the prospect of hospitalization, and the point at which to consider hospice care.

Once diagnosed with SARS-CoV-2 infection, and as soon as possible, we offer any effective available treatment, including antivirals or monoclonal antibodies. Prior vaccination and presumed vaccine effectiveness will also influence the enthusiasm to anticoagulate. We ensure standard interventions to reduce thromboembolic risk are in place, including mobility and hydration (Fig. 1). With a consensus to treat in place, absent alternative effective treatment, we next decide whether to initiate anticoagulation prophylaxis.

How aggressively we advocate for anticoagulation depends on actual or anticipated case severity and bleeding risk [8–11]. Initial decision-making considers the mortality experienced from COVID-19 within a community and national context; if circulating strains have not produced much morbidity or mortality, we would expect less benefit from added anticoagulation. As such, we recommend a nuanced risk assessment for anticoagulation, not just to clinical conditions and a SARS-CoV-2 infection, but also considering local context.

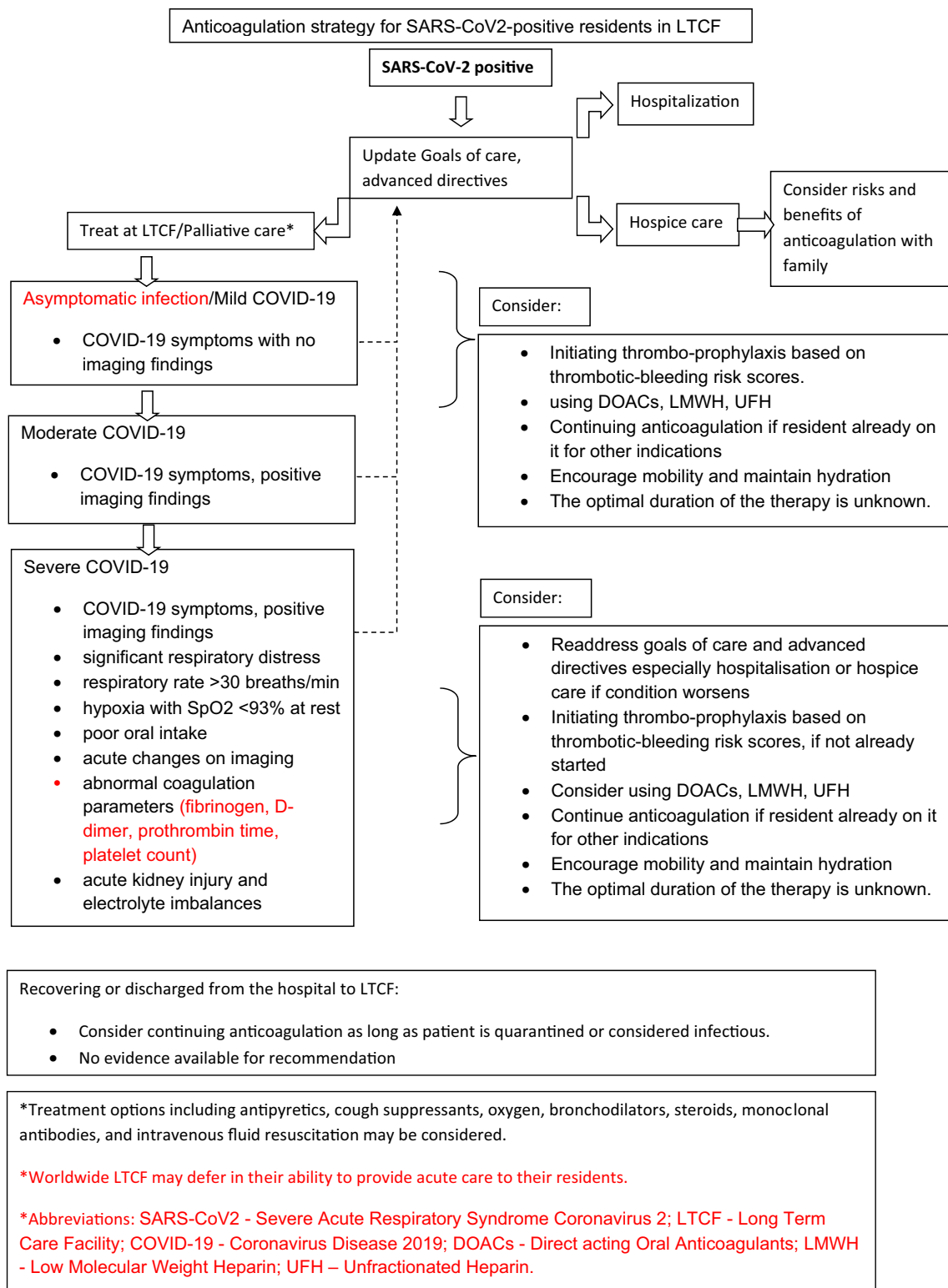


Fig. 1 A Framework for Recommendations for anticoagulation of nursing home residents infected with SARS-CoV-2

In our LTCF, we consider non-immune residents at high risk for severe outcomes. Absent access to definitive therapy, we do not wait for moderate to severe disease to develop;

we provide prophylactic anticoagulation to all residents who are not at the end of life or at high risk for bleeding complications.

We use therapeutic doses of anticoagulants in patients with suspected or proven thrombosis. Contraindications include active bleeding or serious bleeding in the prior 24–48 h, or the use of heparin (e.g., history of heparin-induced thrombocytopenia in which alternative agents such as fondaparinux must be used).

Medications to consider

Next, we choose the anticoagulant, taking into account LTCF-specific issues, such as availability of testing, staffing, vaccination, and personal protective equipment (PPE). We know that LTCFs without in-house diagnostic testing capability can experience delays in results reported by outside laboratories; a delayed D-Dimer result can affect our anticoagulant-specific decisions.

PPE availability may also affect medication choice. An abundance of PPE supplies leaves more room to consider using drugs that require multiple daily doses or direct contact. Severe healthcare worker shortages in LTCFs due to hiring freezes, furloughing, and COVID-19 outbreaks [12] have resulted in a leaning toward the use of direct oral anticoagulants (DOACs) and other medications that are less burdensome to administer or track. These issues give context to the choice of medication for thromboprophylaxis in the LTCF and should be considered.

The next consideration relates to SARS-CoV-2 infection and how it affects clotting. Unfractionated heparin binds to the spike protein, potentially offering added efficacy, in addition to its effects on platelets and antithrombin III. It is also an option in renal insufficiency [13]. LMWH increases the number of healthcare workers exposed to the patient; dose adjustments are required in frail elderly patients and may not be used in patients with chronic kidney disease (CKD) stages 4 and 5. DOACs address thrombogenesis related to inflammation and produce direct thrombin inhibition. Xa inhibition does not generally affect platelet aggregation. Given the propensity of SARS-CoV-2's spike protein to bind to platelets and VWF [14], we might prefer platelet aggregation inhibition. Rivaroxaban has the potential to inhibit tissue factor-mediated platelet aggregation via inhibition of thrombin generation [15], potentially giving it an advantage among the Xa inhibitors. Aspirin has a theoretical advantage due to platelet effects. Observational retrospective data suggest baseline aspirin use, i.e., before infection, may lower mortality rates in patients with COVID-19 [16, 17]. However, randomized controlled trials in which aspirin initiation occurred after infection did not demonstrate a mortality benefit for hospitalized patients with COVID-19 [18, 19]. Additionally, if residents are already on anticoagulants, such as but not limited to warfarin or DOACs for underlying medical comorbid conditions, these should be continued.

To reduce opportunities for SARS-CoV-2 transmission between residents and healthcare workers, missed doses of anticoagulants, and the consumption of PPE driven by extra encounters, consider effective oral once-a-day dosing agents. We need to balance the cost and effectiveness in using unfractionated heparin with safety and PPE expenditure in deciding how best to anticoagulate infected residents in LTCFs.

In considering DOACs, note that most DOACs clear through renal excretion. In one study of 82 LTCFs in the US, about 50% of residents qualified for a diagnosis of CKD [20], and 13% were stage 4 or 5. Yet, few studies have addressed use in the CKD context, limiting guidance. DOAC testing, when available, can help inform us on critical clinical decision-making for concerns regarding drug accumulation with CKD, thrombotic or bleeding events. In our LTCF setting, before the advent of SARS-CoV-2 treatments, we prescribed rivaroxaban because of its once-a-day administration, the desirable potential effect on platelets, and minimal monitoring requirements [15]. If not for resource considerations, such as staffing, need for intravenous administration, and PPE supplies, we would have selected Argatroban as our drug of choice, given its immediate effects and lack of risk for heparin-induced thrombocytopenia [21]. Medication cost was not a factor in our choice but does limit choices in less-resourced settings. Table 1 describes the potential medications, doses, frequency, and monitoring parameters to be considered for empiric TE prophylaxis. Consider therapeutic doses of anticoagulation with suspected or proven thrombosis.

Duration

No guidelines address the duration of TE prophylaxis for SARS-CoV-2 infected LTCF residents; accordingly, residents' clinical status and progression will need to inform this decision. Significant clinical decline and life-limiting prognosis, including admission to hospice justify TE prophylaxis discontinuation. American College of Cardiology and PALTC guidelines recommend extended (post-discharge) TE prophylaxis with DOAC or LMWH for all COVID-19 patients with elevated VTE risk (e.g., reduced mobility, active cancer, low risk for bleeding, and D-dimer greater than two times the upper normal limit) for up to 45 days [22]. In our setting, we continued anticoagulants on residents already receiving them, and initiated treatment for at least 14 days upon diagnosis with an initial positive test confirming current SARS-CoV-2 infection, whether or not they were symptomatic. Because older LTCF residents may shed virus longer due to underlying disease and immune senescence, tend to have more severe disease, and are more likely to have significant functional decline and poor mobility placing them at high risk of TE, they might benefit from longer

Table 1 Commonly used Thromboembolic prophylactic agents

Medication	Dose	Route	Frequency	Therapeutic Target	Risk consideration	Monitoring parameters
Apixaban	2.5 mg (if age > 80 years, weight < 60 kg, serum Cr > 1.5)	Per os	Twice daily	Direct factor Xa inhibitor	Bleeding risk Renal dosing required	CBC, aPTT, PT, serum creatinine, and liver function tests prior to initiation when clinically indicated Routine coagulation testing is not required or necessary; signs of bleeding
Aspirin	81 mg	Per os	Daily	Cyclo-oxygenase (COX) enzyme inhibitor	Lack of evidence, not currently recommended	
*Dabigatran	150 mg (CrCl > 30 unless on P-gp ^a inhibitors;—avoid coad-ministration	Per os	Twice daily	Direct thrombin inhibitor	Bleeding risk. Use extreme caution in > 75 years old Renal dosing required	CBC, aPTT, PT, serum creatinine, and liver function tests prior to initiation, when clinically indicated, signs of bleeding; routine coagulation testing is not required or necessary
*Edoxaban	30 mg (CrCl 15–50 ml/min) Avoid if CrCl > 95 or < 15 ml/min	Per os	Daily	Direct factor Xa inhibitor	Bleeding risk Renal dosing required	CBC, aPTT, PT, serum creatinine, and liver function tests prior to initiation when clinically indicated; routine coagulation testing is not required or necessary
Enoxaparin	40 mg (normal CrCl) 30 mg (if CrCl < 30 ml/min)	Sub-cutaneous	Daily	Factor Xa	Bleeding risk, monitor CBC including platelet count. Renal dosing required	Platelet count, hemoglobin, hematocrit, fecal occult blood, signs or symptoms of bleeding, anti-factor Xa levels
Heparin	5000 units	Sub-cutaneous	Three times a day Twice daily if weight < 50 kg	Antithrombin III	Bleeding risk	creatinine at baseline and during therapy; monitoring of PT and/or aPTT is not necessary Hemoglobin, hematocrit, platelet count, PT, aPTT, signs/symptoms of bleeding, risk factors for bleeding, fecal occult blood test (if indicated); can monitor anticoagulation by anti-Factor Xa activity or aPTT
Rivaroxaban	10 mg (CrCl > 30 ml/min). Avoid use (CrCl < 30 ml/min)	Per os	Daily	Direct factor Xa inhibitor	Bleeding risk, Renal dosing required	Renal function and CBC prior to initiation; hepatic function when indicated or signs of bleeding Routine coagulation testing is not required or necessary
Warfarin	Starting at 2.5 mg	Per os	Daily	Vitamin K epoxide reductase complex I inhibitor	Bleeding risk	Prothrombin time, INR; hematocrit. Warfarin is not recommended due to frequent and close monitoring

*As per Beers criteria

^aP-gp inhibitors—Permeability-glycoprotein inhibitors—Cyclosporine, Ketoconazole, Quinidine, Reserpine, Ritonavir, Tacrolimus, Valspodar (PSC833), Verapamil, Zosuquidar, Elacridar (GF120918) (FDA)

*Edoxaban: Not used in the US, however, used in Europe

duration of thromboprophylaxis [23]. We pair anticoagulation with standard-of-care interventions, such as increased mobilization, thrombo-embolus deterrent stockings, cycled compression devices, and hydration [24].

Meanwhile, the overall thrombotic risk with COVID-19 has decreased with vaccination. Data from England suggest that there was a short interval increase in hematological and vascular events leading to hospitalizations and death after the first doses of mRNA vaccines and adenovirus vectored vaccine [25]. However, these events were notably higher following SARS-CoV-2 infections within the same population and higher in patients with prolonged infection than among those vaccinated.

Perhaps, the one thing to remember about the temporal association of SARS-CoV-2 vaccination and infection to a new coagulopathy is that the spike protein and adenovirus vector can directly contribute to abnormalities in coagulation and COVID-related pathology. When the clinician confronts coagulopathy in the COVID-19 pandemic era, the approach to anticoagulation must consider the added complexities that come with multimorbidity; the pragmatic approach still needs to consider resources, risks, and setting in the risk–benefit assessment to what is ultimately offered.

Conclusion

In this paper we review considerations in the use of TE prophylaxis in LTCF residents contextually with the associated risks, prior vaccination, and access to medication and hospitalization. In facilities where SARS-CoV-2 antiviral therapy and thrombotic risk remain high, thromboprophylaxis may improve outcomes. The LTCF setting has resource limitations requiring consideration of different classes of medications, the use of oral medications, once-a-day dosing and limited options for hospitalization. These strategies limit disease-vectoring among residents and healthcare workers. For LTCFs specifically, currently available evidence leads us to prefer once or twice daily DOACs over injectables for pragmatic reasons, and LMWH better than UFH for pharmacologic reasons. The ultimate choice of medication also depends on its availability in the LTCF, PPE supplies, and facility policies. Whether to prophylactically anticoagulate also depends on access to effective treatment of SARS-CoV-2, including monoclonal antibodies, effective antivirals and the benefits outweighing the risks. As treatments, vaccines, and the selection of anticoagulants improve, risk/benefit considerations will change. We need prospective studies conducted in LTCFs, acute rehabilitation centers, and assisted-living settings to develop future evidence-based recommendations, and to further understand the multi-tiered levels of healthcare and how this can directly affect therapeutic strategies in the context of low-resource settings.

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Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics approval Not relevant.

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