Opinion

Warfarin or Non-Vitamin K Antagonist Oral Anticoagulants: Navigating the Choice of Oral Anticoagulant Drugs in the COVID-19 Pandemic Era

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Abstract

Emerging evidence indicates that thromboembolic complications are a key determinant of inhospital mortality of patients with COVID-19. Prophylactic anticoagulation therapy is an important component of inhospital management of patients with COVID-19. Considering that millions of patients worldwide are prescribed oral anticoagulation therapy, herein, we summarize the pros and cons of non-Vitamin K antagonist oral anticoagulants (NOACs) and warfarin, in terms of pharmacodynamics, and therapeutic efficacy and adverse effect monitoring in the context of the global pandemic of COVID-19. Despite a lack of evidence from high-quality randomized trials, an NOAC, rather than warfarin, would be a scientifically reasonable treatment option for patients with COVID-19 in the outpatient setting.

Keywords: *COVID-19; Non-Vitamin K antagonist oral anticoagulants; Oral anticoagulant; Warfarin*

Introduction

Recent reports from the coronavirus disease 2019 (COVID-19) frontline in China have shown that disseminated intravascular coagulation (DIC), which is featured by thrombocytopenia, an elevated d-dimer level, and prolonged thrombin time, is a common and aggravating factor for the progression of COVID-19 severity.[1,2] Moreover, subsequent studies in China and other countries confirmed a high prevalence of deep venous thrombosis (DVT) by either lower extremity ultrasound or postpartum examination.[3,4] Recognizing the risks of DIC and DVT in critical COVID-19 patients, on March 25 and on April 15, 2020, the International Society on Thrombosis and Haemostasis and the American College of Cardiology published consensus statements aiming to provide risk stratification at admission for COVID-19 patients.[5,6] The guidelines recommend the prophylactic use of unfractionated heparin/low-molecular-weight heparin (LMWH) for DIC and DVT prevention in indicated patients. In support of this recommendation, a recent observational study in China confirmed that among severe COVID-19 patients with sepsis-induced coagulopathy score ≥4, the 28-day mortality was significantly lower in those treated with LMWH than in those who did not receive LMWH treatment.[7] This finding provided proof-of-principle evidence supporting the value of anticoagulation during COVID-19 hospitalization.

Warfarin versus Non-Vitamin K Antagonist Oral Anticoagulants in Clinical Practice

Millions of patients worldwide are prescribed oral anticoagulation therapy. The indications for oral anticoagulation include stroke prevention in nonvalvular atrial fibrillation with CHA_2DS_2-VASc score ≥2 in men or ≥3 in women, valvular atrial fibrillation, intracardiac thrombi, DVT and/or pulmonary embolism, hip or knee replacement surgery, prolonged immobilization, solid tumor (except liver tumor), and thrombotic thrombocytopenic purpura [Figure 1]. In addition, recent evidence from the Cardiovascular Outcomes for People

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Using Anticoagulation Strategies trial has demonstrated the efficacy and safety of a combination of a low-dose non-Vitamin K antagonist oral anticoagulant (NOAC) (rivaroxaban 2.5 mg twice daily) and aspirin in reducing ischemic events in patients with stable coronary heart disease or peripheral artery disease.[8-10] Millions of patients worldwide are prescribed oral anticoagulation therapy in cardiology as well as other medical specialties.

The selection of an oral anticoagulant requires the consideration of comorbidities, such as renal or hepatic dysfunction, thrombocytopenia, and gastrointestinal tract function. Emerging evidence from large randomized clinical trials supports the safety and effectiveness of NOACs (i.e., dabigatran, apixaban, and rivaroxaban) in preventing stroke or systemic embolic events. All NOACs have clinical advantages over warfarin owing to fewer drug–drug and dietary interactions, reproducible pharmacological profiles, decreased risk of intracranial bleeding, and no need for frequent testing of the international normalized ratio (INR) for dose adjustments. However, except in patients with moderate-to-severe mitral stenosis and mechanical heart valve replacement, for whom there is no available clinical evidence to support the use of NOACs, warfarin still has its market share in prescriptions for most of the clinical indications NOACs have been approved for. For example, the NOAC prescription rate for atrial fibrillation is <50% of the warfarin prescription rate across various insurance plans in clinical practice.[11]

Warfarin and Bleeding Complications in Sepsis and COVID-19

Warfarin inhibits the Vitamin K oxidoreductase, thereby preventing γ-carboxylation activation of the coagulation factors II, VII, IX, and X. Thus, warfarin administration can induce a pharmacological depletion of selective coagulation factors. Currently, the mechanisms triggering and factors underlying DIC initiation and progression in the setting of COVID-19 are not well understood. Pathologically, DIC evolution is characterized by systemic microvascular thrombus formation, depletion of coagulation factors, and consequently, overt systemic hemorrhage. The coagulation function is temporally directly or indirectly altered as a result of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and proliferation or viral sepsis-mediated endothelial dysfunction, inflammatory response, and platelet activation.[12,13] These pathological processes would consequently lead to a transient hypercoagulability,[14,15] which, when left uncontrolled, may evolve into pre-DIC and DIC. When taking into account the pharmacological action of warfarin, we would raise the safety concern that warfarin-induced

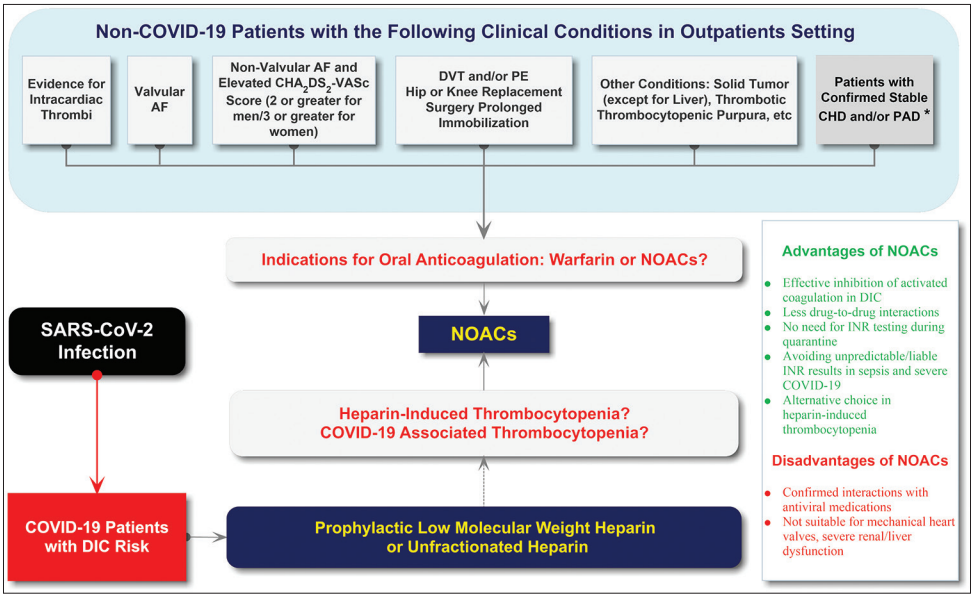

Figure 1: Recommendations for oral anticoagulant selection during the global pandemic of COVID-19, considering the advantages of NOACs over warfarin (listed in the lower right box), we recommend NOACs as the choice of anticoagulant among non-COVID-19 patients in outpatients setting. *Indicating new evidence from the COMPASS trial for patients with stable coronary heart disease or peripheral artery disease. AF: Atrial fibrillation, COVID-19: coronavirus disease 2019, DVT: Deep vein thrombosis, INR: International normalized ratio, NOACs: Non-Vitamin K antagonist oral anticoagulants, PE: Pulmonary embolism, SARS-CoV2: severe acute respiratory syndrome coronavirus 2, CHD: coronary heart disease, PAD: peripheral arterial disease, DIC: disseminated intravascular coagulation

selective depletion of coagulation factors may contribute to aggravation of hemorrhage in COVID-19 patients. In support of this, a registry-based nationwide Danish population study showed that in atrial fibrillation patients who are on warfarin therapy at sepsis, the risk of bleeding is increased within the 3 months following sepsis.[16]

Therapeutic Potential of Non-Vitamin K Antagonist Oral Anticoagulants in Disseminated Intravascular Coagulation

A recent systemic review summarized the available evidence concerning the use of NOACs in the treatment of DIC. Despite the limited sample size (a total of 21 patients in 15 case studies), this review revealed that NOACs seem therapeutically equivalent at least to heparin in patients with prevalent thrombotic phenotypes, including sepsis, vascular malformations, aortic aneurysm, aortic dissection, heparin-induced thrombocytopenia, chemotherapy for cancer, and Klippel–Trenaunay syndrome.[17] Notably, some case studies elegantly demonstrated the role of warfarin versus NOACs in the setting of DIC. For example, the clinical manifestations of aortic aneurysm associated with chronic DIC were dramatically improved when warfarin was replaced with rivaroxaban.[18] Therefore, the inhibition of activated coagulation factors, such as activated factor II (thrombin) or factor X via NOACs, holds promising potential for the treatment of DIC. Conversely, warfarin, which decreases the level of Vitamin K-dependent coagulation factors, cannot inhibit activated coagulation, a key step in initiating DIC, and therefore is ineffective in DIC.

Advantages of Non-Vitamin K Antagonist Oral Anticoagulants over Warfarin during the COVID-19 Pandemic

During the COVID-19 pandemic, the use of NOACs precludes the necessity of frequent testing for INR, which has an obvious advantage in reducing the risk of exposure to SARS-CoV-2 in hospital. In addition, sepsis-associated coagulopathy is typically featured by prolonged thrombin time or elevated INR in conjunction with thrombocytopenia. A recent study showed that abnormal INR provides different information about the coagulation status in patients with DIC than in patients receiving warfarin due to the different nature, which indicates that an equivalent increased INR may predict different bleeding risks in patients with sepsis and those on warfarin therapy.[19] Moreover, a single case report showed that even in the postacute phase of COVID-19, patients on warfarin therapy may have liable INR.[20] These findings add to the complexity of interpreting INR results in patients on warfarin complicated by COVID-19.

Recommendations for Anticoagulant Choice during the COVID-19 Pandemic

Based on warfarin's pharmacological mechanism and the issues of inaccuracy and liability when interpreting INR results in the setting of sepsis and COVID-19, as well as social factors during the COVID-19 pandemic, i.e., home quarantine and the willingness to reduce the risk of exposure to SARS-CoV-2 in hospital, we recommend that clinicians consider NOACs as the optimal choice when oral anticoagulation therapy is indicated in the outpatient setting during the COVID-19 pandemic [Figure 1]. Moreover, if not contraindicated, patients currently on warfarin may benefit from a transfer to NOACs. Although our experience with NOACs for the treatment of DIC is limited, the use of NOACs in the outpatient setting may be at least regarded as a prophylactic approach to reduce the risks of DIC and DVT and may consequently change the clinical course. Moreover, in COVID-19 patients with DIC and DVT risk and currently on LMWH treatment, when the differential diagnosis of the concomitant thrombocytopenia is challenging, i.e., COVID-19-induced versus heparin-induced thrombocytopenia, an alternative choice could be using one NOAC.

It should be noted that despite the advantages of NOACs over warfarin discussed above, among severe COVID-19 patients hospitalized for treatment, the use of antiviral agents (lopinavir, ritonavir, or darunavir) would significantly increase the plasma NOAC level due to drug–drug interaction.[21] Therefore, in COVID-19 patients who are currently on antiviral treatment, all oral anticoagulants should be transferred to unfractionated heparin/LMWH. Currently, the optimal dosing of unfractionated heparin and LMWH for the prophylaxis and treatment of COVID-19 patients remains unknown. The type and dosing should be adjusted based on available guideline recommendations,[6] for example, weight-adjusted dosing. In these times of uncertainty and urgency with the COVID-19 pandemic, despite the unavailability of evidence from high-quality randomized trials, the choice of one NOAC, rather than warfarin, would be a scientifically reasonable option for indicated patients in the outpatient setting.

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Conflicts of interest

There are no conflicts of interest.

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