Anticoagulation therapy in non-valvular atrial fibrillation in the COVID-19 era: is it time to reconsider our therapeutic strategy?

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Non-vitamin K antagonist oral anticoagulants (NOACs) are considered the first-line therapy to prevent stroke in non-valvular atrial fibrillation (AF)[1] and are recommended by the recent ESC guidelines in preference to vitamin K antagonists (VKAs).[1] Non-vitamin K antagonist oral anticoagulants offer many advantages compared to VKAs, which include fixed dosing (up to two times a day), fewer dietary and drug interactions, predictable anticoagulation effect (rapid onset and offset) precluding the need for periprocedural bridging anticoagulation, and no need for regular monitoring of anticoagulant effect. Although NOACs are increasingly used in patients with AF in everyday clinical practice, the use of VKAs is still high, especially in elderly patients living in rural areas.[2] Some physicians are still reluctant to prescribe NOACs in specific populations (i.e. elderly patients, patients with malignancies, patients with severe renal impairment, etc.) that are current under-represented in most studies and most importantly in the pivotal NOAC trials (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48). In patients with creatinine clearance less than 25 mL/min estimated by the Cockcroft–Gault equation, randomized controlled trials-derived data on the effect of NOACs are lacking. These patients were excluded from the NOAC's major clinical trials. Moreover, NOACs are still underused due to their higher costs, while patients on VKA therapy for several years may be averse to convert to new treatments.

Non-vitamin K antagonist oral anticoagulants have been proven to be at least non-inferior to VKAs in large clinical trials in the prevention of stroke, while they are associated with a significant reduction in intracranial haemorrhage. Recently, their safety profile has been strengthened due to the availability of reversal agents, which can achieve a rapid reverse of NOAC's anticoagulation action.[1] Generics of NOACs are expected to be available in the near future, a fact that will make NOACs more attractive from a cost point-of-view.

On the other hand, VKAs require frequent monitoring of their anticoagulant effect and have many food and drug interactions. Moreover, the use of VKAs is limited by the narrow therapeutic interval, and consequently, the necessity for frequent international normalized ratio (INR) monitoring and dose adjustments (INR 2–3 is recommended in most cases with non-valvular AF).[1] Vitamin K antagonists are effective (similar to NOACs) and relatively safe drugs at an adequate time in therapeutic range (TTR), which in daily clinical practice corresponds to TTR >70% (quantified according to the Rosendaal method, or the percentage of INRs in range).[1] However, only a minority of patients manages to achieve TTR >70% and this fact significantly correlates with thromboembolic and bleeding events. Time in therapeutic range >70% requires frequent INR monitoring, good patient's compliance with anticoagulation therapy, and dose adjustment in case of changes in diet or medications known to interact with VKAs.

Coronavirus disease 2019 (COVID-19) pandemic is a new reality in doctors' and patients' lives worldwide. The new coronavirus SARS-CoV-2, which gives rise to the highly infectious COVID-19 disease, has caused a pandemic that is overwhelming healthcare systems worldwide. Governments of many countries have adopted lockdown policies to control the spread of this novel coronavirus. Cardiovascular disease and diabetes mellitus are known risk factors associated with increased mortality from COVID-19 disease.[3] In addition, AF is a common clinical manifestation in hospitalized

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patients with COVID-19 and it is associated with increased mortality and/or requirement for mechanical ventilation.[4,5] Healthcare systems apply technologies of telemedicine and remote monitoring of patients with chronic diseases, such as AF to avoid frequent visits of patients to healthcare centres and/or hospitals.[6] For instance, Li *et al.*[7] conducted a study in China to evaluate the efficacy of remote anticoagulation management with a NOAC (rivaroxaban) by pharmacists for elderly patients with non-valvular AF during the COVID-19 pandemic. This pharmacist-led remote intervention was associated with a reduction in gastrointestinal bleeding complications and skin ecchymoses and with delays in the first outpatient revisit after discharge. These are desirable outcomes during the COVID-19 pandemic since they minimize contact with healthcare workers. According to a position statement of the Working Group on Cardiovascular Thrombosis of the Spanish Society of Cardiology[8] and the NHS 'Clinical guide for the management of anticoagulant services during the coronavirus pandemic', NOACs are recommended to minimize the need for anticoagulation monitoring in AF patients during the COVID-19 pandemic.[6,8] For hospitalized patients under treatment with a VKA who are eligible for prescription of a NOAC, it is recommended to change the VKA into NOAC during hospitalization in order to reduce visits to healthcare centres for subsequent monitoring after discharge, which may expose this high-risk population to SARS-CoV-2 infection.[8] The healthcare departments of some autonomous Spanish communities (e.g. Andalusia, Community of Madrid, Region of Murcia) have already approved anticoagulation with NOACs for patients with a recently diagnosed AF to avoid the frequent INR monitoring required at the start of VKA.[8] In a small, prospective study by Patel *et al.*,[6] telephone switching of warfarin patients to a NOAC was proven safe with good patients' compliance.

Is the anticoagulation therapy with VKAs in patients with AF feasible in the era of the COVID-19 pandemic? Should we replace the VKAs with NOACs in most patients with AF during the COVID-19 pandemic? VKAs are effective and cheap oral anticoagulants, but they require frequent monitoring with blood tests and also have a narrow therapeutic window. Furthermore, TTR of INR recorded is relatively low in population studies (<60–70%), especially in rural and remote regions, thus exposing the patients to severe thromboembolic (INR < 2) or bleeding events (INR > 3). Consequently, frequent monitoring of VKAs is mandatory to avoid thromboembolic and bleeding events, especially in patients with labile INR. It is of clinical significance the fact that the initial letter 'L' in HAS-BLED score[1] (HAS-BLED score has the best evidence for predicting bleeding risk) represents labile INR, which indicates that a patient has TTR <60%. This component of the risk score is relevant only in patients receiving VKAs and consequently, it is not applicable in patients receiving NOACs. This is also of importance among patients with acute coronary syndromes or patients with chronic coronary syndromes undergoing percutaneous coronary intervention in whom a narrower therapeutic range of INR is recommended by the latest guidelines (INR 2–2.5).[1] Frequent INR monitoring equals frequent visits to healthcare centres, which in turn leads to the patients' exposure to SARS-CoV-2 and possible spread of the disease. Additionally, patients with AF are mostly elderly with multimorbidity, suffering from hypertension, and other cardiovascular comorbidities, which make them a population at high risk for severe COVID-19 course and complications.[3] Last but not the least, the well-described COVID-19 coagulopathy can also lead to abnormal coagulation parameters and alters INR levels in patients receiving long-term anticoagulation therapy with VKAs.

Although NOACs seem an attractive treatment option during the COVID-19 pandemic, we have to keep in mind the possible pharmacological interaction of NOACs with antiviral drugs and some immunomodulating agents[3,9] that might be used in patients hospitalized with COVID-19. In this group of patients, low molecular weight

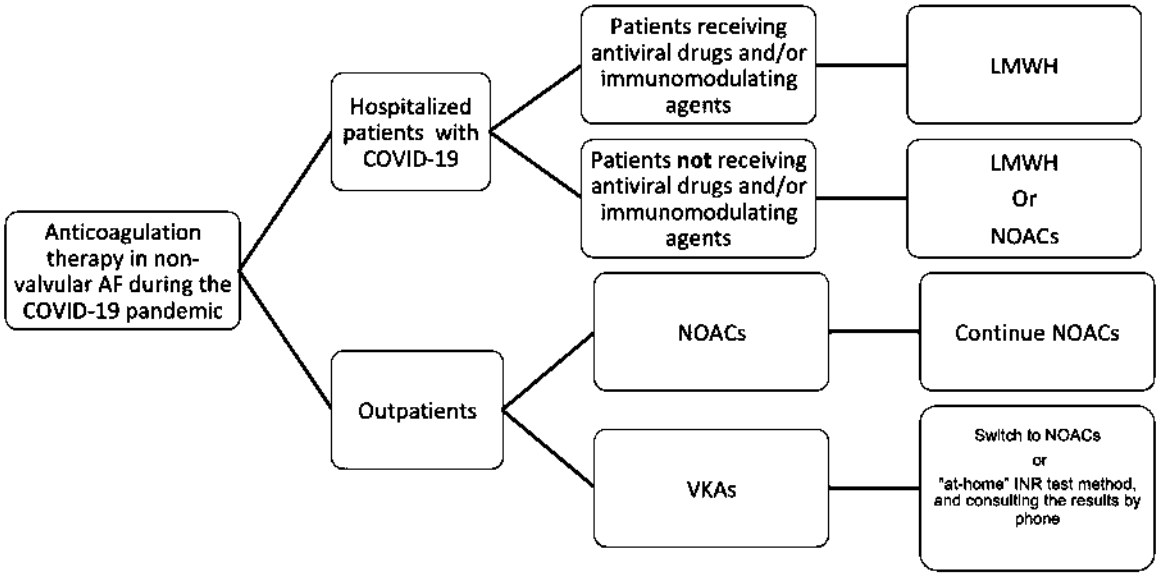

Figure 1 Anticoagulation management in non-valvular atrial fibrillation patients during COVID-19 pandemic. AF, atrial fibrillation; COVID-19, coronavirus disease 2019; LMWH, low molecular weight heparin; NOACs, non-vitamin K antagonist oral anticoagulants; VKAs: vitamin K antagonists.

heparin (LMWH) may be preferable[9] providing not only less drug interactions but also possible antithrombotic, anti-inflammatory, and antiviral activity in COVID-19 disease.[10] However, there is no substantial evidence of significant in-hospital adverse events linked to NOACs continuation in COVID-19 patients undergoing antiviral/immunomodulating treatments.

In conclusion, based on the above data, in the era of COVID-19, anticoagulation therapy in non-valvular AF with NOACs seems to be the safest approach. Non-vitamin K antagonist oral anticoagulants are contraindicated in AF patients with a prosthetic mechanical valve or moderate-to-severe mitral stenosis,[1] and long-term anticoagulation therapy with VKAs is indicated. In these patients with 'valvular AF', the 'at-home' INR test method, and consulting the results by phone may be an alternative solution to minimize healthcare centre visits. In 'valvular AF' patients in whom VKA treatment should be interrupted, bridging using therapeutic doses of LMWH is recommended. For patients with non-valvular AF who receive VKAs and are suitable for NOACs, replacement of VKAs with NOACs should be strongly considered (*Figure 1*).

Conflict of interest: none declared.

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