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Review Article

Novel Oral Anticoagulants in Cardiovascular Practice

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Abstract

In the recent era of medicine, Novel Oral Anticoagulants (Apixaban, Dabigatran, Edoxaban, and Rivaroxaban) have become the preferred drugs for long-term anticoagulation therapy in the majority of cardiovascular conditions, along with non-cardiac co-morbid conditions with few necessary exceptions. This preference is based on their easy availability, therapeutic efficacy, all-cost effectiveness, safety profile, and more convenient usage for both patients and clinicians. Novel Oral Anticoagulants (NOACs) have different pharmacokinetics and pharmacodynamics than oral vitamin K antagonists. This article highlights the basic pharmacology, common complications, available antidotes, and the utility of NOACs in different common cardiovascular diseases requiring long-term oral anticoagulation, including stroke prevention in valvular and non-valvular atrial fibrillation, coronary artery disease, myocardial infarction, left ventricular thrombus and cerebrovascular attacks. NOACs are still underutilized in cardiovascular practice because the concomitant co -morbid conditions hinder a clinician from prescribing these drugs confidently. This manuscript will provide a brief critical overview to help clinicians prescribe NOACs more conveniently.

Key words: noacs; coronary artery disease; lv thrombus; atrial fibrillation; stroke

Introduction

Numerous randomized controlled trials (RCTs) and evidence have shown that Novel Oral Anticoagulants (NOACs) should be the preferred anticoagulant agents concerning safety and efficacy, compared to vitamin K antagonists (VKAs), in the majority of patients with atrial fibrillation (AF) and venous thromboembolism (VTE). [1-3]

NOAC anticoagulation effects are related to the selective and direct inhibition of serine proteases within the coagulation pathway. Apixaban, edoxaban, and rivaroxaban are inhibitors of clotting factor Xa, whereas dabigatran is a direct thrombin inhibitor. [4] Favorable pharmacokinetic characteristics of NOACs include rapid onset of action, short half-lives (about 8– 12 hours), and reduced food and drug interactions compared to VKAs. Moreover, unlike VKAs, NOACs have fixed-dose regimens and do not need regular laboratory monitoring because of their calculable anticoagulant effects. [5] Bleedings that occur during NOAC use are mostly not life-threatening and can be managed by short NOAC interruptions, minor surgery, local compression, or transfusion. However, major bleeding complications like intracranial bleeding have been described in some NOAC-treated patients, leading to a request for NOAC-specific reversal treatment with specific antidotes.6 To treat life-threatening bleeding, idarucizumab (dabigatran antidote) and andexanet alfa (factor Xa inhibitors antidote) have shown efficacy in reversing NOAC anticoagulation and achieving immediate hemostatic control. Currently, idarucizumab has been approved for dabigatran- treated patients in need of urgent surgery. In contrast, andexanet alfa should be used in case of acute, life- threatening bleeding. [7,8] We aim to address the use of NOACs across different cardiovascular conditions within specific patient subgroups. Nowadays, trials are being updated, and our review includes the current indications for NOAC use together with the last released indications.

Critical Overview of The Literature

Stroke Prevention in Valvular and Non- Valvular Atrial Fibrillation: Nowadays, apixaban, dabigatran, edoxaban, and rivaroxaban are recommended to diminish the likelihood of stroke in patients having non-valvular atrial fibrillation (NVAF). NOAC use in valvular heart disease is contraindicated in mechanical prosthetic valves and in moderate to severe mitral stenosis. NOAC utilization is acceptable in bioprosthetic valves. [9,10]

NOACs are the preferable anticoagulant of choice for diminishing the likelihood of stroke in patients having NVAF who qualify for CHA2DS2-VASc score, i.e., ≥ 2 in males or ≥ 3 in females. [11-15] NVAF patients

exclude patients with mechanical prosthetic heart valves or moderate to severe rheumatic mitral stenosis. [11,16,17] These drugs, after being tested in large studies like the ARISTOTLE trial (using apixaban), ROCKET-AF trial (using rivaroxaban), RE-LY trial (using dabigatran), and ENGAGE AF-TIMI 48 trial (using edoxaban) have shown efficacy respectively. [18- 21] NOAC use should be discouraged in patients with mechanical heart valves and moderate to severe rheumatic mitral stenosis until convincing data is available. [22] Recently published INVICTUS study showed a decreased rate of cardiovascular events in patients having rheumatic heart disease associated with AF taking VKA (6.5%) as compared to the rivaroxaban group (8.2%) ($p < 0.001$). Secondary outcomes of ischemic stroke increased in the rivaroxaban group by 0.4% ($p < 0.05$). [23]

RIVER and ENAVLE trials showed non-inferiority of rivaroxaban and edoxaban in patients having AF with bioprosthetic and heart valve repair if started after [8- 12] weeks of surgery.24 In transcatheter aortic valve implantation (TAVI) patients needing anticoagulation for AF, NOACs alone were found beneficial compared to NOACs plus clopidogrel combination with less bleeding events with similar ischaemic events. [25,26] A single AF episode is enough to start NOACs in patients with both obstructive and non-obstructive hypertrophic cardiomyopathy (HCM).[27-30]

Coronary Artery Disease, Myocardial Infarction, and Percutaneous Coronary Intervention: Prolonged oral anticoagulation is indicated in 6-8% of patients undergoing percutaneous coronary intervention (PCI). It has been recommended to perform PCI without holding VKAs or NOACs. In patients taking NOACs, a small modified dose of parenteral anticoagulation (e.g., enoxaparin 0.5 mg/kg i.v. or unfractionated heparin (UFH) 60 IU/kg) needs to be administered without taking into consideration of last NOAC dose. [31]

Generally, in patients with NVAF, NOAC usage is found to be safer than VKA. However, no trials suggest that one NOAC is superior to another in terms of safety or efficacy in the setting of triple therapy. The default triple therapy strategy for such patients is up to 7 days of triple antithrombotic therapy (TAT) (with NOAC and DAPT); this is followed by Dual antithrombotic therapy (DAT) with a NOAC at the recommended dose for stroke prevention and single antiplatelet therapy (SAPT) (preferably clopidogrel, as chosen in more than 90% of cases in available trials) for up to 12 months. [32,33] For patients having an increased risk of bleeding, DAT should be stopped after completing six months (by holding an antiplatelet agent), and only NOAC should be continued further. For patients having an increased risk of coronary ischemia, TAT should be stopped after 30 days, and DAT should be continued further for the next 12 months. [34,35] Based on trial data, the recommended doses for the NOACs in such settings are: Apixaban 5 mg twice a day,34 Dabigatran 110 mg or 150 mg twice a day, [36] Edoxaban 60 mg/daily,[37] Rivaroxaban 20 mg/daily,[38] or in cases where the risk of bleeding is higher than the stent thrombosis or ischaemic stroke risk, a lower dose of rivaroxaban (15 mg once in a day) should be used for the duration of concomitant SAPT or DAPT.[35,38]

Furthermore, a lower dose of rivaroxaban has been investigated as a new regime of dual antithrombotic therapy (DAT) along with aspirin in patients with stable atherosclerotic vascular disease for secondary prevention in the COMPASS trial. [39] This trial investigated rivaroxaban 2.5 mg twice in a day along with aspirin vs. aspirin only vs. rivaroxaban 5 mg twice in a day only. Better cardiovascular outcomes have been observed in patients taking rivaroxaban 2.5 mg twice a day along with aspirin, but more major

bleeding episodes were observed when compared to patients taking aspirin alone. [39]

Left Ventricular Thrombus: Left ventricular (LV) thrombus may occur following acute myocardial infarction (AMI) in the presence of heart failure with reduced ejection fraction or non-ischemic cardiomyopathies. [40] The incidence of LV thrombus associated with MI has been reduced to 3.5–8% in the current era of prompt revascularization, and these most frequently occur in the presence of large akinetic/dyskinetic segments of anterior, anteroseptal or apical wall MI.[41] As patients recovering from MI (complicated with LV thrombus) are at greater risk of thromboembolic events during the first 3-4 months after MI, current clinical guidelines recommend that anticoagulant therapy be administered after MI to be continued for at least three months, and up to 6 months guided by repeated imaging, until thrombus resolution.[42,43] Indeed, using any oral anticoagulant (OAC) for managing LV thrombus in the presence of ACS would constitute triple therapy, with additional considerations.

Although AHA guidelines (2013) endorse using VKA for LV thrombus in the setting of ACS (Class IIa; Level of Evidence: C), recently published ESC guidelines (2023) endorse the use of both VKA or NOACs for LV thrombus resolution post-MI (Class IIa; Level of Evidence: C). 42,43 However, NOACs (i.e., dabigatran, rivaroxaban, or apixaban) can be considered in VKA intolerant patients in the same setting according to the AHA/American Stroke Association (2014) guidelines for stroke prevention (Class IIb; Level of Evidence: C).[44] Warfarin has been the gold standard for anticoagulation, but the increasing data emerging for NOACS necessitates a re-evaluation of our choice for anticoagulation. Although head-to-head comparisons of adverse bleeding complications exist for rivaroxaban vs. dual antiplatelet therapy in the acute management of acute coronary syndrome (ACS), the comparisons have yet to be well documented in the treatment of ACS co-presenting with LV thrombus. [45]

The off-label use of NOACs in LV thrombus, particularly rivaroxaban, and apixaban, has been reported in case reports, as well as large retrospective studies and meta-analyses of pooled data from these studies. These published data have yielded conflicting results, with some observational studies 46 and meta- analyses47 demonstrating comparable rates of thrombus resolution and complications. On the contrary, a recent large retrospective study of 514 patients (236 on warfarin, 185 on any NOAC, of whom 141 on apixaban, [46] on rivaroxaban, and nine on dabigatran) by Robinson et al. challenged the assumption of NOAC equality with warfarin for LV thrombus, by reporting a higher risk of stroke or systemic embolism (SSE) for NOACs, even after adjustment for other factors. [48]

There are three randomized controlled trials investigating NOAC vs. warfarin in LV thrombus.4[9-51] The No-LVT trial was the first RCT to assess NOACs vs. Warfarin for the management of LV thrombus. [49] This non-inferiority design trial randomized 79 patients 1:1 in Egypt and Bulgaria to either warfarin or rivaroxaban 20 mg/day. This trial demonstrated that rivaroxaban 20 mg/day was non-inferior to dose- adjusted warfarin for LV thrombus resolution at one month with numerically greater (but statistically non- significant) LV thrombus resolution at 3 and 6 months. The rivaroxaban arm also had no composite embolic events (0% vs 15%; $p = 0.01$) and numerically fewer major bleeding (5.1% vs 15%; $p = 0.11$). 53.1% of the total patients were on DAPT, and 75% of the bleeding events occurred in patients on DAPT. [49]

Another non-inferiority design RCT by Alcalai et al. enrolled 35 patients with LV thrombus, diagnosed based on 2D-transthoracic echocardiography (TTE), up to 14 days after acute MI at three medical centers in Israel. [50] All patients had an acute anterior MI. Patients were randomly assigned into 2 groups; one group was taking apixaban 5 mg BID, and the other group was taking dose-adjusted warfarin (bridged with therapeutic subcutaneous enoxaparin until the target INR of 2.0–3.0) for three months. Apixaban 2.5 mg BID was prescribed if the usual criteria were met. Echocardiography was done after three months of initiation of anticoagulation to assess the resolution of thrombus, and the difference between both groups remained insignificant ($p>0.001$). According to this trial, apixaban was non-inferior to warfarin. [50]

A smaller single-blinded pilot RCT of 27 patients in Malaysia by Isa et al. found no significant differences between the mean reduction in LV thrombus size in the apixaban arm, 65.1% (SD 31.3) versus the warfarin arm, 61.5% at the 12th-week follow-up ($p = 0.816$). Safety outcomes were also similar between the two arms. [51]

More recently, a small RCT investigated the effects of prophylactic rivaroxaban (2.5 mg twice daily for 30 days in 279 patients with anterior wall MI who had undergone primary percutaneous coronary intervention. In a 30-day follow-up, compared to dual antiplatelet therapy (DAPT) alone, the addition of a lower dose of rivaroxaban to DAPT reduced LV thrombus formation with lower net clinical adverse events and similar bleeding events. [52] There is scarce data on the use of dabigatran or edoxaban in the case of

LV thrombus, and indeed, there is no randomized evidence at all. In addition to AMI, rivaroxaban has also been described in case reports of the treatment of intraventricular thrombus in Chagas disease [53] and dilated cardiomyopathy. [54] Larger RCTs are necessary for more definitive evidence; given the contemporary low incidence of post-MI LV thrombus, performing large prospective studies in this setting remains a challenge. Furthermore, particularly in the setting of LV thrombus with AMI, the issue of triple therapy needs to be weighed into consideration. [55]

Cerebrovascular Accidents: Oral anticoagulant usage in patients with cerebrovascular accidents has always been a grey zone. Many observational studies have shown the safety and feasibility of managing acute ischemic stroke (AIS) with thrombin inhibitors as an adjunct therapy to alteplase or alone. A single- center trial was done on [53] patients with TIA or minor stroke (NIHSS score ≤ 3); these patients were treated with oral dabigatran, and there was no spontaneous ICH observed in the first 30 days.56 To date, the benefit of thrombin inhibitors for the treatment of patients with AIS is not well recognized. [57] Similarly, the usefulness of oral factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban) for the treatment of patients with AIS needs to be better studied, and available data is scarce. Although many studies are ongoing, further clinical trials are still needed for the well-established use of these drugs. [58] Generally, the OAC therapy shortly after cardioembolic and noncardioembolic ischemic strokes is accompanied by hemorrhagic transformations and recurrent ischemic attacks, but according to the available observational studies, the absolute risk of these complications with NOAC therapy is low. However, randomized studies comparing older OACs and antiplatelet drugs are still needed. [59,60] Conceptually, patients with embolic strokes may benefit from OAC therapy the most. On the other hand, currently, OAC therapy is also not indicated after a noncardioembolic stroke. Recently, a study published comparing aspirin and dabigatran treatment for TIA and acute minor noncardioembolic stroke showed a similar incidence of hemorrhagic transformations. [60] Concisely, there are no established recommendations for NOAC therapy soon after embolic and cardioembolic strokes and more clinical trials are needed.

Conclusion

NOACs are providing safe anticoagulation across the spectrum of cardiovascular diseases due to their pharmacokinetics and less drug-food interaction. Due to the safety profile of NOACs over warfarin, we reinforce the use of NOACs wherever indicated. However, the decision to prescribe these novel drugs should always be individualized according to the patient's profile.

Authors' Contribution

SHRN and HNT: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. SHRN, HNT, FAC, JS, and MF: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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