REVIEW ARTICLE

NOVEL ORAL ANTICOAGULANTS IN CARDIOVASCULAR PRACTICE

Syed Haseeb Raza Naqvi[1], Han Naung Tun[2], F. Aaysha Cader[3], Jolanda Sabatino[4], Madiha Fatima[5]

[1]Chaudhry Pervaiz Elahi Institute of Cardiology, Multan, Pakistan, [2]University of Vermont, Burlington City, Vermont State, USA, [3]Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh, [4]University of Padua, Italy, [5]National Institute of Cardiovascular Diseases, Karachi, Pakistan

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.

Keywords: NOACs, Coronary artery disease, LV Thrombus, Atrial Fibrillation, Stroke

Citation: Naqvi SHR, Tun HN, Cader FA, Sabatino J, Fatima M. Novel Oral Anticoagulants in Cardiovascular Practice. Pak Heart J. 2023;56(04):250-255. DOI: https://doi.org/10.47144/phj.v56i4.2618

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 CHA_2DS_2-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.[49-51] 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.

Conflict of interest: Authors declared no conflict of interest.

REFERENCES

1. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. Lancet. 2014;383:955-62.
2. Van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2014;12:320-8.
3. Sabatino J, De Rosa S, Polimeni A, Sorrentino S, Indolfi C. Direct Oral Anticoagulants in Patients With Active Cancer: A Systematic Review and Meta-Analysis. J Am Coll Cardiol Cardio. 2020;2(3):428-40.
4. Rose DK, Bar B. Direct oral anticoagulant agents: pharmacologic profile, indications, coagulation monitoring, and reversal agents. J Stroke Cerebrovasc Dis. 2018;27:2049-58.

5. Stacy Z, Richter S. Practical considerations for the use of direct oral anticoagulants in patients with atrial fibrillation. Clin Appl Thromb. 2017;23:5-19.
6. Tummala R, Kavtaradze A, Gupta A, Ghosh RK. Specific antidotes against direct oral anticoagulants: a comprehensive review of clinical trials data. Int J Cardiol. 2016;214:292-8.
7. Pollack Jr CV, Reilly PA, Bernstein R, Dubiel R, Eikelboom J, Glund S, et al. Design and rationale for REVERSE AD: a phase 3 study of idarucizumab, a specific reversal agent for dabigatran. Thromb Haemost. 2015;114:198-205.
8. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373:2413-24.
9. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369:1206-14.
10. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. J Am Coll Cardiol. 2017;69:1363-71.
11. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42:373-498.
12. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019;140:e125-51.
13. Andrade JG, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C, et al. 2018 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol. 2018;34:1371-92.
14. Chiang CE, Okumura K, Zhang S, Chao TF, Siu CW, Lim TW, et al. 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. J Arrhythm. 2017;33:345-67.
15. Barnes GD, Ageno W, Ansell J, Kaatz S. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13(6):1154-6.
16. Lip GYH, Collet JP, Caterina R, Fauchier L, Lane DA, Larsen TB, et al. ESC Scientific Document Group. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). Europace. 2017;19:1757-8.
17. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38:2739-91.
18. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-91.
19. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-92.
20. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51.
21. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093-104.
22. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369:1206-14.
23. Connolly SJ, Karthikeyan G, Ntsekhe M, Haileamlak A, El Sayed A, El Ghamrawy A, et al. Rivaroxaban in rheumatic heart disease-associated atrial fibrillation. N Engl J Med. 2022;387(11):978-88.
24. Guimaraes HP, Lopes RD, de Barros E, Liporace IL, Sampaio RO, Tarasoutchi F, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. N Engl J Med. 2020;383:2117-26.
25. Nijenhuis VJ, Brouwer J, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, et al. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. N Engl J Med. 2020;382:1696-707.
26. Seeger J, Gonska B, Rodewald C, Rottbauer W, Wohrle J. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. JACC Cardiovasc Interv. 2017;10:66-74.
27. Noseworthy PA, Yao X, Shah ND, Gersh BJ. Stroke and bleeding risks in NOAC- and warfarin-treated patients with hypertrophic cardiomyopathy and atrial fibrillation. J Am Coll Cardiol. 2016;67:3020-1.
28. Dominguez F, Climent V, Zorio E, Ripoll-Vera T, Salazar-Mendiguchia J, Garcia- Pinilla JM et al. Direct oral anticoagulants in patients with hypertrophic cardiomyopathy and atrial fibrillation. Int J Cardiol 2017;248:232-8.
29. Jung H, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation with hypertrophic cardiomyopathy: a nationwide cohort study. Chest. 2019;155:354-63.
30. Lee HJ, Kim HK, Jung JH, Han KD, Lee H, Park JB, et al. Novel oral anticoagulants for primary stroke prevention in hypertrophic cardiomyopathy patients with atrial fibrillation. Stroke. 2019;50:2582-6.
31. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):1289-367. Erratum in: Eur Heart J. 2021;42(19):1908. Erratum in: Eur Heart J. 2021;42(19):1925.
32. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, et al. Safety and efficacy of antithrombotic strategies in patients with atrial fibrillation undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials. JAMA Cardiol. 2019;4:747755.
33. Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. Eur Heart J. 2019;40:37573767
34. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al, AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or pci in atrial fibrillation. N Engl J Med. 2019;380:1509-24.
35. Lip GYH, Collet JP, Haude M, Byrne R, Chung EH, Fauchier L, et al. ESC Scientific Document Group. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed

by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace. 2019;21:192193.
36. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al, RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med. 2017;377:1513-24.
37. Vranckx P, Lewalter T, Valgimigli M, Tijssen JG, Reimitz PE, Eckardt L, et al. Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (PCI) with stent placement: rationale and design of the ENTRUST-AF PCI trial. Am Heart J. 2018;196:105-12.
38. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med. 2016;375:2423-34.
39. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al; COMPASS Investigators. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017;377(14):1319-30.
40. Massussi M, Scotti A, Landi A, Besis G. Direct Oral Anticoagulants and Left Ventricular Thrombosis: The Evidence for a Good Therapeutic Approach. In: Proietti R, AlTurki A, Ferri N, Russo V, Bunch TJ, editors. Direct Oral anticoagulants From Pharmacology to Clinical Practice. Switzerland: Springer Nature; 2021. P.271-280.
41. Weinsaft JW, Kim J, Medicherla CB, Ma CL, Codella NC, Kukar N, et al. Echocardiographic algorithm for post- myocardial infarction LV thrombus: a gatekeeper for thrombus evaluation by delayed enhancement CMR. JACC Cardiovasc Imaging. 2016;9:505-15.
42. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes: Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J. 2023;44(38):3720-826.
43. O'gara PT, Kushner FG, Ascheim DD, Casey Jr DE, Chung MK, De Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary. Circulation. 2012;127(4):529-55.
44. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(7):2160-236.
45. Honan KA, Jogimahanti A, Khair T. An Updated Review of the Efficacy and Safety of Direct Oral Anticoagulants in Treatment of Left Ventricular Thrombus. Am J Med. 2022;135(1):17-23.
46. Abdelnaby M, Almaghraby A, Abdelkarim O, Saleh Y, Hammad B, Badran H. The role of rivaroxaban in left ventricular thrombi. Anatol J Cardiol. 2019;21(1):47-50.
47. Dalia T, Lahan S, Ranka S, Goyal A, Zoubek S, Gupta K, et al. Warfarin versus direct oral anticoagulants for treating left ventricular thrombus: a systematic review and meta-analysis. Thromb J. 2021;19(1):1-8.
48. Robinson AA, Trankle CR, Eubanks G, Schumann C, Thompson P, Wallace RL, et al. Off-label use of direct oral anticoagulants compared with warfarin for left ventricular thrombi. JAMA Cardiol. 2020;5:685-92.
49. Abdelnabi M, Saleh Y, Fareed A, Nossikof A, Wang L, Morsi M, et al. Comparative Study of Oral Anticoagulation in Left Ventricular Thrombi (No-LVT Trial). J Am Coll Cardiol. 2021;77(12):1590-2.
50. Alcalai R, Butnaru A, Moravsky G, Yagel O, Rashad R, Ibrahimli M, et al. Apixaban versus Warfarin in Patients with Left Ventricular Thrombus, A Prospective Multicenter Randomized Clinical Trial. Eur Heart J Cardiovasc Pharmacother. 2022;8(7):660-7.
51. Isa WW, Hwong N, Yusof AM, Yusof Z, Loong N, Wan-Arfah N, et al. Apixaban versus warfarin in patients with left ventricular thrombus: A pilot prospective randomized outcome blinded study investigating size reduction or resolution of left ventricular thrombus. J Clin Prev Cardiol. 2020;9(4):150-4.
52. Zhang Z, Si D, Zhang Q, Jin L, Zheng H, Qu M, et al. Prophylactic Rivaroxaban Therapy for Left Ventricular Thrombus After Anterior ST-Segment Elevation Myocardial Infarction. JACC Cardiovasc Interv. 2022;15(8):861-72.
53. Las Casas Jr AA, Las Casas AA, Borges MA, Melo-Souza SE. Rivaroxaban for treatment of intraventricular thrombus in Chagas disease. J Cardiol Cases. 2015;13(3):75-7.
54. Padilla Pérez M, Salas Bravo D, Garcelán Trigo JA, Vazquez Ruiz, de Castroviejo E, Torres Llergo J, et al. Resolution of left ventricular thrombus by rivaroxaban. Future Cardiol. 2014;10:333-6.
55. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39(3):213-60.
56. Kate M, Gioia L, Buck B, Sivakumar L, Jeerakathil T, Shuaib A, et al. Dabigatran therapy in acute ischemic stroke patients without atrial fibrillation. Stroke. 2015;46:2685-7.
57. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344-418.
58. Gioia LC, Kate M, Sivakumar L, Hussain D, Kalashyan H, Buck B, et al. Early rivaroxaban use after cardioembolic stroke may not result in hemorrhagic transformation: a prospective magnetic resonance imaging study. Stroke. 2016;47:1917-9.
59. Paciaroni M, Agnelli G, Falocci N, Tsivgoulis G, Vadikolias K, Liantinioti C, et al. Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non–Vitamin-K Oral Anticoagulants (RAF-NOACs) Study. J Am Heart Assoc. 2017;6(12):e007034.
60. Butcher KS, Ng K, Sheridan P, Field TS, Coutts SB, Siddiqui M, et al. Dabigatran treatment of acute noncardioembolic ischemic stroke. Stroke. 2020;51(4):1190-8.

Address for Correspondence:

Dr. Syed Haseeb Raza Naqvi, Cardiologist and Cardiac Electrophysiologist at Chaudhry Pervaiz Elahi Institute of Cardiology, Multan, Pakistan.
Email: haseebraza51214@yahoo.com