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The AZALEA-TIMI 71 Study and the Future of Factor XI Inhibition: Reflections from the American Heart Association Scientific Congress 2023

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Interview Summary

Since its earliest days, the effective use of anticoagulation for prevention of stroke and other thromboembolic events has been limited by the risk and fear of bleeding, which was long believed to be inevitable. However, new understanding of the coagulation cascade suggests that, by targeting factor XI, it may be possible to protect patients from pathological thrombosis without significantly affecting physiological haemostasis, and thus greatly reduce the risk of bleeding. The AZALEA-TIMI 71 trial

is the first study to provide definitive evidence that factor XI inhibition substantially reduces bleeding compared to a standard-of-care direct oral anticoagulant (DOAC). Based on an interview with Principal Investigator Christian T. Ruff, Thrombolysis in Myocardial Infarction (TIMI) Study Group, Boston, Massachusetts, USA, this article explains the significance of the AZALEA-TIMI 71 trial results, which showed an unprecedented reduction in the rate of bleeding with abelacimab, an investigational dual-acting factor XI/XIa inhibitor, compared with the DOAC rivaroxaban in patients with atrial fibrillation (AF) at moderate-to-high risk of stroke.

INTRODUCTION

In a Late Breaker session of the 2023 American Heart Association (AHA) scientific congress in Philadelphia, Pennsylvania, USA, Ruff presented the findings of the Phase IIb AZALEA-TIMI 71 trial, which aimed to investigate the hypothesis that anticoagulation with factor XI inhibition may be 'haemostasis-sparing', causing significantly less bleeding than a current standard of care.[1,2] The AZALEA-TIMI 71 trial randomised 1,287 patients with AF at moderate-to-high risk of stroke to receive either abelacimab (90 mg or 150 mg), an investigational factor XI inhibitor given subcutaneously once monthly, or rivaroxaban (20 mg), a commonly used DOAC given orally once daily, with a median follow-up of 21 months. The primary endpoint was the rate of major and clinically relevant non-major (CRNM) bleeding.[1,2] The investigators were optimistic about the outcome, but the magnitude of the reduction across all bleeding endpoints with abelacimab compared with rivaroxaban surpassed all expectations. It led the independent data monitoring committee to recommend early termination of the trial and the establishment of an open-label extension study (OLE), in which patients in the rivaroxaban arm would be transitioned to abelacimab.[1,2] This article is based on an interview conducted with Ruff soon after the presentation of the trial results.

WHY IS ANTICOAGULATION SO IMPORTANT?

Thromboembolic disease, principally ischaemic heart disease and ischaemic stroke, remains the world's biggest modifiable killer, accounting for at least one in four deaths worldwide.[3,4] Many conditions increase the risk, but notable among them is AF, one of the most common medical conditions worldwide. Currently affecting approximately 37 million people globally,[5] the prevalence of AF is expected to rise by 60% by 2050.[6] In the USA alone, the Centers for Disease Control and Prevention (CDC) estimates that 12.1 million people will have AF by 2030.[7] AF is a leading modifiable risk factor for ischaemic stroke, increasing the risk approximately five-fold.[7] Having AF also increases the chances that a stroke will lead to significant disability, and more than doubles the risk that it will be fatal.[8] Anticoagulation is modern medicine's most proven way to protect patients with AF from stroke. When prescribed appropriately and taken consistently over the long term, currently available anticoagulants can reduce the risk of stroke in AF by approximately two-thirds.[8,9]

WHY ARE NEW ANTICOAGULANTS NEEDED?

Since the dawn of modern anticoagulation, the risk of bleeding has been the nemesis of our efforts to lower the risk of thromboembolic disease. Half a century ago, warfarin and other vitamin K antagonists were our only options, but they carried the serious risk of intracranial haemorrhage, with its alarmingly high fatality rate. The advent of DOACs a decade or so ago caused great excitement because they were as effective as warfarin for preventing thromboembolic events, while reducing the risk of intracranial haemorrhage by 50%.[10,11] But it soon became apparent that, with other types of bleeding, including major bleeding which often necessitates hospitalisation, there is only a modest advantage with DOACs over warfarin.[10,11] Concerningly, in the case of gastrointestinal (GI) bleeding, the most common type of bleeding in patients with AF taking anticoagulants, the risk is at least 25% higher with DOACs than with warfarin,[10,11] possibly because DOACs, unlike warfarin, are active drugs in the gut.[12]

It is clear that the risk and/or experience of bleeding, and the fear attached to this, drives substantial undertreatment. Despite the overwhelming evidence for the net benefit of anticoagulation in patients at moderate-to-high risk of stroke, registry studies and claims databases consistently tell us that approximately 40–60% of the AF population receives no anticoagulation at all,[13-17] due to physician and/or patient perception that the risks outweigh the benefits.

It is worth remembering that healthcare providers are often more concerned about the 'sin of commission' (an adverse outcome of an intervention they themselves have prescribed) than the 'sin of omission' (an adverse outcome that is a direct consequence of the patient's condition). For those individuals who do receive anticoagulation, inappropriately low doses are often prescribed.[18-20] In a cohort study of newly diagnosed patients with AF initiating DOAC treatment, almost two in five patients were found to be receiving an off-label reduced dose, which was associated with reduced efficacy (increased risk of stroke/myocardial infarction/death) with no mitigation of bleeding.[18] Renal impairment is often cited as a justification for under-dosing, but, in the ORBIT-AF II registry, DOAC dosing in patients with chronic kidney disease (CKD) was found to be inappropriately low in 42% of cases.[20]

Finally, many patients with AF prematurely discontinue their anticoagulant medication,[16,21,22] again largely due to concerns about bleeding, which perpetually overshadows clinical decision-making in these fragile individuals, who are typically aged over 65 years with multiple co-morbidities. So, we are faced with an immense unmet need: even though we have effective anticoagulants, they are often not seen as safe enough, with the result that significant numbers of vulnerable people are left unprotected or inadequately protected from stroke.

HOW HAS FACTOR XI EMERGED AS A NEW TARGET FOR ANTICOAGULATION?

It has long been believed that bleeding is an inevitable risk with anticoagulants, due to a perceived inextricable link between the pathways leading to pathological thrombosis and physiologic haemostasis.[23] However, a newer model of the coagulation cascade, informed by insights from genetic, epidemiological, and animal studies, has now emerged, revealing two separate pathways with only one section in common: the downstream 'common pathway'.[23-25] The pathway of physiological haemostasis, also known as the extrinsic or tissue factor pathway, is activated in response to trauma and leads to the formation of extravascular haemostatic 'plugs' that seal leaks and injuries in vessel walls. In contrast, the pathway of pathological thrombosis, also known as the intrinsic or contact pathway, is activated when blood is exposed to an inflamed or damaged tissue surface, such as a ruptured atherosclerotic plaque. This leads to the formation of an intravascular clot that ultimately occludes the flow of blood within arteries or veins.[25-29] When considering the targets of currently available anticoagulants, it becomes clear that the vitamin K dependent factors targeted by warfarin are located in both of these pathways, while factor Xa and thrombin, targeted by DOACs, reside in the shared 'common pathway'. This explains why these approaches to anticoagulation, while protecting against thrombosis, also undermine haemostasis, which can lead to bleeding.[23-25] This has prompted interest in more upstream targets, most notably factor XI, which is located only on the pathologic thrombosis pathway. While fundamentally involved in thrombogenesis, factor XI is non-essential for haemostasis, where it plays only a minor, stabilising role in consolidating clots.[29] Thus, by targeting factor XI, the two pathways can be conceptually 'uncoupled', with the prospect of 'haemostasis-sparing' anticoagulation: a vision that has long been seen as the holy grail of anticoagulation therapy.[23,26-29]

There are several sources of evidence to support the potential of factor XI as a promising new target for anticoagulation:

- Congenital factor XI deficiency: Congenital factor XI deficiency (seen in one in 450 Ashkenazi Jews)[30] confers a reduced thrombosis risk[31] with little or no risk of serious or spontaneous bleeding.[32]
- Genetic epidemiology: In large cohort studies, higher factor XI plasma levels have

been associated with a two-fold greater risk of thrombosis,[33] while lower factor XI plasma levels (genetically determined) have been associated with significantly reduced risks of cardiovascular and venous thromboembolic events.[34]

- Animal studies: Experiments in animals show that inhibiting factor XI provides antithrombotic efficacy without increasing bleeding risk.[35]

Thus, strong circumstantial evidence exists to support the hypothesis that factor XI inhibition may offer significantly safer anticoagulation than currently available options. The AZALEA-TIMI 71 clinical trial was a critical test of this hypothesis.

WHY DO YOU REGARD THE AZALEA-TIMI 71 STUDY AS A LANDMARK TRIAL?

The AZALEA-TIMI 71 trial is the largest and longest safety study of an investigational factor XI inhibitor carried out to date, enrolling 1,287 patients with AF at moderate-to-high risk of stroke, who were followed for a median of 21 months, spanning more than 2,000 patient-years.[1,2] Compared with daily oral rivaroxaban 20 mg, abelacimab 150 mg administered subcutaneously once a month (the dosing regimen now being studied in Phase III trials) reduced the composite of major and CRNM bleeding by 67% ($p<0.0001$), major bleeding alone by 74% ($p=0.002$), and GI bleeding by 93% ($p=0.008$).[1,2]

When new investigational therapies are compared with the current standard of care in any medical field, a performance improvement of 20–30% is often cause for celebration, so the AZALEA-TIMI 71 results were truly groundbreaking, leading the independent data monitoring committee to recommend early termination of the trial. The bleeding profile with abelacimab was not dissimilar to what we might expect to see with placebo, and certainly bears no resemblance to anything we have ever seen before in the field of stroke prevention in AF, or even what we are used to with antiplatelet agents. It is fundamentally different. The almost total elimination of GI bleeding might actually be the most important finding. GI bleeding wreaks havoc with our ability to get people to stay on anticoagulants, so the implications for future clinical practice are highly significant.

Another key consideration with anticoagulants is that they typically have to be stopped and restarted if there is any invasive procedure planned. In the AZALEA-TIMI 71 trial, a large number of participants underwent invasive procedures of all sorts while receiving abelacimab, a monoclonal antibody with a long half-life,[36] and thus had full factor XI inhibition at the time. The full analysis of these data will be presented at an upcoming scientific congress, but it is already apparent that bleeding was infrequent in these individuals, which could be a game changer in itself.

WHAT ABOUT THE PARTICIPANTS IN THE AZALEA-TIMI 71 TRIAL? WHAT WILL HAPPEN TO THEM NOW?

Even though AZALEA-TIMI 71 was a Phase IIb trial, the data monitoring committee recommended the establishment of an open-label extension (OLE), to allow all trial participants to receive 150 mg abelacimab going forwards, while Phase III trials for regulatory approval are ongoing. There has been great enthusiasm for this among the AZALEA-TIMI 71 participants. Most of the abelacimab group have chosen to join the OLE, since they had not experienced problems with bleeding or bruising and had found the once monthly injections easy and convenient.

AZALEA-TIMI 71 WAS A SAFETY TRIAL. WHAT EVIDENCE IS THERE SO FAR FOR THE CLINICAL EFFICACY OF ABELACIMAB?

In a Phase IIb study of patients undergoing total knee arthroplasty, a gold standard model for assessing the efficacy of new anticoagulants, abelacimab significantly outperformed standard of care enoxaparin in preventing post-surgical venous thromboembolism (VTE).[37] A single 150 mg intravenous dose of abelacimab showed an 80% reduction in post-surgical VTE, as measured by venography, versus 40 mg enoxaparin administered subcutaneously once daily for 8–12 days.[37]

Although the AZALEA TIMI-71 trial was not powered to show efficacy (there were a total of 25 strokes in the trial across all three arms), we do know from registry studies that the usual risk of strokes in a high-risk patient population like this is around 7% per year in the absence of anticoagulation.[38] In AZALEA TIMI-71, the absolute risk of strokes across all arms was about 1%.[2] Finally, although it was an exploratory endpoint, it is also worth noting that 'net clinical outcome', a composite of ischaemic stroke, systemic embolism, bleeding (major or CRNM), and all-cause death, was approximately 50% less with abelacimab 150 mg versus rivaroxaban ($p<0.001$).[2] This gives researchers confidence that all patients in the trial were receiving safe and effective anticoagulation.

A PHASE III TRIAL WITH THE FACTOR XIa INHIBITOR, ASUNDEXIAN, WAS STOPPED EARLY DUE TO INFERIOR EFFICACY VERSUS THE DOAC, APIXABAN. WHAT ARE THE IMPLICATIONS OF THIS?

The cancellation of the asundexian AF trial[39] highlights the importance of waiting for Phase III research before judging the clinical performance of any investigational agent. Some have speculated that an inadequate dose of asundexian may have been used in the OCEANIC-AF study. Unlike other investigational factor XI inhibitors (and the DOACs early in their clinical development), a Phase II proof-of-concept efficacy study in total knee arthroplasty was not carried out with asundexian, so it is possible the dose selected for Phase III research was not high enough for effective inhibition of factor XI.

Potent suppression of factor XI appears to be critical for efficacy, and available data on the magnitude of factor XI inhibition with asundexian suggest a meaningfully lower level of inhibition compared with abelacimab. In the AZALEA-TIMI 71 trial, abelacimab 150 mg provided sustained factor XI inhibition of approximately 99% throughout the monthly dosing interval,[2] and yet was still strikingly safe.

Important differences between the mechanism of action of abelacimab and small molecule factor XIa inhibitors like asundexian may also help to explain the difference in potency. Abelacimab is a highly selective, fully human monoclonal antibody that binds to factor XI and locks it in the inactive state, thereby preventing its conversion to the activated form, factor XIa. It also inhibits any factor XIa that may already have formed.[36]

In contrast, the small molecule factor XIa inhibitors bind only to factor XIa and do not target the precursor factor XI.[26] The mechanism of action of abelacimab specifically prevents factor XIa from ever forming, closely recapitulating the biology of congenital factor XI deficiency, which has been observed to be associated with significant reductions in both stroke and VTE compared with the general population.[31] So, there are strong reasons to remain optimistic about the efficacy of abelacimab while the results of the Phase III research are pending.

WHAT ARE THE IMPLICATIONS OF USING A LONG-ACTING INJECTABLE MONOCLONAL ANTIBODY FOR ANTICOAGULATION IN THE REAL WORLD?

Apart from the risk of bleeding, current oral anticoagulants have a number of other shortcomings and drawbacks in the real world, which could potentially be addressed by a long-acting injectable monoclonal antibody. First, the bioavailability of DOACs can be altered by both renal and hepatic impairment, resulting in warnings/restrictions or the need for careful monitoring.[40] Notably, over a third of patients with AF have some degree of CKD.[41] In contrast, monoclonal antibodies do not depend on renal or hepatic clearance and no dosage adjustment is needed in the case of CKD or liver disease.

Second, patients with AF are typically burdened by polypharmacy and the risk of drug-drug interactions. In a systematic review and meta-analysis of six AF studies (n=33,602), it was found that 42.7% of patients were taking 5–9 medicines and 20.7% were taking >9 medicines.[42] The risk of drug-drug interactions increases in an almost exponential fashion with the number of drugs taken,[43] and can lead to loss of efficacy or reduced safety of DOACs and of the other medications involved.[44] Since monoclonal

antibodies do not interact with other drugs, this potential risk is avoided.

Third, the effectiveness of long-term medication, like anticoagulation, critically depends on good adherence and persistence with treatment, but unfortunately this is notoriously poor in long-term preventative settings, especially in patients with a high pill burden. This issue largely explains the widely recognised gulf between clinical trial results and real-world outcomes with many preventative daily drugs, including DOACs.

A meta-analysis of 48 studies examining real-world adherence and persistence to DOACs in patients with AF found that DOAC doses were skipped on 1 out of every 4 days, and one-third of patients were adherent <80% of the time.[21] Importantly, suboptimal DOAC adherence was associated with poor clinical outcomes, with a 39% higher hazard of stroke and increased risk of all-cause mortality in nonadherent patients.[21]

A long-acting monoclonal antibody with an infrequent dosing schedule may help to address the thorny problem of adherence. Once we know that a drug has proven safety, a long half-life turns into an advantage, offering sustained protection. Injectables delivered by modern pen-style auto-injectors are increasingly common nowadays in many areas of medicine, and many patients prefer the infrequent administration schedule.

IF ONGOING PHASE III TRIALS OF FACTOR XI INHIBITION ARE SUCCESSFUL, HOW COULD THIS CHANGE THE OVERALL PRACTICE OF ANTICOAGULATION?

Right now, the field of anticoagulation is driven entirely by safety, or perceived safety. People desperately want the safest anticoagulant there is. In the future, if we gain access to a new type of anticoagulant with non-inferior efficacy to current options but with bleeding rates approximately 70% lower than we are used to, there will be enormous appetite for it. In particular, we may finally be able to treat the large proportion of higher-risk individuals who are untreated or inadequately treated with anticoagulants and remain unprotected or poorly protected from stroke. If approved, factor XI inhibition could make a profound difference to the lives of individual patients and exert a dramatically beneficial effect on the epidemiological landscape of thromboembolic disease.

References

1. American Heart Association (AHA). New anti-clotting medication reduces bleeding among people with atrial fibrillation. 2023. Available at: https://newsroom.heart.org/news/new-anti-clotting-medication-reduces-bleeding-among-people-with-atrial-fibrillation. Last accessed: 13 December 2023.
2. Thrombolysis in Myocardial Infarction (TIMI) Study Group. AZALEA-TIMI 71. 2023. Available at: https://timi.org/wp-content/uploads/2023/11/Christian-Ruff-AZALEA-TIMI-71-A-Multicenter-RandomiZed-Active-ControLled-Study-to-Evaluate-the-Safety-and-Tolerability-of-Two-Blinded-Doses-of-Abelacimab-Compared-with-Open-Labe.pdf. Last accessed: 13 December 2023.
3. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. Circ Res. 2016;118(9):1340-7.
4. World Health Organization (WHO). The top 10 causes of death. 2020. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Last accessed: 13 December 2023.
5. Lippi G et al. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. Int J Stroke. 2021;16(2):217-21.
6. Rahman F et al. Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 2014;11(11):639-54.
7. Centers for Disease Control and Prevention (CDC). Atrial fibrillation. 2022. Available at: https://www.cdc.gov/heartdisease/atrial_fibrillation.htm. Last accessed: 13 December 2023.
8. Piccini Sr JP, Fonarow GC. Preventing stroke in patients with atrial fibrillation - a steep climb away from achieving peak performance. JAMA Cardiol. 2016;1(1):63-4.
9. Hart RG et al. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146(12):857-67.
10. Ruff CT et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-62.
11. Carnicelli AP et al.; A Collaboration Between Multiple Institiutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation (COMBINE AF) Investigators. Direct oral anticoagulants versus warfarin in patients with atrial fibrillation: patient-level network meta-analyses of randomized clinical trials with interaction testing by age and sex. Circulation. 2022;145(4):242-55.
12. Feagins LA, Weideman RA. GI bleeding risk of DOACs versus warfarin: is newer better? Dig Dis Sci. 2018;63(7):1675-7.
13. Ko D et al. Trends in use of oral anticoagulants in older adults with

newly diagnosed atrial fibrillation, 2010-2020. JAMA Netw Open. 2022;5(11):e2242964.

14. Hsu JC et al. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: insights from the NCDR PINNACLE Registry. JAMA Cardiol. 2016;1(1):55-62.
15. Piccini JP et al.; Get With The Guidelines-AFIB Clinical Working Group and Hospitals. Adherence to guideline-directed stroke prevention therapy for atrial fibrillation is achievable. Circulation. 2019;139(12):1497-506.
16. Willey V et al. Treatment and persistence with oral anticoagulants among newly diagnosed patients with non-valvular atrial fibrillation: a retrospective observational study in a US commercially insured and Medicare Advantage population. BMJ Open. 2018;8(6):e020676.
17. Sussman M et al. The burden of undertreatment and non-treatment among patients with non-valvular atrial fibrillation and elevated stroke risk: a systematic review. Curr Med Res Opin. 2022;38(1):7-18.
18. Arbel R et al. Effectiveness and safety of off-label dose-reduced direct oral anticoagulants in atrial fibrillation. Am J Med. 2019;132(7):847-55.
19. Steinberg BA et al.; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) II Investigators. Frequency and outcomes of reduced dose non-vitamin K antagonist anticoagulants: results from ORBIT-AF II (the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). J Am Heart Assoc. 2018;7(4):e007633.
20. Yao RJR et al. Variability in nonvitamin K oral anticoagulant dose eligibility and adjustment according to renal formulae and clinical outcomes in patients with atrial fibrillation with and without chronic kidney disease: insights from ORBIT-AF II. J Am Heart Assoc. 2023;12(6):e026605.
21. Ozaki AF et al. Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2020;13(3):e005969.
22. Cools F et al.; Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) Investigators. Risks associated with discontinuation of oral anticoagulation in newly diagnosed patients with atrial fibrillation: results from the GARFIELD-AF Registry. J Thromb Haemost. 2021;19(9):2322-34.
23. Hsu C et al. Factor XI inhibition to uncouple thrombosis from hemostasis: JACC review topic of the week. J Am Coll Cardiol. 2021;78(6):625-31.
24. Koch AW et al. MAA868, a novel FXI antibody with a unique binding mode, shows durable effects on markers of anticoagulation in humans. Blood. 2019;133(13):1507-16.
25. Weitz JI, Fredenburgh JC. Factors XI and XII as targets for new anticoagulants. Front Med (Lausanne). 2017;4:19.
26. Fredenburgh JC, Weitz JI. News at XI: moving beyond factor Xa inhibitors. J Thromb Haemost. 2023;21(7):1692-702.
27. Vedovati MC et al. A new strategy for anticoagulation: the factor XI inhibitors. Eur J Intern Med. 2023;116:8-15.
28. Harrington J et al. Clinical evaluation of factor XIa inhibitor drugs: JACC review topic of the week. J Am Coll Cardiol. 2023;81(8):771-9.
29. Greco A et al. Pharmacology and clinical development of factor XI inhibitors. Circulation. 2023;147(11):897-913.
30. Asselta R et al. Exploring the global landscape of genetic variation in coagulation factor XI deficiency. Blood. 2017;130(4):e1-6.
31. Sharman Moser S et al. The association between factor XI deficiency and the risk of bleeding, cardiovascular, and venous thromboembolic events. Thromb Haemost. 2022;122(5):808-17.
32. Peyvandi F et al.; European Network of Rare Bleeding Disorders Group. Coagulation factor activity and clinical bleeding severity in rare bleeding disorders: results from the European Network of Rare Bleeding Disorders. J Thromb Haemost 2012;10(4):615-21.
33. Meijers JC et al. High levels of coagulation factor XI as a risk factor for venous thrombosis. N Engl J Med. 2000;342(10):696-701.
34. Preis M et al. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. Blood. 2017;129(9):1210-5.
35. Gailani D, Gruber A. Factor XI as a therapeutic target. Arterioscler Thromb Vasc Biol. 2016;36(7):1316-22.
36. Yi BA et al. Pharmacokinetics and pharmacodynamics of abelacimab (MAA868), a novel dual inhibitor of factor XI and factor XIa. J Thromb Haemost. 2022;20(2):307-15.
37. Verhamme P et al.; ANT-005 Total Knee Arthroplasty (TKA) Investigators. Abelacimab for prevention of venous thromboembolism. N Engl J Med. 2021;385(7):609-17.
38. Lip GYH et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72.
39. HCPLive. Bayer halts asundexian afib trial, OCEANIC-AF, for inferior efficacy. 2023. Available at: https://www.hcplive.com/view/bayers-halts-asundexian-afib-trial-oceanic-af-for-inferior-efficacy. Last accessed: 4 January 2024.
40. Chen A et al. Direct oral anticoagulant use: a practical guide to common clinical challenges. J Am Heart Assoc. 2020;9(13):e017559.
41. Washam JB et al. Pharmacotherapy for atrial fibrillation in patients with chronic kidney disease: insights from ORBIT-AF. J Am Heart Assoc. 2018;7:(18):e008928.
42. Gallagher C et al. Polypharmacy and health outcomes in atrial fibrillation: a systematic review and meta-analysis. Open Heart. 2020;7:(1):e001257.
43. Wastesson JW et al. An update on the clinical consequences of polypharmacy in older adults: a narrative review. Expert Opin Drug Saf. 2018;17(12):1185-96.
44. Maher Jr RL et al. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13(1):57-65.