Cureus
Part of SPRINGER NATURE

Open Access Review Article

DOI: 10.7759/cureus.

Uncovering the Role of DOACs in Stroke Prevention for Atrial Fibrillation: A Review of Literature

Sudipta Rao [1], Shailesh Aggarwal [1], Sweatha Mani [2], Abirami Balasubramanian [3], Keerthana Veluswami [4]

1. Department of Internal Medicine, JSS Medical College, Mysore, IND 2. Internal Medicine, K.A.P. Viswanatham Government Medical College, Tiruchirappalli , IND 3. Internal Medicine, Stanley Medical College and Hospital, Chennai, IND 4. Internal Medicine, Stanley Medical College, Chennai, IND

Corresponding author: Sudipta Rao, sudi9ta@gmail.com

Abstract

Atrial fibrillation(AF) is a predominant contributor to morbidity and mortality, and stroke prevention remains the mainstay for the management of AF. The precise mechanism involved in thrombus formation remains unknown. However, factors such as stretch-induced fibrosis, endothelial dysfunction, disordered atrial contractions, and pro-thrombotic states have been postulated for the development of AF. Various risk assessment strategies have been acknowledged for determining the risk of stroke in AF, of which the CHA2DS2-VASc score remains the ultimate risk stratification tool. For the longest time, vitamin K antagonists (VKA) were the only oral anticoagulants available but were associated with an increased risk of bleeding. Recently, direct oral anticoagulants(DOACs) were approved and considered more efficient and safer than or as secure as warfarin in stroke prevention and lowering intra-cranial bleeding events. This article also enlightened the pharmacodynamics and pharmacokinetics of DOACs. This review article compiles current evidence-based data on the role of DOACs, uncovering their underlying mechanisms and comparing their efficacy with warfarin in stroke prevention in AF.

Categories: Neurology, Internal Medicine, Cardiology
Keywords: warfarin, vitamin k antagonists, stroke, pharmacodynamics, direct oral anticoagulants, atrial fibrillation

Introduction And Background

AF is adults' most prevalent cardiac arrhythmia, defined by irregular and disorganized electrical activity that disrupts the heart's normal sinus rhythm [1]. AF has been known for 100 years, but 1905 was a momentous year. William Einthoven (1860-1927) was the first to publish an electrocardiogram showing AF in 1906 [2]. Arthur Cushny, a pharmacologist, cardiologist Thomas Lewis, and two Viennese physicians, Rothberger and Winterberg, established a relationship between pulse irregularity and AF [3]. It is believed to be affecting over 30 million worldwide [4]. More than 5 million Americans in the US have AF [5]. It is anticipated that one in three and one in five persons will develop AF in their lifetime. [6] . Although African Americans and Asians have higher comorbidities, the prevalence and incidence of AF are seen more in the European ancestry [7]. Studies have also shown a sharp rise in the prevalence of AF with an increasing age of more than 65 years [8]. There is conflicting data as to whether sex plays a role in the association of risk factors and AF.

AF is a multifactorial entity. Besides non-modifiable risk factors such as age, ethnicity, and genetics, modifiable risk factors such as systemic hypertension, diabetes, alcoholism, thyroid disorders, obesity, chronic obstructive pulmonary disease (COPD), venous thromboembolism, ischemic heart disease, valvular heart disease have shown to bring forth structural and electrical remodelling of the atria [9]. In contempt of extensive research, uncovering the precise mechanisms for AF remains challenging [10]. Modern literature proposes factors such as stretch-induced fibrosis, epicardial adipose tissue (EAT), chronic inflammation, autonomic nervous system (ANS) imbalances, and genetic mutations contribute incredibly to AF pathogenesis [11]. However, specific treatment targeting the root cause of AF is still unknown. Common symptoms associated with AF include palpitations, dyspnea, chest discomfort, fatigue, and dizziness, which can diminish the quality of life and increase the risk of morbidity and mortality [12]. Over a while, electrocardiograms (ECGs) have delivered as the gold standard for AF diagnosis. Recent advances in wearable devices have reinforced AF diagnosis by offering continuous, non-invasive heart rhythm monitoring, significantly contributing to health providers' detection of AF at an earlier stage [13]. The essence of AF management highlights the control of symptoms, further segmented into rate control and rhythm control, along with diminishing the risk of thromboembolism. An integrated approach to patient care is crucial for this management. Stroke prevention is achieved through anticoagulation therapy by a CHA2DS2-VASc score, which particularly holds significance for patients developing stroke or systemic embolism (SE) [12].

Through this review, we utilize present-day knowledge and ongoing research revolving around the appropriateness of DOACs for the prevention of thromboembolism as a long-term clinical management plan

in patients with AF. This review draws attention to the benefits of implementing DOACs over vitamin K antagonists such as warfarin and explains the underlying mechanisms that aid their efficacy.

Review

Managing AF remains a significant challenge, mainly due to the risk of cardioembolic stroke. Research suggests that the principal cause of thrombus formation in the left atrial appendage (LAA) is disordered electrical signals, uncoordinated atrial contractions, endothelial disjunction, and other thrombotic states. Thrombi formed in the LAA can detach and embolize, often aiming the cerebral circulation, and hence strokes arising from AF -related emboli have been shown to have severe consequences compared to strokes unrelated to AF [14,15]. Various risk criteria have been postulated to assess the probability of developing stroke or SE. In 2010, Lip and colleagues presented the CHA2DS2-VASc score as an advancement over the previously used CHADS2 score [16]. The score was easy to calculate and memorize; the primary goal was explicitly identifying individuals at high risk for thromboembolism. A peculiar feature of the score is its ability to categorize age further, appointing two points for those aged 75 and older and one for those aged between 65-74. Auxiliary risk factors include vascular disease encompassing prior myocardial infarction, aortic plaque, and arterial vascular disease. The CHA2DS2-VASc score has a slightly superior predictive value to its predecessor scores [17-19]. Currently, it is approved as a standard criterion for deciding stroke risk. [20,21]. Although ongoing discussions are underway for the inclusion of female sex as a risk factor.

Evolution of Direct oral anticoagulants.

Earlier in 2009, various studies examined the capacity of oral anticoagulants with VKAs, such as warfarin against placebo or aspirin for preventing AF-related stroke [22]. Every study formulated a different design, targeting specific INR ranges; overall, a target INR range of 2.0-3.0 was urged among high-risk patients [22]. The conclusion of these studies illustrated a substantial benefit in using VKA therapy as compared to aspirin or placebo, after which either VKA therapy or aspirin was recommended for intermediate stroke risk. However, bleeding complications, including intracranial haemorrhage, were the adverse events associated with this therapy. To counter these adverse effects, in 2010, the US Food and Drug Administration (FDA) approved its first DOAC-Dabigatran, followed by Rivaroxaban, Apixaban, Edoxaban, and Betrixaban, which were compared to VKA therapy for stroke prevention in non-valvular AF. Based on their positive effectiveness and safety profile, countries such as North America and Europe sanctioned these drugs. However, specific concerns revolving around the reliability of some data from the ARISTOTLE trial comparing Apixaban vs VKA were put forward [23]. In Defiance of these concerns, the US FDA, after an intensive review, approved the medication with a package label emphasizing the overall stroke and systemic embolism reduction compared to VKA therapy. These drugs Exhibited superior or non-inferior standards compared to VKAs, i.e. warfarin and LMWHs (low molecular weight heparin), lowering thromboembolic rates with equivalent or decreased bleeding risk [24-27]. Later, various evidence-based studies claimed the overall potency and safety of DOACS over VKA [28,29]. Several advantages DOACs offer over warfarin include less frequent follow-ups, no PT/INR monitoring, reduced monitoring needs, quicker onset and offset (significant for pre-procedural and acute bleeding management), and decreased food and drug interactions [30].Subsequently led to increased DOACs prescriptions compared to warfarin by 2013, with Apixaban being the most common DOAC prescribed for patients with nonvalvular AF [31]. DOACs have become the most conventional anticoagulant used in patients with AF; specific concerns regarding its strict compliance and pertinacity to therapy still exist [32]. Analysis from Ontario, Canada, revealed that one-third of the patients prescribed either Rivaroxaban or Dabigatran were no longer taking it following six months of initiation [33]. Elevated rates of stroke and mortality were observed among these patients compared to those who continued taking DOACs as prescribed.

DOACs are categorized into two main groups. The following figure gives an insight into their mechanism of action (Figure *1*).

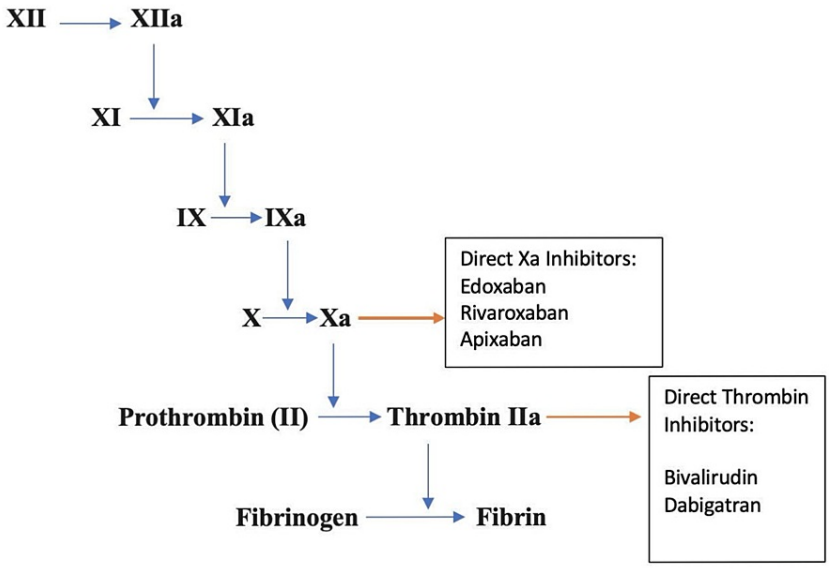

FIGURE 1: Mechanism of action of DOACs

Apixaban, a direct oral factor Xa inhibitor, has prompt absorption, a half-life of 12 hours and 25% excretion through the kidney [34]. Apixaban achieves its maximum concentration (Cmax) 3-4 hours after oral administration [35]. Rivaroxaban (Xarelto), a competitive inhibitor of factor Xa, was first approved by the FDA after its study in the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF) [36]. Apixaban and Rivaroxaban use with either CYP3A4 inducers or inhibitors should be avoided [37]. Their drug is Edoxaban, categorized as a reversible Xa inhibitor [38]. Edoxaban endures transport through P-glycoprotein(pH). Hence, the simultaneous use of potent glycoprotein inhibitors such as verapamil and quinidine can inhibit edoxaban metabolism and increase its toxicity [39]. Dabigatran, a direct thrombin inhibitor, was the first DOAC approved by the FDA based on the reports of the RE-LY (Randomized Evaluation of Long-term Anticoagulant therapy with dabigatran etexilate) trial [40]. It has a bioavailability of (6-7%) which is relatively low [41]. The following table briefly describes the pharmacokinetics and pharmacodynamics of DOACs [Table *1*].

	Characteristics				
Drug Name	Bioavailability	Half Life	Renal Excretion	Hepatic Excretion	Drug Interactions
Apixaban	<50% for 10 mg dose	<12 hours	<25%	Yes	Inhibitors of CYP3A4 and P-gp
Rivaroxaban	66%	6-12 hours	35%	Yes	Inhibitors of CYP3A4 and P-gp
Edoxaban	<60% for 60 mg dose	6-11 hours	<50%	No	Inhibitors of P-gp
Dabigatran	6-7%	11-14 hours	85%	No	Inhibitors of CYP3A4 and P-gp

TABLE 1: Pharmacokinetics and Pharmacodynamics of DOACs

P-gp(P-Glycoprotein)

Summary of DOAC trials

The summary of the following meta-analysis, RE-LY, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI, and EXPLORE Xa, was compared with dose-adjusted warfarin (INR 2-3) in the following tables (Table *2* and Table *3*).

Reference	Study	Study Design	Comparison	Drug and dosage used.	No of cases	Primary outcome	Duration of follow-up	Diagnostic criteria	Conclusion
Robert P. Giugliano et al. (2013) [39]	ENGAGE AF TIMI 48	Randomized, double-blind, double dummy trial.	Edoxaban. Vs warfarin	Edoxaban Low dose :30mg BID EdoxabanHigh dose: 60mg BID	21,105	Stroke and systemic embolism	2.8 years	Twenty-one years or older, ECG findings and CHADS2 score of 2 or more.	Edoxaban was non-inferior compared to warfarin in the reduction of stroke and systemic embolism.
Stuart J Connolly et al. (2013) [42]	EXPLORE - Xa	Randomized Control Trial	Betrixaban vs warfarin	Betrixaban 40,60,80 mg OD	508	Major or clinically relevant non-major bleeding	147 days	18 years of age or older, ECG findings One or more risk factor s for stroke	Betrixaban was associated with equivalent to or lower risk of bleeding as compared to warfarin
Christopher B et al. (2011) [37]	ARISTOTLE	Randomized, double-blind trial	Apixaban vs warfarin	Apixaban 5mg BID	18,201	Ischemic or hemorrhagic stroke and systemic embolism	More than 12 months	21 years of age or older ECG findings one risk factor for stroke CHADS2 score off 2 or more	Apixaban outperformed warfarin in prevention of systemic embolism and stroke .
Manesh R. Patel et al. (2011) [36]	ROCKET AF	Randomized, double-blind, double dummy, event driven trial.	Rivaroxaban vs warfarin	Rivaroxaban 20 mg OD	14,264	Stroke and systemic embolism	More than 14 months	Moderate/ high risk for stroke ECG findings CHADS2 2:10% CHADS2 ≥3: 90%	Rivaroxaban was non inferior to warfarin in prevention of stroke and systemic embolism.
Stuart J et al. (2009) [40]	RELY	Randomized control trial.	Dabigatran vs warfarin	Dabigatran 110mg BID High dose:150mg BID	18,113	stroke and systemic embolism.	2 years	ECG findings , one risk factor for stroke CHADS2 0–1: c. 32% CHADS2 2: c. 35% CHADS2 ≥3: c. 33%	Low dose dabigatran revealed similar rates of stroke and systemic embolism. Lower rates of stroke and systemic embolism were associated with high dose dabigatran.

TABLE 2: Summary of DOAC Trials

ECG-Electrocardiogram

Drug Name	Study Name	Relation with Stroke/Systemic Embolism	Mortality	Adverse Effects		
				Major Bleeding	Gastrointestinal Bleeding	Intracranial Bleeding
Dabigatran 110 mg BID	RE-LY	Non-Inferior	Equivalent	Decreased	Equivalent Re-check	Decreased
Dabigatran 150 mg BID		Superior	Equivalent	Increased	Increased	Decreased
Rivaroxaban 20 mg OD	ROCKET AF	Non Inferior	Equivalent	Equivalent	Increased	Decreased
Apixaban 5 mg	ARISTOTLE	Superior	Decreased	Decreased	Equivalent	Decreased
Edoxaban 30 mg OD	ENGAGE AF TIMI-48	Non Inferior	Equivalent	Decreased	Decreased	Decreased
Edoxaban 60 mg OD		Non Inferior	Equivalent	Decreased	Increased	Decreased
Betrixaban 40 mg OD	EXPLORE Xa	Lower	None	None	NA	NA
Betrixaban 60 mg OD		Equivalent	None	None	NA	NA
Betrixaban 80 mg OD		Equivalent	Not significant	Not Significant	NA	NA

TABLE 3: Effects of different DOACs

NA-Not Applicable

In the ARISTOTLE trial, Apixaban, a direct oral factor Xa inhibitor, was compared to warfarin. Apixaban, given at a dose of 5 mg bid, outperformed warfarin in preventing stroke and systemic embolism, causing less major bleeding, intracranial bleeding events, and lower mortality [39]. A study done by Alexandar T Cohen et al. also demonstrated a lower risk of recurrent VTE (HR [95% confidence interval (CI) 0.72 [0.67-0.78]), major bleeding (MB) (HR [95% CI] 0.70 [0.64-0.76]), and clinically relevant non-major (CRNM) bleeding (HR [95% CI] 0.83 [0.80-0.86]) [43]. Rivaraxoban, administered at a fixed dose of 20 mg OD, was compared with dose-adjusted warfarin in patients with non-valvular AF who were at increased risk for stroke or SE [36]. The primary outcome of the ROCKET AF revealed rivaroxaban to be as good as warfarin in preventing stroke or SE [36].

On the contrary, Apixaban (5mg bid) and high-dose dabigatran (150mg bid) had lower stroke and SE rates [36]. Rivaroxaban revealed equivalent rates of mortality and major bleeding, although less frequent episodes of intracranial cranial bleeding occurred in patients on rivaroxaban [37]. Edoxaban with two dose-based regimens was compared to warfarin in the ENGAGE TIMI 48 trial [39]. The primary outcome indicated that both doses of edoxaban were non-inferior to warfarin in preventing SE and stroke [39]. Edoxaban consistently showed lower rates of all types of bleeding, including primary and intracranial bleeding, except for high-dose Edoxaban (60mg bid), which exhibited increased gastrointestinal bleeding events [39]. Dabigatran, a direct thrombin inhibitor, was studied extensively in the RELY trial. Two fixed-dose regimens of dabigatran (110mg bid and 150mg bid) were compared to warfarin in patients with AF and increased risk for stroke [41]. The study concluded that low-dose dabigatran showed similar rates of SE and stroke compared to warfarin. Still, high-dose dabigatran was associated with a decreased rate of SE and stroke [41]. This difference was primarily seen in incidents of ischemic stroke, whereas hemorrhagic strokes exhibited similar rates in the two dose groups [41]. Higher major bleeding and significant haemorrhage events were noted in high-dose dabigatran; this could be attributed to the absorption of dabigatran, which requires low pH [41]. Hence, dabigatran capsules are coated with a tartaric acid core, leading to increased dyspeptic symptoms and increased gastrointestinal bleeding at higher doses [41].

On the contrary, previous studies compared another thrombin inhibitor with warfarin, named Ximelagatran, which displayed similar efficacy and safety compared to warfarin but was hepatotoxic [41]. In the RELY trial, dabigatran was not found to be hepatotoxic [41]. Lastly, the EXPLORE Xa trial studied betrixaban, a new oral anticoagulant in the pipeline, compared to warfarin, which displayed a lower rate of SE and stroke in patients taking low dose (40mg) betrixaban. In contrast, Betrixaban administered at 60 and 80mg revealed a

similar rate of stroke and SE compared to warfarin [42]. Betrixaban was observed to be permissible in patients with AF at increased risk of stroke [42]. Out of a sample size of 127, no individuals had any major bleeding event.

In contrast, on Betrixaban 40 and 60 mg, respectively, three major bleeding events were seen on Betrixaban 80mg, which was statistically not significant (0.609 (0.145-2.557) [37]. The primary limitation of this study is its small sample size; hence, a thorough conclusion on betrixaban's superiority over warfarin cannot be determined [42]. Another retrospective study on Betrixaban named APEX (Acute Medically Ill Venous Thromboembolism Prevention with Extended Duration Betrixaban) revealed decreased ischemic stroke rates over 77 days of follow-up [44].

Overall, the RELY, ARISTOTLE, ROCKET AF and ENGAGE TIMI 48 studies revealed a significant decrease in all-cause mortality RR 0.90, 95% CI 0.85-0.95, P = 0.0003) [45]. The EXPLORE Xa trial reported two deaths due to a vascular cause, one each in the betrixaban and warfarin group [42]. DOACs contributed a significant reduction of 19% in stroke or systemic embolism events (RR 0·81, 95% CI 0·73-0·91; p<0·0001), compared to warfarin, with a predominant decrease in hemorrhagic stroke [24]. Subdivision analysis catering to factors such as age, sex, prior history of stroke, renal failure, diabetes, CHADS2-score, or competency of anticoagulation with VKA unveiled no substantial relation with stroke or SE [24]. A noteworthy reduction in major bleeding events was ascertained with DOAC therapy paralleled to warfarin when the time within the therapeutic range was less than 66% (RR 0.69 vs 0.93, P =0.022) [24]. This indicated that the reliability and efficiency of DOACs did not depend on the ideality of warfarin treatment [24]. On the contrary, a study done by Goméz-Outes et al. demonstrated that DOACs were inferior to VKA therapy in preventing stroke or SE [45].

Some of the challenges met with DOACs are higher rates of extra-cranial bleeds observed in patients with increasing age on Dabigatran and Rivaroxaban [24]. Major bleeding events were higher in patients aged above 80% years [24]. Hence, a dose alteration of (dabigatran 110 mg bid)and Apixaban (2.5mg) is essential in individuals aged 80 years and above with comorbidities and use of concurrent drugs, which increase bleeding risk [45]. DOACs should be eluded in patients with renal impairment [46]. Patients with less than 30ml/min of creatinine clearance are a significant contraindication for initiating DOACs [46]. Dose alteration of (danigatran 110 mg BD, Rivaroxaban 15 mg OD, Apixaban 2.5 mg BD) is mandatory in patients with moderate kidney dysfunction (creatinine clearance between 30-50 ml/min) [46]. The only DOAC considered to be reliable is Apixaban [46]. VKAs are favoured over DOACs in renal impairment [46].

Limitations

This article focuses on the role of DOACs and their efficacy compared to warfarin in preventing strokes in nonvalvular AF. It does not consider using other anticoagulants, such as heparin, and antiplatelet agents, like aspirin and clopidogrel. The use of DOACs in other thrombotic states, such as pulmonary embolism (PE), deep vein thrombosis (DVT), the perioperative period, and cardioversion, has yet to be covered in this study.

Conclusions

Through this review, we concluded that DOACs exemplify an alluring alternative over VKA therapy for the prevention of incidents of stroke or systemic embolism in individuals with atrial fibrillation. Anticoagulation remains at the forefront of the prevention of stroke. The significant implication of this study was the efficacy and safety of DOACs, which did not depend on the adequacy of warfarin management. These drugs exhibited a quicker onset of action, faster absorption, lesser food or drug interactions, no bridging required with other anticoagulants, and did not demand frequent anticoagulant monitoring; hence, they were preferred in patients with AF. However, bleeding complications, especially intracranial haemorrhage, were found to be significantly lower with this group of drugs, except for GI bleeding. Despite the intense curiosity surrounding DOACs, certain conditions, such as the patient's age, bleeding risk, liver and renal function, should be evaluated before prescribing these agents. One must implement the CHA2DS2 -VASc score for assessing an individual's risk of developing stroke in AF, and further attempts to evaluate stroke risk prediction and stratification are needed. Therefore, the main aim of a clinician should focus on early stroke risk determination and follow a pragmatic approach while managing patients with AF. Lastly, we firmly believe extensive research analyses are mandated on the role of DOACs for stroke prevention in AF to achieve promising patient outcomes.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Saleh K, Haldar S: Atrial fibrillation: a contemporary update . Clin Med. 10.7861/clinmed.2023-23.5.Cardio2
2. Mackenzie J. NEW METHODS OF STUDYING AFFECTIONS OF THE HEART: Br Med J. 1905, 15:812-5. 10.1136/bmj.1.2311.812-a
3. Silverman ME: From rebellious palpitations to the discovery of auricular fibrillation: contributions of Mackenzie, Lewis and Einthoven. Am J Cardiol. 1994, 15:384-9. 10.1016/0002-9149(94)90013-2
4. Chugh SS, Havmoeller R, Narayanan K, et al.: Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014, 25:837-47. 10.1161/CIRCULATIONAHA.113.005119
5. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X: Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am J Cardiol. 2013, 15:1142-7. 10.1016/j.amjcard.2013.05.063
6. Mou L, Norby FL, Chen LY, et al.: Lifetime Risk of Atrial Fibrillation by Race and Socioeconomic Status: ARIC Study (Atherosclerosis Risk in Communities). Circ Arrhythm Electrophysiol. 2018, 11:006350. 10.1161/CIRCEP.118.006350
7. Borzecki AM, Bridgers DK, Liebschutz JM, Kader B, Kazis LE, Berlowitz DR: Racial differences in the prevalence of atrial fibrillation among males. J Natl Med Assoc. 2008, 100:237-45. 10.1016/s0027-9684(15)31212-8
8. Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC Jr, Heckbert SR: Atrialfibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the Multi-Ethnic Study of Atherosclerosis. Ann Epidemiol. 2015, 25:71-6. 10.1016/j.annepidem.2014.11.024
9. W M Feinberg , J L Blackshear, A Laupacis, et al.: Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med.1995 Mar. 13:469-73.
10. Hu D, Barajas-Martinez H, Zhang ZH, et al.: Advances in basic and translational research in atrial fibrillation. Philos Trans R Soc Lond B Biol Sci. 2023, 19:20220174-10. 10.1098/rstb.2022.0174
11. Yamaguchi N, Xiao J, Narke D, et al.: Cardiac Pressure Overload Decreases ETV1 Expression in the Left Atrium, Contributing to Atrial Electrical and Structural Remodeling. Circulation. Circulation; 2021. 23:805-820.. 10.1161/CIRCULATIONAHA.120.048121
12. Hu Z, Ding L, Yao Y: Atrial fibrillation: mechanism and clinical management . Chin Med J (Engl. 202320, 136:2668-2676. 10.1097/CM9.0000000000002906
13. Steinhubl SR, Waalen J, Edwards AM, et al.: Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation: The mSToPS Randomized Clinical Trial. JAMA. 2018, 10:146-155. 10.1001/jama.2018.8102
14. Lamassa M, Di Carlo A, Pracucci G, et al.: Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The. European Community Stroke Project). Stroke. 2001, 32:392-8. 10.1161/01.str.32.2.392
15. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB: Stroke severity in atrial fibrillation. The Framingham Study. Stroke. 1996, 27:1760-4. 10.1161/01.str.27.10.1760
16. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ: 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, 137:263-72. 10.1378/chest.09-1584
17. Larsen TB, Lip GY, Skjøth F, Due KM, Overvad K, Hvilsted Rasmussen L: Added predictive ability of the CHA2DS2VASc risk score for stroke and death in patients with atrial fibrillation: the prospective Danish Diet, Cancer, and Health cohort study. Circ Cardiovasc Qual Outcomes. 2012, 5:335-42. 10.1161/CIRCOUTCOMES.111.964023
18. van den Ham HA, Klungel OH, Singer DE, Leufkens HG, van Staa TP: Comparative Performance of ATRIA, CHADS2, and CHA2DS2-VASc Risk Scores Predicting Stroke in Patients With Atrial Fibrillation: Results From a National Primary Care Database. J Am Coll Cardiol. 2015, 27:1851-9. 10.1016/j.jacc.2015.08.033
19. Shahid F, Lip GYH: Risk Stratification Models in Atrial Fibrillation . Semin Thromb Hemost. 2017, 43:505-513. 10.1055/s-0036-1597285
20. January CT, Wann LS, Calkins H, et al.: 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019, 9:104-132.. 10.1016/j.jacc.2019.01.011
21. Kirchhof P, Benussi S, Kotecha D, et al.: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016, 7:2893-2962. 10.1093/eurheartj/ehw210
22. Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, Singer DE: Antithrombotic therapy in atrial fibrillation. Chest. 2001, 119:1. 10.1378/chest.119.1_suppl.194s
23. Seife C: Research misconduct identified by the US Food and Drug Administration: out of sight, out of mind, out of the peer-reviewed literature. JAMA Intern Med. 2015, 175:567-77. 10.1001/jamainternmed.2014.7774
24. Ruff CT, Giugliano RP, Braunwald E, 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, 15:955-62. 10.1016/S0140-6736(13)62343-0
25. 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. 2014:320-8. 10.1111/jth.12485
26. Kapoor A, Ellis A, Shaffer N, et al.: Comparative effectiveness of venous thromboembolism prophylaxis options for the patient undergoing total hip and knee replacement: a network meta-analysis. J Thromb Haemost. 2017, 15:284-294. 10.1111/jth.13566
27. Cohen AT, Harrington RA, Goldhaber SZ, et al.: Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med. 2016, 11:534-44. 10.1056/NEJMoa1601747
28. Lip GYH, Keshishian A, Li X, et al.: Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular

Atrial Fibrillation Patients. Stroke. 2018, 49:2933-2944. 10.1161/STROKEAHA.118.020232
29. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, Noseworthy PA: Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation. J Am Heart Assoc. 2016, 13:003725. 10.1161/JAHA.116.003725
30. Rose DK, Bar B: Direct Oral Anticoagulant Agents: Pharmacologic Profile, Indications, Coagulation Monitoring, and Reversal Agents. J Stroke Cerebrovasc Dis. 2018, 27:2049-2058. 10.1016/j.jstrokecerebrovasdis.2018.04.004
31. Zhu J, Alexander GC, Nazarian S, Segal JB, Wu AW: Trends and Variation in Oral Anticoagulant Choice in Patients with Atrial Fibrillation, 2010-2017. Pharmacotherapy. 2018, 38:907-920. 10.1002/phar.2158
32. Barnes GD, Lucas E, Alexander GC, Goldberger ZD: National Trends in Ambulatory Oral Anticoagulant Use . Am J Med. 2015, 128:1300-5. 10.1016/j.amjmed.2015.05.044
33. Jackevicius CA, Tsadok MA, Essebag V, et al.: Early non-persistence with dabigatran and rivaroxaban in patients with atrial fibrillation. Heart. 2017, 103:1331-1338. 10.1136/heartjnl-2016-310672
34. Raghavan N, Frost CE, Yu Z, et al.: Apixaban metabolism and pharmacokinetics after oral administration to humans. Drug Metab Dispos. 2009, 37:74-81. 10.1124/dmd.108.023143
35. Frost C, Wang J, Nepal S, et al.: Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. Br J Clin Pharmacol. 2013, 75:476-87. 10.1111/j.1365-2125.2012.04369.x
36. Patel MR, Mahaffey KW, Garg J, et al.: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation . N Engl J Med. 2011, 8:883-91. 10.1056/NEJMoa1009638
37. Granger CB, Alexander JH, McMurray JJ, et al.: Apixaban versus warfarin in patients with atrial fibrillation . N Engl J Med. 2011, 15:981-92. 10.1056/NEJMoa1107039
38. Lip GY, Agnelli G: Edoxaban: a focused review of its clinical pharmacology . Eur Heart J. 2014, 21:1844-55. 10.1093/eurheartj/ehu181
39. Giugliano RP, Ruff CT, Braunwald E, et al.: Edoxaban versus warfarin in patients with atrial fibrillation . N Engl J Med. 2013, 28:2093-104. 10.1056/NEJMoa1310907
40. Connolly SJ, Ezekowitz MD, Yusuf S, et al.: Dabigatran versus warfarin in patients with atrial fibrillation . N Engl J Med. 2009, 17:1139-51. 10.1056/NEJMoa0905561
41. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W: The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. Drug Metab Dispos. 2008, 36:386-99. 10.1124/dmd.107.019083
42. Connolly SJ, Eikelboom J, Dorian P, Hohnloser SH, Gretler DD, Sinha U, Ezekowitz MD: Betrixaban compared with warfarin in patients with atrial fibrillation: results of a phase 2, randomized, dose-ranging study (Explore-Xa). Eur Heart J. 2013, 34:1498-505. 10.1093/eurheartj/eht039
43. Cohen AT, Sah J, Dhamane AD, et al.: Effectiveness and Safety of Apixaban vs Warfarin in Patients with Venous Thromboembolism with Risk Factors for Bleeding or for Recurrences. Adv Ther. 2023, 40:1705-1735. 10.1007/s12325-023-02440-1
44. Gibson CM, Chi G, Halaby R, et al.: Extended-Duration Betrixaban Reduces the Risk of Stroke Versus Standard-Dose Enoxaparin Among Hospitalized Medically Ill Patients: An APEX Trial Substudy (Acute Medically Ill Venous Thromboembolism Prevention With Extended Duration Betrixaban). Circulation. 2017, 14:648-655. 10.1161/CIRCULATIONAHA.116.025427
45. Gómez-Outes A, Terleira-Fernández AI, Calvo-Rojas G, Suárez-Gea ML, Vargas-Castrillón E: Dabigatran, Rivaroxaban, or Apixaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Subgroups. Thrombosis. 20132013, 640723. 10.1155/2013/640723
46. Chadha DS, Bharadwaj P: Direct acting oral anticoagulant: Bench to bedside. Med J Armed Forces India. 2017, 73:274-281. 10.1016/j.mjafi.2016.11.013