

Safety and Efficacy of Novel Oral Anticoagulants as Compared to Warfarin in Treatment of Atrial Fibrillation

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ABSTRACT

BACKGROUND -

Novel oral anticoagulants (NOACs) are a class of medications used to prevent blood clots thereby various studies have demonstrated their potential benefit in their use in atrial fibrillation. They act by inhibiting clotting factors such as factor Xa or Thrombin. Unlike traditional anticoagulants like Vitamin K antagonist (Warfarin), NOACs have a more predictable effect and require less frequent monitoring.

OBJECTIVE –

We aim to explore the safety and efficacy of Novel oral anticoagulants as compared to warfarin in treatment of atrial fibrillation. Additionally, a comparative analysis among NOACs was conducted to determine the most superior among them.

METHODS –

We performed a pair wise systematic review in patients with atrial fibrillation undergoing anticoagulation with help of NOAC as compared to those undergoing anticoagulation on Warfarin by analysing various electronic database from 2005 till 2023 and filtered 11 studies having 70,801 sample size distributed comparably among the two groups based on our inclusion criteria.

RESULTS –

There was slight difference between the safety and efficacy of the NOAC and Warfarin groups. Among the participants, 3019 individuals (8.93%) who were administered Warfarin experienced major bleeding complications, in contrast to 2690 participants (7.26%) who were on NOACs. Regarding the occurrence of stroke, the Warfarin group observed a rate of 987 cases (2.92%), while the NOAC group had 1119 instances (3.02%) of stroke.

CONCLUSION –

The results of recent NOACs studies emphasises on the superiority of them as compared to warfarin in the both rapid onset of action as well as better patient compliance. Our review suggests lower risk of bleeding but a slightly higher risk of stroke occurrence in NOACs as compared to the Warfarin group, thereby showing their superiority in clinical utility, though more robust clinical trials are required to establish long term benefits.

KEYWORDS - Novel oral anticoagulants, atrial fibrillation, Warfarin, Stroke, Bleed.

1. INTRODUCTION

The risk of Atrial Fibrillation is highest among various forms of cardiac arrhythmias. It arises from abnormal electrical activity in the heart's atria, leading them to fibrillate or beat irregularly. This irregular heartbeat significantly increases the risk of stroke, making AF the leading cardiac cause of this condition.[1] The prevalence of atrial fibrillation has been steadily rising worldwide, and it is projected to double or even triple by the year 2050. This deemed the development of a screening programme necessary as given by a multicentric randomised controlled trial SAFE (Screening for Atrial Fibrillation in Elderly).[2] While AF affects approximately 1% of the global population, its incidence rises dramatically among individuals aged 75 and older, with about 9% of this age group being affected.[3]

There are mainly three major types of Atrial fibrillations based on their temporal pattern. These include Recurrent AFib, Paroxysmal AFib and Permanent AFib. The clinical subtypes of atrial fibrillation, along with the symptoms experienced by patients, play a vital role in defining the objectives of management and therapeutic strategies. Regardless of the specific clinical subtype of atrial fibrillation, the administration of appropriate antithrombotic treatment is essential. This treatment should be based on the individual patient's risk factors for stroke and thromboembolism.[4, 5] The risk of stroke in atrial fibrillation is not the same for all individuals, and various clinical factors associated with atrial fibrillation influence this risk.[6] Among the different risk stratification criteria published, CHA₂DS₂-VASc Score (Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, and previous Stroke or transient ischemic attack, Vascular disease) is widely recognized and well-validated. This scheme has been effective in identifying primary prevention patients who are at a high risk of stroke.[7]

Vitamin K antagonists, such as warfarin, have been shown to be highly effective in preventing strokes in patients with nonvalvular atrial fibrillation, especially those at higher risk. Therefore, they are recommended for individuals with such conditions. Vitamin K is essential for the activation of clotting factors II, VII, IX, and X and warfarin inhibits vitamin k thereby preventing their action.[8,9] Its other uses include that in venous thrombosis, recurrent MI, cardiac valve replacement and pulmonary embolism.[10, 11, 12] However, the use of vitamin K antagonists comes with certain challenges. Frequent monitoring of coagulation levels and dose adjustments are necessary due to potential interactions with food and other medications. As a result, many patients find it challenging to comply with the prescribed treatment plan for these drugs in clinical practice.

Since previous decade, several new oral anticoagulants, commonly known as NOACs (Novel Oral Anti-Coagulants), have been introduced. These medications were approved based on their demonstrated efficacy, safety, and noninferiority compared to warfarin, the traditional vitamin K antagonist. NOACs belong to either the group of reversible factor Xa inhibitors or direct thrombin inhibitors. Factor Xa inhibitors like Rivaroxaban disrupt both intrinsic as well extrinsic pathway, preventing thrombin formation as well as subsequent clotting.[13] However, it is important to note that these newer anticoagulants are generally more expensive than warfarin.[14] Despite the cost difference, NOACs offer several advantages over vitamin K antagonists. One of the most significant benefits is that they do not require routine blood testing for international normalized ratio (INR) monitoring. Unlike warfarin, NOACs are administered at fixed daily doses, which simplifies their usage and monitoring. Using NOACs carries a notable apprehension due to the potential risk of intracranial haemorrhage, which can lead to severe and lasting health issues, or even loss of life. Nonetheless, they demonstrated a statistically significant decrease in

intracranial haemorrhage rates when compared to warfarin. [15] Moreover, NOACs have a substantially reduced number of drug interactions compared to warfarin, making them a safer option for many patients. Additionally, they have a rapid onset and offset of action and possess a wider therapeutic window, providing more flexibility in their dosing and administration. [16]

Keywords: Atrial fibrillation, Vitamin K Antagonist, NOACs, Stroke, Bleeding

2. MATERIAL AND METHODS

Various databases like PUBMED, Cochrane Library, G scholar, SCOPUS, EUROPEAN PMC and the EMBASE were searched with no language restrictions from January 2005- July 2023 for studies on management of atrial fibrillation in adults with NOACs (Rivaroxaban, Apixaban, Edoxaban, Ximelagatran and Idraparinux) and Warfarin. Safety and efficacy of two groups were compared focusing mainly on stroke and bleeding complications. Regarding the type of publications - only RCT type studies were picked and reviewed. The literature search was completed by a manual review of reference lists and the resultant review is based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guidelines.[17] We obtained the full text of articles considered eligible to verify that they met inclusion criteria prior to data extraction.

INCLUSION CRITERIA –

1. Patients having Atrial fibrillation being treated by either NOACs or Warfarin
2. Randomised Controlled Trials (RCT) type studies only
3. Studies done between 2005 till July 2023

EXCLUSION CRITERIA –

1. Patients with diseases than atrial fibrillation requiring anticoagulation like MI, DVT, and Cardiac valve replacement.
2. Study types other than RCTs such as observational studies, nonrandomized controlled trials, cohort, retrospective cohort, case control studies, studies performed in animals etc
3. Studies published before 2005

The systematic reviews and meta-analyses that met the inclusion criteria were not subjected to a detailed review. Instead, they were utilized as a resource to identify other potentially relevant articles. Moreover, reference lists of eligible studies were scanned through for other potentially eligible articles. Since our study solely involved the inclusion and analysis of previously published studies, ethical approval was unnecessary.

To minimize bias and uphold the integrity of the randomized controlled trial (RCT) study design, we exclusively considered data from the intention-to-treat analysis in our study's inclusion criteria. In instances where there was duplicate reporting of the same patient populations, we extracted data exclusively from the primary publication.

STATISTICAL ANALYSIS AND SYNTHESIS –

The main goal of our study was to assess the effectiveness of the treatment in terms of occurrence of strokes, and safety was assessed by the occurrence of major bleeding (following the definition by the ISTH [International Society of Thrombosis and Haemostasis] [18]. Additionally, we conducted a secondary

analysis aiming to compare the favourability of different investigated NOACs against each other. This comparison involved analysing the primary efficacy and safety outcomes across all the studies included in our research. Review Manager (RevMan) and Covidence software were used for all systematic analysis.

4. RESULTS

The study selection process began with 650 initial studies identified through electronic searches. Following the removal of 198 duplicated publications, 331 studies were excluded during title and abstract screening due to reasons like being cost-focused, lacking relevance, not being randomized controlled trials (RCTs), or involving patients not afflicted with atrial fibrillation (AF). This step left us with 121 studies that underwent full-text eligibility assessment, resulting in the exclusion of 67 studies. The exclusions encompassed non-RCT studies and meta-analyses. Subsequently, 54 articles remained for a more comprehensive systematic review.

Through manual reference list searches, 3 additional studies were incorporated [19,20]. A further 46 studies were then excluded due to their inclusion of AF patients with other comorbidities or trials that were incomplete. Ultimately, a Meta-analysis was conducted with 11 studies, all of which were RCT [13, 21, 22, 23, 24, 25, 26, 27, 28], encompassing 70,801 patients comparably divided between two groups (NOACs and Warfarin). The study involved a total of 37,010 patients in the NOAC group, while the Warfarin group comprised 33,791 patients. It's important to note that the slight difference in sample sizes between these groups was duly acknowledged and factored in during all calculations and analyses. The results obtained from this comparison were meticulously adjusted to account for this discrepancy in sample sizes, ensuring an accurate assessment of the outcomes.

This systematic review focused on evaluating the safety and effectiveness of novel oral anticoagulants (NOACs) in comparison to warfarin. The review specifically examined the performance of novel oral anticoagulants like Apixaban, Edoxaban, Rivaroxaban, Ximelagatran, and Idaraparinux. During the evaluation, a comprehensive analysis of various anticoagulants was conducted. Specifically, two crucial studies, ARISTOTLE 2011 and LORES et al. 2019, were dedicated to examining the effects of apixaban. Edoxaban's impact was assessed through the ENGAGE 2013 study, which included both its lower (30 mg) and higher (60 mg) dosage forms. The assessment of rivaroxaban's effectiveness was drawn from two pivotal studies, namely ROCKET AF and the study led by Mao L et al. Notably, idraparinix was investigated in the context of the AMADEUS study, while Ximelagatran's implications were derived from the SPORTIF V study. This meticulous evaluation encompassed a wide range of novel anticoagulants, shedding light on their respective safety and efficacy profiles.

Safety Comparison –

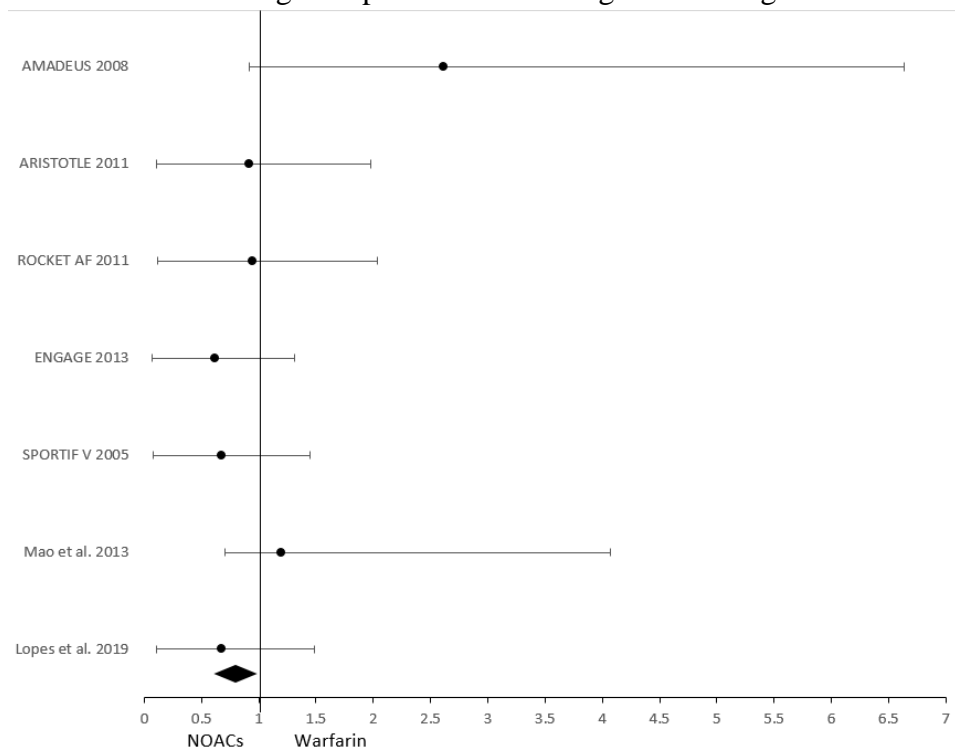
The safety comparison among various NOACs and Warfarin specifically revolved around the assessment of major bleeding risk. This category includes instances of intracranial bleeding, gastrointestinal bleeding, and any clinically significant bleeding at other sites. Within the Warfarin group, a total of 3019 patients (8.93%) experienced bleeding complications. Conversely, in the comprehensive NOACs group, a comparable but notably lower figure emerged, with 2690 patients (7.26%) facing similar bleeding-related challenges as shown in Table 1. This discrepancy in bleeding incidence serves as compelling evidence supporting the assertion that NOACs hold a superior safety profile in contrast to Warfarin. The data suggests that NOACs might offer a more favourable risk-benefit ratio in terms of major bleeding complications, reinforcing their potential advantages in clinical settings.

Table 1: Table Showing Comparison of Bleeding Risk among NOACs and Warfarin.

STUDY	Novel Oral Anticoagulants		Warfarin		Odds Ratio (95% CI)
	Events	Total	Events	Total	
Lopes et al. 2019	241	2290	332	2259	0.68 (0.57-0.81)
Mao et al. 2013	12	177	10	176	1.2 (0.50-2.87)
SPORTIF V 2005	800	1960	987	1962	0.68 (0.60-0.77)
ENGAGE 2013	681	14069	533	7036	0.62 (0.55-0.69)
ROCKET AF 2011	450	7111	470	7125	0.95 (0.83-1.09)
ARISTOTLE 2011	432	9120	462	9081	0.92 (0.81-1.06)
AMADEUS 2008	74	2283	29	2293	2.61(1.69-.4.03)
TOTAL(95% CI)		37010		29932	0.97 (0.90-1.05)
Total Events	2690		2823		

Focusing on individual NOACs, Ximelagatran had the highest bleeding rate at 40.81% (HR 0.81; 95% CI 0.74-0.89), underlining the need for vigilant monitoring. In contrast, Idraparinux showcased the lowest rate at 3.24% (HR 2.56; 95% CI 1.74-3.77), emphasizing its favourable safety profile. In the case of the remaining NOACs, there existed a relatively comparable safety profile. Apixaban demonstrated a bleeding rate of 5.89%, Rivaroxaban exhibited a rate of 6.34%, and Edoxaban displayed a rate of 4.84% (HR 0.63; 95% CI 0.56-0.72). This comprehensive analysis contributes to a deeper understanding of the relative safety profiles of these anticoagulants, thereby aiding informed decision-making within clinical contexts.

Figure 1: Forest Plot Showing Comparison of Bleeding Risk among NOACs and Warfarin.



Efficacy Comparison –

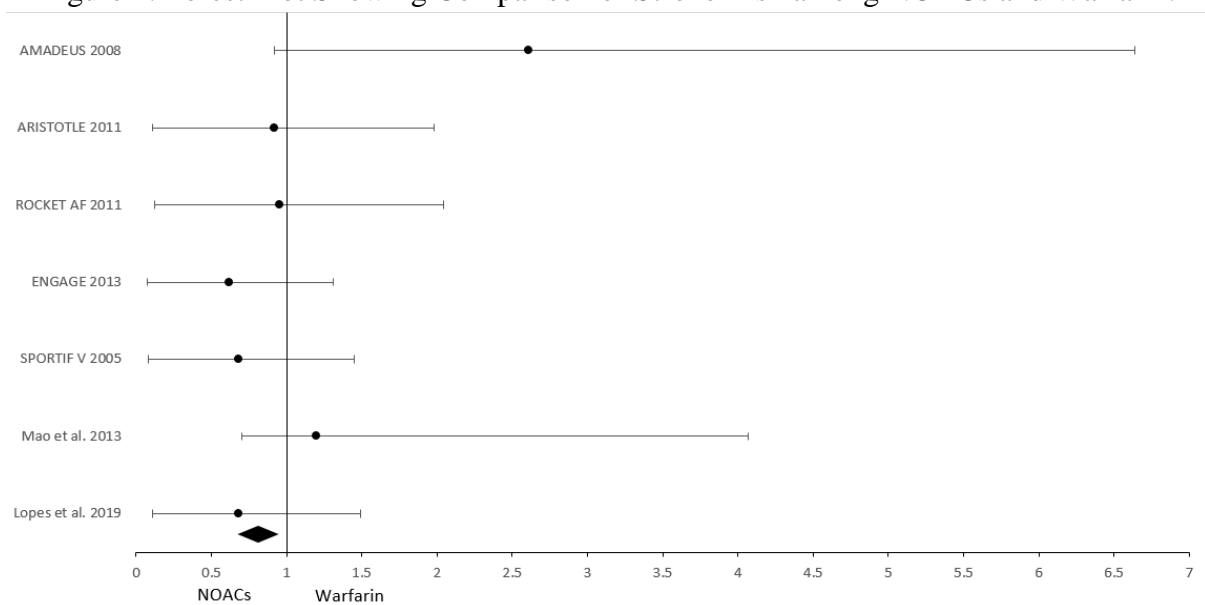
The assessment of stroke risk subsequent to oral anticoagulant usage constitutes a critical dimension encompassing the efficacy of both NOACs and Warfarin. In this context, it is noteworthy that, NOACs collectively demonstrated a slightly elevated stroke incidence rate of 3.02% in comparison to the rate of 2.92% observed with Warfarin as shown in Table 2.

Analysing the individual NOACs, Idraparinux emerged with the lowest stroke risk, with a mere 0.77% (HR 0.68; 95% CI 1.74-3.77) of patients encountering stroke. This contrasts sharply with Edoxaban, which exhibited the highest stroke risk, affecting 4.61% (HR 0.997; 95% CI 0.87-1.13) of patients, emphasizing the need for careful consideration when prescribing this particular anticoagulant. Meanwhile, the other NOACs exhibited relatively comparable stroke profiles: Apixaban had a 1.88% risk, Rivaroxaban showed a 2.63% risk, and Ximelagatran displayed a 2.39% (HR 1.23; 95% CI 0.86-1.89) risk of stroke.

Table 2: Table Showing Comparison of Stroke Risk among NOACs and Warfarin.

STUDY	Novel Oral Anticoagulants		Warfarin		Odds Ratio (95% CI)
	Events	Total	Events	Total	
Lopes et al. 2019	13	2290	26	2259	0.49 (0.25-0.95)
Mao L et al.	4	177	6	176	0.65 (0.18-2.36)
SPORTIF V 2005	47	1960	38	1962	1.24 (0.80-1.91)
ENGAGE 2013	648	14069	325	7036	0.99 (0.86-1.14)
ROCKET AF 2011	188	7111	241	7125	0.77 (0.63-0.94)
ARISTOTLE 2011	202	9120	253	9081	0.79 (0.65-0.95)
AMADEUS 2008	17	2283	25	2293	0.68 (0.36-1.26)
Total (95% CI)		37010		29932	0.98 (0.90-1.08)
Total Events	1119		914		

Figure 2: Forest Plot Showing Comparison of Stroke Risk among NOACs and Warfarin.



This comprehensive analysis contributes significantly to our understanding of the varying stroke risks associated with these oral anticoagulants. It underscores the fine differences in efficacy and safety profiles among NOACs and Warfarin, shedding light on their relative merits and implications for clinical decision-making.

Mortality Comparison –

The examination of mortality defined by deaths stemming from any cause, offers a critical insight into the comparative effectiveness of NOACs and Warfarin. In this realm, NOACs present a marginal advantage over Warfarin, with 7.01% of patients experiencing mortality, as opposed to the 7.22% mortality rate observed in the Warfarin group.

Turning to the NOAC subgroup, it's noteworthy that the mortality rates exhibit variation across different agents. Rivaroxaban stands out with the highest mortality rate at 8.09%. Conversely, Idraparinux displays the lowest rate at 2.72% (HR 1.02; 95% CI 0.71-1.45), highlighting a favourable outcome. Ximelagatran occupies a lower side of the spectrum, recording a mortality rate of 4.8% (HR 1.02; 95% CI 0.76-1.36) as compared to Apixaban and Edoxaban. Apixaban contributes to a 7.53% mortality rate among its patients, reflecting a notable impact. Meanwhile, Edoxaban's mortality rate diverges within its different dosage regimens. The high-dose variant of Edoxaban is associated with a 7.26% (HR 0.89; 95% CI 0.83-0.96) mortality rate, whereas the low-dose Edoxaban demonstrates a slightly lower mortality rate of 6.79%. (HR 0.83; 95% CI 0.77-0.90).

Table 3: Table Showing Mortality Comparison Between NOACs and Warfarin

STUDY	Novel Oral Anticoagulants		Warfarin		Odds Ratio (95% CI)
	Events	Total	Events	Total	
Lopes et al. 2019	538	2290	619	2259	0.8136(0.71 to 0.93)
Mao L et al.	8	177	10	176	0.7858(0.30 to 2.04)
SPORTIF V 2005	94	1960	92	1962	1.0239(0.76 to 1.37)
ENGAGE 2013	988	14069	571	7036	0.8552(0.76 to 0.95)
ROCKET AF 2011	582	7111	632	7125	0.91518(0.81 to 1.03)
ARISTOTLE 2011	321	9120	358	9081	0.8889(0.76 to 1.03)
AMADEUS 2008	62	2283	61	2293	1.0214(0.71 to 1.46)
Total (95% CI)		37010		29932	0.8875(0.83 to 0.94)
Total Events	2593		2343		

This analysis puts light on the intricate web of mortality outcomes across different NOACs and Warfarin. The nuances in these rates underline the complexity of clinical decisions when selecting an anticoagulant regimen for patients with atrial fibrillation. As the clinical landscape evolves and further insights emerge, a deeper understanding of these mortality trends will undoubtedly contribute to more informed therapeutic choices.

Figure 3: Forest Plot Showing Comparison of Mortality among NOACs and Warfarin.

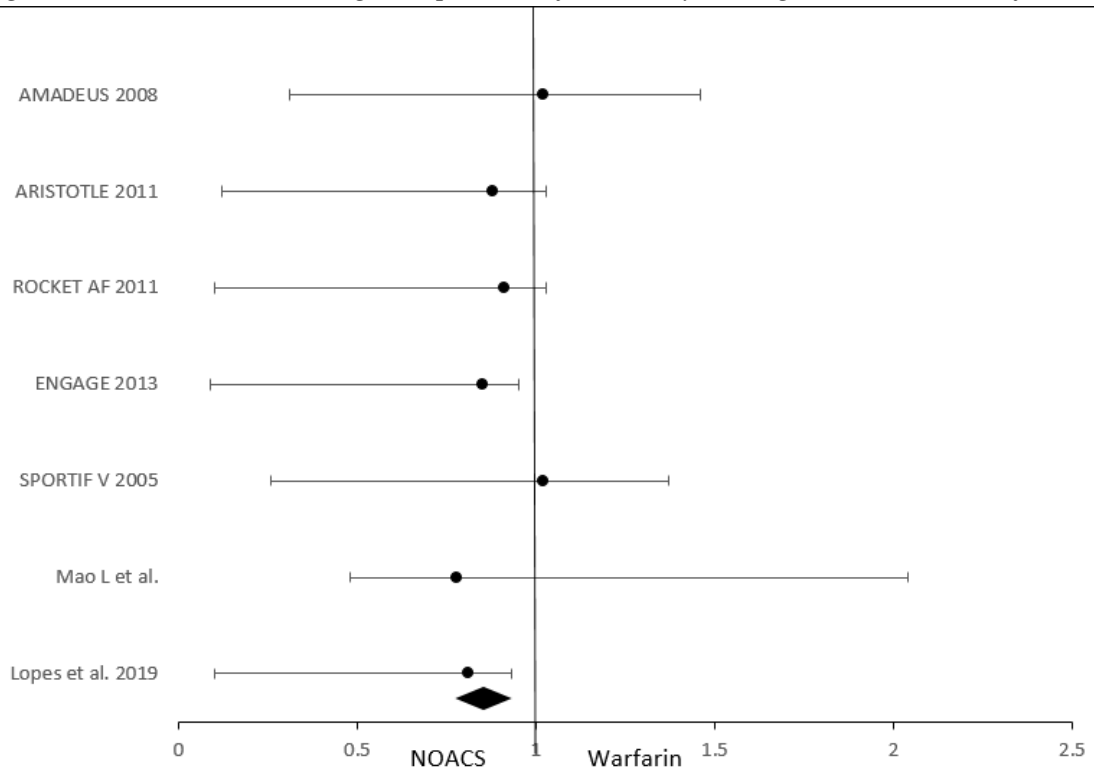


Table 4: Table Showing Warfarin Exclusive Studies

STUDY	Events	Total	Events	Total	Events	Total
JG Cho 2023	9	616	8	616	2	616
Zhu Y 2020	18	507	5	507	0	507
BAFTA	37	488	16	488	107	488
ACTIVE W	159	3371	57	3371	158	3371
Total Events	223		86		267	
Total		4982		4982		4982

In the present landscape of oral anticoagulant therapy, Apixaban stands as one of the most frequently prescribed NOACs for patients with atrial fibrillation.[29] However, the findings from our review introduce an alternative in the form of Idraparinux. Given its triple advantage of both the lowest bleeding complications and stroke risk, and lowest mortality rate, Idraparinux could potentially evolve into the recommended NOAC for patients diagnosed with atrial fibrillation. This recommendation, though, is rooted firmly in the currently available data, particularly when compared to alternatives such as Apixaban and Edoxaban. It is important to note that the body of trials and studies involving Idraparinux remains relatively limited in scope, thus warranting a cautious approach in interpreting these findings.

5. DISCUSSION

The current systematic review and meta-analyses produced three primary insights concerning the utilization of NOACs in comparison to VKAs. Initially, results from randomized controlled trials (RCTs) indicated that NOACs exhibit enhanced efficacy/effectiveness and safety compared to VKAs for atrial

fibrillation (AF). Second, when comparing the stroke percentages for factor Xa inhibitors, apixaban (2.21%) and rivaroxaban (2.63%) came out to be slightly better than edoxaban (4.60%). Even direct thrombin inhibitor Ximelagatran (2.39%) showed stroke rate similar to apixaban and rivaroxaban. Comparison of NOACs for bleeding parameter showed similar percentages for edoxaban and apixaban. A slightly higher bleeding percentage for Rivaroxaban and disproportionately high bleeding percentage of Ximelagatran i.e.40.81 % was found thereby discouraging its clinical utility. And Third, based on mortality rate, All NOACs have lower mortality rate (death due to any cause) than warfarin with the exception of Ximelagatran having slightly higher mortality rate than warfarin.

The individuals engaged in randomized controlled trials (RCTs) may not consistently mirror the diverse array of patients with atrial fibrillation (AF) seen in real-world clinical settings. Evidence stemming from real-world studies can occasionally either enhance or challenge the conclusions derived from RCTs. Meta-analyses that juxtapose the effectiveness and safety outcomes of NOACs against vitamin K antagonists for individuals worldwide with AF in real-world conditions have been documented but updated data in accordance with time has been provided in this review.[30, 31 ,32, 33]

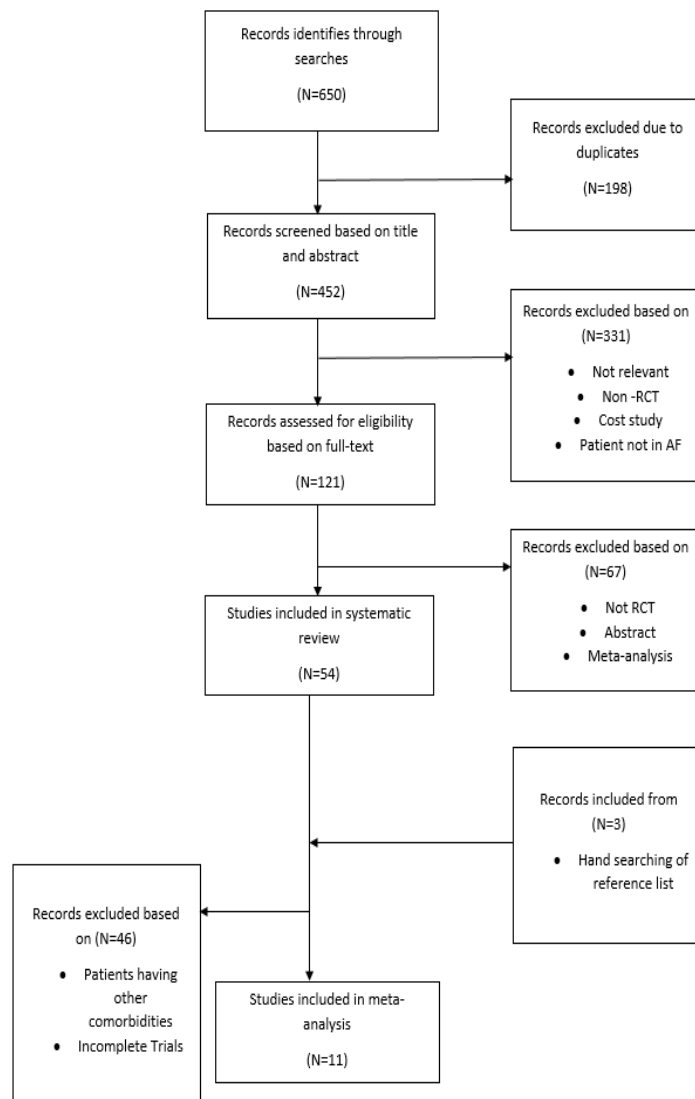
A total of eleven trials were included in our study based on PRISMA guidelines. Among them, six trials were of factor Xa inhibitors and one trial was of direct thrombin (factor IIa) inhibitor i.e. Ximelagatran. The remaining four trials were solely focussed on Warfarin (as shown in Table 4). Our review of the RCTs clearly demonstrates significant reduction in the safety and efficacy outcomes with NOACs as compared to Warfarin, the safety outcome being major bleeding (including Intracranial bleed, Gastrointestinal bleed and major bleed at any other site) while the efficacy outcome being the occurrence of stroke (Ischemic and haemorrhagic stroke). NOACs have greater advantage in respect to bleeding risk (better safety) than in respect to stroke occurrence having greater reduction in bleeding risk than that of stroke risk.

The cornerstone of managing patients with atrial fibrillation (AF) is centered on preventing strokes. Up until recently, the primary focus was to pinpoint individuals at "high risk" and recommend warfarin for them. However, with the advent of NOACs and the heightened emphasis on maintaining precise anticoagulation control with warfarin (as indicated by the average time spent within the therapeutic range of 2.0–3.0 on the international normalized ratio)[34, 35], the current priority has shifted towards initially identifying patients at "low risk" [specifically those with a CHA₂DS₂-VASc score of 0 (for males) or 1 (for females)], who do not necessitate oral anticoagulation therapy. After this decision-making step, effective stroke prevention can subsequently be extended to patients with AF and ≥ 1 stroke risk factor, employing oral anticoagulation, whether in the form of a vitamin K antagonist or an NOAC.(36)

Taking this into consideration, the results of ARISTOTLE[13], ROCKET AF[21], ENGAGE[22] and Mao L et.al(19) were quite similar showing the superiority of their respective NOACs over Warfarin in stroke rate by bringing about a significant reduction. On the contrary, SPORTIF V trial [23] showed ximelagatran to be inferior to warfarin in bringing about the stroke rate reduction. In case of bleeding all the trials except Mao L et.al demonstrated the superiority of NOACs over warfarin. Both high dose and low dose edoxaban data was considered as compared to warfarin in ENGAGE study, though only direct comparison of their rates was considered.

The remaining two trials were solely focussed on Warfarin. Zhu Y et.al [25] demonstrated 0.98% stroke rate and 3.55 % bleeding rate, whereas JG Cho et.al [24] showed 1.29 % stroke rate and 1.46 % bleed rate. In this current analysis, apixaban emerges as a potential primary option for patients, owing to its favourable safety profile and comparable efficacy when contrasted with other NOACs. The conclusions drawn from these findings closely matched those revealed in recently conducted meta-analyses, which were centered on sub analyses of randomized controlled trials (RCTs).[38, 39]

With various non-vitamin K antagonist oral anticoagulants (NOACs) accessible, healthcare providers should have the capacity to tailor the medication to the individual attributes of the patient (and vice versa). This approach provides a broader range of drug choices to ensure effective management in individuals with atrial fibrillation (AF). There are many observational studies on NOACs but based on our inclusion criteria, only RCTs were considered thereby limiting our sample size leading to basing this review only on 11 studies. Therefore, further research and trials on Oral anticoagulants will definitely be of help. Our meta-analysis of data concerning NOACs has provided significant insights that could contribute to addressing the issue of underutilization of oral anticoagulation therapy in AF patients and also puts a light on the type of NOAC to be used.



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