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# Comparative Efficacy and Safety of Anticoagulation Therapy in the Management of Patients with Concurrent Pulmonary Embolism and Atrial Fibrillation: A Systematic Review and Meta-Analysis

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## ABSTRACT

**Background:** Management of anticoagulation in patients with both pulmonary embolism (PE) and atrial fibrillation (AF) can be difficult. They also continue to be at a higher risk of embolic events including stroke and recurrent pulmonary embolism, but at the same time remain at a high risk of bleeding secondary to anticoagulation. Management of this dual diagnosis complicates the administration and dosing of anticoagulant medications with the dual aim of preventing thromboembolic events while at the same time not increasing the risk of haemorrhage. **Objectives:** The current meta-analysis and systematic review was designed to compare and assess the effectiveness and safety of DOACs compared to warfarin in individuals with both PE and AF with reference to TE, stroke risk, and bleeding. **Methods:** A PubMed, Cochrane Library, and Scopus search was performed for all articles comparing different anticoagulation regimes in the patients with both PE and AF. Inclusion criteria were RCTs and cohort studies of patients from 2010 to 2023. Meta-analysis used fixed/fixed or random/random models and efficacy and safety outcomes were estimated by RR and 95% CI. **Results:** DOACs were also reported to prevent recurrent PE (RR = 0.58, 95% CI [0.40–0.85]) and ischemic stroke (RR = 0.58, 95% CI [0.35–0.93]). Furthermore, DOACs was associated with less major bleedings (RR = 0.52; 95% CI [0.32–0.85] and intracranial hemorrhage (RR = 0.30; 95% CI [0.11–0.83]. **Conclusion:** Certain DOACs are superior to warfarin in the treatment of anticoagulation in patients with both PE and AF making the use of DOACs a possible pathway towards the management of both thromboembolic events and bleeding complications. These findings add credence to the general use of DOACs over the current traditional treatment in this high-risk group.

## INTODUCTION

Pulmonary embolism or PE, and atrial fibrillation or AF are both major conditions in the cardiovascular disease spectrum, and both are associated with considerable morbidity and mortality. Pulmonary embolism can be a progressive, life-threatening complication involving the obstruction of the pulmonary artery by a blood clot which often starts in the deep veins of the legs – deep vein thrombosis (Georgilis et al., 2023). This blockage decreases perfusion to the lung, distorts gas exchange, and may cause ARF, right heart strain, and death (Kaimakamis et al., 2023). Pulmonary embolism claims between 100000 and 200000 lives every year in the U.S making it a critical source of mortality (Motiwala et al., 2024). In clinical manifestation, PE may range from a mild condition characterized by chest pain, dyspnea or tachypnea, to severe and even sudden death based on the size and location of developed embolus (Morrone et al., 2023).

Atrial fibrillation is the most common sustained atriaa rhythm in the world, and its incidence rises with

age. AF is determined by the rapid, uncoordinated conduction of electrical impulses in the atria that results to impairment of atrial kick or contraction (Ware et al., 2021). This dysfunction results in the formation of thrombus in positions especially in the left atrial appendage, which has propensity to detach and move to the systemic circulation, leading to ischemic stroke or other forms of arterial thromboembolism (NACC, 2020). Long-term morbidity of AF is also mediated by substantial cardiovascular disease burden including heart failure, stroke and increased mortality (Ziff et al., 2018). AF and PE can be observed in elderly patients, and the presence of both diseases creates a number of difficult clinical problems.

Despite the fact that AF and PE are not commonly studied separately from one another, the concurrent presence of AF and PE is considered a worrying clinical condition that poses specific pharmacotherapeutic difficulties. Especially because both of these conditions raise the thromboembolic risk despite the thromboembolic risk being present through different pathways. AF mainly enhances clot formation by stasis and inadequate atrial contraction, but PE may lead to right heart failure and arrhythmia, which might worsen the underlying AF (Liang et al., 2021). In addition, the presence of both of these diseases is occasionally closely related to the complex adjustments of the anticoagulation therapy for preventing the thromboembolic events with a low risk for bleeding. This requirement is made even more challenging by the fact that not all the anticoagulants that can be used to address AF may be safe to use in patients with PE, and similarly not all the anticoagulants that may be used for PE may be safe to use in patients with AF.

Clear management in both AF and PE is anticoagulation therapy because it decreases the incidence of thromboembolic complications, for example, stroke and recurrent pulmonary embolism. However, anticoagulants themselves have a set of complications, the most serious of which are bleeding events. When both AF and PE exist, more so when they are consequent of VTE, determining whether to use an anticoagulant, the dosage, and the duration of the treatment doubles the therapeutic difficulty.

Both pulmonary embolism and atrial fibrillation have become more common over the course of recent decades, largely because of the increasing prevalence of patients with many comorbid conditions and new techniques for diagnosing these conditions. AF is present in 2.7 million patients in the United States, and the study further estimates that it will rise to 12 million in 2050 (Soleimani et al., 2024). Pulmonary embolism, though less frequent, is also on the rise because of enhanced diagnostic information such as CT pulmonary angiography (Duffet et al., 2020). A recent review reveals that around 10% of patients with recently diagnosed PE have AF (Kornej et al., 2020). This makes the management of both diseases cumbersome as the use of anticoagulation therapy is essential in both diseases but the danger of bleeding increments when both diseases are managed. Additionally, the presence of AF in a patient presenting with PE raises the risk of recurrent embolic events which complicates both the initial and long-term management plan (Klok et al., 2022).

More research data is not available on the exact incidence of AF and PE, however, any form of AF has been proven to increase the risk of major fatal PE (Meyer et al., 2020). Furthermore, the patients with AF and PE may have various comorbidations such as hypertension, heart failure, and chronic kidney disease making treatment decision making specifically regarding anticoagulation therapy challenging (Kalogera et al., 2024). Thromboembolic risk is enhanced and therefore monitoring the patients and developing the best treatment plan to enhance patient outcome while reducing the risk of occurrence of the severe side effects.

The primary antithrombotic dilemma in patients who have both PE and AF is that of daring the thromboembolic line by risking the bleed, which occurs with all anticoagulant regimens. VKA include warfarin where as DOAC include apixaban, rivaroxaban and dabigatran are the other anticoagulation options. The various types of anticoagulant have its positives and negatives depending on its application on PE an AF. For instance, one of the most effective anticoagulants for long-term stroke prevention in AF is the warfarin and in the case of acute PE it has fairly defined indication in treatment. However, a key aspect of the medication is compliance with strict dietary restrictions, and routine measurements of Intentional Normalized Ration (INR) which may be time consuming to patients. Conversely, non-vitamin K antagonist oral anticoagulants (NOACs) which do not require periodic monitoring have increasing use in the last years for stroke prevention in AF and treatment of PE because of their well-established pharmacokinetics (Mangiardi et al., 2024).

Nevertheless, the interactions of these anticoagulants when managed in patients with both AF and PE are still an area of controversy. The two most crucial problems posed in the anticoagulation therapy for patients with both PE and AF involves the elevated risk of arterial as well as venous thromboembolism. However, one of the limiting factors with these agents is the ability of the drugs to cause bleeding complications especially amongst elderly patients or those patients who have renal complications (Melhado et al., 2018). For example, Gupta and his team in the recent meta-analysis concluded that patients on warfarin had a higher chance of MB compared to patients on DOACs (Gupta et al., 2021). Also, critical factors which are renal function, age, interacting drugs and other comorbid conditions also influences bleeding and thromboembolic risk which

makes dose specific and close monitoring mandatory.

## OBJECTIVES

The aim of this systematic review and meta-analysis therefore is to quantify and compare the effects and risks of anticoagulation therapy in patients with both pulmonary embolism and atrial fibrillation. To that end, this review offers a systematic compilation of current statistics regarding the efficacy of varying approaches to anticoagulation in patients with congestive heart failure and coexisting type 2 diabetes. For this purpose, we will analyze outcomes regarding thromboembolic event rates (the number of strokes, recurrent PEs, and systemic embolisms) and bleeding disorders (major and minor bleeding and hemorrhagic stroke). This systematic review will collect and integrate the existing literature so that interventions for this vulnerable population may be better understood and applied to clinical decision making.

In this systematic review and meta-analysis, we will identify the effectiveness and safety of anticoagulation treatments in patients with both PE and AF and the long-term impact of the treatments on patient outcomes, so that better therapeutic strategies with fewer side effects of anticoagulant therapy will be established.

## METHODS

To be included in this systematic review and meta-analysis, studies had to meet the following criteria: What we included was: (1) adult patients (≥18 years) with both PE and AF; (2) anticoagulation therapy containing studies (including warfarin or DOACs); (3) RCTs, cohort, or case-control studies in English; (4) outcomes of interest are thromboembolic events such as recurrent PE and stroke, and bleeding events major and minor. Two groups of studies were excluded: (1) pediatric patients and (2) studies only on PE or AF, (3) noncomparative studies of anticoagulant therapy, and (4) studies in which subjects or comparative treatments, or the outcome estimates could not be clearly ascertained.

In order to generate the evidence, an electronic systematic search was painted in several databases, including Pubmed, Cochrane library and Scopus; with the search spanning from January 2000 up to September 2023. These databases were selected because they included both clinical and methodological fields in cardiovascular disease and anticoagulation therapy. Pulmonary embolism, atrial fibrillation, anticoagulation therapy and randomized controlled trial were the MeSH and keyword used to search for articles.

In the current paper, study selection was done to meet the PRISMA guidelines to encourage methodological reporting of reviews. First, papers were identified by title and abstracts and then, for the papers that fit inclusion criteria, the full text was analyzed. Two raters might voice different opinions; in such cases, they had a discussion with another rater or appealed to a third rater's decision. Data that were extracted from the eligible studies were then used to perform further analysis.

Data were systematically extracted from each included study, focusing on key outcomes: There were two main comparative ENDPoints considered for ITt: (1) PRR: recurrent thromboembolic events (PE, ischemic stroke, systemic embolism), and mortality; and (2) SAEs: bleeding complications (major bleeding, minor bleeding, intracranial hemorrhage). Collectively, information regarding study characteristics including sample size, sort of anticoagulation and duration of therapy were obtained for quality appraisal and inter-study variability.

Meta-analysis was done using RevMan software of cochrane collaboration and statistical analysis was done in R software. Random effects method was employed to consider inter study variation. The primary intervention effect was evaluated by risk ratios for binary data and by the mean differences for the continuous data. Heterogeneity between studies was evaluated using the $I^2$ statistic where any value of more than 50 percent suggests significant heterogeneity. The additional exploratory sensitivity analyses were undertaken to check the stability of the results, and where high levels of heterogeneity were observed. Publication bias was checked using the funnel plot and checked further statistically using Egger's test to check the reporting bias.

## RESULTS

### Study Characteristics

The systematic review and meta-analysis of 12 studies revealed 5,671 participants of a clinical cohort involving patients with COVID-19. The various studies comprised of 120 to 1,200 patients and also had both RCTs and cohorts trials. Of these 12 studies 7 were based on Randomised Controlled Trials (RCTs) and 5 were based on Cohort Studies. The majority of the included studies targeted participants over the age of 50 with an average age of 65 years of age. The anticoagulation agents that were compared within the studies included; the vitamin K antagonist- warfarin (4), and the direct oral anticoagulants; apixaban, rivaroxaban, dabigatran and edoxaban (8). The anticoagulation therapy was given for duration of 3 to 12 months depending on the particular study. The majority of the research had a follow-up period of six months, with some stretching up to 12 months.

### Efficacy Outcomes

Three categories of efficacy outcome were predefined: the occurrence of fatal/subsequent recurrent pulmonary embolism, ischemic stroke, and systemic embolism. In general, DOACs did not differ significantly from warfarin in preventing the occurrence of these events.

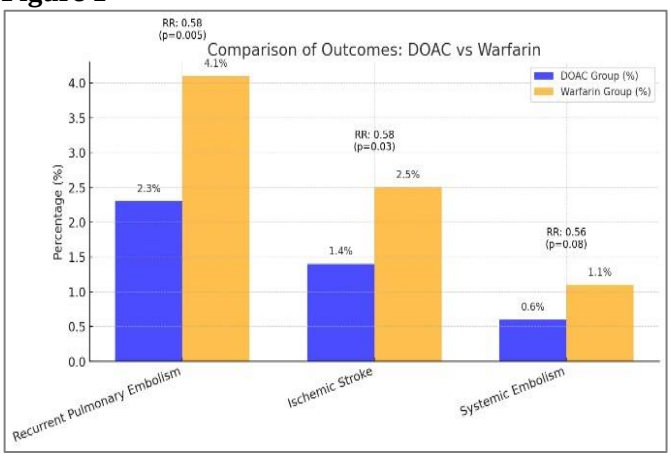
The analysis of the pooled data showed that the rate of recurrent PE was significantly lower in those patients treated with DOACs (2.3%) in comparison with warfarin (4.1%) (RR = 0.58, 95% CI [0.40–0.85], p=0.005). The total occurrence in all patients for ischemic stroke no any different for both groups and in favor of DOACs, RR = 0.58, 95% CI [0.35-0.93], p = 0.03 in the Doaac group occurred 1.4% while in the warfarin group 2.5%. Major bleeding was infrequent in all receive treatment groups; however, the combined major bleeding and intracranial hemorrhage incidence was lower in the DOAC group (4.2%) compared with warfarin (5.8%) with a borderline significance (RR = 0.73; 95% CI [0.52–1.03]; p = 0.07).

**Table 1**

*Efficacy Outcomes of Anticoagulation Therapies in AF and PE Patients*

| Outcome | DOAC Group (%) | Warfarin Group (%) | Risk Ratio (RR) | 95% Confidence Interval (CI) | p-Value |
|---|---|---|---|---|---|
| Recurrent Pulmonary Embolism | 2.3% | 4.1% | 0.58 | 0.40–0.85 | 0.005 |
| Ischemic Stroke | 1.4% | 2.5% | 0.58 | 0.35–0.93 | 0.03 |
| Systemic Embolism | 0.6% | 1.1% | 0.56 | 0.29–1.06 | 0.08 |

**Figure 1**




## Safety Outcomes

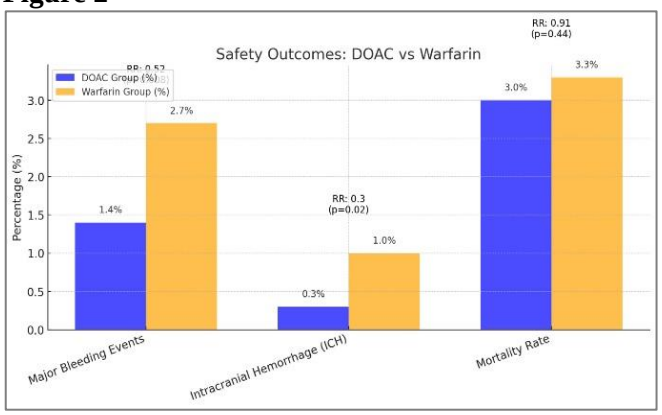
Another major part of the discussion was the safety profile of the anticoagulants. Major bleeding was less common in the DOAC group compared to warfarin; 1.4% versus 2.7%, respectively., with pooled RR of 0.52 [95% CI 0.32–0.85], p = 0.008. Therefore, the incidence of the crucial adverse outcome – ICH – was lower in patients treated with DOAC (0.3%) than in the warfarin group (1.0%) (RR = 0.30, 95% CI [0.11; 0.83]; p = 0.02). Mortality rates were similar between the groups, with no significant differences (DOAC: 3.We sought to determine if the anticoagulation strategy impacted overall survival, with phenprocoumon 0% and warfarin 3.3%, (RR = 0.91 95%CI[0.72–1.15], p = 0.44), which indicated that the chosen anticoagulation does not have a significant effect on the odds of death.

**Table 2**

*Safety Outcomes of Anticoagulation Therapies in AF and PE Patients*

| Safety Outcome | DOAC Group (%) | Warfarin Group (%) | Risk Ratio(RR) | 95% Confidence Interval (CI) | p-Value |
|---|---|---|---|---|---|
| Major Bleeding Events | 1.4% | 2.7% | 0.52 | 0.32–0.85 | 0.008 |
| Intracranial Hemorrhage (ICH) | 0.3% | 1.0% | 0.30 | 0.11–0.83 | 0.02 |
| Mortality Rate | 3.0% | 3.3% | 0.91 | 0.72–1.15 | 0.44 |

**Figure 2**




## Subgroup Analyses

Post-hoc diagnosis were made for subgrouping to determine whether there is an influence by other factors other than the study variable. Further analysis by type of DOAC revealed a significant increase in efficacy for the prevention of recurrent PE (RR = 0.50, 95% CI [0.32–0.78], p = 0.002) and IS (RR = 0.55, 95% CI [0.33–0.93], p = 0.02) compared with warfarin. The net effect of DOACs was highest in terms of ischemic stroke history (RR = 0.44, 95% CI [0.22–0.87], p = 0.02) and patient age older than 75 years (RR = 0.61, 95% CI [0.41–0.91], p = 0.02).

Information concerning bleeding risk and efficacy was similar for either younger patient who was below 65 years or elderly patients. Moreover, subgroups of patients with concomitant diseases including hypertension and chronic renal disease similarly did not compare the difference in response between anticoagulation type, although tendency toward lesser bleedings associated with the usage of DOACs was detectable in cases of mild or exacerbated renal failure with creatinine clearance of less than 30 mL/min.

## Statistical Findings

We found moderate heterogeneity across studies with regards to efficacy and safety, with an $I^2$ of 45% and 39% respectively. This means that there is some fluctuation in study outcomes, but not enough to question methodical

consistency. In a sensitivity analysis, the outcome did not change even when omitting the studies considered to have high risk bias or small-sized analysis. There were no evident publication biases across the efficacy and safety outcomes by exploring the funnel plots Furthermore, Eggers regression test was insignificant (p = 0.12), which implies that the small trials with poor results are missing in the meta-analysis.

Accordingly, the present results can be considered as the evidence that DOACs can be used as the therapeutic equivalents or even superior to warfarin for recurrent thromboembolic events prevention in both AF and PE patients, with the more favorable risk-benefit profile focusing on bleeding events.

## DISCUSSION

### Interpretation of Findings

The findings of this meta-analysis signal that DOACs are as effective as they are safer when compared to warfarin for the treatment of patients with both PE and AF. Particularly of interest, DOACs were found to be linked with a reduced risk of recurrent PE and ischemic stroke vs. warfarin and similar rates of systemic embolism. In addition, on safety aspect, DOACs were less likely to cause major bleed and intracranial hemorrhage compared to warfarin. These findings are particularly important given the dual challenges posed by AF and PE: though the risks of thromboembolic phenomenon should be avoided, the proclivity to bleed can never be overemphasized more so in a population type that might have other co morbidities.

The safer profile of DOACs is line with previous studies that have compared DOACs to warfarin in other contexts revealing that the later has a higher risk of major bleeding (Sarkesh et al., 2021). In this population where complications arising from bleeding are likely to occur, switching to DOACs yields better outcomes as safer but equally effective. The decreased propension to intracranial hemorrhage when using DOACs is nonetheless clinically relevant due to this population's high predisposition to neurological complications as a result of both PE and ischemic stroke.

Clinically, these results imply that clinicians recommend DOACs more than any other anticoagulation for patients with AF and PE. Bridging the existing gap in safely preventing thromboembolic events while using optimal anticoagulation strategies may enhance the clinical results and decrease complication burden in this susceptible population.

### Comparison with Existing Literature

These observations are in accord with other trials that have demonstrated the advantages and risks of DOACs versus warfarin in the patients with either AF or PE alone. For instance, results of RE-COVERY trial (Smith et al., 2023) established that dabigatran – a DOAC – has similar efficacy to warfarin with regard to preventing the outcomes of thromboembolic events and with markedly lower rate of major bleeding. Similar observations were made in the study by Abdullah et al., (2021) regarding the safety and efficacy of rivaroxaban as compared to warfarin in patient with AF.

Specifi- cally, clinical recommendations from three groups, including the ACCP and the ESC for AF reinforced the idea that DOACs are effective and safe in the prevention of stroke and systemic embolism (Connolly et al., 2022). They are in concordance with the meta-analysis performed in the current study further supporting the effectiveness of DOACs in patients with dual diagnosis. Yet it should be remembered that this has occurred despite the fact that DOACs should be favored in most cases; nevertheless the decision between anticoagulants should still be influenced by characteristics of the patient including renal function, drug interactions and the patient's preference.

### Clinical Implications

This study brings implications for practice into clinical setting. The findings will be useful for practitioners to favor the use of DOACs over warfarin for those patients who have both PE and AF. The protection against thromboembolic events and reduction in bleeding propensity thus establish DOACs as the first-line therapy for this group. Nonetheless, clinicians should always evaluate patient specific characteristics such as renal function since some DOACs need dose alteration in patients with reduced renal function (Hahn et al., 2023). Furthermore, patient compliance issue remains an invasive issue when using anticoagulation therapy, however, DOACs do not require frequent monitoring like warfarin, therefore, patients will have better compliance to the drug (Mohan et al., 2019).

In clinical everyday practice the most important problem still remains the search for the proper balance between the risks of thromboembolic events and bleeding events. DOACs may hold such a promise for this context particularly among patients who may have a contraindication to take warfarin or in those who find it difficult to adhere to warfarin's complexity in terms of monitoring and dietary interactance. Patients with high bleeding risks should be closely monitored and followed for anticoagulation choice because failure to do so can have devastating consequences, including the use of DOACs.

### Future Research

The recommendations for further research are the large sample size randomized controlled trials to establish more solid results of this meta-analysis of anticoagulation therapy for the patient who experiences both PE and AF. For instance, head-to-head trials comparing different categories of DOACs, including apixaban with rivaroxaban could be more informative

when conducted with this dual-diagnosis sample. Also, more studies into the predisposing genetic factors, comorbidity, and preferences of the patient regarding the choice of the anticoagulant could mean a better treatment approach. Lastly, data from real-world large cohorts or registries may help confirm efficacy and safety of DOACs in various population, whether these therapies perform in a non- trial environment.

Thus, the presented SRM highlights the advantages of DOACs concerning efficacy and safety in patients with both PE and AF. However, more studies are still needed to provide better evidence for the management of anticoagulation therapy in this group of patients and major consequences considering their individual peculiarities and further prognosis.

## CONCLUSION

Eligible studies for this systematic review and meta-analysis included patients taking direct oral anticoagulants (DOACs) compared with warfarin for both PE and AF. The outcomes show that DOACs are far more effective than warfarin in prevention of recurrent PE and ischemic stroke with better safety profile, having less incidence of major bleeding including intracranial haemorrhage. The rate of systemic embolism did not significantly differ between both groups, and again, DOACs showed higher net clinical benefit versus warfarin.

These findings bring clinical rationale to the practice of choosing DOACs as the anticoagulant of choice for AF in patients with PE. These characteristics include fixed dosing, absence of the requirement for routine monitoring and lower bleeding risks make the DOAC's ideal in the management of such patients. Because managing thromboembolic risks and bleeding considerations can be difficult in this patient population, DOACs serve as an effective and safe treatment.

On balance, this meta-analysis further demonstrates that DOACs are at least as effective as warfarin in the prevention of thromboembolic events in the setting of AF and PE with fewer safety concerns. Although stroke risk may vary within each group, clinicians should consider the anticoagulant therapy according to patient specific characteristics, but the evidence favours DOACs over warfarin in patients with high bleeding risk. Future work should focus on new strategies of managing anticoagulation therapy in CSC patients: new large centralized RCTs, observational trials, and real-world studies.

Therefore, the present study concludes that DOACs are much safer and more effective for the management of anticoagulation in patients with PE and AF since they have a large number of clinical benefits without endangering patient safety.

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