

Review Article

# Recent Advancements in Oral Anticoagulants: A Systematic Review

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## ABSTRACT

Anticoagulants are medications that are administered to patients with clotting issues. Major issues include atrial fibrillation, venous thromboembolism/deep vein thrombosis, and pulmonary embolism. However, recent studies show the increased use of these medications in the treatment and management of COVID-19.

This paper has been designed as a systematic Literature review based on PRISMA strategy. Data were collected by conducting exhaustive research on major electronic databases i.e., SCOPUS, Web of Science, EMBASE, ProQuest, ScienceDirect, and Google Scholar. A total of 52 studies were included in this review. These studies were selected from the period 2011-2021. The overall study revealed the advancements of DOACs or NOACs in comparison to Warfarin, revealed the findings of various food, drug, and another kind of products that interfere with oral anticoagulants, and advancements in terms of treatment of DVT/VTE, pulmonary embolism, and arterial fibrillation by use of oral anticoagulants and the role of anticoagulation in COVID-19.

**Keywords:** Atrial fibrillation; COVID-19; Direct/New oral anticoagulants; Deep Vein Thrombosis; Pulmonary Embolism; Venous thromboembolism; Vitamin K Antagonist

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## INTRODUCTION

Anticoagulants are medications that are administered to patients dealing with clotting issues. These medications; often called blood thinners; interact with the natural clotting system of the body and prevent the formation and occurrence of abnormal clots. These medications don't alter the natural system of the body, rather delay the clotting mechanism, even though the medications are loosely termed as blood thinners, the blood in actuality isn't made any thinner, it just clots as naturally or quickly whilst consumption of anticoagulants. The most common occurrence of abnormal clots is in the legs, a condition known as DVT or deep vein thrombosis, or in the lungs known as pulmonary embolisms. Blood clots are also present in veins, arteries, arrhythmias in the heart or atrial fibrillation, and mechanical heart valves. Anticoagulants are increasingly used for stroke prevention as the occurrence of clots increases the risk of strokes.<sup>1</sup> Anticoagulant is used for the treatment and prevention of blood clots that mainly occur in

the blood vessels. Anticoagulants are used for the prevention of the occurrence of blood clots in the body, and one of the most common conditions treated through these medications is atrial fibrillation.<sup>2,3</sup>

Several types of anticoagulants are available on market and are mainly classified as VKAs and NOACs (factor Xa inhibitors, thrombin inhibitors, Direct Thrombin inhibitors, and Selective Factor Xa inhibitors).<sup>4</sup>

All kinds of anticoagulants work differently to stop blot clots from the formation. These medications cannot break an already formed clot but can prevent the formation of a new one or stop an old one from growing larger.<sup>5</sup> VKAs, such as Warfarin, acenocoumarin, and phenindione, work by blocking the effects of vitamin K which is needed to make some clotting factors described earlier.<sup>6</sup>

Blocking vitamin K prevents blood clots from forming so easily by increasing the time it takes to make fibrin. It usually takes two or three days for these medicines to work fully. The other group of anticoagulant medicines is the direct-acting oral anticoagulants (DOACs) or non-vitamin K antagonists (NOACs).<sup>7</sup>

Historically, the clinical guidelines recommend the administration of low-molecular-weight heparin (LMWH) as the standard procedure for care of CAT and vitamin K antagonists (VKAs) as an optional choice. Moreover, recently, the usage of direct oral anticoagulants (DOACs) like apixaban, dabigatran, rivaroxaban, and edoxaban are becoming widely applicable treatment options for VTE patients as these have indicated better results and responsiveness in comparison to the LMWH and VKAs. The usage of the DOACs also evades frequent laboratory monitoring and discomfort from injections that are associated with the usage of LMWH and VKA.<sup>8</sup>

Another disease treated by anticoagulants is Atrial fibrillation (AF). It causes an uneven heart rate known as cardiac arrhythmia. Cardiac arrhythmia affects more than 2 million people in the US and around 12 million people globally are predicted to be impacted by the year 2050.<sup>9</sup>

AF is also significantly linked to a multitude of other health problems like hypertension, obesity, diabetes mellitus, sleep apnea, and other conditions, all of which can increase the chances of occurrence of an embolism. Thromboembolism combined with atrial fibrillation is an increasing reason for morbidity and mortality.<sup>10</sup>

In addition to the above diseases, anticoagulant use is also seen evident in COVID-19-related coagulatory issues in recent studies and clinical guidelines. However, there is no strict protocol about which medications need to be used. In light of the importance of anticoagulation medications and the need for a guideline for physicians all across the world to evaluate the pros and cons of various options of medications, this review is conducted.

The basic objective of this study is to conduct a systematic review of the available literature regarding anticoagulation medications that can be administered orally.

Other objective includes:

- What are the adverse effects, contraindications, and indications of oral anticoagulant medications that are in use?
- What is the latest advancement and reporting about the use of oral anticoagulants on VTE or DVT, PE, and AF?
- What is the latest advancement and reporting about the use of oral anticoagulants in relation to COVID-19?

The current paper is a review paper that is structured and designed on the basis of PRISMA guidelines. The main purpose of the current study can be explained as to carefully identify and synthesize relevant literature to evaluate the various kinds of oral anticoagulant medications available in the field and to identify their adverse impacts, indications, contraindications, etc.

## Review Design

The current review is designed as a systematic literature review (SLR). This SLR is designed according to the PRISMA methodology (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) which is defined to outline the minimal items that need to be present in a review or a meta-analysis paper. PRISMA is selected by the researcher as it is a well-

known methodology for review papers and is a commonly used technique for writing and reporting systematic reviews. PRISMA also supports the use of transparent reporting techniques of research findings in a review.<sup>11</sup>

## Review Search Methods

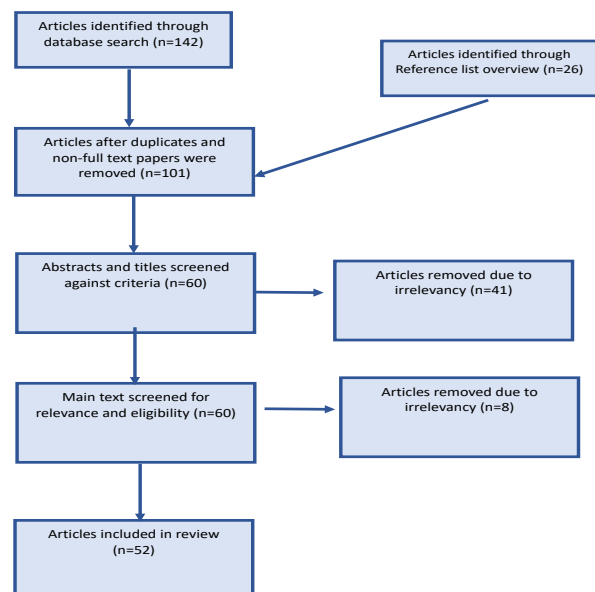
To perform a good review, a researcher needs to conduct a comprehensive search. It is, therefore, advisable to search multiple databases for extracting relevant references for a particular topic, however, this task is long and strenuous. The researcher analyzed the available databases for the selection of papers and of the various databases like SCOPUS, Web of Science, EMBASE, ProQuest, Ebsco, ScienceDirect, and Google Scholar, the researcher selected to derive papers from all possible sources but ensured that the journals are peer-reviewed i.e., journals that have articles written by experts and also reviewed by multiple experts before they are published so that the data collected was reliable. As for the timeline of the papers collected, the researcher restricted it to 10 years i.e., the research between 2011 and 2021 was overviewed and relevant papers were included. For searching, a set of keyword strings were used in the search that includes the following terms: anticoagulation medication\*, Warfarin\*, NOACs\*, DOACs\*, etc.

## Inclusion exclusion criteria for Review

The researcher conducted wide research in this review. Papers included are mostly clinical trials and observational studies but reviews were also not excluded if deemed relevant. The researcher critically evaluated the research published between January 2011 and September 2021. The researcher removed papers that were not published in peer-reviewed journals from the data set of papers included in this review. In addition to the paper, clinical guidelines were also included in this review.

## Data Abstraction and Synthesis Techniques

The data extracted for this review included the following information: author, journal, type of paper, focused issues of academic performance, the future recommendation for improvement in academic performance, and summary of key results of the study. This data was extracted and sorted using Excel Sheets. The themes in this study were divided on the bases of types/classes of medications that classify as oral anticoagulants.



## RESULTS

### Direct/New oral anticoagulants (DOACs/NOACs) versus Vitamin K Antagonists (VKAs)

There are many kinds of anticoagulants but Warfarin is by far the one that was majorly used up until a decade ago. It treats blood clots or prevents them from occurring by decreasing those clotting proteins that are mainly reliant on vitamin K.<sup>6</sup> There is a need for frequent laboratory-based monitoring and dosage adjustments for every patient to ensure that the blood levels are within the INR (international normalized ratio), or the target blood ranges.<sup>12</sup>

It is reported by a multitude of researchers that if the target blood level is not maintained, the patient would be in danger of having an increased risk of clotting if the level is below and an increased risk of bleeding in case it is above the required levels.<sup>12,13</sup>

Researchers have also indicated that the use of Warfarin, like any anticoagulant, leads to an increased risk of bleeding

A clinical study was conducted among veterans aged 65 years and above in Australia and all were new users of warfarin. The bleeding risks were examined using a Poisson GEE model and it

was found that bleeding risks were high in cases where Warfarin was co-prescribed with low-dose aspirin, clopidogrel, both clopidogrel and aspirin, amiodarone, and any kind of antibiotics.<sup>13</sup>

Several researchers examined and compared gastrointestinal bleeding risks of Warfarin with NOACs and found warfarin to be linked to much higher risks in comparison to medications like Apixaban and dabigatran. A study conducted by Hussain et al, indicated that the use of warfarin is linked to an increased risk of bleeding risk in hemodialysis patients that have atrial fibrillation. However, in case of bleeding risk, several reversal strategies can be used like vitamin K supplements or injections or various other blood products that can replace the clotting factors that are impacted by warfarin.<sup>14</sup>

The NOACs or DOACs include many kinds of medications that all individually work by targeting some specific type of individual clotting protein.<sup>15</sup> These medications do not necessarily need to be monitored by using laboratory testing or dose adjustments as they have a specific nature of reaching predictable levels in most patients. One major drawback of this class of medication is based on the shorter-acting life cycles. Warfarin, even if missed by a dose or two, is still acting in the patient's blood.<sup>16</sup> Comparison between warfarin and NOACs are depicted in table 1.

**Table 1: Comparison of Main Features of Warfarin Versus NOACs**

Features	Warfarin	NOACs
Action Onset	Very Slow and prolonged	Rapid Action
Dose	Variable	Fixed
Drug interactions	Many	Some
Food Interactions	Yes	No
Effect Lasting capacity	very long term	Short-lived
Testing and Monitoring	Yes, it is must	no, can be done on doctors' perceptions
Availability of Reversal Agents	Yes	No
Cost	Cheaper	Costlier

It may take up to several days for the blood thinning impacts of Warfarin to completely wear off. However, even if a single dose of a NOAC is missed by the patient, its effects wear off quickly and the patient is left unprotected from clotting of blood.<sup>14</sup>

NOACs are taken either once or twice per day depending on the condition being treated and the NOAC being used. While warfarin effects can be reversed, there is no specific treatment protocol for the reversal of the anticoagulation effect of NOACs in patients that are either bleeding or are at risk of bleeding.<sup>17</sup> Findings of papers published for NOACs and VKAs is depicted in table 2.

**Table 2: Paper Summary for NOACs and VKAs-based papers**

Author	Year	Country	Medicine-Focused	Purpose	Summary of Findings
(13)	2011	Australia	Warfarin	Find the impact of various medications on the excess risk of bleeding-related when the patient is using warfarin	It was found that if the patient is on warfarin treatment and is prescribed low-dose aspirin, clopidogrel, both aspirin and clopidogrel, amiodarone, or any type of antibiotics, bleeding risks are high
(14)	2019	India	Warfarin	To meta-analyzes bleeding risks in warfarin users that need to undergo hemodialysis due to atrial fibrillation	The risk of bleeding in hemodialysis patients with atrial fibrillation is increased if they are on warfarin treatment.

Author	Year	Country	Medicine-Focused	Purpose	Summary of Findings
(15)	2017	USA	NOACs	whether NOACs or warfarin should be the drug of choice for stroke prevention	NOACs are as effective as warfarin in reducing stroke and systemic embolism through anticoagulation. Notably, NOACs have a decreased risk of significant bleeding and other secondary adverse events.
(16)	2021	USA	NOACs	sought to compare outcomes with NOACs vs warfarin for new onset post cardiac surgery AF.	NOACs are associated with a reduction in postoperative length of stay, without excess bleeding or other short-term complications, compared with warfarin. These
(17)	2012	Italy	Warfarin Vs. NOACs	To conduct a meta-analysis of available data on NOACs and warfarin use for AF patients	Patients with NVAF should be treated with NOACs instead of Warfarin as it can be linked to lower risks like systemic embolism, hemorrhage, major bleeding and mortality
(18)	2018	Belgium	All types of Anticoagulants	Compare Warfarin and DOACs for their food-drug and drug-drug interactions.	In terms of food-drug interactions, warfarin is more critical and DOACs may be preferred but still clinical studies need to be conducted for exploring possible drug-drug interactions of DOACs
(7)	2018	Italy	NOACs	Review of drug-drug interactions potential in NOACs. This study is meant to be of help to physicians in choosing the best therapeutic approach for their patients	the results indicate various reactions that may occur due to drug-drug interactions potential in NOACs and is meant to be useful for physicians in making an informed choice for the best possible therapeutic approach
(19)	2020	Germany	DOACs	Overall Review of DOACs in terms of DDIs	Need of more studies that can explore relations of DOACs effectiveness and DDIs.
(20)	2015	China	Warfarin	To examine potential interactions between traditional Chinese herbs or medications and warfarin	Findings indicated possible interactions between 44 commonly consumed herbs and supplements in traditional Chinese medicine and the researcher indicates need of collaboration between western and traditional physicians to increase patient satisfaction and recovery.

### Food, drugs, and herbal medicating interactions

Warfarin is the most widely prescribed oral anticoagulant all over the world, however, there are many factors that are pushing physicians to consider NOACs/DOACs as more viable treatments. One of the most common issues with VKAs like warfarin is that their effectiveness is impacted by food, drugs, and other chemical interactions i.e., pharmacokinetic and pharmacodynamic effects.<sup>18</sup> Another study reviewed various types of drug-drug interactions for NOACs and found that overall, in NOACs, administration of strong P-gp- and CYP3A4-inhibitor can increase the effects of anticoagulants and lead to an increased risk of major bleeding whereas P-gp inducers are responsible for hinder ace of anticoagulant effects by reduction of NOACs plasma concentration.<sup>7</sup> One of the studies conducted cautioned physicians against coadministration of rivaroxaban or apixaban with strong inhibitors of Pgp or CYP3A4 and contraindicated with drugs that inhibit both at once.<sup>19</sup>

In addition to the exploration of food-drug and drug-drug interactions, interaction with herbal medication is also carried out in some studies, one of the studies conducted a review of Warfarin interaction with traditional Chinese medicine (TCM) as it is susceptible to herb-drug interactions given its narrow therapeutic range.<sup>20</sup>

### Anticoagulants use for the treatment of DVT/VTE, PE, and AF

Three kinds of main diseases are treated with anticoagulant medications; pulmonary embolism, atrial fibrillation, and deep

vein thrombosis or venous thromboembolism. A study conducted a network-based meta-analysis to compare DOACs and VKAs for the treatment of elderly VTE patients and found no significant efficiency and efficacy differences, however, a significant decrease in bleeding was observed in the DOACs group. Furthermore, upon the comparison of various DOACs, there was no significant difference in the reoccurrence ratio or the mortality rate. It can be overall concluded that the evidence suggests that DOACs have better clinical efficacy in reducing recurrent VTE in elderly patients.<sup>21</sup>

One of the studies also indicated that increased bleeding risk was related to the use of DOAC therapy in cancer-associated VTE patients and comments that this factor is independent of the death factor i.e., even though the patient may survive, the major bleeding risk was significant.<sup>22</sup>

In one such study data from patients of multiple countries was included and concluded that rivaroxaban and apixaban can be used as an adequate treatment of VTE in patients, no matter what BMI or body weight they possess. Moreover, obese patients undergoing bariatric surgery can opt to use DOACs for the prevention of VTE and DVT safely but there is a need for more research on this perspective.<sup>23</sup> Summary of the various studies performed in the case of VTE/DVT is shown in table 3.

**Table 3: Summary of Advancement Reports on Treatment of VTE**

Author	Year	Country	Medicine-Focused	Purpose	Summary of Findings
(21)	2020	USA	DOACs vs. VKAs	To explore the efficiency of DOACs to treat VTE in elderly patients in comparison to VKAs	DOACs overall offer a better treatment option for VTE in elderly patients as it is linked to lower risks of bleeding
(24)	2018	Sweden	DOACs	Testing DOACs effectiveness in outpatient PE treatment	Overall, it is suggested that in-patient treatment of PE patients can be called as Out-patient treatment efficacy was significant
(25)	2015	France	Warfarin	Examination of benefits and drawbacks of use of warfarin vs placebo for Pulmonary embolism	Warfarin treatment was found to be effective to reduce recurrence of PE, reduced occurrence of VTE development and a major bleeding episode.
(17)	2013	Italy	Warfarin vs. NOACs	To conduct a meta-analysis of available data on NOACs and warfarin use for AF patients	Patients with NVAF should be treated with NOACs instead of Warfarin as it can be linked to lower risks like systemic embolism, hemorrhage, major bleeding and mortality

Several studies explore the impact of anticoagulants in pulmonary embolism treatment. An earlier study conducted a retrospective analysis in Sweden to examine DOACs use in the outpatient treatment of PE. It is found that the outpatient treatment of PE has an acceptable efficacy and safety in patients that can be classified as low risk. In a 6-month follow-up in this retrospective study, it was found that of 245 total patients only 1 death occurred, 1 patient suffered major bleeding, 5 suffered minor bleeding, 9 patients were asked to get objective imaging and were found with a recurrent PE, none had a Recurrent VTE and three patients were diagnosed with a new malignancy.<sup>24</sup>

In one of the studies, placebo and warfarin were used to treat PE patients and it was found that patients that received warfarin led to a reduced recurrence of VTE and major bleeding issues.<sup>25</sup> Summary of the various studies performed in the case of PE is shown in table 4.

**Table 4: Summary of Advancement Reports on Treatment of PE**

Author	Year	Country	Medicine-Focused	Purpose	Summary of Findings
(26)	2020	Italy	DOACs	Complications of bleeding could develop with antiviral drug treatments to patient using DOACs as DOAC plasma level was found to be significantly increased	During the antiviral treatment, it is suggested to withhold the DOACs and some parenteral treatment is advised to keep a check on thrombosis
(27)	2021	England	heparin and combination NOACs/DOACs	pharmacologic thromboprophylaxis treatments were better in clinically ill COVID patients	Overall, more research is required and it is suggested to follow pharmacologic thromboprophylaxis treatments
(28)	2020	Italy	LMWH	Low-molecular-weight heparin (LMWH) was recommended for hospitalized patients, in case that no contraindicative symptoms were presented, right at the time of admission.	LMWH to be started at admission of chronically ill COVID-19 patients
(30)	2021	Germany	Overall anticoagulants	It was found that the patients that were on a long-term oral anticoagulant treatment before contracting COVID-19 disease, suffer from a controlled disease as no complications are may be protected from a more severe course of	Switching to heparin and LMWH is suggested during hospitalization and shifting back to VKAs or NOACs can be done on discharge

In terms of the treatment of atrial fibrillation, many advancements are observed in the past decade. One of the studies in Italy found that in patients that are diagnosed with non-valvular AF, NOACs can be more reliable in comparison to Warfarin as NOACs can be linked to a reduction in hemorrhagic stroke rates, rate of systemic embolism, and overall mortality. Moreover, the switch from Warfarin to NOACs was not found to be linked to an increase in major bleeding risks.<sup>17</sup>



## COVID-19 and Anticoagulants

COVID-19 is a complex disease and is not entirely figured out yet, however, it is being associated with a dangerously high incidence of thrombotic complications. Doctors and researchers explain these complications in terms of a unique blend and complex interplay between the endothelial cells, coronaviruses, inflammatory response systems of the body, and the coagulation system.<sup>26</sup> Several guidelines have already been published and intensified dose of thrombosis prophylaxis is being administered to patients admitted to the hospital with COVID-19.<sup>27</sup>

As soon as the International Society on Thrombosis and Haemostasis presented its guidelines for the management of COVID-19 patients by administration of low molecular weight heparin (LMWH), studies on the link between COVID-19 mortality and use of anticoagulants were started. One of the studies discussed the possible techniques for management of coagulopathy in COVID-19 patients according to the guidelines that were presented by the International Society of Thrombosis and Haemostasis (ISTH) on March 25, 2020. In light of these guidelines, low-molecular-weight heparin (LMWH) was recommended for hospitalized patients, in case no contraindicative symptoms were presented.<sup>28</sup>

A retrospective study with 499 patients was conducted and examined 28-day mortality in both users and nonusers of heparin and concluded that heparin users had a better prognosis. Hence, most of the studies up to now indicate that the use of heparin is beneficial in treating COVID-19-induced coagulopathy, followed by continued oral DOACs or Warfarin post-hospital discharge<sup>3</sup>

One of the studies concluded that a preventive dose of low molecular weight heparin in patients with COVID-19 can reduce mortality as it can provide defense against thrombosis even before the symptoms start.<sup>29</sup>

A study was conducted on COVID-19 patients with a history of non-valvular atrial fibrillation and venous thromboembolism. Such patients were already on VKA or DOACs but the researcher indicated that as the use of heparin or LMWH is more advised

currently for COVID-19 patients, rapid tests must be conducted to find out if switching to heparin or LMWH during the hospital stay may be more beneficial for the patients' prognosis. This study overall concluded that the quantity of NVAF and VTE patients that are significantly presented with severe COVID-19 symptoms is very low and it may be due to the anticoagulant impacts of treatments that they were undergoing using DOAC or VKA prior to contracting COVID-19 and heparinization on admission to hospital, however, need of more clinical research was indicated.<sup>30</sup>

## CONCLUSIONS

In this review, an overall comparison was drawn in oral use of warfarin and NOACs or DOACs. The findings were divided into themes of generic comparison, food and drug-based interactions, treatment of major diseases like AF, VTE, and PE, and use in the treatment of COVID-19. The findings are summarized in the table below and predict that NOACs and DOACs are the future of oral anticoagulation treatment as they offer lower risks in many perspectives and better and easier management as well

The review has indicated a strong need for patient education related to the side effects and risks entailed by the continued usage of these medications. Thus, this review study recounts and discusses all possible areas related to the anticoagulants, and studying this research will enable the patients to address key areas related to their treatment and therefore make informed decisions in the future.

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