GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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From Warfarin to DOACs in modern oral anticoagulant therapy

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GSC Biological and Pharmaceutical Sciences, 2026, 35(03), 089-096

Publication history: Received on 02 May 2026; revised on 08 June 2026; accepted on 11 June 2026

Article DOI: https://doi.org/10.30574/gscbps.2026.35.3.0219

Abstract

Oral anticoagulation therapy plays a critical role in the prevention of thromboembolic diseases. For many years, vitamin K antagonists (VKAs) such as warfarin were the standard treatment. However, direct-acting oral anticoagulants (DOACs/NOACs), which have emerged in recent years, have become the treatment of choice. Direct oral anticoagulants (DOACs), also known as non–vitamin K antagonist oral anticoagulants, are a newer class of anticoagulant agents that directly target key components of the coagulation cascade. These agents include oral direct thrombin inhibitors and factor Xa inhibitors. DOACs are currently approved for several clinical indications, including the prevention of stroke in patients with atrial fibrillation, as well as the treatment and secondary prevention of venous thromboembolism.

Compared with traditional anticoagulants such as warfarin, DOACs offer several practical advantages, including predictable pharmacokinetics, fewer dietary and drug interactions, and no routine coagulation monitoring requirements. Emerging evidence from both preclinical and clinical studies suggests that DOACs exhibit a favorable safety profile, particularly with respect to reduced risk of major bleeding events. Despite these benefits, conventional anticoagulants are still widely used in clinical practice due to long-term experience, cost considerations, and specific patient-related factors.

This review provides a comprehensive overview of the pharmacological characteristics of DOACs, with particular emphasis on their mechanisms of action, clinical efficacy, and safety profiles. Furthermore, current laboratory assessment strategies and available reversal agents are discussed in light of recent advances and evidence from experimental and clinical studies.

Keywords: Anticoagulation; Direct oral anticoagulants; Warfarin; Venous thromboembolism

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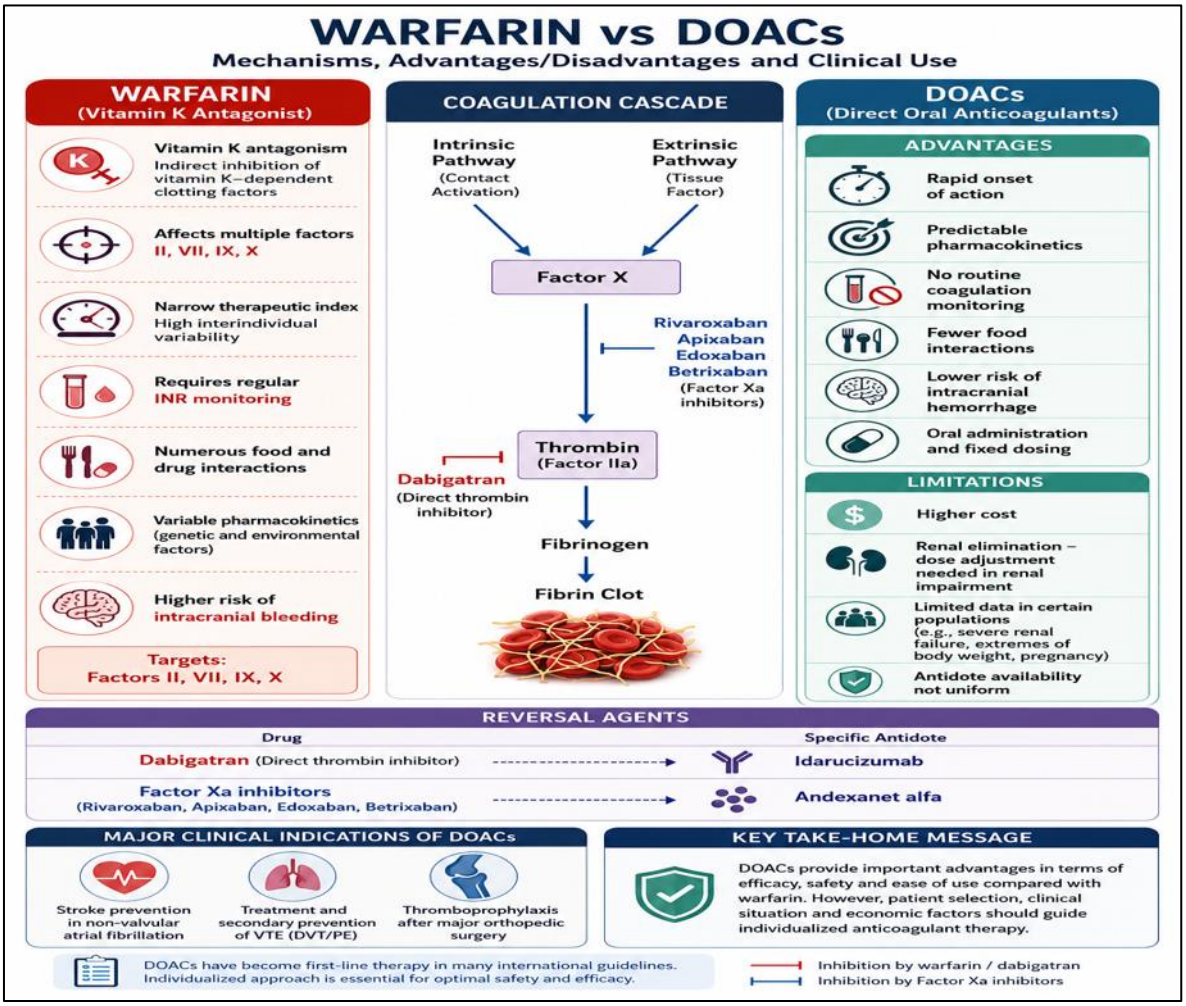
Graphical abstract



1. Introduction

The clinical condition encompassing deep vein thrombosis and pulmonary embolism is recognized as a major cause of morbidity and mortality among vascular diseases. Venous thromboembolism (VTE) is a significant health issue that affects more than 10 million people worldwide each year and is considered the third most common acute cardiovascular syndrome after myocardial infarction and stroke [1]. For many years, the primary approach to managing this clinical condition has been the use of vitamin K antagonists, which indirectly affect the coagulation cascade. However, the narrow therapeutic range of these agents, their variable pharmacokinetic properties among individuals, common drug and food interactions, and the need for regular laboratory monitoring are among the primary factors limiting their clinical use [2,3].

While dabigatran inhibits thrombin (Factor IIa), rivaroxaban, apixaban, edoxaban, and betrixaban target Factor Xa. These medications have been in clinical use since the 2010s and are now included among the first-line treatments in many international guidelines [4,5].

In clinical practice, DOACs are widely used for thrombosis prophylaxis following major orthopedic surgeries, to reduce the risk of thromboembolism in non-valvular atrial fibrillation, and in the treatment of VTE [6-8]. The advantages of oral administration, rapid onset of action, and predictable pharmacological properties, which eliminate the need for routine coagulation monitoring, make these agents easier to use. In addition, their lower risk of intracranial hemorrhage compared with conventional anticoagulants is considered a significant clinical advantage [9,10].

However, there are also some limitations to DOAK treatment. The need for dose adjustments or usage restrictions in patients with advanced renal insufficiency, the lack of sufficient clinical data in certain patient groups, and the relatively

high cost of these medications are among the factors influencing their use [11,12]. Although specific reversal agents have been developed (such as idarucizumab for dabigatran and andexanet alfa for Factor Xa inhibitors), access to these treatments is not equally available at every healthcare facility [13].

In conclusion, DOACs offer significant convenience and safety benefits in anticoagulant therapy. However, an individualized approach should be adopted, taking into account patient selection, clinical condition, and economic factors.

1.1. Pharmacodynamics and Pharmacokinetics

Table 1 Pharmacokinetic properties [14-16]

	Dabigatran	**Rivaroxaban**	**Apixaban**	**Warfarin**
Bioavailability	~6–7%	80–100%	~50%	~95-100%
T1/2 (half-life)	12–18 h	5–9 h (↑ elderly)	~12 h	36–42 h
Plasma protein binding	~35%	90–95%	~93%	~99%
Renal excretion	~80%	~66%	~27%	Minimal
Fecal excretion	~20%	~28%	~46–56%	Biliary
Antidote / Reversal	Idarucizumab	Andexanet alfa	Andexanet alfa	Vitamin K

1.1.1. Warfarin

Warfarin is a classic anticoagulant administered orally that affects the coagulation cascade through indirect mechanisms. It exerts its effect by inhibiting the vitamin K epoxide reductase enzyme, thereby reducing the synthesis of vitamin K-dependent clotting factors (Factors II, VII, IX, and X) in the liver [17,18]. Because of this mechanism, warfarin's anticoagulant effect does not take effect immediately; the clinical effect generally develops within a few days, depending on the half-life of the clotting factors already present in the circulation [19,20].

From a pharmacokinetic perspective, warfarin has high oral bioavailability (over 95%) and is rapidly absorbed from the gastrointestinal tract [21]. Maximum plasma concentrations are typically reached within 1–2 hours. The plasma protein binding rate is very high (>99%), and the volume of distribution is low. Warfarin is metabolized in the liver primarily by the cytochrome P450 enzyme system, particularly CYP2C9; this sets the stage for numerous drug interactions. In addition, genetic polymorphisms (particularly variations in CYP2C9) lead to significant differences in dosage requirements among individuals [22].

The elimination half-life is long, averaging around 36–42 hours, which results in the anticoagulant effect persisting even after the drug's active effects have worn off. To ensure therapeutic efficacy and safety during warfarin therapy, monitoring of the INR (International Normalized Ratio) is required, and dose adjustments are made based on this parameter [23,24].

A significant advantage in clinical practice is that warfarin's anticoagulant effect is reversible. To this end, Vitamin K1 (phytonadione) is used to restore the synthesis of clotting factors [25]. In emergencies, prothrombin complex concentrates (PCC) or fresh frozen plasma (FFP) may be administered for a faster effect. Although FFP provides immediate clotting factors, its preparation requires large volumes and time; this can pose a problem in emergencies. However, warfarin's narrow therapeutic range, numerous drug and food interactions, and the need for regular laboratory monitoring are significant factors that complicate its clinical use [24].

1.1.2. Oral Direct Thrombin (Factor IIa) Inhibitors

Dabigatran is administered orally as a prodrug (dabigatran etexilate) rather than in its clinically active form and is rapidly converted to active dabigatran by esterases in the gastrointestinal tract [26]. Since this transformation occurs independently of the cytochrome P450 enzyme system, it offers advantages in terms of classical drug interactions. Although the drug's oral bioavailability is approximately 6–7% and is considered relatively low, therapeutic efficacy is achieved at appropriate doses, and a critical step in the coagulation cascade is effectively inhibited through direct thrombin inhibition [27].

Pharmacokinetically, maximum plasma concentration is reached within 1–3 hours, and this process is not significantly affected by age or gender [28]. The drug is primarily excreted from the body via the kidneys; therefore, kidney function is a key factor in treatment planning, and dose adjustment is necessary, particularly in patients with renal insufficiency [29]. The volume of distribution is approximately 50–70 L, and the plasma protein binding rate is approximately 35% [30]. Steady-state plasma levels are typically reached within 2–3 days, while the elimination half-life ranges from 12 to 17 hours on average. Dabigatran's predictable pharmacokinetic properties eliminate the need for routine coagulation monitoring. However, advanced age, comorbidities, and drug interactions should be carefully evaluated [31,32].

A clinically significant advantage is that the anticoagulant effect of dabigatran can be reversed with a specific antidote. Idarucizumab, which is used for this purpose, binds to dabigatran with high affinity, rapidly neutralizing its free and active form, and provides effective reversal, particularly in cases of life-threatening bleeding, situations requiring emergency surgery, and cases of overdose [33,34].

1.1.3. Oral Direct Factor Xa Inhibitors

Factor Xa inhibitors provide effective anticoagulation by targeting the central step in the formation of thrombin within the coagulation cascade, thereby reducing the risk of thrombosis [35]. Rivaroxaban, apixaban, edoxaban, and betrixaban, which are included in this group, are widely preferred in clinical practice due to their predictable pharmacokinetic properties and fixed-dose regimens [36].

Rivaroxaban is rapidly absorbed after oral administration and typically reaches peak plasma concentrations within 2–4 hours. Bioavailability increases, particularly when taken with food at high doses, and exceeds 80% [37,38]. It is primarily metabolized in the liver via the CYP3A4/5 and CYP2J2 enzymes, and is also associated with the P-glycoprotein transport system. Elimination occurs via both renal and hepatobiliary pathways. Rivaroxaban is primarily metabolized in the liver; two-thirds of the absorbed dose is processed via oxidative and hydrolytic pathways [39]. Approximately 36% of the dose is excreted unchanged via the kidneys. While the elimination half-life of rivaroxaban is approximately 7–11 hours in younger individuals, it has been reported to increase to 11–13 hours in the elderly population [38,40].

Edoxaban is rapidly absorbed after oral administration, reaching peak plasma levels within approximately 1–2 hours, and has moderate to high bioavailability [45,46]. It is minimally metabolized and is excreted largely unchanged. A significant portion of its elimination occurs via the kidneys. Its half-life is 10–14 hours, making it suitable for once-daily dosing [47].

Unlike other Factor Xa inhibitors, betrixaban undergoes minimal hepatic metabolism and is excreted largely unchanged [48,49]. Although its oral bioavailability is relatively low, its long half-life (approximately 19–27 hours) ensures a prolonged duration of action [50]. Elimination occurs primarily via the hepatobiliary route and through P-glycoprotein. Due to these characteristics, it has been developed specifically for extended thromboprophylaxis in hospitalized medical patients [49].

A key advantage of these agents in current clinical practice is the availability of specific reversal options. The effects of Factor Xa inhibitors can be rapidly reversed with andexanet alfa, a recombinant modified Factor Xa analog [51].

1.2. Indications and Contraindications

Table 2 Indications and Contraindications of Direct Oral Anticoagulants (DOACs) and Warfarin [52-56,19]

Drug / Group	Main Indications	Contraindications / Special Considerations	
Dabigatran	Stroke and systemic embolism prevention in non-valvular atrial fibrillation Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) Prevention of recurrent venous thromboembolism (VTE)	Contraindicated in patients with mechanical heart valves Use with caution in renal impairment due to renal elimination	
Rivaroxaban / Apixaban / Edoxaban / Betrixaban	Stroke and systemic embolism prevention in non-valvular atrial fibrillation	Active major bleeding Severe hepatic disease	

	Treatment of acute DVT and PE Prevention of recurrent VTE	Use with caution in advanced renal impairment	
Warfarin	Mechanical heart valves (DOACs contraindicated) Atrial fibrillation with moderate-to-severe mitral stenosis Treatment and prevention of VTE when DOACs are unsuitable Long-term anticoagulation	Severe renal impairment (GFR < 15 mL/min) Antiphospholipid syndrome (especially triple-positive patients)	

DOACs are increasingly preferred due to predictable pharmacokinetics and fewer interactions; however, warfarin remains essential in specific clinical conditions.

Although DOACs have more predictable pharmacokinetic properties and a lower potential for drug interactions compared to warfarin, they are not entirely free of interactions [57]. In contrast, while DOACs have fewer drug interactions, they may be affected by strong CYP3A4 and P-glycoprotein inducers or inhibitors, depending on the specific drug. Certain herbal products can also affect these pathways. Continuous monitoring of these interactions is critical for the safe use of oral anticoagulants [57,58].

In the pharmacokinetics of DOAKs, P-glycoprotein (P-gp) and cytochrome P450 (particularly CYP3A4) systems play key roles. For this reason, while potent inhibitors (such as azole antifungals and protease inhibitors) may increase the risk of bleeding by raising plasma levels [19], inducers (such as rifampin and St. John's wort) may increase the risk of thromboembolism by lowering drug levels [56]. In addition, while taking rivaroxaban in high doses with food increases its bioavailability, dabigatran absorption may be delayed; apixaban and edoxaban, however, are not significantly affected by food [37,45,56].

From a pharmacodynamic perspective, the use of DOACs in combination with antiplatelet agents or nonsteroidal anti-inflammatory drugs significantly increases the risk of bleeding. Recent clinical studies show that the combination of a DOAC and a P2Y12 inhibitor is associated with a lower risk of bleeding compared to triple therapy regimens containing warfarin, particularly in patients with atrial fibrillation and those undergoing percutaneous coronary intervention [59,60].

Warfarin, on the other hand, has a much broader spectrum of drug interactions because it is metabolized via cytochrome P450 (particularly CYP2C9) and is directly linked to vitamin K [61,62]. Changes in dietary vitamin K intake, as well as antibiotics, antifungals, and many cardiovascular medications, can either increase or decrease the effects of warfarin. Therefore, monitoring the INR is essential, and dose adjustments must be made frequently and on an individualized basis. [62,63].

2. Conclusion

Recent developments in the field of anticoagulant therapy have led to a significant paradigm shift, particularly with the introduction of direct oral anticoagulants (DOACs) into clinical practice. These agents target specific steps in the coagulation cascade, offering a more predictable efficacy profile and are easier to use compared to traditional vitamin K antagonists. In particular, the fact that they can be administered at a fixed dose and do not require routine laboratory monitoring provides a significant advantage in terms of patient compliance and treatment continuity.

Factor Xa inhibitors and direct thrombin inhibitors are at least as effective as warfarin in the treatment and prevention of venous thromboembolic events, and in some studies have even been associated with a lower risk of major bleeding. In particular, the reduced risk of intracranial hemorrhage is a key factor highlighting the safety profile of DOACs. For this reason, current international guidelines frequently recommend DOACs as first-line therapy for appropriate patient groups. However, it is also clear that DOAKs are not ideal for all patient populations. For patients with mechanical heart valves, individuals with severe mitral stenosis, and those with specific conditions such as antiphospholipid syndrome, vitamin K antagonists remain the preferred treatment option. In addition, renal function must be carefully assessed in patients receiving agents that are primarily excreted by the kidneys. The high cost of medications and limited access to specific antidotes in some centers are other significant practical constraints. Despite all its drawbacks, warfarin remains

an important treatment option due to its long history of clinical use, broad range of indications, and low cost. However, the need for frequent INR monitoring and the presence of numerous drug and dietary interactions limit its use in modern treatment approaches.

In conclusion, DOACs have become increasingly preferred agents that offer significant advantages in the management of venous thromboembolic diseases today. However, the choice of optimal treatment should be tailored to the individual patient, taking into account their specific clinical characteristics, comorbidities, renal function, and economic factors. Future large-scale studies will provide clearer data on the safety and long-term outcomes of DOAK use, particularly in specific patient groups.

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