

Antithrombotic Therapy in Atrial Fibrillation: A Review of Current Guidelines, Anticoagulant Options, and Bleeding Risk

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Abstract

Atrial fibrillation (AF) increases thromboembolic risk, primarily stroke, due to stasis and abnormal atrial function. Antithrombotic therapy is central to AF management to prevent stroke and systemic embolism. Guidelines historically recommended vitamin K antagonists like warfarin, but the introduction of direct oral anticoagulants dabigatran, rivaroxaban, apixaban, edoxaban has shifted practice. These agents offer predictable pharmacokinetics and reduced need for monitoring. However, anticoagulation carries bleeding risk, particularly intracranial and gastrointestinal hemorrhage. Balancing ischemic prevention against bleeding risk remains a clinical challenge, guided by risk scores such as CHA₂DS₂-VASc for stroke and HAS-BLED for bleeding. Current guidelines from ESC, ACC/AHA, and AHA/ASA recommend oral anticoagulation for AF patients with CHA₂DS₂-VASc ≥ 2 in men and ≥ 3 in women. DOACs are preferred over warfarin in non-valvular AF due to comparable or superior efficacy and lower rates of intracranial hemorrhage. Meta-analyses show apixaban has the lowest bleeding risk among DOACs, while dabigatran 150 mg has higher gastrointestinal bleeding but lower stroke risk. Warfarin remains an option for mechanical valves and severe mitral stenosis. Bleeding risk assessment using HAS-BLED identifies modifiable factors like uncontrolled hypertension and concomitant antiplatelet use. Recent trials support low-dose DOACs in high bleeding risk patients, though efficacy may be reduced. Left atrial appendage closure is considered for patients with contraindications to anticoagulation. Real-world data confirm DOAC adherence improves outcomes, but renal function monitoring is essential to avoid accumulation and bleeding. Antithrombotic therapy in AF should be individualized based on stroke and bleeding risk. DOACs are first-line for most patients with non-valvular AF due to favorable safety profiles. Ongoing evaluation of bleeding risk and renal function is critical. Future research should refine risk stratification and explore safer anticoagulant strategies for high-risk populations. Guideline adherence improves outcomes, but clinical judgment remains essential in balancing efficacy and safety.

Keywords: Atrial fibrillation, Anticoagulation, Antithrombotic therapy, Bleeding risk, and Antagonist

INTRODUCTION

The most common sustained cardiac arrhythmia seen in clinical practice and the most significant and rapidly rising global public health concern. In recent decades, its prevalence has soared, which is expected given that the population is living longer; other causes of cardiovascular

death have decreased and there is an increase in other risk factors such as hypertension, diabetes mellitus, metabolic syndrome and obesity (Ding *et al.*, 2020).

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52.55 million were estimated to be living with atrial fibrillation (AF) or atrial flutter in 2021 compared with 1990 and this figure is up by 137% (Cheng *et al.* 2024).

There are also studies that suggest by the late 2010's this figure stood at nearly 59 million worldwide and the number will continue to rise at a similar or greater rate for many years to come especially in societies with an increasingly aging population (Linz *et al.* 2024). In the USA alone nearly 4% of adults suffer from this condition with figures for the over 90s reaching over 24% (Oltman *et al.* 2024) and in all demographics it is predicted that there is a lifetime risk of nearly 1 in 3 after the age of 40/45.

This epidemic is leading to a greater burden on mortality, morbidity and also costs. AF patients are associated with higher levels of stroke, cognitive decline/dementia, heart failure and lower quality of life. This condition is a cause of 1.5-2 fold increased cardiovascular mortality (Karatela *et al.* 2025) and these causes billions of dollars in expenditure as a result of treatment of stroke, rhythm control therapies and anti-coagulation monitoring.

The heightened thromboembolic risk in AF stems directly from the disruption of normal atrial physiology, best understood through Virchow's triad of stasis, endothelial dysfunction, and hypercoagulability. In sinus rhythm, organized atrial contraction ensures complete emptying of the left atrium and particularly the left atrial appendage. During AF, however, rapid and disorganized electrical activity (typically 350–600 impulses per minute) results in ineffective mechanical contraction and blood stasis within the atrium, most prominently in the trabeculated left atrial appendage. This stasis is compounded by progressive atrial remodeling, often described as atrial myopathy or cardiopathy. Chronic or recurrent AF promotes inflammation, oxidative stress, fibrosis, and endothelial or endocardial dysfunction, which impair the natural antithrombotic properties of the atrial wall. Concurrently, a prothrombotic state emerges through upregulation of coagulation factors, enhanced platelet reactivity, and reduced fibrinolysis. These changes collectively fulfill Virchow's triad, explaining why both paroxysmal and persistent forms of AF elevate thromboembolic risk, with the degree of risk often correlating with the overall AF burden (Watson *et al.*, 2009; Ding *et al.*, 2020).

The clinical consequences of this prothrombotic milieu are profound. Nonvalvular AF increases the risk of ischemic stroke approximately fivefold compared with individuals in sinus rhythm, while valvular AF associated with conditions such as moderate-to-severe mitral stenosis elevates this risk even higher (Ding *et al.*, 2020). AF-related strokes tend

to be more severe, resulting in greater long-term disability, higher recurrence rates, and increased mortality. Beyond stroke and systemic embolism, AF contributes to other thromboembolic events and exacerbates heart failure, while also being linked to cognitive decline (Win *et al.*, 2016).

Given these risks, oral anticoagulation therapy has become the cornerstone of stroke prevention in patients with AF. Landmark clinical trials have consistently shown that anticoagulation reduces stroke risk by roughly two-thirds relative to placebo or antiplatelet therapy. Contemporary guidelines strongly endorse its use in patients whose estimated annual thromboembolic risk exceeds 2%, typically assessed through validated tools such as the CHA₂DS₂-VASc score. Direct oral anticoagulants (DOACs) are now preferred over vitamin K antagonists such as warfarin in most eligible patients because of their superior efficacy, lower risk of intracranial hemorrhage, and greater convenience without the need for routine coagulation monitoring (Joglar *et al.*, 2024).

Nevertheless, antithrombotic therapy introduces a persistent and challenging clinical dilemma. While effectively mitigating thrombotic risk, anticoagulation inevitably heightens the potential for bleeding complications, ranging from nuisance bleeds to major or life-threatening events such as intracranial or gastrointestinal hemorrhage (Win *et al.*, 2016). This risk is particularly pronounced in elderly patients, those with renal impairment, prior bleeding history, or concurrent use of other antithrombotic agents. Consequently, clinicians must continuously balance the absolute benefits of stroke prevention against individualized bleeding hazards. Fear of bleeding frequently leads to undertreatment, resulting in preventable strokes, whereas inappropriate therapy in truly low-risk patients exposes them to unnecessary harm. Tools such as the HAS-BLED score assist in this assessment, yet the ultimate decision requires shared decision-making that incorporates patient preferences, life expectancy, comorbidity burden, and modifiable risk factors ((Joglar *et al.*, 2024).

The aim of this review is to provide a comprehensive, evidence-based synthesis of current antithrombotic strategies in atrial fibrillation. Drawing from the most recent major guidelines, including the 2023 ACC/AHA/ACCP/HRS recommendations, as well as high-quality meta-analyses and indexed studies, this study examines contemporary risk stratification approaches, compares available anticoagulant options with their respective efficacy and safety profiles, and offers practical guidance

on bleeding risk evaluation and mitigation. By presenting a balanced, clinically oriented perspective grounded in the latest data, this review seeks to support healthcare providers in optimizing therapy for diverse AF populations while identifying remaining uncertainties and future research directions in this rapidly evolving field.

CURRENT GUIDELINES FOR ANTITHROMBOTIC THERAPY IN ATRIAL FIBRILLATION

Current major guidelines provide structured, evidence-based frameworks for antithrombotic therapy in patients with atrial fibrillation. The 2023 American College of Cardiology/American Heart Association/American College of Chest Physicians/Heart Rhythm Society (ACC/AHA/ACCP/HRS) guideline and the 2024 European Society of Cardiology (ESC) guideline represent the most authoritative and up-to-date sources (Joglar *et al.*, 2024; Van Gelder *et al.*, 2024). These documents emphasize individualized risk assessment, preference for direct oral anticoagulants in most patients, and a balanced approach that prioritizes stroke prevention while addressing bleeding hazards through modifiable risk factor optimization rather than blanket withholding of therapy.

STROKE RISK ASSESSMENT

Stroke risk stratification forms the foundation of decision-making for antithrombotic therapy. Both guidelines endorse the CHA₂DS₂-VASc score as the primary validated tool for estimating annual thromboembolic risk in patients with nonvalvular atrial fibrillation (Joglar *et al.*, 2024; Van Gelder *et al.*, 2024). The score incorporates congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, prior stroke or transient ischemic attack (2 points), vascular disease, age 65–74 years, and female sex. According to the 2023 ACC/AHA/ACCP/HRS guideline, anticoagulation decisions should be guided by estimated yearly thromboembolic risk, with a threshold of approximately $\geq 2\%$ per year generally warranting therapy (Joglar *et al.*, 2024). This corresponds roughly to a CHA₂DS₂-VASc score of ≥ 2 in men or ≥ 3 in women. The guideline allows flexibility beyond strict score cutoffs, encouraging consideration of additional risk modifiers or alternative validated scores when uncertainty exists, particularly in patients with intermediate risk.

The 2024 ESC guideline similarly relies on clinical risk factors but has evolved toward a simplified CHA₂DS₂-VA score (removing the sex category as a standalone point) while maintaining emphasis on a default strategy of offering oral anticoagulation to eligible patients except those at truly low risk (Van Gelder *et al.*, 2024). Both guidelines stress that the thromboembolic risk associated with atrial fibrillation persists across paroxysmal, persistent, and

permanent patterns, as well as in device-detected atrial high-rate episodes when risk factors are present. The ESC framework integrates this assessment within the broader AF-CARE pathway, placing comorbidity and risk factor management first, followed by stroke avoidance (Van Gelder *et al.*, 2024).

BLEEDING RISK ASSESSMENT

Bleeding risk assessment is essential for informed shared decision-making but should not serve as the sole reason to withhold anticoagulation in patients with elevated thromboembolic risk. The HAS-BLED score remains the most widely validated and practical tool endorsed across guidelines (Pisters *et al.*, 2010). This score evaluates hypertension, abnormal renal or liver function, prior stroke, bleeding history or predisposition, labile international normalized ratio (for patients on vitamin K antagonists), elderly age (>65 years), and concomitant drugs or alcohol excess. A score of ≥ 3 identifies patients at higher risk of major bleeding, prompting closer monitoring and aggressive correction of modifiable factors such as uncontrolled hypertension, unnecessary concomitant antiplatelet agents, or excessive alcohol intake.

The 2023 ACC/AHA/ACCP/HRS guideline explicitly states that bleeding risk scores should not be used in isolation to determine anticoagulation eligibility but rather to identify and address reversible risks (Joglar *et al.*, 2024). Similarly, the 2024 ESC guideline advises against using bleeding scores to exclude patients from therapy; instead, they recommend focusing on modifiable bleeding risks while proceeding with anticoagulation when thromboembolic benefit outweighs harm (Van Gelder *et al.*, 2024). Both documents highlight that fear of bleeding frequently results in undertreatment, leading to preventable strokes.

INDICATIONS AND CONTRAINDICATIONS FOR ANTICOAGULATION

Guidelines converge on strong recommendations for oral anticoagulation in patients whose estimated annual thromboembolic risk reaches or exceeds 2%. Direct oral anticoagulants are preferred over vitamin K antagonists in most patients with nonvalvular atrial fibrillation due to superior safety regarding intracranial hemorrhage and comparable or better efficacy (Joglar *et al.*, 2024; Van Gelder *et al.*, 2024). Exceptions include patients with moderate-to-severe mitral stenosis or mechanical heart valves, where vitamin K antagonists remain the standard. Antiplatelet therapy alone is no longer recommended for stroke prevention in atrial fibrillation.

Contraindications to long-term oral anticoagulation include active major bleeding, severe uncontrolled

hypertension, or conditions with prohibitive bleeding risk where left atrial appendage occlusion may be considered as an alternative (Class 2a recommendation in the 2023 ACC/AHA guideline) (Joglar *et al.*, 2024). For

patients undergoing percutaneous coronary intervention, guidelines advocate minimized duration of triple therapy and early transition to dual therapy to reduce bleeding. Both major guidelines stress shared decision-making,

Table1. Current guideline recommendations for anticoagulation in AF

Clinical Situation	Recommended Therapy	Guideline Source	Recommendation Strength
CHA ₂ DS ₂ -VASc ≥ 2 (men) or ≥ 3 (women)	Oral anticoagulation (DOAC preferred)	ACC/AHA 2023 & ESC 2024	Strong
Intermediate risk (CHA ₂ DS ₂ -VASc 1 men/2 women)	Consider anticoagulation after shared decision-making	ACC/AHA 2023 & ESC 2024	Moderate
Low risk (CHA ₂ DS ₂ -VASc 0 men/1 women)	No anticoagulation	ACC/AHA 2023 & ESC 2024	Strong
Mechanical valves or moderate-severe mitral stenosis	Vitamin K antagonist	Both guidelines	Strong
High bleeding risk (HAS-BLED ≥ 3)	Anticoagulation with risk modification and monitoring	Both guidelines	Conditional

Sources: Joglar *et al.* (2024); Van Gelder *et al.* (2024)

incorporating patient preferences, life expectancy, and values, particularly in borderline or complex cases (Joglar *et al.*, 2024; Van Gelder *et al.*, 2024).

Current antithrombotic management in atrial fibrillation centers on oral anticoagulants that target key steps in the coagulation cascade. Vitamin K antagonists have historically served as the standard therapy, while direct oral anticoagulants now predominate due to their targeted mechanisms, predictable pharmacokinetics, and favorable efficacy-safety profiles established in large-scale trials and meta-analyses (Carnicelli *et al.*, 2022; Karakasis *et*

al., 2024). Antiplatelet agents play a very limited role in stroke prevention for atrial fibrillation.

WARFARIN AND TRADITIONAL ANTICOAGULATION

Warfarin is a vitamin K antagonist that exerts its anticoagulant effect by interfering with the vitamin K cycle. In the normal cycle, vitamin K hydroquinone (VK-H₂) acts as a cofactor for the γ -carboxylation of glutamic acid residues on clotting factor precursors (II, VII, IX, X, and proteins C, S, Z). This carboxylation, catalyzed by the carboxylase enzyme, enables these factors to bind calcium

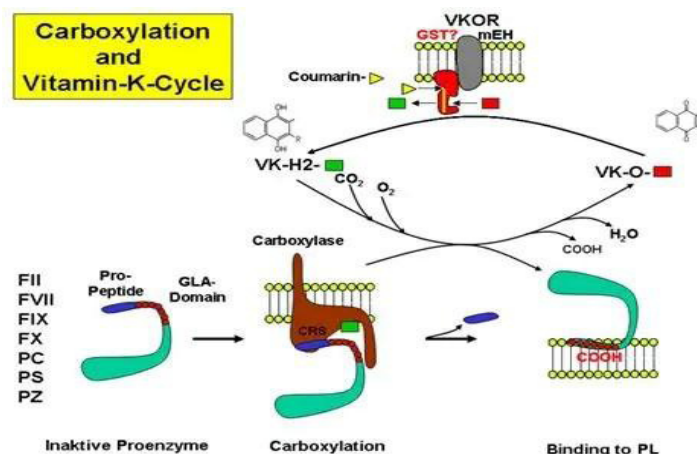


Fig1. Carboxylation and vitamin K cycle

Sources: Hindley *et al.* (2023)

and attach to phospholipid surfaces, which is essential for effective coagulation. During this process, VK-H₂ is oxidized to vitamin K epoxide (VK-O), which must be

recycled back to VK-H₂ by the enzyme vitamin K epoxide reductase (VKOR) (Hindley *et al.*, 2023).

As shown in Fig. 1, Warfarin blocks VKOR, preventing

the regeneration of VK-H₂. Without sufficient VK-H₂, the carboxylase enzyme cannot activate clotting factors, leaving them in an undercarboxylated, inactive state. This results in impaired coagulation and a reduced ability to form fibrin clots. Because Warfarin acts indirectly by depleting active vitamin K, its onset of action is gradual (4–5 days), allowing time for existing functional clotting factors to degrade (Carnicelli *et al.*, 2022). Clinically, Warfarin therapy requires frequent INR monitoring to maintain a therapeutic range of 2.0–3.0. Its pharmacokinetics are highly variable due to genetic polymorphisms (notably CYP2C9 and VKORC1), numerous drug–drug and food interactions (such as antibiotics or vitamin K-rich foods), and a narrow therapeutic window (Ding *et al.*, 2020). These factors make Warfarin effective but challenging to manage, necessitating individualized dosing and careful follow-up.

In patients with atrial fibrillation, warfarin reduces stroke risk by approximately 60–70% compared with placebo but carries a substantial bleeding risk, including intracranial hemorrhage rates of around 0.7–1.0% per year in clinical trials. Real-world time in therapeutic range often remains suboptimal, further limiting effectiveness (Carnicelli *et al.*, 2022).

DIRECT THROMBIN INHIBITORS

Dabigatran etexilate is an orally administered prodrug that is rapidly converted by esterases into its active form, dabigatran. Unlike traditional anticoagulants that act indirectly, dabigatran binds directly and reversibly to thrombin (Factor IIa). In the coagulation cascade shown in Fig. 2, thrombin sits at the critical junction of the common pathway, converting fibrinogen (Factor I) into fibrin (Factor Ia) and amplifying clot formation by activating platelets. By occupying thrombin's active site, dabigatran prevents both fibrin generation and thrombin-induced platelet aggregation, effectively halting clot propagation (Ferri *et al.*, 2022).

Pharmacologically, dabigatran has rapid absorption, reaching peak plasma concentration within 1–3 hours, and a half-life of 12–17 hours. Its elimination is primarily renal (~80%), which means dosing must be adjusted in patients with moderate renal impairment (CrCl 30–50 mL/min) and it is contraindicated in severe renal failure (CrCl <30 mL/min) (Hindley *et al.*, 2023). This dependence on renal clearance distinguishes dabigatran from warfarin, which is metabolized hepatically and requires INR monitoring. Clinically, dabigatran offers predictable anticoagulation

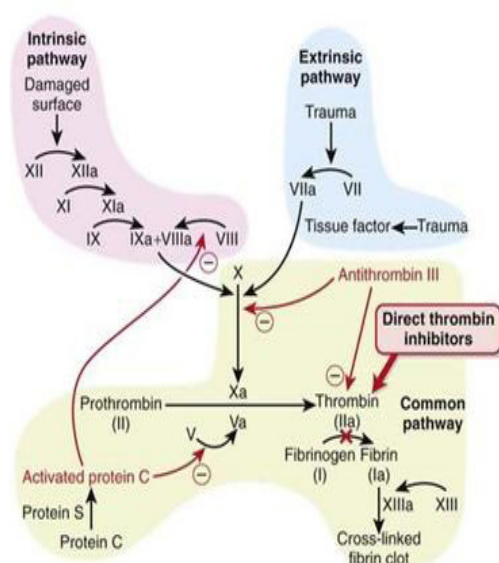


Fig2. Coagulation cascade and direct thrombin inhibition Figure 2 shows how dabigatran blocks thrombin (Factor IIa) within the common pathway, preventing fibrin formation and platelet activation.

Sources: Hindley *et al.* (2023)

without routine monitoring, but its use requires careful patient selection to balance the stroke prevention benefit against the bleeding risk burden, particularly gastrointestinal bleeding (Ferri *et al.*, 2022).

In large trials and meta-analyses, dabigatran (150 mg twice daily) demonstrated superiority to warfarin for

stroke/systemic embolism prevention, with significant reductions in intracranial hemorrhage. The 110mg dose showed similar efficacy with lower bleeding rates. Major bleeding risk was comparable or lower than warfarin, though gastrointestinal bleeding was higher with the 150 mg dose (Karakasis *et al.*, 2024; Zhang *et al.*, 2024).

FACTOR Xa INHIBITORS

Factor Xa inhibitors such as apixaban, rivaroxaban, and edoxaban act by selectively and reversibly inhibiting Factor Xa, a pivotal enzyme in the coagulation cascade. As shown in Fig. 3 (Coagulation Cascade and Factor Xa Inhibition), both the intrinsic and extrinsic pathways converge at Factor Xa, which combines with Factor Va to convert prothrombin (Factor II) into thrombin (Factor IIa). By blocking Factor Xa, these drugs prevent thrombin generation, thereby halting the conversion of fibrinogen into fibrin and ultimately suppressing thrombus formation. This direct inhibition produces a rapid onset of action, with

peak plasma levels achieved within 1–4 hours, and shorter half-lives compared with warfarin (Hindley *et al.*, 2023).

Among the oral Factor Xa inhibitors, apixaban is administered twice daily and has approximately 27% renal elimination. It consistently demonstrates the most favorable bleeding profile among DOACs, significantly reducing stroke/systemic embolism, major bleeding, and intracranial hemorrhage compared with warfarin (Carnicelli *et al.*, 2022; Zhang *et al.*, 2024). Rivaroxaban, taken once daily with food (for the 20 mg dose), undergoes about 36% renal clearance. It shows comparable efficacy to warfarin for stroke prevention, with reduced intracranial

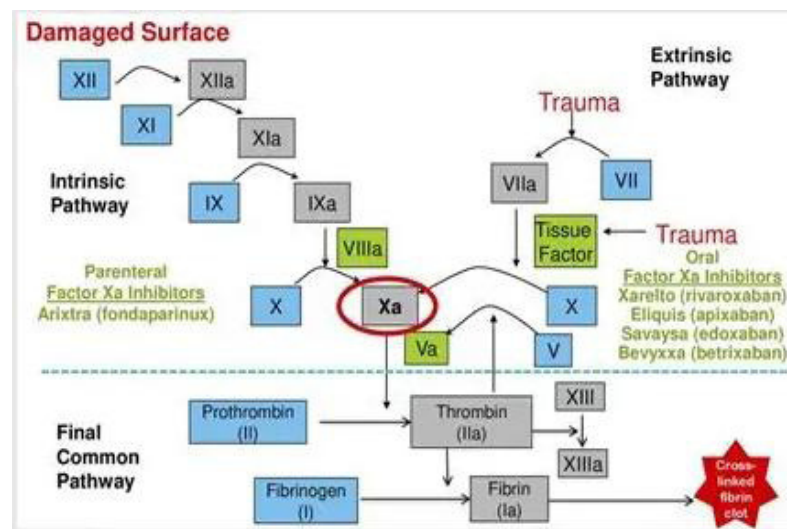


Fig3.Coagulation cascade and factor Xa inhibition

Source: Karakasis *et al.* (2024)

hemorrhage, though gastrointestinal bleeding risk may be slightly higher than with apixaban (Karakasis *et al.*, 2024). Edoxaban, dosed once daily with 50% renal elimination, is unique in that it is not recommended for patients with CrCl >95 mL/min due to reduced efficacy. Nevertheless, it achieves lower intracranial hemorrhage rates than warfarin while maintaining stroke prevention efficacy (Zhang *et al.*, 2024; Hindley *et al.*, 2023).

Overall, DOACs as a class reduce stroke/systemic embolism (HR 0.81), death (HR 0.92), and intracranial bleeding (HR 0.45) compared with warfarin, while maintaining similar or lower rates of major bleeding (Carnicelli *et al.*, 2022). This balance of efficacy and safety has made Factor Xa inhibitors the preferred choice in many patients with atrial fibrillation requiring anticoagulation.

COMBINATION THERAPY AND LEFT ATRIAL APPENDAGE OCCLUSION

Antiplatelet agents (aspirin or dual antiplatelet therapy)

have a limited role in atrial fibrillation stroke prevention. They are markedly inferior to oral anticoagulation and are no longer recommended as monotherapy for patients with elevated CHA₂DS₂-VASc scores (Kumbhani *et al.*, 2021).

In patients requiring concomitant antiplatelet therapy (e.g., recent percutaneous coronary intervention), guidelines favor minimizing triple therapy duration and transitioning to dual therapy (oral anticoagulant plus P2Y₁₂ inhibitor, preferably clopidogrel) to reduce bleeding risk while maintaining efficacy (Kumbhani *et al.*, 2021).

For patients with contraindications to long-term oral anticoagulation, left atrial appendage occlusion provides a nonpharmacologic alternative. Percutaneous devices reduce stroke risk compared with no anticoagulation and serve as a reasonable option in selected patients after shared decision-making (Goldsweigt *et al.*, 2025).

BLEEDING RISKS AND SAFETY CONSIDERATIONS

Bleeding remains the primary safety concern with

antithrombotic therapy in atrial fibrillation, requiring careful balance between thromboembolic risk reduction and hemorrhage potential. Major bleeding complications

encompass events that are fatal, involve critical sites, or necessitate transfusion or intervention. Gastrointestinal bleeding and intracranial hemorrhage constitute the most

Table2. Comparison of major anticoagulants used in AF

Drug	Mechanism	Advantages	Limitations	Major Bleeding Risk
Warfarin	V i t a m i n K antagonist	Established use; reversible	Variable response; monitoring required; interactions	Higher ICH
Dabigatran	Direct thrombin inhibitor	Rapid onset; renal clearance	High renal dependence; GI bleeding	Similar or lower than warfarin
Apixaban	FactorXa inhibitor	Best bleeding profile; BID dosing	Twice daily	Lowest among DOACs
Rivaroxaban	FactorXa inhibitor	Once daily	Food requirement; GI bleeding	Similar to warfarin
Edoxaban	FactorXa inhibitor	Once daily	Not for high CrCl	Low ICH

Sources:Kumbhani *et al.* (2021); Goldsweig *et al.* (2025).

clinically significant subtypes (Karakasis *et al.*, 2024; Zhang *et al.*, 2024).

GASTROINTESTINAL BLEEDING RISKS

Gastrointestinal bleeding occurs more frequently with certain direct oral anticoagulants compared with warfarin. Standard-dose direct oral anticoagulants were associated with a higher hazard of major gastrointestinal bleeding compared with warfarin (HR 1.31 [95% CI, 1.08–1.57]) (Carnicelli *et al.*, 2022). Among individual agents, rivaroxaban and higher-dose dabigatran (150 mg) demonstrate elevated gastrointestinal bleeding risk, while apixaban consistently shows the lowest rates. In patients with high gastrointestinal bleeding risk factors, apixaban was associated with lower major bleeding risk (HR 0.59 [95% CI, 0.56–0.63]) and dabigatran with lower risk (HR 0.78 [95% CI, 0.70–0.86]), whereas rivaroxaban showed higher risk (HR 1.11 [95% CI, 1.05–1.16]) compared with warfarin (Lip *et al.*, 2021).

Risk factors for gastrointestinal bleeding include advanced age, prior gastrointestinal bleeding history, concomitant antiplatelet or NSAID use, uncontrolled hypertension, and renal impairment. History of gastrointestinal bleeding significantly increases subsequent major gastrointestinal bleeding risk (adjusted HR up to 5.16 when recent) (Sherwood *et al.*, 2015; Martin *et al.*, 2023).

INTRACRANIAL HEMORRHAGE

All direct oral anticoagulants demonstrate substantial reductions in intracranial hemorrhage compared with warfarin. Standard-dose direct oral anticoagulants were associated with markedly lower intracranial bleeding (HR 0.45 [95% CI, 0.37–0.56]) and lower-dose regimens showed even greater reduction (HR 0.28 [95% CI, 0.21–0.37]) (Carnicelli *et al.*, 2022). Apixaban, dabigatran 110

mg, and edoxaban consistently rank among the lowest for intracranial hemorrhage risk in network meta-analyses (Zhang *et al.*, 2024).

Intracranial hemorrhage carries high mortality and disability. Restarting or initiating oral anticoagulation after intracranial hemorrhage in atrial fibrillation patients reduced ischemic stroke/systemic embolism (aHR 0.64 [95% CI, 0.55–0.67]) and all-cause death (aHR 0.53 [95% CI, 0.35–0.80]) without significantly increasing recurrent intracranial hemorrhage overall (aHR 1.07 [95% CI, 0.66–1.74]), although regional differences (e.g., higher recurrent risk in Asians) exist (Zhou *et al.*, 2023).

MANAGEMENT OF BLEEDING COMPLICATIONS

Clinical management strategies focus on risk stratification, modifiable factor correction, and individualized therapy. Bleeding risk scores such as HAS-BLED guide identification of high-risk patients but should prompt optimization (blood pressure control, avoidance of unnecessary antiplatelets/NSAIDs, alcohol moderation) rather than therapy withdrawal in those with high thromboembolic risk. Dose adjustment based on renal function, age, and weight is critical for direct oral anticoagulants to maintain safety. Drug interactions with P-glycoprotein or CYP3A4 modulators require careful review (Karakasis *et al.*, 2024).

In patients with bleeding, temporary interruption, supportive care (transfusion, endoscopic hemostasis for gastrointestinal bleeding), and resumption timing are key. Resumption of anticoagulation after gastrointestinal bleeding should be individualized, weighing thrombotic versus recurrent bleeding risks (Martin *et al.*, 2023).

REVERSAL AGENTS AND EMERGENCY CARE

Specific reversal agents improve outcomes in life-

threatening bleeding. Idarucizumab provides rapid reversal for dabigatran, while andexanet alfa reverses apixaban and rivaroxaban in uncontrolled or life-threatening hemorrhage. Four-factor prothrombin complex concentrate serves as a nonspecific option when specific agents are unavailable (Gómez-Outes *et al.*, 2021; White *et al.*, 2022).

For warfarin, prothrombin complex concentrate is preferred over fresh frozen plasma for urgent reversal. Emergency care protocols emphasize rapid assessment of bleed severity, anticoagulation type and timing of last dose, and multidisciplinary involvement (Levy *et al.*, 2024).

Table3. Major bleeding risks associated with anticoagulants

Anticoagulant	Common Bleeding Site	Risk Factors	Reversal Strategy
Warfarin	Intracranial, Gastrointestinal	Labile INR, Drug interactions, Diet	Vitamin K, PCC
Dabigatran	Gastrointestinal	Renal impairment, High dose	Idarucizumab
Apixaban	Lower overall	Age, Renal function	Andexanet alfa
Rivaroxaban	Gastrointestinal	Concomitant antiplatelets	Andexanet alfa
Edoxaban	Variable	High CrCl (reduced efficacy)	PCC (nonspecific)

Sources: Gómez-Outes *et al.* (2021); White *et al.* (2022); Levy *et al.* (2024)

to move beyond one-size-fits-all approaches toward individualized care that better balances thromboembolic protection with safety (Goldsweig *et al.*, 2025; Xue *et al.*, 2025).

Left atrial appendage occlusion (LAAO) devices have gained prominence as a nonpharmacologic option for stroke prevention, particularly in patients with contraindications to long-term oral anticoagulation. The 2025 SCAI/HRS guidelines provide the first major evidence-based framework for transcatheter LAAO, recommending its consideration in patients with nonvalvular atrial fibrillation who have absolute or relative contraindications to oral anticoagulation (Goldsweig *et al.*, 2025). Devices such as Watchman and Amulet reduce stroke risk relative to no anticoagulation, with growing evidence supporting concomitant use with ablation procedures. The OPTION trial demonstrated reduced non-procedural bleeding with LAAO plus ablation compared to continued anticoagulation, while maintaining non-inferior efficacy for stroke prevention (Goldsweig *et al.*, 2025; Reed *et al.*, 2025). However, challenges persist, including peri-device leaks associated with increased thromboembolism risk and the need for short-term post-procedural antithrombotic therapy.

Personalized anticoagulation strategies are advancing through integration of clinical, imaging, and biomarker data. Biomarker-guided therapy using the ABC-AF (Age, Biomarkers, Clinical history) scores incorporates NT-proBNP, high-sensitivity troponin, growth differentiation

The balance between efficacy and safety favors direct oral anticoagulants in most patients, with apixaban often demonstrating the most favorable profile. Individualized approaches incorporating patient-specific factors remain essential for optimal outcomes.

EMERGING THERAPIES AND FUTURE DIRECTIONS

The field of antithrombotic therapy in atrial fibrillation continues to evolve rapidly, with a strong emphasis on precision medicine, reduced bleeding risk, and nonpharmacologic alternatives. Future strategies aim

factor-15, and hemoglobin to refine stroke and bleeding risk estimates beyond traditional scores (Hijazi *et al.*, 2025; Wallentin *et al.*, 2025). A recent registry-based randomized trial evaluating ABC-AF-guided multidimensional treatment (including anticoagulant selection) did not demonstrate overall superiority in reducing stroke or death compared to usual care, highlighting the need for further refinement in implementation (Hijazi *et al.*, 2025).

AI-assisted risk prediction models represent a promising frontier for precision medicine. Machine learning models have outperformed conventional scores such as CHA₂DS₂-VASc and HAS-BLED in predicting stroke and bleeding events, incorporating comprehensive electronic health record data for individualized recommendations (Chaudhary *et al.*, 2025; Lin *et al.*, 2026). Mount Sinai's AI model, validated on large cohorts, suggested that up to half of patients currently recommended for anticoagulation might safely avoid it, potentially transforming decision-making (Antoun *et al.*, 2025). These tools enable dynamic, patient-specific risk assessment and may guide optimal anticoagulant choice and dosing.

Novel anticoagulants targeting factor XI or XIa are under active development with the goal of decoupling antithrombotic efficacy from bleeding risk. Agents such as abelacimab (a monoclonal antibody inhibiting both factor XI and XIa), asundexian, and milvexian have shown substantial reductions in bleeding compared to direct oral anticoagulants in phase 2 and 3 trials while maintaining

promising efficacy signals in atrial fibrillation (Xue *et al.*, 2025; Piccini *et al.*, 2025; Kumar *et al.*, 2024). The AZALEA-TIMI 71 trial demonstrated markedly lower bleeding with abelacimab versus rivaroxaban, and ongoing phase 3 studies (LILAC-TIMI 76, LIBREXIA-AF) will clarify their role in broader populations (Xue *et al.*, 2025). These agents exploit the differential roles of factor XI in pathological thrombosis versus hemostasis, offering a potential safety advantage.

Overall, these emerging approaches signal a shift toward precision antithrombotic management in atrial fibrillation. While challenges in validation, accessibility, and long-term data remain, integration of LAAO, biomarkers, AI, and novel agents holds substantial promise for optimizing outcomes through truly individualized care (Antoun *et al.*, 2025; Goldsweig *et al.*, 2025; Xue *et al.*, 2025).

Table 4. Emerging strategies in AF antithrombotic management

Emerging Approach	Potential Benefit	Current Limitation
LAAO Devices	Reduced long-term bleeding; nonpharmacologic stroke prevention	Procedural risks; peri-device leaks
Biomarker-Guided (ABC-AF)	Improved risk stratification	Limited outcome improvement in trials
AI-Assisted Prediction Models	Highly personalized, dynamic decisions	Needs broader validation and integration
Factor XI/XIa Inhibitors	Lower bleeding risk with preserved efficacy	Efficacy in high-risk patients uncertain; ongoing trials

Sources: Xue *et al.* (2025); Antoun *et al.*, 2025 Chaudhary *et al.* (2025); Lin *et al.* (2026).

CONCLUSION

Antithrombotic therapy remains the cornerstone of stroke prevention in patients with atrial fibrillation. Contemporary guidelines from the ACC/AHA and ESC have refined risk stratification using tools such as CHA₂DS₂-VASc and HAS-BLED, while strongly favoring direct oral anticoagulants over vitamin K antagonists in most eligible patients due to their superior safety profile, particularly with regard to intracranial hemorrhage. Apixaban consistently demonstrates the most favorable balance of efficacy and bleeding risk across multiple analyses. Clinicians must continue to individualize therapy through shared decision-making, carefully weighing thromboembolic benefits against bleeding hazards, optimizing modifiable risk factors, and selecting the most appropriate agent or strategy based on patient-specific characteristics including renal function, age, comorbidities, and preferences. The integration of left atrial appendage occlusion as a nonpharmacologic alternative has further expanded therapeutic options for those with contraindications to long-term anticoagulation.

Looking ahead, the management of atrial fibrillation is entering a new era of precision medicine. Emerging therapies, including factor XI inhibitors, biomarker-guided approaches, artificial intelligence-assisted risk prediction models, and improved left atrial appendage

occlusion devices, hold promise for further decoupling antithrombotic efficacy from bleeding risk. As these innovations mature, they are expected to enable more personalized and safer treatment strategies. Ultimately, successful implementation will depend on ongoing education, multidisciplinary collaboration, and a continued commitment to patient-centered care that dynamically reassesses risk and therapy needs over time. By translating the latest evidence into thoughtful clinical practice, healthcare providers can meaningfully reduce the burden of stroke while minimizing harm in this growing patient population.

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Conflict of Interest

The authors declared that there are no conflicts of interest.

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