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Anticoagulation in Atrial Fibrillation Patients

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia and may cause thrombo-embolic events, typically stroke. Advances in pharmacological approaches to anticoagulation and groundbreaking large randomized controlled trials of non-vitamin K antagonist oral anticoagulants (NOACs) have changed the paradigm of anticoagulation therapy. Furthermore, observational studies support the efficacy and safety of NOAC. Few studies address the differences among NOACs, but prescriptions should be based on a thorough understanding of their pharmacological differences, including interactions, side effects, reversibility, and practical approach. In a subset of patients with AF, warfarin may still be the preferable option. Consequently, an individualized approach to oral anticoagulation is crucial.

Keywords: anticoagulation, apixaban, atrial fibrillation, dabigatran, edoxaban, rivaroxaban, vitamin K antagonist, warfarin

1. Introduction: the changing paradigm for anticoagulation

Atrial fibrillation (AF) is a prevalent arrhythmia possessing a well-known association with thromboembolic events, especially stroke. In AF, atrial pumping ends, and blood tends to pool in the left atrium rather than be pumped into the left ventricle. Thrombi can form in the sluggish blood pool in the atrial region known as the left atrial appendage (LAA). A typical LAA thrombus can cause stroke or peripheral embolism should it break free. Indeed, AF-related strokes tend to be more life-threatening than strokes caused by other reasons [1].

Anticoagulation therapy prevents strokes and warfarin; the most commonly used vitamin K antagonist (VKA) has been the standard agent used to reduce stroke risk in certain AF patients with risk factors since the 1950s [2]. Historically, warfarin has been the drug of choice, but it has often been underused due to its narrow risk-benefit interval and the need for frequent monitoring. It is being gradually eclipsed by a variety of non-vitamin-K antagonist oral anticoagulants (NOACs) that are demonstrating excellent safety and effectiveness without the need for frequent monitoring and subsequent dose adjustment.

The availability of several pharmacological approaches to anticoagulation as well as a more thorough understanding of risk factors for embolization and bleeding has improved patient care but also complicated prescribing choices. The paradigm for anticoagulation in AF patients has changed. In addition, there are now options for patients that suffer from AF but who, for one reason or another, are unable to take

anticoagulants. These patients can often undergo closure of the LAA, the site of the majority of the thrombi.

2. Valvular vs. nonvalvular atrial fibrillation

The distinction between valvular and nonvalvular AF is not helpful in terms of defining the nature of the arrhythmia, but it may be of value in better defining the patient's risk for thromboembolism and which type of anticoagulation therapy (if any) is indicated [3]. AF may be paroxysmal or persistent, for example, or symptomatic or asymptomatic ("silent"). When decisions concerning anticoagulation are to be reached, the main factors that may affect prescribing choices are valvular versus nonvalvular forms of AF. Moreover, it should be noted that patients with nonvalvular AF may have concomitant valvular heart disease.

2.1 Nonvalvular AF

In 2016, the European Society of Cardiology (ESC) defined nonvalvular AF as an exclusion of moderate to severe mitral valve stenosis or metallic prosthetic heart valves [4]. The American Heart Association (AHA) and American College of Cardiology (ACC) went a bit further in the exclusion and stated nonvalvular AF was AF not associated with rheumatic mitral stenosis, metallic or bioprosthetic heart valves, or mitral valve repair [5]. It has even been stated by experts that perhaps the terms "nonvalvular" and "valvular" AF are outmoded and no longer useful. See **Table 1**.

Anticoagulation therapy helps to mitigate the risk of stroke in patients with nonvalvular forms of AF [14]. As such, anticoagulation may be indicated for patients with nonvalvular AF, but other factors may come into play. Surgery can affect the anticoagulation decision, both in terms of whether the AF patient needs anticoagulation therapy before and after surgery or just perioperatively for a short window of time [6].

2.2 Valvular AF

As seen in **Table 1**, valvular heart disease encompasses such conditions as mitral stenosis, mitral regurgitation, aortic stenosis, and aortic insufficiency. Valvular heart disease has an age-dependent prevalence of about 0.7% for 18–44-year-olds and 13.3% in patients ≥75 years, and it is considered a risk factor for stroke and systemic embolism. Valvular heart disease may coexist with arrhythmias, including AF [15]. Prosthetic heart valves are associated with thrombin growth, and heart valve surgery may expose the blood pool to mechanical hardware, both of which may activate intrinsic coagulation pathways. Valvular AF has been associated with platelet activation, which may contribute to further thromboembolic risk [3]. Since patients with mechanical heart valves were considered to be at risk for thromboembolism, they should always be prescribed with VKA for anticoagulation as no data exist for the use of NOAC in this subgroup [13]. Distinguishing characteristics for valvular and nonvalvular heart diseases appear in **Table 2**.

2.3 Other patient populations

AF is a prevalent condition and occurs in many patient subpopulations that merit a short discussion in terms of anticoagulation and AF classification.

Society or source	Definition of valvular AF	Definition of nonvalvular AF
American College of Cardiology Expert Consensus 2017 [6]	AF associated with rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair	All AF not associated with rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair
American College of Chest Physicians 2018 [7]	Moderate to severe mitral stenosis or mechanical heart valve	AF not associated with moderate to severe mitral stenosis or mechanical heart valve
Canadian Cardiovascular Society 2016 [8]	Rheumatic mitral stenosis, mitral valve repair, mechanical or bioprosthetic heart valve	AF not associated with mitral stenosis, mitral valve repair, and mechanical or bioprosthetic heart valve
Canadian Cardiovascular Society 2018 [9]	Rheumatic mitral stenosis, moderate to severe non-rheumatic mitral stenosis, or mechanical heart valve	AF not associated with rheumatic mitral stenosis, moderate to severe non-rheumatic mitral stenosis, or mechanical heart valve
De Caterina, Camm (Expert Opinion) 2016 [10]	Proposes the use of "mechanical and rheumatic mitral AF" or MARM-AF as alternative	AF not associated with mechanical and rheumatic mitral AF
European Heart Rhythm Association and European Society of Cardiology Working Group on Thrombosis 2017 [11]	The term is outdated and should be replaced by a functional Evaluated Heartvalves, Rheumatic or Artificial (EHRA) category, based on the anticoagulation therapy used. EHRA typically is described as Types 1 and 2 Type 1 is valvular heart disease requiring VKA anticoagulation Type 2 is valvular heart disease requiring VKA or NOAC therapy	
European Society of Cardiology 2016 [4]	Avoids the term, preferring "AF related to hemodynamically significant mitral stenosis or prosthetic mechanical heart valves"	AF not related to hemodynamically significant mitral stenosis or prosthetic mechanical heart valves
National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand 2018 [12]	Moderate to severe mitral stenosis or mechanical heart valve	AF not associated with moderate to severe mitral stenosis or mechanical heart valve
UMBRIA-Fibrillazione Atriale Study (Clinical Trial) 2019 [13]	Favors the term Type 2 valvular heart disease, defined as moderate to severe mitral or aortic regurgitation, moderate to severe aortic stenosis, or mild mitral stenosis (mitral valve areas >2.0 cm^2 on echocardiography)	AF not associated with moderate to severe mitral or aortic regurgitation, moderate to severe aortic stenosis, or mild mitral stenosis

Table 1.
The definitions for nonvalvular and valvular AF, which can be crucial to selecting appropriate anticoagulation therapy, are blurred and may even be outmoded. Note that some guidelines did not define these terms at all.

2.3.1 Transcatheter aortic valve procedures

Transcatheter aortic valve replacement (TAVR) is often recommended for low-risk patients with severe symptomatic aortic stenosis, but less is elucidated about the role of postsurgical anticoagulation therapy in this population [16]. TAVR candidates have a 40% rate of pre-existing AF and a further 10% chance of developing new-onset AF following TAVR [17]. Most patients discharged following TAVR (n = 16,694) are on dual antiplatelet therapy without anticoagulation (81.1%) [18].

Aspects of heart disease	Valvular heart disease Type 1	Valvular heart disease Type 2	Nonvalvular AF	Comments
Aortic regurgitation		Yes		
Aortic stenosis			Yes	High risk for stroke
Mechanical heart valve	Yes			High risk for thromboembolism
Mild mitral stenosis		Yes		
Mitral regurgitation		Yes		Common form of valvular heart disease
Moderate to severe aortic stenosis			Yes	
Moderate to severe mitral stenosis	Yes			May be of rheumatic origin

Table 2.
An overview of distinguishing characteristics for valvular heart disease (Types 1 and 2) versus nonvalvular heart disease [13].

In a study of 172 patients who underwent TAVR plus a pacemaker implant, 25% of the patients developed new-onset AF or atrial flutter over the median follow-up period of 15 months. Of these patients, 14.7% had at least an episode of asymptomatic AF, which was detected by device diagnostics in the pacemaker but not on their electrocardiogram (ECG). The cumulative incidence of stroke in this population was 1.4% for patients in normal sinus rhythm compared to 12.5% for new-onset AF patients. Patients with obvious AF, detected on ECG, were significantly more likely to be given anticoagulation therapy than those with subclinical new-onset AF (70% vs. 15%, respectively, p = 0.02) [19]. The rate and characteristics of AF in this particular patient population as well as those with new transcatheter aortic valve implantation (TAVI) are not extensively studied.

2.3.2 Catheter ablation patients

Patients undergoing catheter ablation for AF typically receive perioperative anti-coagulation treatment that is discontinued following surgery providing they have no other risk factors. In the Role of Coumadin in Preventing Thromboembolism in AF Patients Undergoing Catheter Ablation (COMPARE) study, it was shown that continuing warfarin for 48 hours after the procedure was associated with fewer periprocedural strokes and fewer minor bleeding events compared to bridging using low-molecular-weight heparin [20].

Results are mixed in terms of the safety and effectiveness of warfarin versus newer agents. In a prospective cohort of 290 AF ablation patients, periprocedural administration of dabigatran compared to warfarin was associated with a higher rate of thromboembolic events (2.1% vs. 0.0% for dabigatran and warfarin, respectively) and major bleeding complications (6% vs. 1%, p = 0.019) [21]. However, in a case-control analysis of 763 patients undergoing radio-frequency AF ablation, dabigatran patients had similar anticoagulation effectiveness and safety compared to warfarin patients [22]. A meta-analysis of 14 studies on the use of dabigatran vs. warfarin for periprocedural anticoagulation in patients undergoing catheter ablation for AF (n = 4782) reported dabigatran patients had a similar incidence of major bleeding events and thromboembolic events compared to warfarin patients, and both agents were associated overall with low rates of complications [23].

NOACs have been evaluated in patients undergoing catheter ablation for AF. In the RE-CIRCUIT, it was shown that uninterrupted dabigatran is associated with fewer bleeding complications than uninterrupted warfarin in this population [24]. The AXAFA-NET 5 trial found that continuous apixaban is safe and effective following catheter ablation to treat AF in terms of bleeding, stroke, and cognitive function [25]. Uninterrupted rivaroxaban was shown to be feasible in this population with event rates similar to that of uninterrupted VKA [26].

2.3.3 Cardiac implantable electronic device patients

In some cases, patients on anticoagulation therapy are subsequently indicated for implantation of a cardiac implantable electronic device (CIED). In a randomized study of patients undergoing implantation of an implantable cardioverter defibrillator (ICD), 343 patients were randomized either to undergo bridging to heparin during the procedure or to be continued on warfarin. Major thromboembolic complications in this study were rare and similar between groups (the heparin patients reported one case of cardiac tamponade and one case of myocardial infarction, while the warfarin group had one transient ischemic attack). Device pocket hematoma of clinical significance occurred in 3.5% of warfarin patients compared to 16.0% of heparin patients [27].

2.3.4 Clinically silent AF

The prevalence of asymptomatic or "clinically silent" (subclinical) AF is unknown but likely substantial [28]. Clinically silent AF is often captured by device diagnostics in CIED patients. In a study of dual-chamber pacemaker patients (411 without known AF and 267 with known AF), it was found that at a median 38 months of follow-up, 30% of those without known AF had silent AF verifiable by the pacemaker. Risk factors for silent AF in this study were heart failure (p = 0.03) and age > 75 years (p = 0.0002). Sixty-two percent of patients who developed silent AF (n = 125) were administered with anticoagulation therapy; of those with known AF at implant (n = 216), 80% took anticoagulation therapy. The annual rate of stroke was 1.9% for patients who developed silent AF postimplant compared to 2.1% for those with known AF at implant. Vascular dementia developed in 11.2% of those with known AF at implant compared to 6.2% of those who developed silent AF postimplant (p = 0.048) [29].

2.3.5 Clinically silent stroke

Silent stroke may be defined as asymptomatic cerebral infarction, which is typically discovered when brain lesions are found during imaging procedures. Indeed, silent stroke is one of the most common incidental findings in brain scans [30]. The incidence and prevalence of this condition is not known nor are risk factors, although it appears that patients with AF are at elevated risk compared to those without this arrhythmia [31, 32]. The role of anticoagulation for patients at risk for silent stroke is not clear [30].

3. Risk stratification for thrombosis

The goal of anticoagulation therapy in AF patients is to reduce their risk for stroke or systemic embolism. The CHA_2DS_2-VASc scoring system has been

developed to calculate the numerous factors that may increase the likelihood of thrombus: hypertension, heart failure, older age, diabetes, stroke, transient ischemic attack, vascular disease, and female sex [5, 33]. For patients who score ≥ 1 on this scoring metric, oral anticoagulation therapy is preferred over antiplatelet therapy. However, scoring tools are imperfect. A large retrospective review of 140,420 AF patients found the annual rate for ischemic stroke with those scoring ≤1 was lower than previously stated (0.1–0.2% for women and 0.5–0.7% for men) [33]. A retrospective cohort study found that age between 65 and 74 years was a stronger predictor of stroke compared to the other items on the CHA$_2$DS$_2$-VASc scoring system. People in that age bracket had an annual stroke risk of 1.78%. By the same token, AF patients <50 years of age had low risk (0.53%) [34].

4. Safety issues and bleeding risks

Hemostatic alteration introduces the risk of potentially devastating bleeding, typically intracranial hemorrhage [35]. The consequences of a bleeding event are of greater clinical importance than the amount of bleeding itself, for instance, a small amount of pericardial bleeding following cardiac surgery may have potentially life-threatening consequences, while a much larger bleeding event may be clinically manageable. Bleeding is a high-risk situation and is not the subject of clinical trials. In fact, most of the evidence about bleeding rates and risks is derived from safety reports in clinical trials. Thus, expert consensus often overrides data-driven evidence in terms of bleeding risks.

In addition to procedure-related bleeding risks, individual patient factors for bleeding must also be taken into account. The HAS-BLED score, based on a survey of almost 4000 patients in the Euro Heart Survey on AF, offers a way to create a numerical score based on several factors. The acronym encapsulates some of the key risks: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), and drugs and/or alcohol concomitantly [36]. The HAS-BLED has seen a wide adoption, but two important points must be considered. Firstly, many risk factors in the HAS-BLED score are shared with other risk-scoring schemes for calculating the risk of thrombosis, e.g., hypertension and stroke. Secondly, a high HAS-BLED score is not necessarily indicative that oral anticoagulation should be omitted but may be used to select patients in need for regular follow-up.

5. Drug therapies and prescribing options

For over half a century, the anticoagulation regimen for AF was the use of VKA, also called coumarins. They included acenocoumarol, phenprocoumon, fluindione, and warfarin [37]. Warfarin is by far the most common of these and is the most commonly used anticoagulant [38]. These are effective agents, but they have certain disadvantages: a narrow therapeutic range, required laboratory monitoring, good patient adherence for safety and effectiveness, and certain risks for drug-drug and drug-food interactions [39].

The emergence of NOAC drugs has changed the paradigm for anticoagulation therapy. These agents have been shown noninferior to warfarin with respect to thromboembolism. They may alleviate some of the disadvantages of VKA anticoagulation, but some of them do not have reversal agents. A short summary of anticoagulants appears in **Table 3**.

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Dosing	5 mg × 2 but 2.5 mg × 2 if two of the following: age > 80 years, weight < 60 kg, or creatinine >133 µmol/l	150 mg × 2 or 110 mg × 2 if either: age > 80 h, GFR 30–50 ml/min, GI disease, increased risk of bleeding	60 mg × 1 but 30 × 1 if one of the following: weight ≤ 60 kg, concomitant ciclosporin, dronedarone, erythromycin, ketoconazole	20 mg × 1 but 15 mg × 1 if GFR 15–50 ml/min	Strat dose 5–7.5 mg, daily, and then adjustment to INR
Renal failure	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Approved indication
Risk of intracranial bleeding vs. warfarin	Lower	Lower	Lower	Lower	—
Interactions with other drugs or food	Few	Few but note dronedarone	Few	Few	Numerous
Possible to crush tablet	Yes	No	Yes	Yes	Yes
Independent of timing of food intake	Yes	Yes	Yes	No	Yes
Laboratory follow-up	6–12 months	6–12 months	6–12 months	6–12 months	Frequent, typically 1–2 every month
Specific antidote	No	Yes, instant effect	No	No	Yes, slow effect

Table 3.
A short summary of anticoagulation agents.

5.1 Vitamin K antagonists

Vitamin K antagonists (VKA) act by reducing the synthesis of the coagulation factors that rely on vitamin K. They inhibit the liver's ability to synthesize the precursors to clotting factors, Factor II (prothrombin), Factor VII, Factor IX, and Factor X. For that reason, it may take up to 2 weeks before all of these factors are eliminated and the drug is effective [35]. Warfarin may be reversed with oral or intravenous vitamin K, although the reversal may take hours to take effect [40]. Warfarin is an effective anticoagulant as long as blood concentrations fall within a relatively narrow therapeutic range; regular monitoring for time in therapeutic range is required. There is a wealth of clinical experience with VKA to inform prescribing choices.

Although warfarin may seem to be eclipsed by newer and more convenient agents, warfarin is still frequently prescribed and may be the optimal choice for some patients. VKA anticoagulation therapy decreases the risk of ischemic stroke in AF patients by >60%, although it does present a slightly increased risk for bleeding (<0.3%/year) [41].

Prescribing considerations for warfarin must include its narrow therapeutic index (overdosing may cause bleeding, and underdosing may cause thrombosis). Thus, warfarin patients must be followed with regular assessment of their international normalized ratio (INR). While genetics influence how an individual responds to VKA, such tests are not often used, and there is little guidance in terms of how to apply the findings from such genetic tests to therapeutic choices [42, 43]. Warfarin can be monitored at home with a home-based system and weekly test strips. The direct cost of warfarin is lower than for NOAC medications.

An important safety concern about warfarin involves hemorrhagic stroke which may occur in patients on VKA therapy. In fact, about 12–14% of cases of intracerebral hemorrhage are associated with warfarin [44]. VKA agents appear to contribute to vascular calcification to a greater extent than NOACs [45]. Drug-drug or food-drug interactions often occur with VKA therapy, particularly involving foods and drugs that induce or inhibit the CYP 450 enzymes [39, 46].

5.2 Non-vitamin-K antagonist oral anticoagulants (NOACs)

Four NOAC medications are approved and indicated for stroke prevention in patients with nonvalvular AF in the USA with some international variations. The NOAC category offers drugs in two classes: those that inhibit Factor Xa (apixaban, edoxaban, rivaroxaban) and direct thrombin inhibitors (dabigatran). Trials have demonstrated they are effective anticoagulation options with reasonable safety profiles. The advantages of NOACs compared to VKA therapy include predictable pharmacokinetics, rapid onset and offset of action, recent promising evidence from clinical trials showing reductions in stroke, intracranial hemorrhage, and all-cause mortality [46]. NOACs offer advantages, but the lingering concern with such medications is the lack of a reversal agent to stop the anticoagulatory effect in the event of a bleeding emergency for all these agents except dabigatran. The monoclonal antibody idarucizumab is available as a specific, with rapid onset, reversal agent for dabigatran [47].

5.2.1 Apixaban

Apixaban is a highly selective direct inhibitor of activated coagulation Factor X that can indirectly inhibit thrombin-induced platelet aggregation. It is an oral anticoagulant with linear and predictable pharmacokinetics and rapid onset/offset

of action and has relatively few potential drug-drug or drug-food interactions [48]. In a meta-analysis of 16 studies, apixaban was more effective in reducing the rate of thromboembolic events compared to warfarin but similar to warfarin in reducing the risk of stroke [49]. However, it may reflect patient selection, and it is important to stress that no head-to-head studies with a randomized controlled have been conducted.

A post hoc analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study compared clinical characteristics and outcomes in AF patients with a history of cancer taking either apixaban or warfarin. The outcomes were stroke, systemic embolism, major bleeding, and mortality [50]. In the study, 157 patients had active cancer, the remaining 1079 had remote cancer, and they were compared to 16,947 patients without cancer. No significant relationships between cancer and stroke, systemic embolism, ischemic stroke, or death could be determined, and the relationship between cancer and myocardial infarction was not significant after statistical adjustment. Apixaban was associated with improved rates of the composite endpoint (stroke, systemic embolism, myocardial infarction, and mortality) in those with active cancer and in those without cancer but not in those with remote cancer [50]. In a post hoc analysis of the ARISTOTLE study, 76.5% of patients were found to be on polypharmacy, defined as ≥5 or more drugs, and mortality, stroke, and systemic embolism rates increased with the greater number of concomitant medications [51]. Apixaban was deemed to be more effective than warfarin in AF patients on polypharmacy compared to warfarin and at least equivalent in terms of safety. An analysis of ARISTOTLE study data found 104 patients had a bioprosthetic heart valve replacement, and 52 had undergone valve repair. The safety and effectiveness of apixaban in this subpopulation was consistent with the larger study results, that is, apixaban may be an appropriate choice for a patient with valve replacement or repair [52]. Using data from this study, it was found that 30.5% of patients were taking potentially interacting medications at the time of the study (2722 apixaban and 2824 warfarin patients), which is common among AF patients. For the primary outcome endpoint (stroke or systemic embolism), both apixaban and warfarin were similar, and interacting medications had no effect on this outcome [53]. Apixaban results were also consistent in the multimorbid population (64% of ARISTOTLE population, defined as ≥3 comorbid conditions); apixaban was similarly effective in the general ARISTOTLE population as in the multimorbid subpopulations, including those with high multimorbidity (≥6 comorbid conditions) [54].

Using a Markov model and a population model from 2017 to 2030, apixaban was compared to warfarin in the German population of nonvalvular AF patients. The study showed that apixaban use instead of a VKA could avoid 52,185 major clinical events, including 14,319 all-cause deaths and 15,383 nonfatal strokes [55]. A Department of Defense study in the USA (n = 41,001) found apixaban was associated with a significantly lower risk of stroke, systemic embolism, or major bleeding compared to warfarin and to rivaroxaban [56].

5.2.2 Dabigatran

Dabigatran, a prodrug, is a direct thrombin inhibitor with predictable pharmacokinetics and pharmacodynamics, no need for laboratory monitoring, and fewer drug-food and drug-drug interactions compared to VKA. Unlike other NOAC drugs, dabigatran has an approved specific reversal agent, idarucizumab [57]. Dabigatran holds the distinction of being the first NOAC agent to be approved for nonvalvular AF patients [58].

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) study (n = 18,113) compared dabigatran at two doses (150 or 110 mg twice a day) to warfarin in a trial of AF patients that excluded those with mechanical heart valves, moderate to severe mitral stenosis, or valvular heart disease requiring intervention (patients with valvular heart disease not requiring intervention could be included) [59]. For dabigatran 150 mg twice daily, the rate of stroke or systemic embolic events was significantly lower than that of patients taking warfarin, but for those on 110 mg twice daily, rates were similar to warfarin. Intracranial bleed rates and mortality rates were significantly lower in both dabigatran groups compared to warfarin regardless of whether or not the patient had valvular heart disease [59].

The randomized phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN) study was terminated early when it compared VKA therapy to dabigatran and the dabigatran group experienced a high rate of thromboembolic and bleeding adverse events [60]. The study enrolled patients undergoing atrial and/or mitral mechanical valve implantation who were administered with 150 or 300 mg of dabigatran twice a day to determine relative safety and effectiveness of dabigatran compared to warfarin [61]. Dabigatran patients experienced higher rates of adverse events: 5% had strokes, 2% transient ischemic attacks, and 2% myocardial infarction compared to only transient ischemic attacks only at a rate of 2% in the warfarin group. The reasons for this have been speculated: dabigatran doses were too high, dabigatran was introduced too soon after valve surgery, or there remain factors to be elucidated about thromboembolic risks associated with artificial heart valves [62].

5.2.3 Edoxaban

Edoxaban, a factor Xa inhibitor, is approved for the prevention of stroke in nonvalvular AF patients. Factor Xa is a protease that serves to convert prothrombin into thrombin which, in turn, converts fibrinogen into fibrin and allows for clotting. Edoxaban has a dual mechanism of action in that it inhibits both free Factor Xa and also the by-product Factor Xa produced by prothrombinase [63]. Like other NOAC medications, it requires less laboratory monitoring, has fewer drug-drug and food-drug interactions, and lowers the risk of major bleeding compared to warfarin. It is not metabolized via the CYP450 enzyme system (which is the case for apixaban and rivaroxaban), and it was shown in the ENGAGE AF-TIMI study to be noninferior to warfarin. It is an oral agent that need be taken only once daily [63]. The safety and efficacy of edoxaban seem to be similar to other NOAC medications for the control of venous thromboembolism to reduce the risk of stroke in nonvalvular AF patients.

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombosis in Myocardial Infarction 48 study (ENGAGE-AF-TIMI 48) compared edoxaban to warfarin in AF patients with and without valvular heart disease [64]. Valvular heart disease is associated with an increased risk for major adverse cardiovascular events, major bleeding, and death. Higher-dose edoxaban was found to be similarly effective to warfarin for all endpoints (stroke, systemic embolic event, major bleeding) in a trial of 18,222 patients [64].

A substudy of ENGAGE AF-TIMI 48 examined the effect of patient age on bleeding risk (risk is greater with older age) and favored edoxaban over warfarin for AF patients ≥75 years [65]. As such, edoxaban may be preferred over warfarin in elderly patients at risk for falls [66].

5.2.4 Rivaroxaban

Rivaroxaban is an NOAC that acts as a selective, direct inhibitor of activated coagulation Factor Xa. It is an oral medication with a rapid onset/offset of action and short half-life. It does not require laboratory monitoring and has predictable pharmacokinetics and pharmacodynamics and relatively few drug-drug and drug-food interactions compared to warfarin [67]. There is currently no approved reversal agent for rivaroxaban.

The ROCKET-AF study (n = 14,264) compared rivaroxaban to warfarin and found rivaroxaban had a 1.7% risk of stroke or systemic embolism at 1 year compared to 2.2% for warfarin. The composite safety endpoint was major bleeding or major bleeding plus clinically relevant non-major bleeding and occurred at a rate of 14.9% for rivaroxaban and 14.5% for warfarin patients [68]. The study concluded that rivaroxaban was noninferior to warfarin in prevention of stroke and systemic embolism. There was no significant difference in major or non-major but clinically relevant bleeding between rivaroxaban and warfarin. Gastrointestinal bleeding occurred more often in rivaroxaban than warfarin patients, but rates of major bleeding were similar.

5.3 Rotation of anticoagulation

There may be cases when it becomes necessary to change from warfarin to an NOAC or vice versa. In the case of moving from VKA to an NOAC, INR monitoring is needed throughout the shift [14]. The opposite transition, from NOAC to VKA, may require bridging to heparin or starting off with a lower dose of the NOAC medication at first, INR twice a week (minimum), and adjustment of VKA until the INR reaches ≤2.0 [69].

5.4 Risks of anticoagulation

In an elderly population (262,611 patients ≥60 years free of dementia and stroke), it was observed that incident AF was associated with an increased risk of dementia independent of stroke, while anticoagulation therapy decreased the risk for dementia [70]. The association between AF and dementia is not well elucidated, but white matter lesions, silent brain infarcts, and microbleeds in the brain are more common in AF patients, and it is not clear whether anticoagulation might play a role in this decreased risk for dementia [71].

Patients with liver disease are at risk for increased bleeding with anticoagulation therapy (but not increased thromboembolic events) [72]. However, NOAC therapy was shown in a clinical study (n = 39) to be safe and effective in cirrhosis patients [73].

Warfarin is teratogenic and should not be administered to pregnant women or women of childbearing potential without a clear understanding that they must not get pregnant while taking this drug [74].

6. Emergency anticoagulation and emergency anticoagulation reversal

NOAC anticoagulation offers advantages over VKA anticoagulation but also poses new challenges in the management of emergency situations. Emergency thrombolysis for treatment of ischemic stroke requires that the coagulation system be intact and, for this reason, is contraindicated in patients taking NOAC

drugs, unless the agent is completely reversed before [75]. Prothrombin time and other laboratory tests are often faster and easier to accomplish with VKA therapy than NOAC in emergencies. For major bleeding events, rapid reversal of anticoagulation may be required which is likewise easier with VKA; however, reversing VKA agents such as warfarin may still take hours. Among the NOAC options, only dabigatran has a reversal agent, while the reversal agents for the other NOAC medications are in development.

7. Evidence from clinical trials

The NOAC medications and warfarin have been the subject of large published clinical trials, but head-to-head studies among the NOACs have not yet been carried out, and attempts to analyze data across trials have been challenged by differences in study methodologies, the AF populations evaluated, definitions (stroke, AF, major bleeding, and so on), and composite endpoints [76]. A meta-analysis (n = 17 studies) comparing rivaroxaban, dabigatran, and warfarin in real-world settings found that rivaroxaban was similar to warfarin in terms of the risks for major bleeding, myocardial infarction, and all-cause mortality; rivaroxaban was associated with a lower risk for stroke or systemic thromboembolism compared to warfarin; however, rivaroxaban had a higher risk for gastrointestinal bleeding than warfarin. Compared to dabigatran, rivaroxaban had similar risks for stroke and systemic thromboembolism and myocardial infarction, but the risks for major bleeding, gastrointestinal bleeding, and all-cause mortality were higher with rivaroxaban than dabigatran [77]. A retrospective study found that rivaroxaban and apixaban elevate the INR to levels above the high cutoff for normal (84.2% of rivaroxaban and 78.3% of apixaban with rivaroxaban significantly higher than apixaban, p < 0.001); however the clinical implications for these elevated INR values are not known [78].

A retrospective study of 1365 geriatric patients with head trauma found that NOAC therapy was a safer alternative than warfarin, although warfarin and NOACs were associated with similar mortality rates. NOAC patients had a lower rate of intracranial hemorrhage progression [79]. A retrospective database study of nonvalvular AF patients newly started on rivaroxaban, apixaban, or warfarin matched 11,411 rivaroxaban users to 11,411 warfarin patients and reported that the risk of ischemic stroke or intracranial hemorrhage was significantly lower in the rivaroxaban patients than in the warfarin patients. The study further matched 4083 apixaban patients to 4083 warfarin patients and found the combined endpoint (ischemic stroke or intracranial hemorrhage) was nonsignificantly reduced by apixaban versus warfarin. Apixaban reduced the risk of intracranial hemorrhage (hazard ratio 0.38, 95% confidence interval, 0.17–0.88) compared to warfarin, but the risk of ischemic stroke was nonsignificantly increased by apixaban versus warfarin (hazard ratio 1.13, 95% confidence interval, 0.49–2.63). The study did not compare rivaroxaban to apixaban [80].

In a study of 962 consecutive TAVR patients prescribed with NOAC (n = 326) or VKA therapy (n = 636) after surgery, the composite study endpoint were all-cause mortality, myocardial infarction, and any cerebrovascular event. After 1 year of follow-up from TAVR, the composite endpoint occurred in 21.2% of NOAC and 15.0% of VKA patients. Rates of bleeding and all-cause mortality were similar, but NOACs had a higher rate of ischemic events than VKA therapy [81]. In a systematic review of anticoagulation therapy in AF patients with valvular heart disease and bioprosthetic heart valves, edoxaban 30 mg was associated with the least rate of major bleeding compared to rivaroxaban, VKA, and other similar agents. Overall, NOAC medications were more effective in this population than warfarin, and NOACs were similar with the exception of edoxaban and major bleeding rates [82].

Evidence from clinical trials shows promise but does not yet provide clinicians with a complete picture. For example, patients with moderate to severe mitral stenosis or those with a mechanical heart valve are both at elevated risk from thromboembolism and typically excluded from head-to-head clinical trials that compare VKAs to specific NOACs. There are also patient groups who have been included in some, but not other trials, for example, patients who had a previous heart valve surgery (but not a mechanical valve) were excluded from RE-LY but included in ROCKET-AF, ARISTOTLE, and ENGAGE-AF. Patients with AF and a mechanical heart valve are routinely excluded from most head-to-head trials on anticoagulation. Thus, there are gaps in the evidence as to which types of anticoagulation treatments are most effective in specific populations.

8. Clinical considerations for oral anticoagulants

Although it is well known that anticoagulation therapy can help prevent stroke in AF patients at risk for thromboembolic events, only about half of the indicated patients actually are prescribed with therapy [83]. There is an inverse relationship between antiplatelet prescription and non-prescription of anticoagulation therapy. However, antiplatelet therapy is not as effective as anticoagulation medications for stroke prevention [84]. When prescribing anticoagulation therapy, the clinician must evaluate several factors: the indications for anticoagulation therapy, individual patient characteristics, whether or not the patient is taking other medications, patient preferences (if any), clinician and institutional preferences, and cost [14]. When antiplatelet therapy is combined with anticoagulation, the risk for bleeding increases [14]. Among patients with nonvalvular AF, those with heart failure and/or left-ventricular dysfunction have higher rates of bleeding and stroke/systemic embolism. Although some large trials of NOACs have included such patients, there have been no specific studies to investigate the safety of such drugs in these populations [85], and there is little evidence to guide prescribing choices.

Comorbidities must be considered when selecting the optimal anticoagulation regimen for a specific patient. Hepatic disease may increase the patient's risk for bleeding and impairs hepatic drug metabolism and clearance. In NOAC trials, patients with liver disease were excluded, so there is a paucity of evidence about how to use NOAC therapy in this population. A retrospective database study from Korea (12,778 warfarin patients and 24,575 NOAC patients) found NOACs reduced the risk for ischemic stroke, intracranial hemorrhage, gastrointestinal bleeding, major bleeding, and all-cause death compared to warfarin. In the 13% of this study population with active liver disease, there was a lower rate for the composite endpoint (all endpoints above) for NOAC than warfarin [86].

Renal failure, common in AF patients, has an inflammatory pathophysiology and puts patients at risk for both thromboembolitic events and bleeding [87]. Since NOACs are cleared by the kidneys, renal failure has an adverse effect on NOAC pharmacokinetics but not on warfarin. However, warfarin likewise can interact with other drugs including drugs taken by patients managing kidney disorders [88]. A retrospective database study in Germany, RELOAD, compared outcomes of nonvalvular AF patients with compromised renal function taking either rivaroxaban or phenprocoumon (VKA therapy) and found that for patients with no evidence of cancer, rivaroxaban was associated with a lower rate of ischemic stroke and intracranial hemorrhage compared to phenprocoumon [89]. Warfarin is also more commonly prescribed to nonvalvular AF patients on hemodialysis, and while no head-to-head clinical trials have compared warfarin to NOACs in this population, dialysis patients are sometimes prescribed with NOAC

therapy. The preference for NOACs in the hemodialysis population may be due to several concerns: it is difficult to maintain warfarin at INR in the therapeutic range, warfarin may calcify vasculature, and dialysis patients have an elevated risk of intracranial hemorrhage. Hemodialysis patients are challenging for anticoagulation, because they often are multimorbid, have extensive antibiotic exposure, and may have vitamin K deficiency. Adherence can also be especially problematic in the hemodialysis population [90].

The role of anticoagulation in cancer patients becomes complex as many cancer patients are at increased bleeding risk and may be taking antiplatelet agents and nonsteroidal anti-inflammatory drugs, have renal impairment, or be on chemotherapy. Many chemotherapeutic agents increase the patient's risk of arterial and venous thrombosis, and chemotherapy that induces thrombocytopenia may elevate bleeding risks [91]. There is also the risk that anticoagulants may interact with chemotherapeutic agents or supportive-care drugs. Many chemotherapeutic regimens (cisplatin, melphalan, cyclophosphamide) and some monoclonal antibodies increase the risk of nonvalvular AF. Cancer patients with AF have an increased risk for thromboembolism [92]. There is only limited knowledge of the risk of ischemic stroke attributable to cancer, and many risk assessment tools do not incorporate cancer. Further, cancer is not just one disease, and there may be important clinical variations with respect to the type of cancer, AF risk, and risk of thromboembolism and stroke [93].

Patient factors may also influence prescribing choices. Patient adherence must be considered in long-term anticoagulation therapy; the continuously adherent rate is under 45% for those newly diagnosed AF patients prescribed with some form of anticoagulation therapy [94]. Patient education may play a role in improving adherence. In a study of 339 adults on anticoagulation treatment for nonvalvular AF, participants evidenced moderate knowledge about AF but had a more limited understanding of anticoagulation and stroke [95]. Thus, better educational efforts may be helpful. Culture and ethnicity may also be a consideration when making prescribing determinations. In a multinational survey of 937 adults on anticoagulation treatment for nonvalvular AF, national differences emerged such that US patients perceived AF as a serious condition, whereas the Japanese were less concerned about AF, but both were quite concerned about stroke risks. French patients preferred the physician to select AF therapy, while German, US, and Canadian patients preferred to be involved in therapeutic choices [96]. A cross-sectional survey of 226 physician specialists in Bulgaria also reports that 68% of patients who have an indication for anticoagulation therapy preferred a shared decision-making approach, and only 19% wanted the physician to make all anticoagulation therapy choices [97]. Improved understanding about the risk of stroke, the nature of stroke, and anticoagulation treatment may improve adherence and empower patients in their own care.

Women taking warfarin have a greater risk of stroke/embolism than men, but this sex difference is not maintained for all of the NOACs [98]. Moreover, there is some evidence that with NOACs, women have less risk of major bleeding than men. The differences have been discussed in the literature and do not seem to apply to anticoagulation effectiveness [99]. Further studies are needed, but it appears that NOAC drugs may have some sex-based differences that at this time seem clinically unimportant.

9. Device-based approaches

Some patients have a relative or absolute contraindication to anticoagulation therapy. Device-based approaches may be important options for these patients.

It exceeds the scope of this chapter to describe these devices, their implantation, and results in detail, but a brief introduction is offered. Direct closure of the LAA via a minimally invasive surgical procedure is well established. It is a safe, effective procedure that can generally be performed in 30–40 min. Initially, the LAA was closed utilizing an endoscopic stapler, but more recently a minimally invasive LAA surgical clip is used (AtriClip, AtriCure, Inc., Cincinnati, Ohio, USA). The clip offers complete closure immediately, and no postoperative anticoagulation is needed.

A device implanted under fluoroscopic control into the orifice of the LAA by transseptal puncture may also be used (Watchman, Boston Scientific, Inc., Boston, Massachusetts, USA). This device has a high leak rate, and the US Food and Drug Administration requires postoperative anticoagulation for several weeks after implantation. Five-year outcomes from two large randomized clinical trials (PREVAIL and PROTECT AF) found that LAA closure with the WATCHMAN device offered stroke prevention in patients with nonvalvular AF comparable to that of warfarin with additional reductions in major bleeding and mortality [100].

In contrast to these is a suture-based occluding device (Lariat, SentreHEART, Redwood City, California, USA) that requires transseptal implantation. Unlike WATCHMAN, this device does in fact close the LAA, but in addition to a transseptal puncture, it requires access to the pericardium. A large randomized multicenter controlled trial is ongoing to determine the 30-day safety of this device and freedom from documented episodes of AF, atrial flutter, or atrial tachycardia >30 s at 12 months with a secondary composite endpoint of cardiovascular death or stroke [101].

10. Conclusions

New anticoagulation therapies are changing the paradigm of anticoagulation treatment for patients with certain forms of AF. This shift is further complicated by the fact that the definition and understanding of nonvalvular versus valvular AF are under scrutiny and evolving. Vitamin K antagonism (warfarin and other drugs) had been the standard of care for decades and still represents an important anticoagulation option. The main drawbacks to VKA are the need for laboratory monitoring and strict therapy adherence to maintain anticoagulation efficacy plus the potential for drug-drug and food-drug interactions. A benefit for warfarin and other VKA treatments is the fact that the anticoagulation effect can be pharmacologically reversed. The arrival of the NOAC agents presents improved effectiveness in many key endpoints such as stroke prevention and similar or enhanced safety with respect to bleeding risks. There are four of these drugs (apixaban, dabigatran, edoxaban, and rivaroxaban), but as yet there are no head-to-head clinical trials among them for clinical guidance. Except for dabigatran, there are presently no reversal agents for these drugs. Clinicians must evaluate these anticoagulation approaches to make individualized decisions for patients. Further study is needed, particularly for specific subpopulations of AF patients: those with heart failure, implanted devices, renal compromise, and cancer.

Conflicts of interest

Peter Magnusson has received speaker fees or grants from Abbott, Alylam, Bayer, AstraZeneca, BMS, Boeringer-Ingelheim, Lilly, Novo Nordisk, Octupus

Medical, and Pfizer. Joseph Pergolizzi is a principal at Native Cardio, Inc. Randall K. Wolf is a paid consultant to the engineering team at AtriCure, Inc. Morten Lamberts has received speaker fees from BMS. Jo Ann LeQuang has no relevant disclosures.

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