

REVIEW

# Pharmacological and Non-pharmacological Treatments for Stroke Prevention in Patients with Atrial Fibrillation

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## ABSTRACT

Atrial fibrillation (AF) is associated with significant risk of stroke and other thromboembolic events, which can be effectively prevented using oral anticoagulation (OAC) with either vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, or edoxaban. Until recently, VKAs were the only available means for OAC treatment. NOACs had similar efficacy and were safer than or as safe as warfarin with respect to reduced rates of hemorrhagic stroke or other intracranial bleeding in the respective pivotal randomized clinical trials (RCTs) of stroke prevention in non-valvular AF patients. Increasing “real-world” evidence on NOACs broadly confirms the results of the RCTs. However, individual patient characteristics including renal function, age, or prior bleeding should be taken into account when choosing the OAC with best

risk–benefit profile. In patients ineligible for OACs, surgical or interventional stroke prevention strategies should be considered. In patients undergoing cardiac surgery for other reasons, the left atrial appendage excision, ligation, or amputation may be the best option. Importantly, residual stumps or insufficient ligation may result in even higher stroke risk than without intervention. Percutaneous left atrial appendage occlusion, although requiring minimally invasive access, failed to demonstrate reduced ischemic stroke events compared to warfarin. In this review article, we summarize current treatment options and discuss the strengths and major limitations of the therapies for stroke risk reduction in patients with AF.

**Keywords:** Atrial fibrillation; Left atrial appendage ligation and closure; Oral anticoagulation; Percutaneous left atrial appendage occlusion; Stroke, thromboembolic events; Vitamin K antagonists; Non-vitamin K antagonist

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## INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults, representing a substantial health care burden [1]. The arrhythmia is associated not only with impaired quality of life and frequent hospitalizations but

also a higher risk of stroke, other thromboembolic events, and increased mortality [2, 3]. A fibrillating left atrium (LA) meets all the requirements for thrombus formation of Virchow's triad, especially in the LA appendage (LAA) [4]. The risk of stroke in AF patients varies according to the individual risk profile, but the overall ischemic stroke rate without oral anticoagulation (OAC) is approximately 3.20 per 100 person-years [5]. Patients with AF-related strokes have worse outcomes compared to other stroke etiologies [6]. Individual stroke risk assessment and the use of optimal stroke prevention strategy are mandated in all AF patients. The use of OAC should be considered first or, if contraindications are present, an interventional or surgical LAA occlusion or amputation could be considered.

In this review we outline contemporary pharmacological and non-pharmacological treatments for stroke prevention in AF patients.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

## THROMBUS FORMATION IN AF

More than 90% of LA thrombi in nonrheumatic AF are formed in the LAA [7]. Representing a remnant of the original embryonic LA, the LAA is not only a simple attachment but also shows a complex sequence of filling and emptying with substantial volume changes over the cardiac cycle [8]. Irregular electrical activation of the LA and the LAA during AF facilitates thrombus formation due to abnormal blood flow. Abundance of LAA morphologies has been described recently [8, 9] with a simplified classification of four LAA types with the descriptive names cactus, windsock, chicken wing, and cauliflower [10]. The different LAA morphologies are currently evaluated with respect to the specific morphology-associated risk for thrombus formation, and the results published so far are inconsistent regarding the "high-risk" morphology [10–12].

Endothelial and blood component-specific factors promoting blood clot formation in AF,

e.g., endothelial dysfunction, alterations in coagulation, inflammation, and hemoconcentration, have been described in detail elsewhere [4]. Although the association of AF and ischemic stroke depending on the individual stroke risk factors has been clearly established, studies in patients with cardiac implantable devices and hence accurate AF detection showed a surprising lack of clear temporal relation between AF episodes and thromboembolic events [13, 14], which is currently under intensive investigation [15].

## ORAL ANTICOAGULANT DRUGS FOR STROKE PREVENTION IN AF

The use of OAC [either vitamin K antagonists (VKAs) or non-vitamin K oral anticoagulants (NOACs)] should be considered in all AF patients at risk of stroke in the absence of contraindications. The risk of AF-related stroke is commonly assessed using the CHA<sub>2</sub>DS<sub>2</sub>-VASc [congestive heart failure, hypertension, age ( $\geq 75$ ), diabetes mellitus, stroke history or TIA, vascular disease, age 65–74, sex category female] score, which is recommended by international AF guidelines [16–19]. Recently, a concern has been raised about the necessity of OAC use for stroke prevention in AF patients with a single additional CHA<sub>2</sub>DS<sub>2</sub>-VASc stroke risk factor due to low observed stroke rates in a few AF cohorts [20]. However, even though not all risk factors in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score carry an equal risk, the other study demonstrated a higher observed stroke risk in AF patients with a single additional risk factor [20, 21]. In addition, other studies clearly showed that the use of OAC in AF patients with a single additional stroke risk factor was associated with reduced risk of stroke and mortality [22, 23]. Consequently, all AF patients with one or more additional stroke risk factors (i.e., a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 in men and 2 in women) should be considered for OAC therapy. Additional stroke risk factors not covered by the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, such as the LAA morphology [10], LA enlargement [24], African ethnicity [25], renal function [26], and other factors [27–29], are currently under investigation. Besides, evolving ablation

strategies including electrical isolation of the LAA further complicate stroke risk assessment. Whether electrical LAA isolation leads to higher stroke risk because of reduced LAA blood flow velocity is subject to ongoing discussions [30–32].

A drawback of OAC use is the risk of OAC-related bleeding. Of various proposed tools for bleeding risk assessment, the HAS-BLED [uncontrolled hypertension, advanced renal or liver disease, a history of stroke, previous bleeding, labile international normalized ratio (INR), age > 65 years, concomitant drugs predisposing to bleeding (aspirin or nonsteroidal anti-inflammatory drugs, excessive alcohol use)] score provides well-balanced simplicity and predictive ability for bleeding events and is most commonly used [33]. Individualized and balanced risk stratification remains the most challenging task. In clinical practice and outside clinical trials it is especially the patient with “special” risk profile due to, e.g., chronic kidney disease on dialysis, prior ischemic stroke or prior intracranial bleeding, malignancies, special genetic features, and substantial co-medication who demands attention [34].

### Vitamin K Antagonists

Since the isolation of 4-hydroxycoumarin in 1940 by Link and colleagues [35], VKAs have been proven to be effective and safe in the prevention of AF-related thromboembolic complications, and large randomized controlled trials (RCT) on VKA therapy reported a two-third risk reduction in strokes compared to placebo [36]. However, it is important to note that the overall efficacy and safety of VKAs are highly dependent on the quality of VKA management.

As VKAs disable the “regeneration” of vitamin K within the vitamin K epoxide cycle via inhibition of the vitamin K epoxide reductase enzyme and thus interrupt the carboxylation of inactive blood coagulation factors, the effect of VKAs does not occur immediately but after 48–72 h, because coagulation factors that are already carboxylated and active still work. Furthermore, at the beginning of VKA therapy a transient hypercoagulable state can occur as a

result of the decrease of baseline protein C and protein S levels before decrease of vitamin K-dependent clotting factor levels respectively [37]. Besides the complex initiation phase of VKA therapy, which closely depends on liver function, the inhibition of the vitamin K epoxide reductase enzyme can be compensated with higher concentrations of vitamin K thus influencing the dose–response relationship. It seems that a predominantly higher vitamin K intake at a day-by-day level leads to greater body stores and thus a stronger resilience when variations in vitamin K intake occur. Apparently, stable dietary habits support stable INR values, but large-scale prospective trials are lacking [38, 39]. On the other hand, it is thus possible to initiate reversal or antagonization of VKAs in case of exaggerated anticoagulation states using vitamin K compounds.

Regular monitoring of the INR, a measure of VKA anticoagulation intensity, is mandatory because of the narrow therapeutic window of VKAs. Since a single INR value is not a reliable indicator of the quality of VKA anticoagulation over a time period, the time in therapeutic range (TTR) is used as a measure of the quality of VKA management. Unfortunately, the target TTR values of at least 65–70% are often difficult to maintain in routine clinical practice. A recently published summary of various meta-analyses showed that the TTR is located most of the time below the target value of 65% in patients on VKAs [40]. Evidently, both the efficacy in stroke prevention and safety concerning the VKA-related bleeding risk are strongly influenced by the achieved TTR [40–42]. The SAME-TT<sub>2</sub>R<sub>2</sub> score [sex category female, age < 60 years, medical history (more than two comorbidities), treatment (interacting drugs, e.g., amiodarone for rhythm control), tobacco use, race (non-Caucasian)] has been developed as a simple tool to identify patients at higher risk for poor TTR control [43].

The anticoagulant effect of VKAs is also influenced by genetic factors and numerous food or drug interactions contributing to substantial inter- and inpatient variability in anticoagulation intensity [44]. Genetic mutations in cytochrome P450 (CYP) 2C9 and the vitamin K epoxide reductase enzyme gene

*VKORC1* are of great importance, but routine use of genetic testing to guide VKA therapy has not been recommended because of a lack of randomized data [45–47]. Noteworthy, an ongoing US trial (the “Genetics informatics trial”), will be the first adequately powered trial to detect a difference in thrombotic and major bleeding events with genotype-guided VKA dosing [48].

### Non-vitamin K Oral Anticoagulants

Numerous difficulties in the long-term management of VKA therapy, including slow onset and offset of anticoagulant effect, the narrow therapeutic window, pronounced inter- and intraindividual variability in the anticoagulant intensity related to the genetic factors and numerous food and drug interactions, thus necessitating regular laboratory monitoring of anticoagulation intensity, as measured by the INR, and the need for frequent dose adjustments, as guided by the INR values, prompted the efforts to develop alternative oral medication. The ideal anticoagulant should target a specific coagulation factor, with a predictable, dose-related anticoagulant effect, and comparable efficacy as VKAs and possibly better safety than VKAs [49]. NOACs [also referred to as DOACs (direct oral anticoagulants)] fulfill most of these criteria, but still have some limitations (Table 1).

#### Oral Direct Thrombin Inhibitors

The oral direct thrombin inhibitor dabigatran etexilate was the first approved non-vitamin K oral anticoagulant [50] (Fig. 1, Table 1).

The pivotal, randomized, phase III clinical trial that established the efficacy and safety of dabigatran in comparison to dose-adjusted warfarin for the prevention of stroke and systemic embolism in patients with non-valvular AF, the “RE-LY” (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, showed non-inferiority of dabigatran 110 mg twice daily and superiority of dabigatran 150 mg twice daily in comparison to warfarin in the reduction of stroke and systemic embolism, with lower rates of major bleeding in the

110-mg-dose treatment arm and comparable major bleeding rates in the 150-mg-dose treatment arm relative to the warfarin-treated patients [51, 52].

Both dabigatran doses tested in the RE-LY trial (i.e., 150 and 110 mg) were subsequently approved in Europe, whilst in the USA only the 150 mg dose and the 75 mg dose, which was never tested in a RCT, were approved. Numerous large observational studies investigating the “real-world” safety and effectiveness of dabigatran in routine clinical practice broadly confirmed the RE-LY findings [53–60]. Dabigatran 150 and 110 mg twice daily showed comparable results in the prevention of ischemic stroke and systemic embolism compared to VKAs. Key findings concerning bleeding complications have been a significant reduction in the risk of intracranial hemorrhage and comparable or lower major bleeding rates with dabigatran compared to VKAs, whereas the reports on the risk of gastrointestinal bleeding with dabigatran were conflicting, with overall tendency towards the higher gastrointestinal bleeding risk with dabigatran relative to warfarin [60, 61].

Dabigatran is predominantly eliminated renally (~ 80% of the ingested dose). The pre-specified RE-LY subgroup analysis revealed consistent effects of both dabigatran doses relative to warfarin in patients with moderate renal dysfunction [62]. However, major bleeding rates were higher in all three treatment arms in patients with impaired renal function compared to those with preserved renal function. Importantly, patients with severe renal failure [creatinine clearance (CrCl) < 30 ml/min] were excluded from the RE-LY study. As per the European label, dabigatran should not be used if CrCl is below 30 ml/min, whilst the US label allows the use of 75 mg twice daily in patients with a CrCl of 15–30 ml/min [17, 19, 63]. Despite the lack of high-quality evidence, dabigatran has been prescribed to hemodialysis patients. However, reported results with higher rates of hemorrhagic deaths in patients on hemodialysis and on dabigatran compared to warfarin were alarming [64].

The RE-LY trial showed an age-related risk of bleeding with benefits of 110 over 150 mg dose

**Table 1** Overview of non-vitamin K oral anticoagulant drugs [50, 52, 62, 68, 72, 74–77, 89–91, 96–100, 105, 158]

	<b>Dabigatran etexilate</b>	<b>Rivaroxaban</b>	<b>Apixaban</b>	<b>Edoxaban</b>
EMA approval	March 2008	September 2008	May 2011	June 2015
FDA approval	October 2010	July 2011	December 2012	January 2015
Pivotal phase III clinical trial	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Prodrug	Yes	No	No	No
Mechanism	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Absolute bioavailability (%)	6.5	≥ 80	50	62
Time to peak concentration (h)	0.5–2	2.5–4	3–4	1–2
Half-life (h)	12–17	5–13	8–15	6–11
Metabolism by CYP	No	Yes	Yes	Yes
P-glycoprotein substrate	Yes	Yes	Yes	Yes
Excretion via urine as unchanged active drug (%)	80	33–50	25	50
Dose monitoring	Modification of the thrombin generation test Diluted thrombin time (dTT) Activated partial thromboplastin time (aPTT) Ecarin clotting time (ECT)	Anti-FXa assay	Anti-FXa assay	Anti-FXa assay
Dosing recommendation (according to prescribing information)				
Standard dose	150 mg bid	20 mg qd	5 mg bid	60 mg qd
Reduced dose	110 mg bid <sup>a</sup>	15 mg qd	2.5 mg bid	30 mg qd
Reduce dose if	Age ≥ 80 years	CrCl 15–49 ml/min	Two out of three:	One or more of the following:
	Co-medication with verapamil		Age ≥ 80 years	CrCl 15–50 ml/min
	Consider dose reduction:		Body weight ≤ 60 kg	Low body weight ≤ 60 kg

**Table 1** continued

	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
	CrCl 30–49 ml/min		Serum creatinine $\geq 1.5$ mg/dl	Co-medication with strong P-gp inhibitors (e.g., dronedarone)
	Age 75–80 years			
	Gastritis, gastroesophageal reflux disease			
	Increased risk of bleeding			
If CrCl 15–29 ml/min	Not recommended	Reduced dose	Reduced dose	Reduced dose
Gastrointestinal intolerance	Dyspepsia and esophagitis	None	None	None
Antidote/reversal agent	Idarucizumab	Andexanet alfa <sup>b</sup>	Andexanet alfa <sup>b</sup>	Andexanet alfa <sup>b</sup>

*bid* twice a day, *CYP* cytochrome P450, *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *qd* once a day, *CrCl* creatinine clearance

<sup>a</sup> 75 mg bid available in the USA

<sup>b</sup> Manufacturer currently seeking licensure in North America and Europe

in patients 75 years or older, as was also demonstrated in a recent meta-analysis [65, 66]. Dose reduction depending on additional patient-specific risk factors should therefore be considered [34].

In addition, caution should be exercised regarding simultaneous administration of P-glycoprotein inhibitors and inducers, as dabigatran etexilate is a P-glycoprotein substrate [67].

The most common side effect is dyspepsia and it has been recently suggested that it is not only the upper abdominal pain but definite esophagitis, maybe due to the tartaric acid in dabigatran etexilate capsules [68]. The increased risk of myocardial infarction amongst patients on dabigatran is currently under debate [69–71].

#### **Oral Direct Thrombin Inhibitors Antidote**

The weak point of nonexistent reversal agents in NOAC therapy has now been overcome with the new antidote idarucizumab. Idarucizumab, a monoclonal antibody fragment, binds

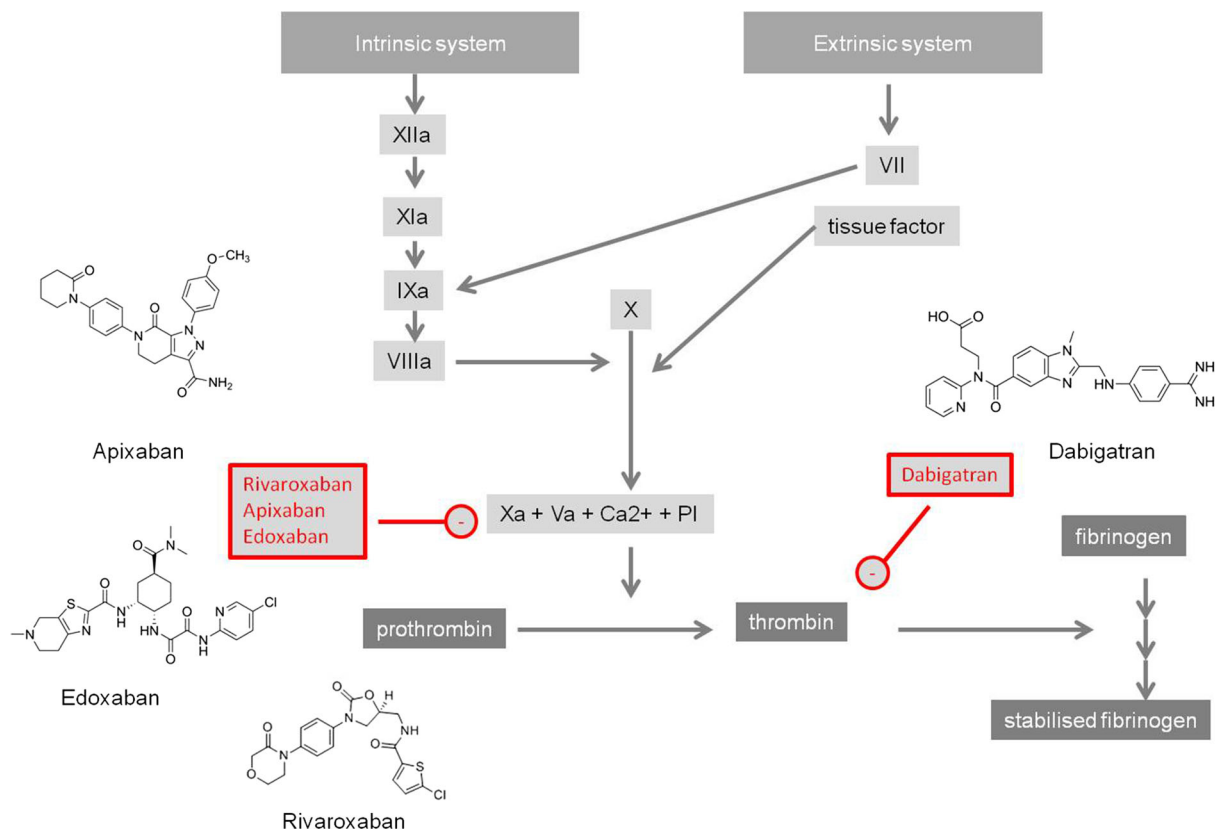
dabigatran with a 350 times higher affinity compared to thrombin and acts rapidly [72]. The full-cohort analysis of the “RE-VERSE AD” (Reversal Effects of Idarucizumab on Active Dabigatran) study showed recently that idarucizumab is effective for dabigatran reversal among patients with uncontrollable or life-threatening bleeding or patients who were about to undergo urgent surgery or invasive procedures [73].

#### **Oral Factor Xa Inhibitors**

##### **Rivaroxaban**

The direct oral factor Xa inhibitor rivaroxaban inhibits free, clot-bound, and within-prothrombinase-complex factor Xa (Fig. 1) [74] and has an oral bioavailability of nearly 100% when taken with food. The pivotal, randomized, phase III clinical trial “ROCKET AF” (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF)





**Fig. 1** Schematic coagulation cascade and anticoagulants. Extrinsic and intrinsic coagulation pathways are displayed showing targets of direct factor Xa inhibitors and direct thrombin inhibitor. The chemical structure information for rivaroxaban, apixaban, edoxaban, and dabigatran are available in the PubChem Substance and Compound

database through the following identifier numbers: rivaroxaban—PubChem CID 9875401, CAS 366789-02-8; apixaban—PubChem CID 10182969, CAS 503612-47-3; edoxaban—PubChem CID 10280735, CAS 697761-98-1; dabigatran—PubChem CID 216210, CAS 211915-06-9 [159]

showed non-inferiority for prevention of stroke or systemic embolism compared to warfarin in 2011 [75]. One-third of rivaroxaban is eliminated in the urine and 7% in the feces [76] (Table 1). In the ROCKET AF patients received 20 mg rivaroxaban daily with normal renal function or mild impairment and 15 mg daily with a CrCl between 30 and 49 ml/min. Rivaroxaban is also approved in Europe for patients with severely reduced kidney function (CrCl 15–29 ml/min) with the reduced dose regime, i.e., 15 mg daily [77].

Notably, there has been a large debate about the ROCKET AF results and in particular with regard to the INR measurements, as the device used to measure INR values in the warfarin arm was recalled by the FDA in December 2014

because of lower INR values compared to those found by a laboratory method [78]. However, subsequent analyses have shown that this could not have altered the main trial results [79].

The “XANTUS” trial (Xarelto on Prevention of Stroke and Non-central Nervous System Systemic Embolism in Patients with Non-valvular Atrial Fibrillation), a prospective, non-interventional study conducted at 311 centers across Europe, Canada, and Israel reported low stroke rates and even lower rates of major bleedings than in ROCKET AF with the selected dose regime at the discretion of the treating physician [80]. Other “real-world” data reports and large registries also confirmed safety of rivaroxaban treatment in heterogeneous patient populations [81, 82]. Although rivaroxaban has

been reported to have an inferior profile concerning major bleeding in “real-world” pairwise comparisons to dabigatran and apixaban but comparable to warfarin [83–86], such comparisons have numerous limitations. Indeed, the risk for intracranial hemorrhage has been proven to be lower in patients on rivaroxaban compared to warfarin as shown in the “REVISIT-US” (Real-World Evidence on Stroke Prevention in Patients with Atrial Fibrillation in the United States) study. The REVISIT-US is a retrospective administrative claims database study, wherein 11,411 rivaroxaban users were propensity score matched 1:1 to warfarin users and rivaroxaban use was associated with a 47% reduction in hazard ratio concerning intracranial hemorrhage compared to warfarin [82].

Rivaroxaban has been associated with better compliance in real-world data due to once-a-day dosing compared to twice-daily dosing of apixaban and dabigatran, although this finding could not be consistently validated in all recent studies [87, 88]. On the other hand, as the anticoagulant effect declines rapidly after even one missed dose, strict adherence to the prescribed dosing regime is crucial.

### **Apixaban**

Apixaban is the third approved NOAC, a potent direct factor Xa inhibitor (Fig. 1) which is predominantly eliminated hepatically [89] (Table 1).

Apixaban has been evaluated in two key clinical trials. The AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial was a randomized, double-blinded study that compared apixaban to aspirin in patients unsuitable for VKA therapy [90]. Patients received a dose of 5 mg apixaban twice daily or a reduced dose of 2.5 mg twice daily when meeting two out of three of the following criteria: age  $\geq 80$  years, body weight  $\leq 60$  kg, and serum creatinine  $\geq 133$   $\mu\text{mol/l}$ . The patients randomized to the aspirin therapy arm received one to four 81 mg aspirin doses per day at the discretion of the treating physician. The trial was terminated prematurely because of the marked superiority of apixaban for preventing strokes

and systemic embolism, with comparable bleeding risks between the two arms [90].

The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF) trial was a randomized trial comparing apixaban with warfarin to prevent stroke and systemic embolism among 18,201 patients with AF [91]. The recommended study doses of apixaban were the same as described in the AVERROES trial. Besides non-inferiority it also demonstrated superiority over warfarin in terms of primary outcomes, i.e., stroke or systemic embolism, major bleeding, and all-cause mortality [91].

Since its approval, apixaban has been evaluated in large registries [84, 92, 93] and showed a particularly favorable risk profile concerning major bleeding risk, that has been found consistently in recent studies [84, 85]. Recommended dose has been reduced in ARISTOTLE and AVERROES as stated above in patients meeting two of the following criteria: age  $\geq 80$  years, serum creatinine  $\geq 1.5$  mg/dl (133  $\mu\text{mol/l}$ ), or weight  $\leq 60$  kg, which represents the current recommendation of the European label. In a recently published renal function-centered analysis of the ARISTOTLE trial, efficacy and safety were reported to be similar in patients with normal, poor, and worsening renal function compared to warfarin [94].

As apixaban has the highest percentage of hepatobiliary metabolism of all NOACs, caution should be taken in the setting of advanced hepatic failure as studies concerning risk profile of this specific patient population are lacking [95]. Apixaban is metabolized via the CYP450 system leading to certain drug interactions and, just like the other factor Xa inhibitors, apixaban is a substrate of P-glycoprotein [96].

### **Edoxaban**

Edoxaban, a direct factor Xa inhibitor, is the fourth NOAC approved for prevention of stroke and other thromboembolic events in patients with atrial fibrillation [97].

Like rivaroxaban, edoxaban is applied once daily, on the basis of a randomized clinical phase II study that found significantly higher bleeding rates compared to warfarin for the twice daily dose regime compared to the once



daily application [98]. Although edoxaban is promoted as trouble-free concerning CYP450 system interactions because it is metabolized via hydrolysis, it shows interaction with P-glycoprotein (P-gp) inhibitors, but is the only factor Xa inhibitor not contraindicated in co-medication with strong inhibitors of both CYP3A4 and P-glycoprotein, such as dronedarone (Table 1) [99]. Excretion is 50% renal leading to a recommended dose reduction to 30 mg daily in patients with renal impairment (Table 1) [97]. The pivotal, randomized, phase III clinical trial to evaluate edoxaban, ENGAGE AF-TIMI 48 (The Effective Anticoagulation with Factor Xa Next Generation in AF-Thrombolysis in Myocardial Infarction 48), compared two different doses of edoxaban (30 and 60 mg) to warfarin [100]. In the ENGAGE AF-TIMI 48 trial the edoxaban dose was halved if the estimated CrCl was 30–50 ml/min, patient's body weight was 60 kg or less, or if there was concomitant use of verapamil or quinidine as they represent potent P-glycoprotein inhibitors. The trial showed non-inferiority of edoxaban to warfarin in the prevention of stroke or systemic embolism and significantly lower rates of bleeding and death from cardiovascular causes. Of note, the TTR in the warfarin arm was 68.4% and thus higher than in all the other pivotal NOAC trials [52, 75, 91]. Worthy of discussion, a post hoc analysis of the ENGAGE AF-TIMI 48 trial reported higher efficacy in patients with mild kidney dysfunction compared to patient with normal kidney function with a CrCl > 95 ml/min. In patients with normal CrCl the risks of stroke and systemic embolism were in favor of warfarin therapy [101] perhaps due to lower drug exposure in patients with normal kidney function. This is currently under debate and calls for further investigation concerning optimal edoxaban dosing in patients without renal impairment [102, 103]. Gathering of real-world data on safety and effectiveness of edoxaban is currently under way.

### Factor Xa Inhibitor Antidote

Andexanet alfa is a recombinant factor Xa molecule with higher affinity for natural factor

Xa inhibitor than endogenous factor Xa, thus reversing factor Xa inhibition. In the two randomized controlled trials ANNEXA-A (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXa Inhibitors-Apixaban) and ANNEXA-R (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXa Inhibitors-Rivaroxaban), the new antidote was tested in older healthy volunteers, showing reversing effects within 2–5 min after bolus administration, sustaining during continuous infusion, and fading effects approximately 1–3 h after cessation of administration [104]. More recently, the reversal agent was tested in 67 patients with acute major bleeding [105]. Further clinical trials on efficacy and safety are pending.

### From VKA to NOAC: Implicated Challenges

In clinical practice, patients switch more and more often from VKA to NOAC therapy. Whether the switching process involves a higher risk for bleeding complication has been the subject of current studies. A recently published French matched-cohort study, based on administrative national health-insurance data in combination with a hospital discharge database, investigated a total of 6705 switchers, defined as patients previously on VKA therapy who switched to NOACs, compared to 10,705 patients remaining on VKAs. With the limitation of a relatively short follow-up period, no difference between groups for bleeding events was observed [106]. Another hot topic in NOAC therapy is co-medication with antiplatelet drugs (triple therapy) due to coronary artery disease and consecutive interventions and has been discussed in detail elsewhere [107]. In addition, special situations, e.g., new-onset atrial fibrillation post cardiac surgery and anticoagulation during cardioversion or catheter ablation, are currently extensively studied [108–110]. Although the problem of slow therapeutic onset and offset of anticoagulant effect in warfarin treatment could be overcome with NOACs, there is some evidence that the skipping of one dose has a more detrimental effect, especially in NOACs with

once-daily dosing [111]. The compliance of NOAC intake and measures to maximize it are therefore currently studied extensively [112]. Another important topic is the medical costs, which are *prima facie* higher in NOAC than in VKA therapy and thus may limit access to NOACs [113]. However, recently published cost-effectiveness analyses showed that NOACs provide a decent cost-effectiveness owing to clinical benefits and this has been shown in several countries [113, 114]. It will be interesting how world-wide anticoagulation standards will change in the next few years. The Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) provides interesting insights into the world-wide prescription changes during the conversion period with introduction of NOACs [115, 116].

### Future NOACs in the Pipeline

At the moment, there are additional NOACs in clinical testing [49]. Betrixaban is a specific and reversible factor Xa inhibitor that has been developed to overcome dose adjustment in patients with renal impairment. Betrixaban is excreted in the gut (82–89%), but uses the P-glycoprotein efflux pump like the other factor X inhibitors [117]. RCTs for stroke prevention in atrial fibrillation are lacking to date but the phase III clinical trial “APEX” (Acute Medically Ill Venous Thromboembolism Prevention with Extended Duration Betrixaban) [118, 119] retrospective substudy showed a reduced all-cause stroke and ischemic stroke through 77 days follow-up [120]. TTP889, a selective factor IXa antagonist, and GCC-4401C, a direct factor Xa inhibitor, are two other anticoagulants currently in clinical testing [121, 122].

## LEFT ATRIAL APPENDAGE LIGATION AND CLOSURE

Different approaches have been evaluated to get rid of “our most lethal attachment” [123]. Currently available and broad applied techniques and devices include surgical ligation and

excisions, stapling tools as well as epicardial clips [124, 125].

Surgical left atrial appendage closure has been performed for decades and it also a convenient supplemental procedure in hearts that are already exposed during cardiac surgery. However, profound evidence through randomized controlled prospective trials supporting this approach for stroke prevention is lacking [126]. In 2005 the Left Atrial Appendage Occlusion Study (LAAOS), the first randomized, non-blinded study of surgical LAA occlusion was conducted, comparing the two arms LAA occlusion or control with a 2:1 randomization favoring LAA occlusion. Not addressing stroke prevention itself but safety and feasibility, the study reported LAA occlusion in 66% of the patients randomized to the LAA occlusion arm. Two mechanisms of failure of sufficient LAA closure using either stapling devices or surgical sutures have been described: (1) persistent flow across suture lines and (2) stapling too distally with a residual LAA stump greater than 1 cm [127]. A more recent study from Lee et al. even identified insufficient LAA closure with surgical techniques via intraoperative transesophageal echocardiography (TEE) in up to 63% [125]. Of note, insufficient closure seems to be more harmful and thrombogenic than no closure at all [128, 129].

Introduced in 2014, the LAAOS III trial aims to determine stroke risk by comparing patients undergoing elective cardiac surgery with concomitant surgical LAA closure and without LAA closure, respectively [130]. Although final results after the 4-year follow-up period are eagerly awaited, it has to be pointed out that anticoagulation will be continued in both groups. Current guidelines recommend to continue anticoagulation in at-risk patients after surgical occlusion or exclusion of the LAA as well. However, even if different stroke risk components are addressed (anatomic region of thrombus formation versus decreased affinity of thrombus formation) it appears controversial to continue OAC after LAA occlusion or exclusion *per se* [16].

Another method for LAA occlusion during cardiac surgery is a clip device (“AtriClip”) that is placed epicardially at the base of the left atrial

appendage. Study reports from the “EXCLUDE” (Exclusion Device in Patients Undergoing Concomitant Cardiac Surgery) trial suggested a fast, atraumatic, and highly successful left atrial appendage occlusion [131], and possible application of the device in off-pump surgery has been shown very recently [132]. Another recently developed tool favors access via mini-thoracotomy and occluding LAA via a clamp consisting of two tubes connected by an elastic bow [133].

## INTERVENTIONAL PERCUTANEOUS ENDOCARDIAL AND EPICARDIAL LAA CLOSURE

In 2002 early experiences with a new device for interventional, percutaneous LAA occlusion were reported. The percutaneous left atrial appendage transcatheter occlusion (PLAATO) device enabled non-invasive occlusion of the left atrial appendage via an implant and delivery catheter [134]. The device was built as a self-expanding nitinol cage covered with an occlusive expanded polytetrafluoroethylene membrane to occlude blood flow into the remaining orifice equipped with three anchors. After the first promising results and implantations the tool was withdrawn from the market in 2006.

The next upcoming device has been the WATCHMAN, which received the CE mark in 2005. The device has a self-expanding nitinol frame covered with a permeable polyethylene terephthalate membrane and ten active fixation anchors. In the multicenter, randomized WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) trial, the device was implanted successfully in 91% of all cases [135]. It showed non-inferiority in comparison to continued warfarin therapy in the primary composite endpoint stroke, systemic embolism, and cardiovascular death event rates. The rate of the primary adverse procedure-related events, with the most frequent one pericardial effusion, led to the demand of a further trial for FDA approval. Hence, the answer was the “PREVAIL” (Prospective Randomized Evaluation of the

Watchman LAA Closure Device in Patients with AF Versus Long Term Warfarin Therapy) trial that showed significant improvement of procedural safety but failed to meet the non-inferiority criteria [136]. Then again, the extended analysis of the PROTECT AF trial, after 3.8 years of follow-up, concluded both non-inferiority and superiority of the WATCHMAN device compared to warfarin for the combined outcome of stroke, systemic embolism, and cardiovascular death [137]. However, it is important to mention that the patient-level meta-analysis comparing left atrial appendage closure versus systemic therapy (warfarin) published in 2015 also failed to prove non-inferiority in the device group concerning the most interesting isolated endpoint of ischemic stroke but showed a significant reduction of hemorrhagic stroke leading to no significant difference in the rate of all stroke or systemic embolism [138]. In summary, conclusive data concerning left atrial occlusion devices is lacking to date.

The third LAA closure device, the Amplatzer Cardiac Plug (ACP), has a self-expanding nitinol mesh forming a lobe and disk, connected by a central neck. The lobe is implanted 10 mm inside of the LAA orifice to anchor the device, supported by distally located stabilizing wires arranged crown-like. A procedural success rate of 97.3% was reported in a multicenter study including a total of 1053 patients from 22 centers [139]. It has been highlighted, however, that the number of periprocedural complications was “moderate” with cardiac tamponade as the leading adverse event. The next generation of the ACP, the Amulet or ACP2, has to be implanted 12 mm inside the LAA cavity, features stiffer stabilizing wires, and is available in larger disc diameters than its predecessor [140]. Besides the same basic structure, implantation of the Amulet device has been accompanied by a lower rate of non-relevant pericardial effusions, compared to the ACP in an early-experience dual-center cohort study [141].

As it is the case in every intervention, the procedural complication rate is dependent on the interventionist’s expertise. Apparently, greatly feared adverse events of left atrial appendage occlusion device implantation are pericardial effusion and device embolization

which have an occurrence rate of up to 2% [142]. Pre-interventional imaging aims to maximize procedural safety and success, improving assessment of individual relationships to anatomical adjacent structures [143, 144]. However, a sufficient infrastructure with post-device monitoring interval is mandatory. The European Heart Rhythm Association survey provided insights into clinical practice in 2012 and found out that 73% of the responding centers performed at most 10 procedures per year. The intervention itself is most often performed by the interventional cardiologist or the electrophysiologist as the primary operator with the patient either under sedation or under general anesthesia. Interestingly, the top three limiting factors in clinical practice have been the cost-intensive acquisition of LAA occlusion devices, the limited efficacy data, and the relevant risk of complications [145].

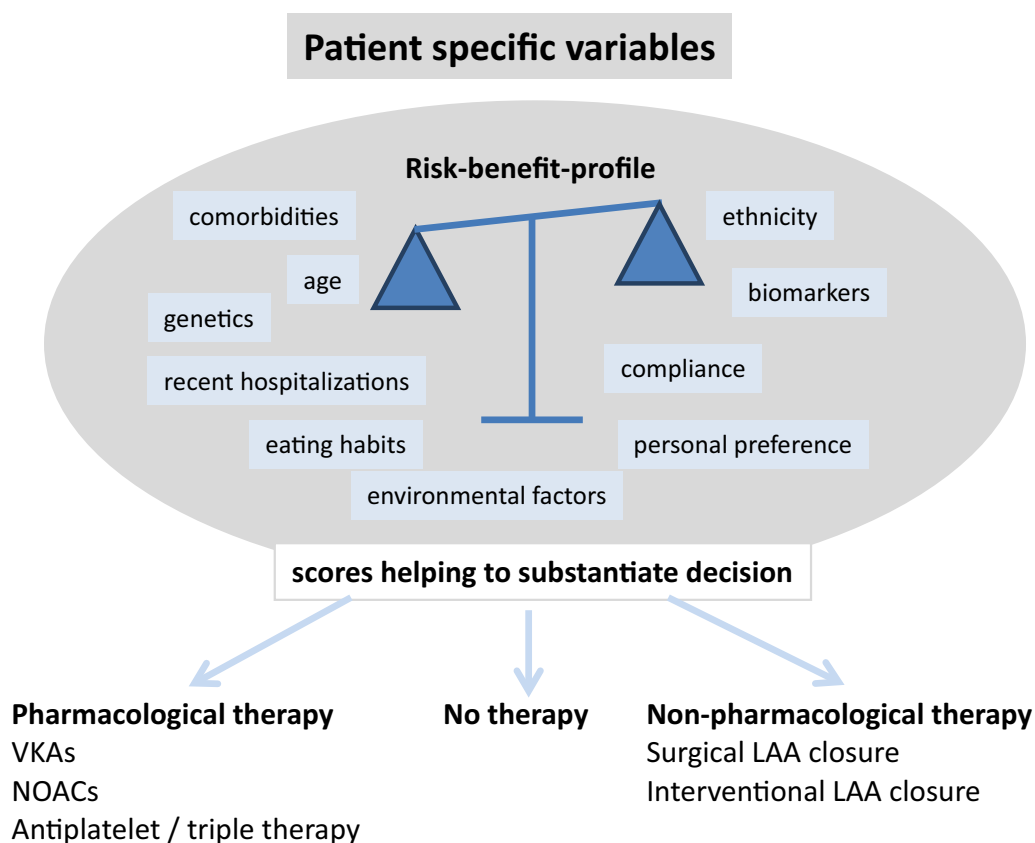
Current European guidelines recommend left atrial appendage occlusion with class IIb level of evidence B in patients with AF and contraindications for long-term OAC as well as in patients with AF undergoing cardiac surgery or thoracoscopic AF surgery [16].

Pursuant to the goal to reduce bleeding complications, a current matter of debate is the antithrombotic management following left atrial appendage occlusion device implantation [146]. On the one hand, patients selected for device implantation present themselves with a high risk of stroke and high risk of bleeding complications. On the other hand, after successful device implantation, there is a risk for clot formation on the artificial device surface until complete endothelialization has occurred. In the RCTs PROTECT AF and PREVAIL evaluating WATCHMAN performance, patients received postprocedural VKA therapy in combination with aspirin for 45 days followed by 6 months of dual platelet inhibition with clopidogrel and aspirin if closure was successful [135, 136]. As a result of the high bleeding risk in most patients with indication for left atrial appendage occlusion, this regime appears difficult. Another approach is to treat patients after device implantation for 6 months with dual antiplatelet therapy and with lifelong aspirin thereafter [147]. A randomized controlled trial

in OAC-contraindicated patients determining which medical regime is best following left atrial appendage occlusion is lacking, and the antiplatelet and anticoagulation regime after left atrial appendage occlusion is currently diverse in clinical practice.

The LARIAT procedure, a percutaneous catheter-based LAA ligation with a suture delivery component, uses a combined endo- and epicardial approach for LAA closure. Following initial reports of bleeding and perforation due to the epicardial access, it has been developed further. The basic principle of pericardial and trans-septal access followed by the placement of the endocardial magnet-tipped guidewire in the LAA and connection of the epicardial and endocardial magnet-tipped guidewires for stabilization, positioning of a snare, and release of a pretied suture for LAA ligation, however, has not changed [148]. In 2014 safety and efficacy outcomes of 154 patients enrolled for the LARIAT procedure were reported with quite a few major complications: emergency surgery was required in three patients (2%) because of right ventricular perforation, and LAA perforation and major bleeding in a total of 14 patients [149]. Up to now, the LARIAT procedure has not managed to establish itself firmly.

Overall, there are three main open issues in the field of left atrial appendage occlusion: First, the available data cannot be considered sufficient. It is remarkable that our current practice is mainly based on data from 1114 patients randomized in the PROTECT AF and PREVAIL studies [136, 138]. This is a small number of patients from which to draw conclusions for a new treatment strategy for stroke prevention in AF. Second, there is no randomized comparison of interventional LAA occlusion against NOACs. This is important considering the significant reduction of hemorrhagic stroke under NOACs compared with warfarin [150] and the reduced overall risk of major bleeding under NOACs [91]. Third, there is no sufficient data for the patient population for which this technique is currently recommended, namely patients that have a contraindication for OAC. Although non-randomized data suggest that in these patients, at least the short-term outcome is



**Fig. 2** Patient-specific factors influencing decision-making about oral anticoagulation [10, 25–29, 160]

similar to the group of patients without contraindication against the use of oral anticoagulants [151], the long-term benefit of LAA occlusion in this patient population needs to be confirmed [152].

## FUTURE DIRECTIONS

Albeit often ignored and quoted as having “minimal useful function” [123], the LAA does fulfill a variety of physiologic tasks. It is not just that it operates as a blood reservoir, contracts and thus supports hemodynamics, but it also has a substantial endocrine activity with an atrial natriuretic peptide production of approximately 30% of the whole heart [153]. Furthermore, it serves as a reservoir for cardiac progenitor cells [154]. Little is known about post-device implantation effects on the aforementioned functions [155, 156]. Besides new direct OACs and improved LAA device

technology there is currently no other idea to eliminate stroke risk. New directions would include possibilities for local release of blood-thinning agents to decrease whole body adverse effects of anticoagulation, LAA occlusion devices coated with endogenous cell layers to diminish formation of thrombus at the device surface, and 3D printed LAA models to facilitate guiding and device sizing [157].

## CONCLUSIONS

AF and risk for stroke are closely interwoven. Thus, a variety of pharmacological and non-pharmacological treatments have been evaluated to reduce thromboembolic risks (Fig. 2). Pharmacological treatment is appropriate and comfortable for a large proportion of patients. Recently, new OACs have been developed with several advantages over classic VKAs. Despite the initial enthusiasm, all of the new



drugs do have distinct limitations and caution has to be exercised when severe comorbidities are present. Furthermore, the potential for drug interaction is not to be underestimated. Worthy of note is the development of antidotes and reversal agents, which had been a major demand in the last few years.

For patients with a high bleeding risk and thus not suitable for oral anticoagulation, a palette of surgical and non-surgical methods for LAA occlusion are available. Of note, LAA occlusion always entails the possibility of severe complications due to the necessary access or complex device positioning. Currently, this therapy is reserved in clinical practice for patients who have a clear indication for anticoagulation but also a contraindication for such a treatment.

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