

Strategies for primary and secondary stroke prevention in atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) is the most common type of cardiac rhythm abnormality in adults, affecting 1 to 1.5% of the general population in the Western world and is the major risk factor for stroke with a fivefold risk compared with the general population. Pharmacological and nonpharmacological strategies are available for controlling recurrent or permanent AF as well as for prevention of AF. Prevention of recurrent AF is one of the best protections against AF-related stroke and reduces the prevalence of stroke by almost 25%. Antiplatelet compounds are indicated for CHAD scores 0-1 and reduce the risk of stroke from AF by 20 to 25%. For CHAD scores >1 oral anticoagulation with vitamin K antagonists is indicated and reduces the risk of stroke by 62%. Since inhibitors of coagulation factors Xa, VII, or IIa have either not been clinically tested for their efficacy for prevention of stroke from AF, did not show a comparable effect to well-established drugs, or had excess side effects (idraparinux, ximelagatran), and since mechanical devices are highly questionable concerning their long-term effect, there is currently no alternative to oral anticoagulation with vitamin K antagonists as primary or secondary stroke prevention in high-risk AF patients.

KEYWORDS

Anticoagulation, coagulation factors, stroke prevention, prophylaxis, side effects, drug safety

INTRODUCTION

Atrial fibrillation (AF) is the most common type of cardiac rhythm abnormality in adults, affecting 1 to 1.5% of the general population in the Western world and is the major independent risk factor for stroke.^{1,2} The prevalence of AF increases with age, occurring in less than 1% of the general population at age <60 years, but in almost 10%

of those >80 years.¹ AF may be categorised as valvular or nonvalvular, lone or associated with other cardiac disease, permanent or paroxysmal, or as hereditary or acquired. Irrespective of the cause of AF, it is associated with a fivefold increased risk of stroke or embolism compared with patients without AF.² The annual risk of ischaemic stroke in patients with lone AF is 1.3% and increases to 10 to 12% in patients with previous stroke or transient ischaemic attack.³ Strokes from AF are usually more severe and associated with an increased risk of morbidity, mortality, and poorer functional outcome than strokes from other causes.² The risk of stroke from AF is enhanced by the presence of additional risk factors, such as age >65 years, arterial hypertension, diabetes mellitus, heart failure, or previous stroke, as expressed by the CHAD score.⁴ Age >65 years, presence of heart failure, arterial hypertension, and diabetes mellitus count 1 point each in this score, and previous stroke/embolism 2 points.⁴

PHARMACOLOGICAL STRATEGIES FOR STROKE-PREVENTION IN ATRIAL FIBRILLATION

Upstream therapy and risk factor modification

Pharmacological and nonpharmacological strategies for controlling AF as well as primary prevention of AF by 'upstream' therapy and risk factor modification are likely to contribute substantially to the reduction of stroke rates in the general population (*table 1*).² Despite recent advances and promising new approaches, prevention of recurrent AF may be one of the best protections against AF-related stroke and may reduce the prevalence of stroke by almost 25%.⁵

Antiarrhythmic drugs can approximately double the maintenance rate of sinus rhythm in recurrent AF.⁶ Antiarrhythmic drugs are indicated for symptoms of short AV nodal conduction time with a high ventricular heart rate in

Table 1. Strategies for primary or secondary stroke prevention in AF, clinically applicable or under clinical development

<p>Pharmacological</p> <p>Upstream therapy and risk factor modification (ACEI, ARBs (sartans), statins, digitalis, amiodarone, β-blockers, calcium antagonists)</p> <p>Platelet inhibitors (aspirin, clopidogrel, ticlopidine (withdrawn))</p> <p>Multitargeted coagulation inhibitors</p> <ul style="list-style-type: none"> • Vitamin-K antagonists (warfarin, phenprocoumon, acenocoumarol) • Heparins (UFH or LMWH) <p>Selective inhibitors of coagulation factors</p> <ul style="list-style-type: none"> • Factor Xa inhibitors <ul style="list-style-type: none"> - Short-acting, direct inhibitors (rivaroxaban (BAY 597939)) - Long-acting, indirect inhibitors (idraparinix, biotinylated idraparinix) • Factor IIa (thrombin) inhibitors <ul style="list-style-type: none"> - Direct oral thrombin inhibitors (ximelagatran/melagatran (withdrawn because of liver toxicity), dabigatran (BIBR-1048)) <p>Nonpharmacological</p> <p>Nonpharmacological upstream measures and risk factor modification</p> <p>Electrical cardioversion</p> <p>Electrical ablation of right atrial conductive tissue</p> <p>Percutaneous left atrial appendage occlusion (PLAATO)</p> <p>Minimally invasive surgical isolation of the LAA (Maize, COX procedure)</p> <hr/> <p>ACEI = angiotensin-converting enzyme inhibitors; ARBs = angiotensin-II-receptor-blocking drugs; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; LAA = left atrial appendage.</p>
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recurrent or sustained AF.⁶ Pharmacological cardioversion is indicated if AF lasts less than one year and if the left atrium is normally sized. It is carried out by application of digitalis (in case of normal contractility), amiodarone (in case of reduced contractility), β -blockers, calcium antagonists, or propafenon (in case of normal contractility). Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor-blocking drugs (ARB) may further improve the maintenance of sinus rhythm through cardiac remodelling⁶ or prevention of atrial endocardial dysfunction by rapid atrial pacing.⁷ Retrospective, cross-sectional and longitudinal analysis of the SPORTIV III and V data, however, did not demonstrate a significant benefit of ACEI or ARB in AF patients, except in patients >75 years.⁸ Preliminary studies suggest that also statins, such as atorvastatin, which have pleotropic effects, such as reduction of vascular inflammation, could reduce the AF incidence after cardiac surgery and the recurrence rate of AF after electrical cardioversion,^{9,10} particularly together with β -blockers,¹¹ although other studies with paravastatin did not confirm these findings.¹²

Platelet inhibitors

An effective approach for reducing the risk of stroke from AF in primary stroke prevention is platelet inhibitors.

If the CHAD score is <2, (low-risk patients) platelet inhibitors, such as acetylsalicylic acid (ASA), clopidogrel, or ticlopidine, are indicated as primary stroke prevention in AF.³ Antiplatelet compounds reduce the risk of stroke from AF by 20 to 25%.² Although clopidogrel has proven efficacy and superiority compared with ASA to prevent systemic vascular events in at-risk patients, it currently does not play an important role in the prevention of AF-related thromboembolic events.³ In a recent study (CHARISMA trial) clopidogrel plus ASA was not more effective than ASA alone in preventing strokes in AF patients.¹³ In a substudy of the ACTIVE W trial the combination of clopidogrel plus ASA had a higher risk of bleeding compared with vitamin K antagonists (VKA), irrespective of whether patients suffered from paroxysmal or sustained AF.¹⁴ Whether the combination of extended-release dipyridamol and ASA and the combination of clopidogrel with ASA are superior to ASA in monotherapy for stroke prevention in AF has not been investigated.¹⁵

Multitargeted (acting on a number of coagulation factors) Vitamin K antagonists

Although VKA have been in clinical use for more than 50 years, they were not proven to be beneficial in primary or secondary stroke prevention until about a decade ago.¹⁶ In high-risk patients (CHAD score >1) oral anticoagulation (OAC) with VKA (warfarin, phenprocoumon, acenocoumarol) is a class I ACC/AHA indication, unless there are contraindications.³ Pooled data from trials comparing antithrombotic treatment with placebo have shown that VKA reduce the risk of stroke from AF by 62% with an absolute reduction of about 3% per year.^{3,5,16} In high-risk patients, warfarin is superior to ASA in preventing strokes, with a relative risk reduction of 36%. The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study additionally showed that VKA (warfarin) also reduce the risk of stroke in patients >75 years compared with ASA without increasing the bleeding risk.¹⁷ The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) study has shown that warfarin is also superior to antiplatelet therapy with clopidogrel plus ASA in the prevention of embolic events from AF.^{3,5,18} VKA were also superior over a combination of ASA and clopidogrel in a study on 70 patients with nonvalvular AF with regard to plasma markers of thrombogenesis (levels of fibrin D-dimer, β -thromboglobulin, soluble P-selectin, plasma prothrombin fragment 1 + 2).¹⁹ The combination of ASA and clopidogrel, however, was superior over ASA alone in preventing thromboembolic events in AF.²⁰ In a nonrandomised study VKA also proved effective regarding the long-term prognosis of patients with AF who survived a severe, disabling stroke (modified Rankin scale 4-5).²¹ Independent predictors of mortality were

increasing age, increasing handicap, and ASA vs VKA. Previous transitory ischaemic attack and ASA vs VKA were predictors of vascular recurrence. Thus, VKA lengthen survival and decrease the risk of recurrent thromboembolic events.²¹ In patients under antiplatelet therapy for previous peripheral artery disease or stroke who develop AF, switching from antiplatelet therapy to VKA might be all that is required.²² The combination of VKA and antiplatelet therapy only provides additional benefit over VKA alone in patients with prosthetic heart valves.²² The appropriateness of a combination of VKA with antiplatelet therapy in patients with an indication for VKA (AF) who also have an indication for antiplatelet therapy (coronary heart disease) is unsolved.²² Compared with a combination of clopidogrel and ASA, VKA also reduce the risk of stroke in AF patients with a CHAD score <2.²³

Shortcomings of VKA include slow onset of action, numerous drug/drug and drug/food interactions, narrow therapeutic window, complexity of dose adjustment for one third of the patients, need for frequent monitoring, necessity of daily intake, genetic variation in metabolism, and the risk of bleeding.^{16,24} The risk of major haemorrhage under warfarin is twice that with ASA.²⁵ Treatment with VKA needs to be tailored individually on the basis of age, comorbidities, and contraindications.²⁵ Less than 60% of patients without a contraindication to VKA actually receive them.³ Of those who receive VKA <50% are consistently within therapeutic targets.³ Limitations of VKA therapy prompted the development of new anticoagulants with predictable pharmacokinetics, which do not require regular monitoring.²⁵ VKA act nonspecifically, as they inhibit the coagulation cascade at various steps. Desired characteristics of new anticoagulants include good bioavailability, no food/food or food/drug interactions, rapid onset of action, wide therapeutic window, absent necessity of monitoring, availability of an antidote, absence of side effects, absence of interactions with other drugs, and low costs.^{26,27}

Heparins and heparinoids

Unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) are supportive to OAC for preventing stroke in AF or if there are contraindications for OAC. The anticoagulant properties of UFH were detected in 1916 and by the 1930s their therapeutic use was evaluated.²⁸ UFH and LMWH act nonspecifically on a number of coagulation factors. UFH has equipotent activity against factors IIa and Xa but also acts on factors IXa, XIa, and XIIa.²⁹ UFH and LMWH do not require antithrombin-III as a cofactor. Disadvantages of UFH are that it can only be used intravenously, that its laboratory control is difficult, that it stimulates platelets leading to activation, aggregation, and clot formation, and that it rarely (incidence 0.2%)³⁰ causes heparin-induced thrombocytopenia (HIT).^{28,31} Although

LMWH has a predictable half-life, its subcutaneous mode of administration and long-term risks, particularly osteoporosis, mean that it is not feasible for long-term use.³ In a study on 431 patients with acute ischaemic stroke and AF, they did not profit from LMWH (dalteparin) as compared with ASA with regard to primary outcome, measured by the International Stroke Trial scale at three months, and secondary outcome variables.³²

Selective inhibitors of coagulation factors

More recent approaches to primary and secondary prevention of stroke from AF include selective inhibitors of specific coagulation factors involved in the initiation or propagation of the coagulation cascade (factors Xa, II) (*table 1*). To understand the mechanisms of action and side effects, it is important to know that coagulation factors, which are targets of the inhibitory activities of their inhibitors, also affect coagulation independent processes, such as wound healing, inflammation, immune response, tissue repair, angiogenesis, mitogenesis, tumour growth, apoptosis, and cell survival.

Factor Xa inhibitors

Coagulation factor Xa is an attractive target for drug development because of its position at the convergence of the intrinsic and extrinsic clotting pathways.³³ There are two different strategies for inhibiting factor Xa that are being pursued, indirect or direct inhibition, depending on whether factor Xa is inhibited with or without the mediation of antithrombin-III. Direct inhibitors without antithrombin-III mediation have a high bioavailability, a short half-life, and are thus short-acting and orally applicable. They include rivaroxaban (BAY 597939), YM150, apixaban, razaxaban, otamixaban, DX-9065a, LY517717, DU-176b, or betrixaban (*tables 1 and 2*).^{33,34} Indirect inhibitors have a low bioavailability, a long half-life, and are thus long-acting, and are subcutaneously administered. They include idraparinux, biotinylated idraparinux, and fondaparinux (SSR-126517-E). Only those compounds experimentally or clinically applied for preventing stroke/embolism from AF are further discussed.

Direct, short-acting factor-Xa inhibitors

Rivaroxaban is a nonpeptidic, orally bioavailable small molecule, which directly inhibits clot-associated or free Xa activity, prothrombinase activity, and reduces thrombin generation.^{29,32} Rivaroxaban has a high oral bioavailability, a rapid onset of action, a half-life of five to nine hours, and predictable pharmacokinetics. Rivaroxaban has undergone extensive phase II studies for venous thromboembolism prevention after orthopaedic surgery and phase III studies have begun.³⁰ Rivaroxaban demonstrated superiority to enoxaparin for prophylaxis of thromboembolism after total knee arthroplasty with similar low bleeding complications.³⁵

Table 2. Potential or experimental strategies for primary or secondary stroke prevention in AF

Pharmacological		
<i>Selective inhibitors of coagulation factors</i>		
Factor Xa inhibitors	Short-acting, direct inhibitors:	
	Apixaban	Experimental
	Razaxaban	Experimental
	Otamixaban	Clinical development
	Betrixaban	Clinical development
	YM-150	Clinical development
	DX-9065a	Experimental
	LY517717	Clinical development
	DU-176b	Clinical development
	Tick anticoagulant peptide (TAP)	Experimental
	Antistatin (ANT)	Experimental
	Antithrombin-heparin covalent complex (ATH)	Experimental
	JTV-803	Experimental
	PRT05402 (Portola)	Experimental
	Long-acting, indirect inhibitors:	
Fondaparinux (SSR-126517-E)	Approved for VTE	
Factor IIa (thrombin) inhibitors	Nelagatran	Experimental
	Argatroban	Approved for HIT, ACS
	Efegatran	Clinical development
	Desirudin	Approved for ACS
	Lepirudin	Approved for HIT, ACS
	Bivalirudin	Approved for HIT, ACS
	Hirudin	
Factor VIIa inhibitors	Nematode anticoagulant peptide (NAPc2)	Experimental
	Active site-blocked factor VIIa (FVIIai)	Experimental
	Recombinant tissue factor pathway inhibitor (rTFPI)	Experimental
<i>Stimulators of fibrinolysis</i>	Protein-C derivatives	Experimental
	Soluble thrombomodulin	Experimental
Nonpharmacological	Carotid filtering devices (emboli diverted from internal to external carotid artery)	Experimental
	Catheter-based isolation of the pulmonary veins ⁶	Experimental

VTE = venous thromboembolism; HIT = heparin-induced thrombocytopenia; ACS = acute coronary syndrome.

Rivaroxaban is currently being assessed for the treatment and secondary prevention of venous thromboembolism, prevention of stroke from AF, and secondary prevention in acute coronary syndrome.³⁵

Indirect, long-acting factor-Xa inhibitors

Idraparinux is a synthetic O-sulphated, O-methylated pentasaccharide, which tightly binds to antithrombin-III and thereby and specifically induces the inactivation of the procoagulant protease, factor X.³⁶ Idraparinux not only differs structurally from fondaparinux for its additional methyl groups, but also for its half-life of about 80 hours, which is why it is dosed once weekly.³⁷ Idraparinux does not elevate liver enzymes.³⁸ In the AMADEUS trial idraparinux turned out to have a similar effect to warfarin but was significantly more frequently associated with bleeding events than warfarin.³⁹ In deep venous thrombosis, idraparinux had a similar effect to heparin plus a VKA but was less effective in patients with pulmonary embolism.⁴⁰ Idraparinux has a mechanism of action similar to that of heparin.⁴¹ It was developed as an antithrombotic for venous and arterial thrombosis, acute coronary syndrome, stroke, or as adjunct to thrombolytic therapy.³⁷ The biotinylated

form of idraparinux, which has avidin as an antidote, is currently being evaluated in the range of an ongoing phase III trial (BOREALIS-AF study) for its effect on stroke prevention in AF.²⁹

Coagulation factor II (thrombin) inhibitors

Thrombin is a central enzyme in haemostasis exerting potent procoagulant effects and activating platelets.³¹ Thrombin converts fibrinogen to fibrin and activates factors V, VIII, XI, XIII, and platelet protease-activated receptors.²⁹ In addition to its role in haemostasis and coagulation, thrombin exhibits numerous other biological activities affecting inflammation by controlling the expression of cytokines,⁴² immune responses, tissue repair, tumour growth, apoptosis, cell survival, wound healing, endothelial cytoprotection,⁴³ and angiogenesis.⁴⁴ In the cerebrum thrombin induces injury of cortical neurons,⁴⁵ facilitates epileptic seizures,⁴⁶ mediates neurodegeneration or neuroprotection via protein-activated receptors,⁴⁷ induces angiogenesis,^{48,49} and induces the expression of the MKP-1 gene in endothelial cells.⁵⁰ Thrombin inhibitors inhibit thrombin by directly binding to exosite I and/or the active site of thrombin and are applied orally, which is why they

are also termed direct, oral thrombin inhibitors.²⁹ Direct oral thrombin inhibitors include ximelagatran/melagatran, dabigatran, argatroban, efegatran, hirudin, desirudin, lepirudin, and bivalirudin (tables 1 and 2). Only those clinically or experimentally tested for the prevention of stroke/embolism in AF patients are further discussed.

Ximelagatran is an oral prodrug and undergoes rapid enzymatic conversion to melagatran.⁵¹ Melagatran has poor oral bioavailability, must be given subcutaneously, and is active in the prevention and treatment of venous thromboembolic events, coronary thrombotic events,⁵² or of arterial thromboembolic events from AF.⁵² Ximelagatran has rapid onset of action, fixed twice-daily dosing, stable absorption, low potential to interact with other medication, does not require monitoring of drug levels or dose adjustment, and has a short plasma elimination half-life of approximately four hours.^{3,51} According to the SPORTIF III and V trials, comparing ximelagatran with warfarin for stroke prevention in AF and at least one additional risk factor, ximelagatran was not inferior to warfarin.¹⁶ Ximelagatran was also found to be as efficient as warfarin in the secondary prevention of embolic events, but had to be withdrawn because of potential liver toxicity.^{2,5,53-56} Elevation of liver enzymes occurred in 5 to 10% of the included patients and was more common in older patients, particularly women.^{16,54} The nonrandomised, concomitant treatment with ASA and VKA was associated with increased bleeding without indication of reducing primary outcome events.³³

Dabigatran appears to have a better safety profile than ximelagatran and can be given without regard to age, gender, or weight and has minimal drug interactions.^{2,24} Dabigatran is the only oral direct thrombin inhibitor in late-stage development. Since November 2005, a phase II trial (Re-LY trial) has been initiated, which compares the effect of dabigatran vs VKA for the prevention of stroke/embolism from AF.^{29,31,57} Dabigatran has been proven to be equivalent to LMWH in deep venous thrombosis prophylaxis and did not show excess bleeding.²⁴ The plasma half-life of dabigatran is 14 to 17 hours, allowing once-daily dosing, and elimination is primarily via renal excretion.²⁹ In a dose-finding, warfarin-controlled study on 542 AF patients, the prevalence of stroke did not differ between the dabigatran and warfarin group.⁵⁸

Nonpharmacological approaches

Electrical cardioversion is indicated when AF lasts less than one year and the left atrium is not enlarged. Even when sticking to this rule, the recurrence rate is 32% after one year.¹¹ Whether radiofrequency ablation is helpful for the prevention of embolic events in AF is questionable since the majority of AF patients are too old for the procedure, since candidates for ablation have a low risk of embolism, since the procedure

itself may increase the embolic risk, and since it is uncertain how long the embolic risk persists after the procedure. Specific mechanical approaches to stroke prevention in AF include various models of percutaneous left atrial appendage occluders (PLAATO), minimally invasive surgical isolation of the left atrial appendage (Maize procedure, COX procedure); PLAATO was long regarded to be a safe and reasonable method for patients with contraindications to OAC or those who continue to embolise despite sufficient anticoagulation. PLAATO has already been frequently applied, but meanwhile it turned out to be more harmful than beneficial due to its strong negative influence on the regulatory function of the left atrial appendage and the frequently insufficient closure of the left atrial appendage orifice.⁵⁹

MONITORING

The anticoagulant effect of platelet inhibitors does not require monitoring. The effect of VKA is best monitored by determination of the international normalised ratio (INR). Sufficient oral anticoagulation in AF patients at high risk for stroke is provided if the INR is between 2 and 3. The anticoagulant effect of UFH is usually monitored by determination of the activated partial thromboplastin time (aPTT). A therapeutic effect is achieved if the aPTT is elevated two to three times the normal upper reference limit. The therapeutic effect of LMWH is usually monitored by determination of the anti-factor Xa activity. A therapeutic effect is achieved if the plasma anticoagulant level ranges between 0.6 to 1.0 U/ml. The anticoagulant effect of UFH, LMWH, and direct thrombin inhibitors can also be monitored by measuring the prothrombinase-induced clotting time (PiCT).⁶⁰ PiCT is actually the only method to measure the effect of thrombin inhibitors in contrast to the prothrombin time, aPTT, Heptest, ecarin clotting time, or chromogenic assays.⁶⁰ Fondaparinux and idraparinux prolong the coagulation time in the PiCT, Heptest, and chromogenic assays in a dose-dependent manner but not in the aPTT.⁶⁰ PiCT is a suitable test to determine the anticoagulant effect of the long-acting, indirect factor Xa inhibitors.⁶⁰ Idraparinux increases the thrombin generation time, the aPTT, the thrombin time and reduces the prothrombin fragments 1+2.⁶¹ Lepirudin can be monitored by the aPTT, which should be maintained at 1.5 to 2.0 times baseline.²⁹ The anticoagulant activity of argatroban is monitored using the aPTT at 1.5 to 3.0 times baseline.²⁹

ANTAGONISTS

UFH can be antagonised by protamin. LMWH can be antagonised by protamin and prothrombin complex concentrate. VKA can be antagonised by vitamin K (slow

or by prothrombin complex concentrate in cases of urgency. Idraparinux may be effectively antagonised by recombinant factor VIIa.⁶¹ There is no specific antidote available for ximelagatran⁶¹ or hirudin.

CONCLUSIONS

Although many of the phase II and phase III studies with new anticoagulants were promising, clinical use for stroke prevention in AF, whenever approved, has been disappointing so far. Currently, there is no alternative to VKA for primary and secondary stroke prevention in patients with AF and additional risk factors. The VKA days cannot be left behind since the currently available new anticoagulants cannot be recommended for stroke prevention in AF and since new strategies require ongoing pharmacological research and clinical trials, which may last another few years before becoming available on a widespread basis. However, the ongoing basic research on new anticoagulants is promising and may be successful with time. Meanwhile, all measures should be taken to avoid under-usage of VKA for stroke prevention in AF patients at high risk for stroke embolism.⁶²

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