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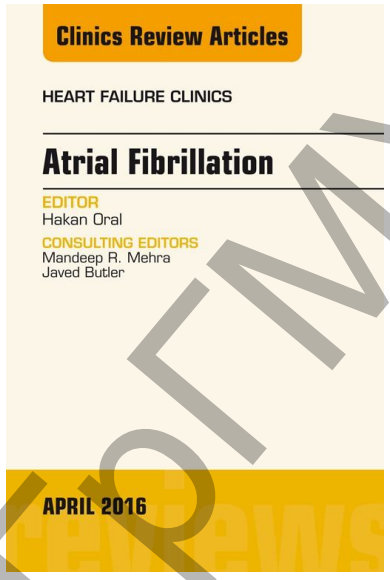

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Antithrombotic and anticoagulant therapy for atrial fibrillation

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Abstract

Atrial fibrillation (AF) substantially increases the risk of stroke and other thromboembolic events. Hence, the vast majority of AF patients require appropriate antithrombotic prophylaxis. Oral anticoagulation (OAC) with either dose-adjusted vitamin K antagonist (VKA, e.g. warfarin) or non-VKA oral anticoagulants (NOACs, e.g. dabigatran, apixaban, rivaroxaban) can be used for this purpose unless contraindicated. Therefore, stroke and bleeding risk assessment is an obligatory part of AF management and risk has to be weighed individually. Antiplatelet drugs (e.g. aspirin and clopidogrel) are inferior to OACs, both alone and in combination, with comparable risk of bleeding events. Exclusion of the left atrial appendage as major source of embolism in AF is an alternative option for stroke prevention in the few high risk patients with contraindications for anticoagulation.

Key words: atrial fibrillation, stroke risk, bleeding risk, antithrombotic prophylaxis, oral anticoagulants, antiplatelet drugs

Key points

- Prophylaxis of stroke and other thromboembolic events is central to the management of patients with AF.
- All patients with AF but those with low stroke risk (non-valvular AF and CHA_2DS_2-VASc score = 0 in males, or 1 in females) require treatment with OACs unless they are contraindicated.
- In patients CHA_2DS_2-VASc score = 1 apart from those getting the score of 1 by virtue of female gender OAC should be considered according to European guidelines however American guidelines support either OAC or aspirin or no antithrombotic therapy in this risk stratum.
- Vitamin K antagonists and non-VKA OACs (NOACs, e.g. dabigatran, rivaroxaban, apixaban) can be administered depending on the clinical situation.
- VKAs can be used in patients with either valvular or non-valvular AF, NOACs are approved for patients with non-valvular AF only.
- No universal definition of non-valvular AF is available so far. Currently it states for AF in the absence of haemodynamically significant rheumatic valvular disease (first of all, mitral stenosis) or prosthetic mechanical heart valves.
- Antiplatelet drugs either alone or in combination are inferior to OAC for antithrombotic prophylaxis but they have to be used in combination with OAC in AF patients undergoing percutaneous intervention with stent implantation.
- In high risk patients with contraindications for anticoagulation left atrial appendage exclusion is an alternative option.

Competing interests

G.Y.H.L. has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo and has been on the

speakers bureau for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. MD – none declared.

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia which is associated with high morbidity and mortality. The upward trend for AF prevalence translates into approximately 3% of adults being affected with the arrhythmia in the more recent report.[1,2]

AF confers a 5-fold elevated risk of stroke, which is characterized with prolonged hospitalizations, greater disability and higher mortality when associated with the arrhythmia in comparison with patients without AF.[3] In the real life, involvement of AF in stroke development seems to be even more profound as in substantial proportion of so-called cryptogenic strokes AF has been detected via prolonged ECG monitoring as AF per se is often asymptomatic.[4]

Oral anticoagulation (OAC) is the recommended effective option for the prevention of stroke and other thromboembolic events in AF, with either dose-adjusted vitamin K antagonists (VKA, e.g. warfarin) or non-VKA anticoagulants (e.g., dabigatran, apixaban, rivaroxaban, or edoxaban).[5,6] Antithrombotic prophylaxis with the adherence to guidelines improved significantly during the last decade but the rate of antiplatelet drugs administration instead of OAC remains significant, especially amongst the elderly and those at high bleeding risk. In the EURObservational Research Programme Atrial Fibrillation General Pilot Survey (EORP-AF), for example, 95.6% of patients amongst those with the CHA_2DS_2-VASc score ≥1, ie. with indications for OAC, received antithrombotic prophylaxis, with 80.5% amongst them were taking OAC.[7] Another unfavorable trend found in the EORP-AF study was a common administration of combination of OAC with antiplatelet drugs in stable coronary artery disease (CAD).[7]

The present article aims to provide an overview of current evidence for antithrombotic therapy in patients with AF.

Stroke and bleeding risk assessment

Stroke risk is not homogeneous in AF patients. Thus, decision for initiation of OAC therapy has to be justified by patient's individual risk assessment, and the net clinical benefit balancing stroke reduction against serious bleeding. A variety of risk factors for stroke development has been established, which subsequently gave the basis for the derivation of various stroke risk stratification schemes. [8,9]

The CHA_2DS_2-VASc score[10] (see the table 1 for acronym), is recommended by the 2012 ESC and 2014 AHA/ACC/HRS guidelines for the management of AF as the only stroke risk assessment tool in patients with non-valvular AF.[5,6]

The annual rate of thromboembolic events (including ischaemic stroke, pulmonary embolism and peripheral artery embolism) increased gradually with increasing CHA_2DS_2-VASc score, ranging from 0.78 (95% confidence interval [CI] 0.58-1.04) per 100 person years with CHA_2DS_2-VASc = 0, rising to 23.64 (95% CI 10.62-52.61) with CHA_2DS_2-VASc = 9.[11]

The major advantage of the CHA_2DS_2-VASc score in comparison to other stroke risk stratification schemes, including the older $CHADS_2$ score (heart failure, hypertension, age ≥75 years, diabetes and stroke/transient ischaemic attack)[12] is its ability to reliably distinguish the group of patients with a low risk of stroke, i.e. CHA_2DS_2-VASc score 0 for males or 1 for females, that has been validated in several large real-world AF cohorts.[13-15] For example, in a retrospective analysis performed in the Danish nationwide cohort study which involved 19444 patients with $CHADS_2$ score=0, annual stroke rates ranged from 0.84 (95% CI 0.65-1.08) % in CHA_2DS_2-VASc score 0 to 3.2 (95% CI 1.60-6.40) % in CHA_2DS_2-VASc score 3.[13]

Following the identification of these 'truly low risk' patients who do not need any antithrombotic therapy, effective stroke prevention (i.e. OAC) can be offered to those with ≥1 stroke risk factors given the positive net clinical benefit for these patients.[16-18,53] Noteworthy, current American guidelines allow choice between OAC, aspirin or no antithrombotic therapy in patients with a

CHA_2DS_2-VASc score = 1.[6] On the contrary, European guidelines offer for consideration OAC only.[5] For AF patients with ≥1 stroke risk factors, the net clinical benefit of OAC therapy is positive, meaning that stroke risk reduction outweighs potential increase risk of haemorrhage. Moreover, the net clinical benefit is greater in patients with the higher bleeding risk; thus, high bleeding risk has not to be considered as a reason avoid OAC.[16-18]

The HAS-BLED score (see the table 1 for acronym) has to be used for evaluation of individuals' risk of major bleeding.[19] This score performs well in comparison to other bleeding risk stratification schemes in different clinical settings: both AF and non-AF patients, warfarin or other anticoagulants, in case of bridging therapy.[20-23] Also, it is able to predict ICH independently of other bleeding events.[21,22]

Of note, risk stratification is a dynamic process and both stroke and bleeding risk should be assessed each time during patient's follow-up. Also, the HAS-BLED score includes risk factors which can be modified and thus, reducing individual's bleeding risk and potentially making OAC therapy safer.[5,6]

Anticoagulation therapy

Vitamin K Antagonists (e.g. warfarin)

Until recently, the VKA class (eg. warfarin) were the only available OACs for stroke and thromboembolism prevention in AF patients. VKAs reduce stroke by 64 (95% CI 49-74) %, both in primary (2.7% annual absolute risk reduction) and secondary (8.4% annual absolute risk reduction) prevention, as well as all-cause mortality, by 26% (95% CI 3–43).[24]

Warfarin inhibits the synthesis of the vitamin K-dependent coagulation factors (II, VII, IX, X) by interfering vitamin K reduction in the liver from vitamin K epoxide (inactive form that appears during oxidation of hydroquinone form) back to active one with the enzyme, called vitamin K epoxide reductase complex subunit 1 (VKORC1). Oxidation of hydroquinone form is coupled with

the posttranslational modification of vitamin K-dependent proteins which includes carboxylation of glutamic acid residues and formation of the γ-carboxyl glutamic acid domains. These domains are capable of binding calcium ions (with positive charge), thereby making proteins attractable to injured cells surface, which carries negative charge. Proteins lacking sufficient amount of calcium-binding domains (partially carboxylated and decarboxylated) have significantly reduced coagulant activity.[25] Pharmacological characteristics of warfarin are summarised in the table 2.

Despite high antithrombotic efficacy, warfarin has a range of disadvantages, which make it inconvenient for use both from patients' and clinicians' point of view, specifically because of high intra- and inter-individual variability of anticoagulant effect (patient can develop bleeding complications with the minimal dose or may have warfarin resistance), food and drug interaction, slow onset of action, long half-life, etc.[25] This results into significant underuse of warfarin in patients with AF in the real world, particularly if estimated bleeding risk is high, in association with CAD and in the elderly.[7,26-28]

Genetic polymorphism of enzymes involved in the warfarin metabolism (cytochromes CYP2C9, CYP3A4, CYP2C19, CYP1A2) and target enzyme for warfarin (VKORC1) are of particular importance in its pharmacology, and several attempts have been made to develop algorithm for warfarin dosing based on pharmacogenetic approach, however, genetic testing cannot be applied routinely given the growing population with AF who requires OAC.[29-31]

To reach optimal anticoagulation effect slow titration in the beginning of therapy and regular monitoring of international normalized ratio (INR) is required because of narrow therapeutic window for warfarin (INR 2.0-3.0). Time in therapeutic range (TTR) is used to evaluate quality of anticoagulation with warfarin and the average individual TTR has to be as high as >70% to expect efficacious stroke risk reduction with a low bleeding risk.[32] For example, in 27458 patients taking warfarin from the UK General Practice Database, who spent at least 70% of time within therapeutic range, significantly lower stroke and mortality rate was achieved in comparison to

patients with <30% of time in range.[33] Also, whilst translating data on warfarin effectiveness from clinical trials, it is important to keep in mind that TTR in real life population from every day practice is usually lower. In their systematic review Walraven et al found significantly more poor control in the community practices than either in anticoagulation clinics or clinical trials (-12.2%; 95% CI -19.5 to -4.8).[34]

Non-VKA oral anticoagulants

Given the limitations of the VKAs, new classes of OACs have been developed, which allow overcoming the challenges of warfarin therapy as they selectively inhibit key factors in the coagulation cascade. These non-VKA oral anticoagulants (NOACs, previously referred to as new or novel OACs) include direct thrombin (factor II) inhibitors (e.g. dabigatran) and factor Xa inhibitors (e.g. apixaban, rivaroxaban and – most recently - edoxaban).[35-37]

Direct thrombin inhibitors bind to active catalytic site of thrombin, either free thrombin in plasma or clot (fibrin)-bound thrombin, thereby interfering with multiple effects realized with thrombin: fibrin production from fibrinogen and its stabilization; activation of coagulation factors V, VIII, XI and XIII; platelet activation, inhibition of fibrinolysis, proinflammatory changes.[38,39]

Factor X represents place of intrinsic and extrinsic coagulation pathways convergence. One molecule of activated factor Xa as a result of cascade of enzymatic reactions eventually leads to conversion of up to 1000 molecules of prothrombin to thrombin. Direct factor Xa inhibitors not only block free factor Xa via binding to its active site, but also inactivate it within the prothrombinase complex bound to platelets.[38,39]

The principal differences of the NOACs from VKAs are the fixed dose administration and no need for intensive INR control, as well as a more rapid onset and shorter offset of action, fewer drug and no food interactions and kidney elimination.[35-37] Pharmacological characteristics of the NOACs are summarised in the table 2.

Four large phase III prospective randomized clinical trials on the safety and effectiveness of NOACS in comparison to warfarin have been completed (Table 3): RE-LY with dabigatran[40], ROCKET AF with rivaroxaban[41], ARISTOTLE with apixaban[42], and ENGAGE AF – TIMI 48 with edoxaban[43] (see the Table 3 for acronyms). Trials on the oral direct factor Xa inhibitors were double-blind, whereas trial on dabigatran was open label between dabigatran and warfarin arms, but double blind between 2 arms with different doses of dabigatran (150 mg versus 110 mg bid).

Patients in the ROCKET AF trial cohort were at higher stroke risk (based on the $CHADS_2$ score), with more patients with the history of stroke, TIA or systemic embolism, and a lower mean TTR (55%).[44]

All-cause (ischaemic, haemorrhagic or indeterminate) stroke and/or systemic (non-central nervous system) thromboembolic event were analysed as primary efficacy endpoint. Major bleeding (broadly defined as decrease of haemoglobin by at least 2 g/dl, transfusion of at least two units of red blood cells (within 24 hours in the ARISTOTLE trial), bleeding at a critical site or resulting in death) were used as primary safety end-point (clinically relevant non-major bleedings were accounted as well in the ROCKET AF trial).[40-43]

In the effectiveness analyses, all NOACs appeared to be noninferior to warfarin in the risk reduction in the primary endpoint of stroke or systemic embolism. However, apixaban and dabigatran 150 mg were found to be superior to warfarin.[40,42] All NOACs appeared to be effective for secondary prophylaxis of stroke and/or TIA.[45-47]

In the safety analysis the rate of major bleeding was found to be at least similar between NOACs and warfarin, or even significantly less with dabigatran 110 mg bid, apixaban and edoxaban, of note a reduced risk of intracranial haemorrhage was apparent for all NOACs.[40-43]

A favorable trend in mortality was seen for all three NOACs compared to warfarin, which reached statistical significance when apixaban or edoxaban 60mg was used.[40-43] Interestingly, a numerical but non-significant trend towards higher rate of myocardial infarction was found for dabigatran,

which was nonsignificant with inclusion of previously unidentified events[40,48]) and low-dose edoxaban[43].

As regards to long-term follow-up, dabigatran was further evaluated in the RELY-ABLE study, which included 5851 dabigatran-treated patients from the RE-LY study, followed-up for an additional 2.3 years, as well as in 'real-world' Danish nationwide cohort study, which both showed consistent results with the original trial.[49,50]

In the meta-analysis of phase II and phase III randomized trials comparing NOACs versus VKAs these agents were found to reduce total mortality (relative risk [RR] 0.89, 95% CI 0.83–0.96), cardiovascular mortality (RR 0.89, 95% CI 0.82– 0.98), and stroke/systemic embolism (RR 0.77, 95% CI, 0.70–0.86), intracranial hemorrhage (RR 0.46, 95% CI 0.39–0.56).[51] These results are consistent with another systematic review using data from three pivotal studies (RE-LY, ROCKET AF, and ARISTOTLE): 8 (3 to 11) fewer deaths per 1000 patients (RR 0.88, 95% CI 0.82 to 0.96), 4 (2-5 fewer) fewer hemorrhagic strokes per 1000 patients (RR 0.48, 95% CI 0.36 to 0.62) with obvious trend towards reduced risk of ischaemic stroke (RR 0.89, 95 CI% 0.78 to 1.02).[52] Administration of the NOACs appeared to be particularly advantageous in patients with high risk of stroke and/or bleeding.[53] Considering the noninferiority of the NOACs for stroke/thromboembolism prevention and better safety profile, the NOACs are given a preference over VKAs in current guidelines (Figure 1).[5]

Since no head-to-head studies have been conducted, there is no direct evidence of important differences of the efficacy and safety between the NOACs. Several indirect comparisons between dabigatran, rivaroxaban and apixaban have been carried out with broadly similar results obtained. These indirect comparisons found apixaban to be less causative of bleeding when compared with the dabigatran 150 mg or rivaroxaban. Also, rivaroxaban seemed to be less effective than dabigatran 150 mg for stroke prevention. There were no compelling differences between the NOACs in reduction in ischemic strokes or mortality.[54,55]

In another comparison analysis performed separately for primary and secondary prevention of stroke no significant differences in safety and efficacy endpoints between dabigatran 150 mg, rivaroxaban, and apixaban were found for secondary prevention, apart from higher rate of myocardial infarction with dabigatran 150 mg. For the primary prevention of stroke, there were some differences between the agents, e.g. apixaban was associated with more strokes in comparison with dabigatran 150 mg, but less major bleeding in comparison with both dabigatran 150 mg and rivaroxaban.[56]

In a recent indirect comparison of high dose edoxaban with other NOACs there were no significant differences in the efficacy endpoints (apart from higher rate of stroke, stroke or systemic embolism, haemorrhagic stroke when compared with dabigatran 150 mg). Higher rate of major and clinically relevant nonmajor bleeding was observed when compared with apixaban, but lower one, when compared with rivaroxaban. There were higher bleeding rates with all NOACs in comparison to low-dose edoxaban whilst it was less effective for stroke/systemic embolism prevention.[57]

Importantly, limitations of indirect comparisons (differences in study design, patient population, definitions of outcomes) have been acknowledged in all analyses.

The advantages of the NOACs in particular clinical situations may become disadvantageous. No need for anticoagulation monitoring may result in decreased patients' adherence to treatment, that given the short half-lives of the NOACs place them at higher risk of adverse events. Also, there are no routine anticoagulation tests to evaluate reliably effect of the NOACs, which is essential in acute settings (e.g., acute ischaemic or haemorrhagic stroke). Those available in everyday practice, and supply physicians only with tentative qualitative information.[36,58]

Also, there are no specific antidotes for NOACs. Prothrombin complex concentrates (either activated or non-activated) appeared to be standard for bleeding management for the NOACs.[36] Other reversal agents (anti-dabigatran antibody fragments, recombinant factor VIIa, factor Xa

missing Gla (carboxyglutamic acid) residues in Gla domains, etc) are mostly investigational thus far although early results appear promising.[59]

Finally, the NOACs are currently approved for non-valvular AF and are contraindicated in patients with severe kidney dysfunction (i.e. creatinine clearance <30 ml/min).[5,6]

Defining non-valvular AF in clinical practice is a subject for controversy as no universal definition of non-valvular AF is available so far. European guidelines refer non-valvular AF to AF in the absence of rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.[5] American guidelines define non-valvular AF as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.[6] Patients populations in pivotal trials on NOACs can be taken into account as well. Patients with moderate or severe mitral stenosis or prosthetic mechanical heart valve were excluded in all trials.[40-43] However, in the RE-LY trial patients with any hemodynamically relevant valve disease were excluded.[40] Also, ROCKET AF cohort included patients with annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty[41], and ENGAGE AF-TIMI 48 - those with bioprosthetic heart valves and/or valve repair[43].

Given no compelling evidence for superiority of the NOACs over well-controlled VKA (i.e. high TTRs, >70%) and limited data of NOACs performance in the real-world population, attempts have been made to identify reliably proportion of AF patients who will reach a high TTR on VKA. The SAMe-TT_2R_2 score (Table 4) is a decision tool which may help to discriminate patients with anticipated high TTR (i.e. suitable for warfarin therapy) against those with anticipated low TTR (i.e. suitable for NOACs). [60,61]

Antithrombotic therapy

Aspirin (acetylsalicylic acid) has previously been considered as an alternative to OACs, particularly in patients with moderate risk of stroke development[62], i.e. up to 60% of AF population as being

classified with the $CHADS_2$ score (congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/TIA).[63]

Aspirin use was supported by the results of few old trials, which together showed a non-significant relative risk reduction of stroke by of 19% (95% CI -1 to 35) in aspirin versus placebo/control, with no effect on all-cause mortality.

The non-significant 19% reduction was driven by the results of only one single positive trial for aspirin, the SPAF I trial (Stroke Prevention in Atrial Fibrillation), which used aspirin 325 mg od and found a 42% of stroke risk reduction, vs control but with marked internal heterogeneity for the aspirin effect in the OAC-eligible and OAC-ineligible arms of SPAF-I.[24] In SPAF-I, aspirin did not have any benefit in those age>75 nor did it prevent severe strokes. Also, no significant reduction in stroke (either all stroke, ischaemic, disabling or fatal) nor all-cause mortality was found in Cochrane review.[64]

More contemporary trials do not support aspirin use. Aspirin was found to be non-effective for stroke prevention in low-risk patients with AF in the Japan Atrial Fibrillation Stroke Trial.[65] Importantly, aspirin did not benefit the elderly in BAFTA trial (the Birmingham Atrial Fibrillation Treatment of the Aged Study) where warfarin was superior to aspirin, and importantly warfarin and aspirin had similar risks of major bleeding and intracranial haemorrhage.[27]

Aspirin was also clearly inferior to apixaban in the AVERROES trial (Apixaban VERsus acetylsalicylic acid to prevent stroke in atrial fibrillation patiEntS who have failed or are unsuitable for vitamin K antagonist treatment), in which apixaban therapy resulted in 55% relative risk reduction in the stroke rate (particularly ischemic and disabling strokes) with no difference between aspirin and apixaban for major bleeding or intracranial haemorrhage.[66,67]

Dual antiplatelet therapy of aspirin and clopidogrel may be marginally better than aspirin monotherapy – 11% (95% CI 2-19) % risk reduction for major vascular events (stroke, systemic embolism, myocardial infarction, death from vascular causes), 28% (95% CI 17-38) risk reduction

of stroke development was seen in the ACTIVE (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) trial for aspirin-clopidogrel combination therapy but at cost of increased major bleeding.[68] However, the combination of aspirin and clopidogrel still remained inferior to OAC.[69] Considering aforementioned assertions antiplatelet therapy as a mean of stroke prophylaxis is only recommend for AF patients unsuitable or with contraindications for any form of OAC (Figure 1).[5]

Antiplatelet agents in AF patients, undergoing PCI/stenting

The lower ability of antiplatelet drugs to prevent stroke and systemic embolism can perhaps be explained from pathophysiological point of view. Thrombi in AF are fibrin-rich and activation of coagulation factors plays greater role in their development than platelet activation. In contrast, platelet activation and development of platelet-rich thrombi is the hallmark of thrombotic complications in CAD (acute coronary syndrome [ACS], stent thrombosis, etc.).[70-72]

Given the high prevalence of AF associated with CAD[73] and need to undergo percutaneous intervention, often with stent implantation, these patients require therefore combination of OAC and anti-platelet agents (triple therapy) to cover both pathways and reduce risk of complications.[74]

Obviously, triple therapy is associated with a higher risk of bleeding complications, and its duration of use depends on several factors including initial bleeding risk, type of stent (bare metal or drug-eluting stent and its generation), clinical setting (ACS or elective procedure) to balance risk of bleeding and thrombotic/thromboembolic complications (Table 5).[74]

Considering increased risk of major bleeding in triple therapy[75-77] and low adherence to it (specifically, underuse of OAC)[78], several studies attempted to compare effectiveness and safety of different prophylactic regimens against triple therapy.

Broadly similar effectiveness and safety for triple therapy, dual antiplatelet therapy or warfarin plus single antiplatelet agent was observed in the AFCAS registry (Atrial Fibrillation Undergoing Coronary Artery Stenting) and Danish nationwide registries.[79,80] In the WOEST study (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) there was significantly lower bleeding rate and mortality was found in the warfarin plus clopidogrel arm versus triple therapy (HR 0.36, 95% CI 0.26–0.50 and HR 0.39, 95% CI 0.16–0.93, respectively) with no significant differences in the rate of thrombotic events.[81]

However, these studies cannot change current practice as the data are non-conclusive (small sample, heterogeneity in design, combinations and doses of antithrombotic agents, etc.). Larger, prospective, randomized trials are required to prove the efficacy and safety of the various combinations of oral anticoagulants (including NOACs) and antiplatelet drugs (including newer P_2Y_{12}-receptor inhibitors prasugrel and ticagrelor).

Noteworthy, in patients with stable CHD and AF, treated chronically with OAC, antiplatelet medications bring no significant benefits with respect to reduction of stroke, acute coronary events or mortality, but they are associated with increased risk of serious bleeding (HR 1.5 [95% CI 1.23-1.82] for aspirin or HR 1.84 [95% CI 1.11-3.06] for clopidogrel), particularly ICH.[82]

Nonpharmacological stroke and thromboembolism prevention

A range of comorbidities may make patients with AF ineligible for chronic OAC (e.g., hepatic and/or kidney dysfunction, mechanical valve prostheses, hereditary coagulation disorders).

Because the left atrial appendage (LAA) is known to be the major source of the stroke-causing thrombi in AF because of loss of coordinated contraction, dilation and blood stasis, LAA exclusion offers an alternative to OAC option for stroke prevention in AF.

This can be achieved via percutaneous access (with closure devices) or during open heart surgery for any other reason (by ligating, stapling, amputation).[83] Overall, LAA devices were found to be

noninferior to warfarin, for example WATCHMAN device (Boston Scientific, Natick, MA, USA) in the PROTECT AF study (LAA System for Embolic Protection in Patients With Atrial Fibrillation).[84] However, LAA occlusion may not eliminate completely risk of stroke because of other than LAA sources of thrombi[85], which taken together with risk of procedural complications and scarce data allow to apply this option only for high stroke risk patients who are unable to tolerate OAC (Figure 1)[5] Surgical excision of LAA may be considered in patients undergoing cardiac surgery.[6]

Conclusion

Optimal prevention of thromboembolic events in vast majority of AF requires oral anticoagulation. With the NOACs became available antithrombotic prophylaxis seemed to overcome range of inconveniences associated with the warfarin treatment. The role of antiplatelet agents for stroke prevention in AF has diminished significantly but may still be required for the prevention of thrombotic complications in coronary disease, which appear to be common in AF. An informed assessment of the risk of stroke (using CHA_2DS_2-VASc) and bleeding (using HAS-BLED) is of importance when balancing risks and considering the net clinical benefit of thromboprophylaxis.

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Table 1. Stroke and bleeding risk stratification with the CHA_2DS_2-VASc[10] and HAS-BLED[19] scores

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension (systolic blood pressure >160 mmHg)	1
Hypertension	1	Abnormal renal or liver function	1 or 2
Age ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INRs (if on warfarin)	1
Vascular disease (prior MI, PAD, or aortic plaque)	1	Age (e.g., >65, frail condition)	1
Aged 65–74 years	1	Drugs (e.g., concomitant antiplatelet or NSAIDs) or alcohol excess/abuse	1 or 2
Sex category (i.e. female gender)	1		
Maximum score	9		9

CHA_2DS_2-VASc: heart failure [moderate-to-severe left ventricular systolic dysfunction refer to left ventricular ejection fraction ≤40% or recent decompensated heart failure requiring hospitalization], hypertension, age ≥75, diabetes, stroke/transient ischaemic attack [TIA], vascular disease [specifically, myocardial infarction, complex aortic plaque and peripheral artery disease], age 65–74 years, female sex.
HAS-BLED: uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [e.g. age >65, frail condition], drugs [e.g., antiplatelet, non-steroidal anti-inflammatory drugs]/excessive alcohol.
INR, international normalized ratio; LV, left ventricular; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; TIA/TE, transient ischemic attack/thromboembolism; PAD, peripheral artery disease.

Table 2. Pharmacological characteristics of warfarin and non-VKA oral anticoagulants[36,86-87]

Parameter	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Inhibition of VKORC1	Direct thrombin inhibitor (free or bound), reversible	Factor Xa inhibitor (free or bound), reversible	Factor Xa inhibitor (free or bound), reversible	Factor Xa inhibitor (free or bound), reversible
Onset of action	Slow, indirect inhibition of clotting factor synthesis	Fast	Fast	Fast	Fast
Offset of action	Long	Short	Short	Short	Short
Absorption	Rapid	Rapid, acid-dependent	Rapid	Rapid	Rapid
Bioavailability, %	>95	6.5	>80	>50	62
T_{max}, hour	2.0-4.0	1.0-3.0	2.5-4.0	1.0-3.0	1.0-2.0
V_d, L	10	60-70	50-55	21	>300
Protein binding, %	99	35	95	87	40-59
$T_{1/2\beta}$, hour	40	12-17	9-13	8-15	9-11
Renal clearance	None	80	35	27	50
Non-renal clearance	None	20	65	73	50
CL/F, L/hour	0.35	70-140	10	5	30.2-33.7
Accumulation in plasma	Dependent on CYP2C9 metabolic efficiency	None	None	1.3-1.9	Negligible
Food effect	No effect on absorption; dietary vitamin K influence on pharmacodynamics	Delayed absorption with food with no influence on bioavailability	Delayed absorption with food with increased bioavailability	None	None
Age	Yes, lower CL/F as age increases	Yes, lower CL/F as age increases	None	Yes, lower CL/F as age increases	NR
Body weight	Yes, higher dose for increased weight	None	None	Yes, higher exposure with low body weight (< 60 kg)	NR
Sex	Yes, lower CL/F in women	Yes, lower CL/F in women	None	Yes, higher exposure in women	NR
Ethnicity	Lower dose in Asian patients; higher dose in African-American	None	Lower dose in Japanese patients	None	None

	patients				
Drug transporter	None	P-gp	P-gp, BCRP	P-gp, BCRP	P-gp
CYP-mediated metabolism	CYP2C9, CYP3A4, CYP2C19, CYP1A2	None	CYP3A4/5, CYP2J2 (equal)	CYP3A4/5, CYP2J2 (minor), CYP1A2 (minor)	CYP3A4 (4%)
Drug-drug interactions*	Numerous	Potent P-gp inhibitors (verapamil, reduce dose; dronedarone: avoid) and inducers (avoid)	Potent CYP3A4 and P-gp inhibitors (avoid) and inducers (use with caution)	Potent CYP3A4 and P-gp inhibitors (avoid) and inducers (use with caution)	Potent P-gp inhibitors (reduce dose) and inducers (avoid)
Coagulation measurement	INR	TT, dTT, aPTT, ECA	PT, anti-FXa	anti-FXa	PT, aPTT, anti-FXa
Reversal agents	Vitamin K (slow reversal, prolonged inhibition), FFP or PCCs (rapid reversal)	Activated charcoal or haemodialysis (overdose); PCCs or recombinant FVII (uncontrolled bleeding)	Activated charcoal, FFP, PCCs, activated FVII	Activated charcoal, FFP, PCCs, activated FVII	Activated charcoal, FFP, PCCs, activated FVII
Dosing for AF	Individualised for each patient according to INR response (0.5-16 mg qd)	150 mg bid or 110 mg bid in high bleeding risk Contraindicated if CrCl < 30 mL/min	20 mg qd if CrCl > 50 mL/min or 15 mg qd if CrCl 15-50 mL/min	5 mg bid or 2.5 mg bid if • CrCl 15-29 mL/min or • any 2 of the following are present: ○ age ≥ 80 years ○ body weight ≤ 60 kg ○ serum creatinine ≥ 133 φmol/L	Awaiting EMA approval

AF, atrial fibrillation; aPTT, activated partial thromboplastin test; BCRP, breast cancer resistance protein; bid, twice daily; CL/F, apparent clearance; CrCl, creatinine clearance; CYP, cytochrom P450 isozymes; dTT, diluted thrombin test; ECT, ecarin chromogenic assay; EMA, European Medicines Agency; F, factor; FFP, fresh frozen plasma; INR, international normalized ratio; NR, not reported; qd, once daily; PCC, prothrombin complex concentrate; P-gp, P-glycoprotein; PT, prothrombin time; T_{max}, time to maximum plasma concentration; TT, thrombin time; $T_{1/2\beta}$, terminal half-life, V_d, volume of distribution; VKORC1, vitamin K epoxide reductase enzyme subunit 1.

*Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole, intraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir, atanazavir). P-gp inhibitors include verapamil, amiodarone, quinidine, and clarithromycin. P-gp inducers include rifampicin, St. John's wort (Hypericum perforatum), carbamazepine, and phenytoin. Potent CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, and St. John's wort.

Table 3. Summary of pivotal clinical trials of non-VKA oral anticoagulants in patients with nonvalvular AF

Clinical trial	RE-LY[40]		ROCKET AF[41]	ARISTOTLE[42]	ENGAGE AF - TIMI 48[43]	
Non-VKA OAC examined	Dabigatran		Rivaroxaban	Apixaban	Edoxaban	
Patients	18113		14 264	18 201	21105	
Age, years	71		73	70	72	
Mean $CHADS_2$ score	2.1		3.5	2.1	2.8	
Non-VKA OAC dosing arm	110 mg bid	150 mg bid	20 (15*) mg qd	5 (2.5**) mg bid	60 mg qd	30 mg qd
Prior vitamin K antagonist treatment, %	50		62	57	58.8	59.2
Prior stroke or transient ischemic attack, %	20 (including systemic embolism)		55	19 (including systemic embolism)	28.1	28.5
Mean TTR, warfarin arm; %	64		55	62	68.4	
Relative risk (95% CI) for non-VKA OAC versus warfarin						
Stroke or systemic embolism	0.90 (0.74-1.10)	0.65 (0.52-0.81)	0.88 (0.75-1.03)	0.79 (0.66-0.96)	0.87 (0.73-1.04)	1.13 (0.96-1.34)
Major bleeding	0.80(0.70-0.93)	0.93 (0.81-1.07)	1.04 (0.90-1.20)	0.69 (0.60-0.80)	0.80 (0.71-0.91)	0.47 (0.41-0.55)
Intracranial hemorrhage	0.30 (0.19-0.45)	0.41 (0.28-0.60)	0.67 (0.47-0.93)	0.42 (0.30-0.58)	0.47 (0.34-0.63)	0.30 (0.21-0.43)
Gastrointestinal bleeding	1.09 (0.85-1.39)	1.49 (1.19-1.88)	1.47 (1.20-1.81)	0.88 (0.67-1.14)	1.23 (1.02-1.50)	0.67 (0.53-0.83)
Myocardial infarction	1.29 (0.96-1.75)	1.27 (0.94-1.71)	0.81 (0.63-1.06)	0.88 (0.66-1.17)	0.94 (0.74-1.19)	1.19 (0.95-1.49)
Death	0.91 (0.80-1.03)	0.88 (0.77-1.00)	0.85 (0.70-1.02)	0.89 (0.80-0.99)	0.92 (0.83-1.01)	0.87 (0.79-0.96)

ARISTOTLE, Apixaban for Reduction In STroke and Other ThromboembоLic Events in atrial fibrillation; bid, twice daily; CHADS2, congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke or transient ischemic attack (2 points); CI, confidence interval; ENGAGE AF – TIMI 48 Effective aNticoaGulation with factor Xa next GEneration in Atrial Fibrillation – Thrombolysis In Myocardial Infarction 48; OAC, oral anticoagulant; qd, once daily; RE-LY, Randomized Evaluation of Long-term anticoagulation therapy; ROCKET AF, Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; TTR, time in therapeutic range.

* in patients with creatinine clearance 30 to 49 mL/min.

** in patients with 2 or more of the following criteria: age >80 years, body weight <60 kg, or serum creatinine >133 φmol/L.

Table 4. Quality of anticoagulation control assessment with the SAMe-TT_2R_2score[60]

Risk factors	Score
Sex category (i.e. female gender)	1
Age <60 years	1
Medical history (≥2 of the following: hypertension, DM, CAD/MI, PAD, CHF, previous stroke, pulmonary, hepatic or renal disease)	1
Treatment with interacting drugs(e.g., amiodarone)	1
Tobacco use (within 2 years)	2
Race (i.e. non-caucasian)	2
Maximum score	8

CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; MI, myocardial infarction; PAD, peripheral artery disease

Table 5. Recommended antithrombotic strategies following coronary artery stenting in patients with atrial fibrillation at moderate-to-high thromboembolic risk

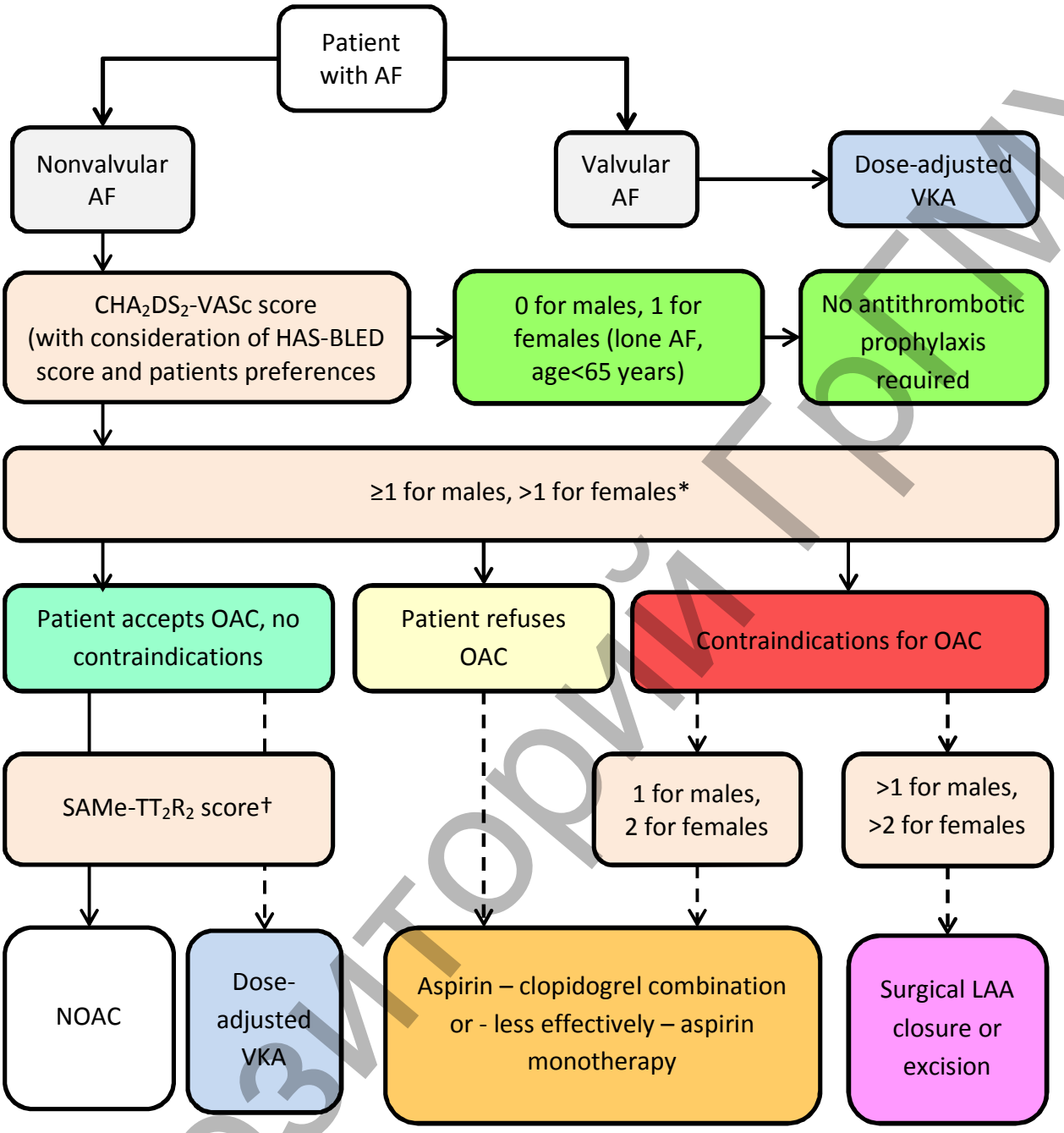
(adapted from Lip et al. [74])

Haemorrhagic risk	Clinical setting	Stent implanted	Recommendations in timeline		
			Triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day	Dual therapy of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)	Monotherapy of warfarin (INR 2.0–3.0)
Low or moderate	Elective	Bare metal	1 month	-	Lifelong
		Drug eluting	3-6 months	12 months	
	ACS	Bare metal / Drug eluting	6 months	12 months	
High	Elective	Bare metal*	2-4 weeks	-	Lifelong
	ACS		4 weeks	12 months	

* drug eluting stents should be avoided

ACS, acute coronary syndrome; INR, international normalized ratio.

Figure 1. Recommendations for prevention of thromboembolism in non-valvular AF[5]



* 2014 AHA/ACC/HRS guideline for the management of patients with AF allows either OAC or aspirin or no antithrombotic therapy in patients with a CHA_2DS_2-VASc score = 1[6]

† currently not in the guidelines

Solid line, best option; dashed line, alternative option.

CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74 years, sex category

(female); HAS-BLED, hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile international normalized ratio, elderly (≥65 years old), drugs/alcohol concomitantly (1 point each); SAMe-TT_2R_2, female sex, age less than 60 years, medical history (2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral artery disease, heart failure, previous stroke, pulmonary, hepatic or renal disease), treatment with interacting drugs (e.g. amiodarone), tobacco use (within 2 years, doubled), non-Caucasian race (doubled).

LAA, left atrial appendage; NOAC, novel (non-VKA) oral anticoagulant; OAC, oral anticoagulation; VKA, vitamin K antagonist