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MODERN MANAGEMENT OF ATRIAL FIBRILLATION

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The article describes the modern approaches to the correction of atrial fibrillation.
Key words: *atrial fibrillation, correction*

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia seen in clinical practice.[1] Its prevalence continues to rise in the aging European population with more than one in ten of subjects being affected after age of 80.[2, 3] AF represents a major public health problem by significantly affecting quality of life and being linked to increased cardiac and cerebrovascular morbidity and mortality. One of the most devastating but preventable in most patients complication of AF is stroke. Strokes developed due to AF have higher morbidity and mortality than strokes due to other causes. In the absence of antithrombotic therapy, the annual risk of stroke in nonvalvular AF increases from approximately 5% in patients less than 65 years old to about 8% in patients 75 years of age or older.[4] AF is responsible for only 1.5% of strokes at age 50–59 years of age, but its impacts raises more than 15-fold among 80–89 year old patients when AF is accountable for more than 20% of strokes.[5] Women with AF over the age of 75 years are at particularly high risk for AF.[6]

Also AF has a direct impact on cardiac hemodynamics. For example, it reduces left ventricular ejection fraction by approximately 15-20%, particularly if the heart rate is poorly controlled. AF is very common in patients with heart failure with both reduced and preserved ejection fraction where it is associated with poor prognosis.[7-9].

AF is accompanied by loss of coordinated atrial contractions which predisposes to atrial thrombus formation with risk of its consequent dislocation downstream and an embolic stroke. Nonvalvular AF increases the risk of stroke and thromboembolism about 5-fold, whilst valvular AF poses 17-fold raise in stroke risk.[10] As many as 1 in 6 of all strokes in the USA are attributable to AF.[4] Also AF is associated with frequent admissions to emergency departments, hospital admissions and repeated pharmaceutical and electrical cardioversions despite the use of antiarrhythmic medications.

Ageing is associated with diffuse cardiac changes including atrial fibrosis degenerative changes in the sinus node and supraventricular conduction as well as increase in left ventricular diastolic pressure.[11] All these factors contribute in higher risk of AF. Other risk factors for AF such as hypertension, diabetes coronary artery disease, heart failure are common in older people further increasing propensity to AF development. AF can also result from non-cardiac caused, such as various systemic or respiratory illnesses, acute and chronic alcohol abuse, thyrotoxicosis, use of illicit drugs. Prompt treatment of those conditions is essential for prevention of AF recurrences.

Several guidelines for the management of AF are available of which guidelines of the European Society of Cardiology have been recently updated and represent state-f-the art information on best management of the arrhythmia.[8, 9].

Diagnosis

AF can often be detected by irregular pulse and heartbeats. However in all cases the diagnosis has to be confirmed by an ECG showing absence of P waves. Accordingly ECG should be always be recorded when the patient is suspected to have AF. If paroxysmal AF is suspected based on temporary symptoms ECG monitoring may be needed. A 24-hour Holter monitor is useful for frequent palpitation episodes. In many cases, when the palpitations are less frequent a 7-day event recorder will provide a more suitable option for the arrhythmia detection. In some cases of very symptomatic events implantation of loop recorders may be required. Of note, asymptomatic AF is very common and can be often detected on 24-hour Holter monitoring this facilitating the diagnosis.[12] Upon assessment for AF careful attention should also be given to possible caused of secondary AF, comorbidities and complications. A transthoracic echocardiogram should be performed in most patients with AF for the diagnosis of underlying structural heart disease and to help decision making for treatment strategies.

Classification

Five clinical types of AF are distinguished by current AF guidelines based on the presentation and duration of the arrhythmia: (i) *first diagnosed AF* - every patient who presents with AF for the first time, irrespective of the arrhythmia duration; (ii) *paroxysmal AF* - self-terminating AF lasting for up to 7 days (usually less than 48 hours); (iii) *persistent AF* - when an AF episode lasts more than 7 days or needs termination by cardioversion (either pharmaceutical or electrical); (iv) *long-standing persistent AF* - when AF has lasted for e”1 year but a rhythm control strategy is still considered; and (v) *permanent AF* - when the arrhythmia is accepted by the patient (and his doctor) and rate control rather than rhythm control is aimed.[8, 9].

Management

Rhythm control

Rhythm control strategy aims to restore and maintain sinus rhythm in patients with AF. Cardioversion of AF to sinus rhythm can be achieved pharmacologically or electrically. In patients with structural heart disease, antiarrhythmic drugs such as amiodarone or sotalol can be administered prior to cardioversion to increase its success. However, long-term maintenance of sinus rhythm after successful cardioversion can be challenging in many patients despite antiarrhythmic therapy with only about half of patients aiming pharmaceutical rhythm control actually remaining AF free by one year. This dictates careful individualised choice of preferable strategy of AF management for every patient. As a general rule maintenance of sinus rhythm should be considered in symptomatic patients, in those with treatable precipitants and when AF could lead to hemodynamic compromise (e.g., in congestive heart failure). For maintenance of sinus rhythm control in patients with paroxysmal AF, administration of a beta-blocker is a common first choice. Class Ic antiarrhythmics, such as flecainide, amiodarone or dronedarone can be used if beta-blockers are ineffective or contraindicated. Flecainide is an

effective antiarrhythmic drug for patients without structural heart disease/ischaemic heart disease.

Dronedarone is a novel antiarrhythmic agent structurally similar to amiodarone but designed to minimise numerous side effects common with amiodarone. Althouhg dronedarone is usually well tolerated its antiarrhythmic activity appears to be inferior to amiodarone. Also dronedarone has been shown to increase mortality in subjects with congestive heart failure and should thus be contraindicated in this category of patients. Nevertheless dronedarone could be an antiarrhythmic drug of choice for AF patients without heart failure where it was shown to reduce hospitalisation rates and cardiovascular mortality compared with placebo.[13] Amiodarone apparently remains a sole antiarrhythmic agent to be utilised in patients with congestive heart failure in whom beta-blockers cannot cope with AF burden.

Restoration and maintenance of sinus rhythm in AF aims improvement in symptoms, exercise tolerance and quality of life as well as reduction in risk of stroke and prevention of tachycardia-related cardiomyopathy. However, all major clinical trial agree on that rate control vs. rhythm control strategies suggest that control of the evidence from clinical trials suggests the contrary.[14-16] These trials show that a rhythm-control strategy is non-superior to the rate control approach in terms of mortality, which appears to be associated with lower rates of thromboembolism and hospital admissions.[14] Moreover the rate control strategy was more cost-effective and less frequently complicated by side effects of the treatments used. Of importance, subanalyses of the largest of those studies, the AFFIRM trial revealed that attempts to maintain sinus rhythm in patients 65 years or older can even lead to higher mortality compared to the rate control approach.[14].

Rate control

The rate control approach aims to minimise the symptoms and haemodynamic consequences of AF, particularly those related to uncontrolled tachycardia. At present there is no robust evidence of what the optimal heart rate should be in AF. Generally the reasonable target for heart rate is considered to be 60 to 90 beats per minute at rest and less than 110 beats per minute during exertion. Beta-blockers and rate-limiting calcium channel blockers (diltiazem and verapamil) should be used as the preferable initial agents for rate control unless contraindicated. [17] Of note rate limiting calcium channel blockers should not be used in patients with systolic heart failure. Combination of beta-blockers or rate-limiting calcium channel blockers with digoxin can be used when monotherapy is not sufficient. In some cases when the heart rate is particularly difficult to control amiodarone can be tried. Occasionally, when pharmacological agents fail to reduce ventricular heart rate atrioventricular node ablation may be performed add followed by implantation of permanent pacemaker.[18] Where urgent rate control is essential in the acute setting, an intravenous beta-blocker (e.g. metoprolol or esmolol) or a rate-limiting calcium channel blocker, verapamil can be administered. Intravenous amiodarone is a useful alternative in situations where beta-blockers or calcium channel blockers are ineffective or contraindicated.

Antithrombotic therapy

Adequate antithrombotic therapy is the keystone of management of AF. Administration of warfarin in suitable patients reduced risk of stroke by two thirds, thus being one of the most effective cardiovascular medicines. Evidence of extremely high efficacy of oral anticoagulation therapy (e.g. warfarin) for stroke prophylactics in AF derives from multiple large clinical trials. A meta-analysis of 13 trials including over 14000 patients with AF, an adjusted-dose of warfarin with target international normalised ratio (INR) 2-3 prevented two thirds of cases of ischaemic stroke or systemic thromboembolism and significantly reduced all-cause mortality.[19] Of note, a similar treatment approach is currently recommended for patients with paroxysmal, persistent and permanent forms of AF who have been shown to be at similar risk of stroke. This is partly due to the fact that patients with paroxysmal AF often suffer from asymptomatic episodes of the arrhythmia when patients with perceived good rhythm control remain unprotected from the risk of thromboembolism when silent AF occurs. It should also be pointed out that in AF warfarin is clearly superior to aspirin in reducing the risk of ischemic stroke [19]. Importantly, there is no significant difference in risk of major bleeding between the oral anticoagulants and aspirin.

How should patients be selected for initiation of oral anticoagulation? The current European guidelines on management of AF recommend stratification of stroke risk using the well validated CHA2DS2-VASc score (Table 1).[8, 20] Oral anticoagulation therapy is indicated in AF patients with “high risk” of stroke who have score e”2. Patients with genuinely “low risk” of stroke who have score = 0 do no not require any antithrombotic therapy. In patients with a score=1, either oral anticoagulation or aspirin can be used, with a preference for oral anticoagulation [20, 21]. Also the new guidelines recommend formal assessment of the bleeding risk in patients considered for oral anticoagulation. For this purpose the HAS-BLED bleeding score should be used (Table 2) [8, 22]. The HAS-BLED score predicts patients at a “high risk” of bleeding (i.e. HAS-BLED score e”3) who need extra caution after initiation of the oral anticoagulation, but does not imply that such treatment is contraindicated.

Tabl. 1 - The CHA_2DS_2-VASc stroke risk score

Letter	Risk factor	Points
C	Congestive heart failure/left ventricular dysfunction	1
H	Hypertension	1
A	Age >75 years	2
D	Diabetes mellitus	1
S	Stroke/transistor ischemic attack/thrombo-embolism	2
V	Vascular disease	1
A	Age 65–74 years	1
S	Sex category (i.e. female sex)	1

Maximum 9 points. Based on Lip et al [37]

Tabl. 2 - The HAS-BLED bleeding risk score

Letter	Clinical characteristic	Points	Definition
H	Hypertension	1	Systolic blood pressure >160 mmHg
A	Abnormal renal and/or	1	Presence of chronic dialysis/renal transplantation/serum creatinine ?200 mmol/L
	Abnormal liver function	1	Chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin .2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase .3 x upper limit normal, etc.)
S	Stroke	1	History of stroke
B	Bleeding	1	Previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc.
L	Labile INRs	1	Unstable/high INRs or poor time in therapeutic range (e.g., 60%).
E	Elderly	1	Age >65 years, , frail condition
D	Drugs or alcohol (1 point each)	1 or 2	Concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse

Maximum 9 points. INR, international normalized ratio. Adapted from Pisters et al.[22]

Novel oral anticoagulants

Oral anticoagulants acting by inhibition of the vitamin K inhibition (for example, warfarin) achieve their pharmacological effects inhibition of coagulation factors II (prothrombin), VII, IX and X via interruption of their carboxylation.[23] Despite their high effectiveness for stroke prevention in AF administration of the vitamin K antagonist is complicated by the need of regular INR monitoring, numerous food and drug interactions.[24] According to the AFFIRM study, the vast majority of strokes in both arms of the trial developed in subjects who stopped warfarin or was not able to maintain therapeutic INR levels.[25-28] Accordingly development of novel oral anticoagulant directed to block activity of specific coagulation factors crucial for activation of both intrinsic and extrinsic coagulation pathways, factor Xa and factor IIa (thrombin) was initiated. Three of the novel oral anticoagulant, apixaban, rivaroxaban and dabigatran have been successfully tested in large clinical trials in patients with AF.

Apixaban

Apixaban is a selective reversible inhibitor of factor Xa.[29, 30] The drug is promptly absorbed after oral intake and shows bioavailability of 60-70%. It peak plasma concentrations are achieved 3-4 hours after the administration and the steady-state blood levels of apixaban are evident within three days of initiation of treatment. Apixaban has a half-life of 10-14 hours on continues therapy.[30, 31] The drug is removed by several mechanism, involving intestinal (about 50–55%) and renal (about 25–30%) secretion and oxidative metabolism. It plasma levels can increase when the drug is used simultaneously with the cytochrome P450 inhibitors.[29, 30].

In the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) double-blind noninferiority trial 18,201 patients with AF who had at least one additional risk factor for stroke were randomized for apixaban (typical dose of 5 mg twice daily) or warfarin (target INR 2.0-3.0).[29] During the median 1.8 year follow-up apixaban was found to be superior to warfarin in relation to the primary study outcome of stroke or systemic embolism (hazard ratio 0.79; 95% confidence interval 0.66-0.95; p=0.01 for superiority). Apixaban was also associated with lower rate of major bleeding (hazard ratio 0.69; 95% confidence interval 0.60-0.80; P<0.001) and ultimately with lower rates of death from any cause (hazard ratio 0.89, 95% confidence interval 0.80-0.99, p=0.047). Also apixaban almost halved the risk of haemorrhagic stroke compared with warfarin (hazard ratio 0.51; 95% confidence interval 0.35-0.75, p<0.001).

Rivaroxaban

Rivaroxaban is another oral direct factor Xa inhibitor.[32, 33] It has oral bioavailability of over 80% which is independent of food intake. The maximum plasma levels are seen 0.5-3 hours after oral administration of the first dose and 2–3 hours after multiple dose intakes. The steady state half-life is 4-9 hours in young healthy individuals, but it is longer in older people (up to 12 hours) and subjects with renal failure due to delayed elimination.[34] About two thirds of rivaroxaban is metabolized in the liver with the rest being eliminated by various enzymatic mechanisms.[32] About 30% of the administered dose is excreted unchanged by kidneys.[33, 35] The rest of the drug is metabolized into inactive metabolites and eliminated by renal and intestinal secretion.

In the double blind non-inferiority Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial[32] 14264 patients with AF were randomised for rivaroxaban (20 mg once daily or 15 mg once daily in patients with creatinine clearance 30-49 ml/min) or dose-adjusted warfarin. During a median 1.9 year follow up the primary end point of stroke or systemic embolism annually occurred in 1.7% of patients treated with rivaroxaban and in 2.2% of participants receiving warfarin this proved noninferiority of the new drug compared to warfarin. Annual rate of major bleeding was 3.6% in patients receiving rivaroxaban and 3.4% in those treated by warfarin, thus also demonstrating non-inferiority. Of importance, treatment with rivaroxaban was associated with significant reduction in intracranial haemorrhage (0.5% vs. 0.7% with warfarin, p=0.02) and fatal bleeding (0.2% vs. 0.5% with warfarin, p=0.003).

Dabigatran etexilate

Dabigatran is a direct, reversible thrombin inhibitor. A highly polar hydrophilic molecule of dabigatran has very limited absorption after oral intake. Consequently a prodrug, dabigatran etexilate has been developed to address the problem, still with bioavailability of about 6%. Following to conversion to an active drug by plasma esterases reaches its peak plasma levels 1-2 hours after administration and shows a half-life of approximately 14-17 hours.[36] Eighty percent of dabigatran is removed by kidneys. Cytochrome P450 enzymes is not involved in the drug metabolism thus minimizing risks of significant interdrug interactions.[36] Unlike ximelagatran, dabigatran does not induce hepatotoxicity, which was clearly demonstrated by both clinical trials and post marketing data.

In the noninferiority open label Randomized Evaluation of Long-term anticoagulant therapy (RE-LY) trial[32] 18113 patients with AF were randomised to either 110 mg or 150 mg twice daily or unblinded warfarin. During the follow up of median 20 year duration the annual rate of the primary outcome of stroke or systemic embolism was 1.69% in the warfarin group, with evidence of non-inferiority for 110 mg dabigatran dose (1.53%) superiority of the 150 mg dose (1.11%, p<0.001 for superiority). The annual rate of major bleeding was did not differ significantly between warfarin (3.36%) and the 150 mg dabigatran dose (3.11%), but 110 mg dabigatran dose produced significantly less bleeding events (2.71% per year) than warfarin. Of note, the rate of haemorrhagic stroke was lower in both dabigatran doses (0.12% per year with 110 mg of dabigatran and 0.10% per year with 150 mg of dabigatran) than in the warfarin group (0.38% per year). The death rate in the warfarin group was 4.13% which was statistically similar to the 110 mg of dabigatran (3.75%). There was a strong trend towards a lower risk (3.64% per year) with 150 mg of dabigatran than with warfarin (p=0.051).

Conclusions

The rata control strategy with appropriate anticoagulation results in similar rate of thromboembolic complications to rhythm control approach with currently available antiarrhythmic drugs. Novel oral anticoagulants are effective and safe in patients with non-valvular AF and benefit from no need in blood monitoring. Possible limitations of these agents include lack of established treatment able to reverse their activity when this is urgently needed. Also their effectiveness and safety have not be established in patients with severe renal failure which is not uncommon in AF. Also effectiveness of the new agents in valvular AF and patients with concomitant acute coronary syndromes is still to be determined. Despite these limitations the novel oral anticoagulants open a new era of stroke prevention in AF and they are likely to become dominant antithrombotic agents used in AF in the future.

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СОВРЕМЕННЫЕ ПОДХОДЫ К ЛЕЧЕНИЮ ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ

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В статье изложены современные подходы к коррекции фибрилляции предсердий.
Ключевые слова: *фибрилляции предсердий, коррекция.*

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