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REVIEW ARTICLE

New concepts in the therapy of atrial fibrillation

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Abstract

Atrial fibrillation is a frequent arrhythmia with increasing prevalence. The paper reviews the most important present aspects and paradigms in the treatment of the arrhythmia. The main aim of treatment is directed to improve the quality of life while reducing morbidity and mortality. A large experience derived from epidemiological registers and clinical research, impressive advances in interventional electrophysiological therapies and the introduction of non-vitamin K antagonists had a dramatic impact on the medical approach. Recommended steps to classify and treat atrial fibrillation are presented and discussed. (Cardiol J 2016; 23, 1: 3–11)

Key words: atrial fibrillation

Introduction

Atrial fibrillation (AF) is a common arrhythmia. At present AF affects up to 2% of the general population [1] and in Europe has an estimated prevalence of 6 million. In United States, AF incidence will double, from 1.2 million cases in 2010 to 2.6 million cases in 2030 and given this increase in incidence, AF prevalence is projected to increase from 5.2 million in 2010 to 12.1 million cases in 2030 [2]. Its frequency is augmenting due to the worldwide increasing patients' age and contributing cardiovascular risk factors [2, 3]. Data on AF would fill a textbook. We review the most important recent aspects.

Diagnosis and risk stratification

The recommended steps to classify and treat AF (Table 1) are a) anamnesis and clinical findings, to diagnose whether AF is paroxysmal, persistent, long-standing (> 1 year), or permanent; b) a clinical and laboratory check-up; c) a 12-lead electrocardiogram (ECG); d) an echocardiographic assessment, and e) a long-term dynamic ECG [1, 3].

The main aim of treatment of AF is directed to increase the quality of life while reducing morbidity and mortality. The degree of symptoms and co-existing pathologies are the basis for choosing the therapy. A large experience, derived from epidemiological registers and clinical research, impressive advances in interventional electrophysiological therapies, and the introduction of non-vitamin K antagonists (NOAC) had a dramatic impact in the medical approach [4–7].

Thromboembolic prophylaxis

The reduction of thromboembolic complications is a capital aim of therapy. The CHA_2-DS_2-VASc score (Table 2), developed when only vitamin K antagonists (VKA) and antiplatelet agents were available [1, 3–5] and also used for NOAC has replaced previous scores and influences the thromboembolic prophylaxis in AF [5].

Antiplatelet agents

The use of aspirin, other antiplatelet agents, or their combination in the thromboembolic prophylaxis in AF is now generally not recommended. The therapeutic effect is uncertain or insufficient and yet there is an increased bleeding risk [1, 3–7].

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Table 1. Recommended steps to classify and treat atrial fibrillation.

Diagnosis	Therapy
General	**Anticoagulation**
• Symptoms (EHRA score)	• CHA$_2$-DS$_2$-VASc score
• Clinical check-up	• Oral anticoagulation (VKA, NOAC)
• Coexisting pathologies?	**Antiarrhythmic strategies**
• Laboratory	• Drugs controlling heart rate
Specific	• Sinus conversion if indicated and possible
• 12-lead ECG	• Catheter ablation when indicated
• Echocardiography	**Treatment of co-morbidities**
• Long-term dynamic ECG	• Heart failure
	• Hypertension
	• Diabetes mellitus
	• Apnea/hypopnea
	• Respiratory pathology
	• Renal failure
	• Dyslipidemia
	• Inflammatory pathology

ECG — electrocardiogram; NOAC — non-vitamin K antagonists; VKA — vitamin K antagonists

Table 2. CHA$_2$-DS$_2$-VASc score.

Letter	Explanation	Points
C	Congestive heart failure, also treated	1
H	Hypertension, also treated	1
A$_2$	Age > 75 years	2
D	Diabetes mellitus, also treated)	1
S$_2$	Stroke: transient ischemic attacks/stroke, cerebral stroke	2
V	Vascular disease, also treated	1
A	Age, 65–74 years	1
S	Sex, female	1

≥ 2 points = indication for anticoagulation

Table 4. HAS-BLED score.

Letter	Explanation	Points
H	Hypertension, also treated	1
A	Abnormal renal or liver function (1 point each)	1–2
S	Stroke: transient ischemic attacks/stroke, cerebral stroke	1
B	Bleeding	1
L	Labile international normalized ratio (for VKA)	1
E	Age > 65 years	1
D	Drugs or alcohol (1 point each)	1–2

Maximum 9 points; VKA — vitamin K antagonists

Table 3. Yearly cardio-embolic risk and CHA$_2$-DS$_2$-VASc score.

Score	Yearly % risk
2	4
3	5
4	8.5
5	12.5
6	18.2

Oral anticoagulation

Oral anticoagulation (OAC) is indicated with a CHA$_2$-DS$_2$-VASc score ≥ 2. The yearly stroke rate is related to the score as shown in Table 3. However, before using OAC it is necessary to consider general bleeding and safety profiles, and also possible interactions. It is recommended to use the HAS-BLED score (Table 4).

Vitamin K antagonists

These drugs are loosely called VKA because they inhibit vitamin K epoxide reductase. Their

Table 5. Relevant pharmacokinetics of acenocoumarol, phenprocoumon and warfarin.

	Acenocoumarol	**Phenprocoumon**	**Warfarin**
Clot formation	Yes*	Yes*	Yes*
Inhibition**	The liver enzyme vit. K reductase (thus reduced form of vit. KH2)	The liver enzyme vit. K reductase (thus reduced form of vit. KH2)	The liver enzyme vit. K reductase (thus reduced form of vit. KH2)
	Factors II, VII, IX, and X, ultimately reduced cleavage of fibrinogen into fibrin and decreased coagulability of the blood	Factors II, VII, IX, and X, ultimately reduced cleavage of fibrinogen into fibrin and decreased coagulability of the blood	Factors II, VII, IX, and X, ultimately reduced cleavage of fibrinogen into fibrin and decreased coagulability of the blood
Dose adjustment	Individual	Individual	Individual
Activity***	Effects of genetic factors: unknown	Effects of genetic factors: unknown	Activity is determined partially by genetic factors
	Patients older than 60 years and Asian patients appear to exhibit greater than expected INR response to the anticoagulant effects VKA	Patients older than 60 years and Asian patients appear to exhibit greater than expected INR response to the anticoagulant effects VKA	Patients older than 60 years and Asian patients appear to exhibit greater than expected INR response to the anticoagulant effects VKA
Half-life	8 ± 0.5 h	157 ± 12 h	Mean 40 h (range 20–60 h)
Routine monitoring	Mandatory, INR	Mandatory, INR	Mandatory, INR
Interactions	Cytochrome P450: 2C9 and 2C8	Cytochrome P450: 2C9 and 2C8	CYP450: 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4
	Vitamin K	Vitamin K	Vitamin K

*When newly started, VKA may promote clot formation temporarily, because the level of protein C and protein S are also dependent on vit. K activity. For example, warfarin causes decline in protein C levels in first 36 h. In addition, reduced levels of protein S lead to a reduction in activity of protein C (for which it is the co-factor) and to a reduced degradation of factor Va and factor VIIIa. The hemostasis system becomes temporarily shifted towards thrombus formation, leading to a prothrombotic state; **Full doses of VKA produce a precipitous decline in factor VII, resulting in an initial prolongation of the INR. Full antithrombotic effect does not take place until significant reduction in factor II occurs (4–5 days later); ***Polymorphisms in two genes (VKORC1 and CYP2C9) play a particularly large role in response to warfarin. However, the clinical use of pharmacogenomic testing in warfarin dosing is controversial; INR — international normalized ratio; VKA — vitamin K antagonists

action may be antagonized by administration of vitamin K. In some countries non-coumarin VKA, especially 1,3-indandione derivatives (e.g., fluindione and phenindione) are available. However, 4-hydroxycoumarins (coumarins), especially warfarin, are the commonly used VKA. Especially in some European countries, acenocoumarol and phenprocoumon are frequently used. VKA are still used, but the number of patients with AF who are first treated with NOAC or are switched from VKA to NOAC is steadily increasing. VKA are given with an individualized dosage in patients with AF to reach an international normalized ratio (INR) 2–3. It is noteworthy that to avoid the early prothrombotic state induced by VKA until a therapeutic INR is achieved [8] patients who are at high risk of cardio-embolic events should receive a bridging therapy with low-molecular heparins in the early phase (4–5 days) of treatment, or should directly be treated with an NOAC (Table 5).

It should also be considered that OAC with VKA is problematic in patients with severe hepatic dysfunction: under this condition the validity of the prothrombin-time test and related tests for assessing the risk of hemorrhage and guiding OAC is strongly questioned [9] and this conditions may explain the problems related to the use of VKA in this pathology.

Vitamin K antagonists are highly effective in reducing thromboembolic complications in patients with AF [1, 3–7]. However, patients must take VKA throughout their lives and as with any other therapy there are also some 'shadows'. It has been known since the 1970s that women receiving VKA between the 6th and 12th week of pregnancy give birth to children with severe bone abnormalities. Recently it has been demonstrated that patients on coumarin-therapy develop cardiac valvular pathologies induced by basophilic-amorphous calcified deposits; it is hypothesized that treatment with coumarins induces incomplete γ-carboxylation of the matrix-gla protein with a consequent decreased protection against tissue calcification [10]. Furthermore, more vitamin K is needed for carboxylation of bone production than for activation of clotting factor and concern has arisen that VKA could interfere with bone metabolism, putting patients at risk for osteoporosis. The impact of VKA

Table 6. Pharmacokinetics of available non-vitamin K antagonists.

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Inhibition	Thrombin	Factor Xa	Factor Xa	Factor Xa
Prodrug	Yes	No	No	No
Dose adjustment	Related to age and eGFR	Related to age, eGFR and weight	Related to eGFR, co-medication and weight	Related to eGFR
Bioavailability	6%	70%	62%	80%
Protein binding	35%	90%	55%	90%
Dosage intervals	bid	bid	oad	oad
Half-life	12–14 h	12 h	8–10 h	7–11 h
Renal excretion	40%	25%	40%	35%
Routine monitoring	No	No	No	No
Interactions	p-glycoprotein	cytochrome P3A4 and p-glycoprotein	cytochrome P3A4 and p-glycoprotein	cytochrome P3A4 and p-glycoprotein

eGFR — estimated glomerular filtration rate; bid — twice per day; oad — once per day

in this setting is not well established, but there is evidence that these drugs have a negative effect on bone turnover [11].

Non-vitamin K antagonists

Non-vitamin K antagonists were mentioned in the 2010 guidelines of the European Society of Cardiology. In the 2015 guidelines, one finds 15 suggestions about the use of NOAC in different scenarios. In our paper, we deal only with the use of NOAC in prevention of thromboembolic events in patients with AF. Large data from the use of NOAC have revolutionized and simplified OAC. At present available NOAC are dabigatran, apixaban, edoxaban and rivaroxaban. Their most important pharmacokinetic data are shown in Table 6. The available data [5, 6] show that NOAC are equivalent and possibly better than VKA in the thromboembolic prophylaxis of patients with AF. Of note, compared to VKA, NOAC have a smaller risk for intracerebral bleeding [6, 7, 12, 13].

The mechanism of action of dabigatran differs from that of other available NOAC because it blocks directly and selectively thrombin. The most commonly reported side-effects of dabigatran are gastro-intestinal adverse-effects. When compared to people treated with VKA, patients taking dabigatran had fewer life-threatening bleeds, fewer minor and major bleeds, including intracranial bleeds, but the rate of gastro-intestinal bleeding was significantly higher. Dabigatran capsules contain tartaric acid, which is required for adequate absorption and lowers the gastric pH. The lower pH has been associated with dyspepsia and it is

hypothesized that this plays a role in the increased risk of gastrointestinal bleeding. A small but significantly increased risk of acute coronary events has been noted when combining the safety outcome data from multiple trials [14].

Apixaban, edoxaban and rivaroxaban exert their anticoagulant effect via direct inhibition of a single factor (factor Xa). Major bleeding and fatal bleeding occurred significantly less frequently with these NOAC than with VKA, but gastro-intestinal and nasal bleeding is not rare [15–17]. It is hypothesized that these side effects may be related to anticoagulatory active metabolites, which are absent in VKA. Rare side effects of edoxaban are abnormal liver function and rash [16]. Non-bleeding gastro-intestinal adverse effects of rivaroxaban (e.g. nausea) are very rare [17].

A recent interesting paper [17] with data collected from countries with a reputed experience in the therapy with VKA shows that patients switched from VKA to NOAC have higher stroke risk profiles than patients directly treated with NOAC. Therefore, it seems possible that patients with AF who have been previously treated with VKA are different from those who have been untreated [18].

When using OAC it is important to consider the renal and to a certain extent the hepatic function. We have insufficient reports about the use of NOAC in patients with severe renal and/or hepatic dysfunction. It is proven, however, that a severe renal dysfunction (and also a severe hepatic dysfunction) may increase the bleeding risk, in NOAC mostly by inducing accumulation [12]. Research for specific antidotes for NOAC is ongoing, but

Table 7. Antiarrhythmic therapy and/or rhythm control in atrial fibrillation.

Structurally normal heart				
First line therapy • Flecainide • Propafenone • Sotalol • Dronedarone[+]	Second line therapy • Ablation			
Known cardiac pathology				
	Significant LVH	**CAD**	**Cardiomyopathy**	**Severe renal failure**
First line therapy	• Amiodarone	• Sotalol[++] • Dronedarone[+] • Dofetilide	• Amiodarone • Dofetilide	• Amiodarone
Second line therapy		• Amiodarone	• Amiodarone • Dofetilide	
	• Ablation	• Ablation	• Ablation	

+Dronedarone is contraindicated in patients with long-standing or permanent atrial fibrillation; ++Sotalol is contraindicated in the presence of severely impaired left ventricular function or severe renal failure; CAD — coronary artery disease; LVH — left ventricular hypertrophy

specific antidotes are not yet available with few exceptions in hospital settings. Some patients were successfully treated with prothrombin concentrate complex.

Alternative thromboembolic prophylaxis when oral anticoagulation is contraindicated

Some patients with AF and high risk for thromboembolic complications cannot be safely treated with OAC because they also have an excessive bleeding risk or contraindicating co-morbidities. Thromboembolic events originate from the left atrium. Thus, in selected patients with AF in whom necessary OAC is contraindicated, left atrial appendage closure with an occluding device can be used [19–21]. The technique is quite effective in reducing thromboembolic events in AF [1, 3, 4, 19–21], but several complications may occur [21]. For example, apixaban had to be used to treat protruding thrombus over left atrial appendage occlusion device [22].

Antiarrhythmic therapies

We have discussed the need for thromboembolic prophylaxis but, of course treatment of the arrhythmia has also a central role. The therapy is adjusted to the symptoms and the duration of the AF, taking into proper account the co-morbidities. Possible therapeutic approaches are presented in Table 7.

Pharmacologic options

Table 8 shows antiarrhythmic drugs which may be used in the therapy AF. AF is a dynamic disease and altogether available antiarrhythmic drugs have a limited efficacy. Therefore, long-term antiarrhythmic treatment of AF is often less effective than required [3, 4, 23].

Heart rate control

In asymptomatic patients and, especially, in the elderly polymorbid patients with AF, heart rate control is often the 1st choice therapeutic option [3, 4, 23–25].

The use of digoxin is bond to a long-time debate. Especially in recent years, it is stated that, when used in patients with AF and manifest cardiac failure, digoxin increases the mortality [22–28]. Vamos et al. [28] suggest several potential mechanisms of digoxin-associated mortality increase: in many studies detected digoxin serum levels were higher (> 1.2 ng/mL) than the level now recommended; at toxic levels, digoxin may induces severe arrhythmias; digoxin has many interactions, e.g. with amiodarone and other antiarrhythmic drugs (and these drugs were used in the analyzed studies; digoxin increases vagal tone, reduces atrioventricular conduction and shortens atrial refractory periods, effects which may have pro-arrhythmic effects in AF; also, digoxin was found to be associated with doubling of relapses of

Table 8. Antiarrhythmic drugs used in chronic therapy of atrial fibrillation.

Class	Example	Pro-arrhythmic potential	Other relevant adverse events	Contraindications
IC[+]	Flecainide and propafenone	Atrial flutter with 1:1 conduction[++], VT/VF	Nausea, dyspepsia, paresthesia	CAD, LVH, long QT-time, LVD, HF NYHA IV
III	Sotalol	Torsades de pointes	Bradycardia	Severe LVD or severe RF
	Dofetilide	Torsades de pointes		
	Dronedarone[++]	Rare	Decompensated HF, hepatic dysfunction (rare)	HF NYHA II with decompensation in the last weeks, long QT-time, previous SCD (with LVD, HF) permanent AF, relevant hepatic failure or RF
	Amiodarone	Rare	Thyroid, lung, hepatic toxicity, optic neuropathy, polyneuropathy	Hepatic disease, interstitial lung disease
	Digoxin	Possible	Dizziness, nausea, fainting, pounding, or irregular heartbeat or pulse, bradycardia. Less common: black, tarry stools, bleeding gums, blood in the urine or stools, pinpoint red spots on the skin, rash with flat lesions or small raised lesions on the skin, stomach pain, unusual bleeding or bruising, gynecomastia, anxiety, confusion, impaired vision	Bradycardia, relevant RF or hepatic failure, electrolyte pathologies
		Toxicity	Proarrhythmic effect	

+To counteract this pro-arrhythmic effect of IC class agents should be used in combination with drugs which reduces the AV-conduction (*β*-blocker, verapamil or diltiazem); ++Dronedarone is contraindicated in patients with long-standing or permanent atrial fibrillation (AF); CAD — coronary artery disease; HF — heart failure; LVD — left ventricular dysfunction; LVH — left ventricular hypertrophy; NYHA — New York Heart Association; RF — renal failure; SCD — sudden cardiac death; VF — ventricular fibrillation; VT — ventricular tachycardia

AF following cardioversion. However, the statistically increased mortality in AF-patients treated with digoxin is open to debate [29–33]. Digoxin has been used for a long time, mostly in polymorbid patients, when other drugs have failed and there is no alternative pharmacologic treatment. It is well known that the therapeutic safety profile of digoxin is narrow, and overdose and/or an interaction with antiarrhythmic drugs, diuretics etc. may induce toxic effects. Most recent studies describe dangerous electrophysiological effects which were described as digoxin-induced arrhythmias, but the serum levels were higher than safe, the electrolytic state (K$^+$, Na$^+$ etc.) were rarely reported: were the arrhythmias evidence for toxicity? Adverse-events due to improper use and toxicity should not be taken and evidence for increased mortality at low-dose levels. Meta-analysis studies reporting effects and increased mortality of digoxin are difficult to be evaluated, because the use of digoxin and the treated patients cannot be properly compared [32, 33]. Indeed, if properly titrated, taking into account digoxin pharmacokinetics and the co-morbidities (renal function, electrolytes) digoxin is effective in improving cardiac symptoms and (even not during physical exercise) it has a regulatory effect on heart rate. The impetus for novel methodologies regarding analysis and reporting of results should not solely be driven by concerns of statistical power, but by a desire to better understand how therapies influence a broader characterization of total disease burden. Most disease progressions are associated with the realization of multiple complications and analysis may sometimes obfuscate the findings. Analysis of event arms may lend itself to conflicting interpretations such as those presented in recent trials, there is the concern of type I error rate inflation due to multiple testing [34]. Thus, the reader is cautioned with this approach [34]. An exclusive focus on mortality may obscure important effects of medications [35]. Thus, the real effect of old digoxin on increased mortality (especially in polymorbid elderly patients) must be taken into consideration. Using two standardized

bias scoring systems, D. Kotecha (annual congress of the ESC in London 2015) has demonstrated that reviews reporting an association between mortality and digoxin were highly biased. No studies have evaluated the impact of digoxin in patients with AF without heart failure. The higher the observational study's bias score, the greater the reported association between digoxin and mortality. In contrast, well conducted and randomized controlled trials all score a very low bias and carry a consistent message that digoxin had a neutral effect on mortality. The best available evidence demonstrates that digoxin reduces hospital admission and has no effect upon all-cause mortality in patients with heart failure with or without atrial fibrillation.

Pharmacologic therapy aimed to restore/maintain sinus rhythm

First choice drugs are β-blockers or, when contraindicated, verapamil or diltiazem [3, 4, 23–26].

Asymptomatic patients and patients with impaired cardiac function often are effectively treated with a rhythm control strategy [1, 3, 22–25].

In patients with AF without structural cardiac pathology antiarrhythmic agents of class IC (e.g., flecainide or propafenone), combined with a β-blocker, are the first choice [1]. In patients with relevant cardiac pathology, especially with an impaired left ventricular systolic function, amiodarone and dofetilide (class III antiarrhythmic drugs) are the first choice [1, 4, 25].

Amiodarone (class III agent) is the most effective therapeutic agent but, unfortunately its use is severely limited because of its many interactions and adverse effects; amiodarone should be used for a relatively short period [3, 4, 23–25].

Dronedarone (class III agent) should be used with many restrictions and is contraindicated in patients with heart failure and in those with permanent AF [4, 5, 23–25].

Vernakalant is a new antiarrhythmic drug that acts selectively in the atrium, targeting atrial specific channels: the Kv1.5 channel which carries IK (ur), and the Kir3.1/3.4 channel which carries IK (Ach): it can also work to block Ito, late Ina, and exert a minor blockade of IKr currents. Vernakalant is available in both intravenous and oral forms. Intravenous vernakalant has been shown to be effective in terminating acute onset AF whose duration is > 3 h and < 7 days (~50% efficacy vs. 10% for placebo). It does not appear to be effective for AF whose duration is > 7 days, nor does it appear to be effective for atrial flutter. Studies with oral vernakalant have been designed to evaluate its efficacy and safety in the prevention of AF recurrence. Up to date have the therapeutic efficacy was moderate; the most common side effects being dysgeusia, sneezing, paresthesia, nausea, and hypotension. In the clinical trials, there were minimal drug-induced ventricular arrhythmias observed.

Electrophysiological options to achieve sinus rhythm

The MAZE procedures were the first attempts to obtain and maintain sinus rhythm in AF [36]. A recent review [37] focuses on surgical options in the curative treatment of AF. Especially the hybrid approach, which combines the advantages of catheter and surgical ablation (with the excision or exclusion of the left atrial appendage), is a promising approach for the future. The knowledge about AF pathophysiology is steadily increasing and new data affect the therapeutic strategies. Because of the increased experience and good therapeutic results catheter-based ablation procedures (isolation of the pulmonary veins either by radiofrequency or cryoablation) have become a routine intervention in cardiology and are increasingly used in AF. Indeed, the ablation therapy is becoming the 1st choice therapy for symptomatic patients with AF [1, 4, 20, 36]. Patients' preferences play without doubt a central role. The efficiency of the ablation is increasing. Nonetheless, the risk-advantage profile must be taken into account and some indications must be respected. The type and duration of AF, the type of cardiac disease, and the size and function of the atria must be considered to deliver a successful therapy. In centers with large numbers of interventions complications occur in less than 4% of cases. Complications at the inguinal entrance occur in about 2% of cases. In less than 1% of cases cardiac tamponade may follow and require drainage. Transient ischemic complications or cerebral strokes occur in less than 1% of cases. Atrio-esophageal fistula is a feared complication, which occur in less than 0.2% of cases. Recent meta-analyses [3, 36] report that 77% of the ablation-treated patients are asymptomatic at a 1-year follow-up, in comparison to 52% of medically treated patients. It should be noted that up to a third of patients requires a 2nd ablation (redo-ablation) to achieve a long-lasting symptom-free life [3, 4, 23, 25, 38]. We still lack enough information to personalize ablation in each individual, which could results in more efficacious and less extensive ablation in some patients [39].

In some cases, pharmacologic treatment does not suffice to reduce sufficiently heart rate. In these

patients, an approach could be the interruption of the atrioventricular conduction by catheter ablation and the implantation of a cardiac pacemaker [3]. This therapy has a 99% efficacy and has the advantage that many drugs to control the arrhythmia can be discontinued.

Treatment of risk factors and co-morbidities

In recent years, the term 'upstream therapy' has been used to describe treatment of AF [3, 4, 23–25]. It has been demonstrated that the effective treatment of cardiovascular risk factors (e.g., arterial hypertension, diabetes mellitus, tobacco consumption, sleep apnea/hypopnea, renal dysfunction, pulmonary diseases, inflammatory disorders, and dyslipidemia) has positive therapeutic effects on AF [3–7, 23–26]. A study [40] has shown that, in overweight patients with AF, a significant weight decrease, associated with a good control of metabolic pathologies, reduces symptoms related to AF and also has a positive effect on cardiac remodeling. Among the drugs used to treat patients with AF it seems that angiotensin-converting enzyme inhibitors/angiotensin-2 receptor antagonists, and statins (HMG CoA reductase inhibitors) are effective in slowing the evolution of AF. These drugs may reduce pathologic factors such as inflammation and fibrosis.

Lastly, it has been found that non-steroidal anti-inflammatory drugs increase the risk of AF [41] and it might be advisable, if possible, to use other analgesic drugs to treat patients at risk for AF.

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References

1. Camm AJ, Lip GYH, De Caterina R et al. Focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J, 2012; 33: 2719–2747, doi: 10.1093/eurheartj/ehs253.
2. Colilla S, Crow A, Petkun W et al. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am J Cardiol, 2013; 15: 1142–1147. doi: 10.1016/j.amjcard.2013.05.063.
3. Pillarisetti J, Lakkireddy D. Atrial fibrillation in Europe: State of the state in disease management. Eur Heart J, 2014: 35: 3326–3327. doi: 10.1093/eurheartj/ehu415.
4. Camm AJ, Kirchhof P, Lip GYH et al. Guidelines for the management of atrial fibrillation. The task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Eur Heart J, 2010; 31: 2369–2429. doi: 10.1093/eurheartj/ehq278.
5. Gage BF, Waterman AD, Shannon W et al. Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. JAMA, 2001; 285: 2864–2870. doi: 10.1001/jama.285.22.2864.
6. Lip GYH. Stroke and bleeding risk assessment in atrial fibrillation: When, how, and why? Eur Heart J, 2013; 34: 1041–1049. doi: http://dx.doi.org/10.1093/eurheartj/ehs435.
7. Heidbuchel H, Verhamme P, Alings M et al. EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. Eur Heart J, 2013; 34: 2094–2106. doi: 10.1093/eurheartj/eht134.
8. Diener HC, Granger C, Patel MR. Is there a period of liability with initiation of warfarin in patients with atrial fibrillation? Eur Heart J, 2014; 35: 1834–1835. doi: 10.1093/eurheartj/ehu042.
9. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. New Engl J Med, 2011; 14: 147–156.
10. Schurgers LJ, Aebert H, Vermeer C et al. Oral anticoagulant treatment: Friend or foe in cardiovascular disease? Blood, 2004; 104: 3231–3232. doi: 10.1182/blood-2004-04-1277.
11. Stenova E, Steno B, Killinger Z et al. Effect of long-term oral anticoagulant therapy on bone mineral density and bone turnover markers: A prospective 12 month study. Bratisl Lek Listy, 2011; 112: 71–76.
12. Hart RG, Eikelboom IW, Alistair J et al. Anticoagulants in atrial fibrillation patients with chronic kidney disease. Nat Rev Nephrol, 2012; 8: 569–578.
13. O'Donoghue ML, Ruff CT, Giugliano RP et al. Edoxaban vs. warfarin in vitamin K antagonist experienced and naive patients with atrial fibrillation. Eur Heart J, 2015; 36: 1470–1477. doi: 10.1093/eurheartj/ehv014.
14. Uchino K, Hernandez AV; Hernandez. Dabigatran associated with higher risk of acute coronary events – metaanalysis of non inferiority randomized controlled trial. Arch Intern Med, 2012; 5: 397–302. doi: 10.1001/archinternmed.2011.1666.
15. Granger CB, Alexander JH, John JV, McMurra JJV et al. Apixaban versus warfarin in patients with atrial fibrillation. New Engl J Med, 2011; 365: 981–992.
16. http://www.mayoclinic.org/drugs-supplements/edoxaban-oral-route/side-effects/drg-20137330.
17. http://www.rxlist.com/xarelto-side-effects-drug-center.htm.
18. Podokorney SD, Granger CB. Should patients on vitamin K antagonists be treated differently? Eur Heart J, 2015; 36: 1431–1433. doi: 10.1093/eurheartj/ehv032.
19. Reddy VY, Sievert H, Halperin J et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: A randomized clinical trial. JAMA, 2014; 312: 1988–1998.
20. John Camm A, Colombo A, Corbucci G et al. Left atrial appendage closure: A new technique for clinical practice. Heart Rhythm, 2014; 11: 514–521.
21. Reddy VY, Holmes D, Doshi SK et al. Safety of percutaneous left atrial appendage closure. Results From the Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT AF) clinical trial and the continued access registry. Circulation, 2011; 123: 417–424. doi: 10.1161/CIRCULATIONAHA.110.976449.
22. Feixa X, Scalone G, Martín-Yuste V, Vidal B. Large protruding thrombus over left atrial appendage occlusion device successfully treated with apixaban. Eur Heart J, 2015; 36: 1427. doi: 10.1093/eurheartj/ehv081.

23. Kevin M. Trulock, Sanjiv M et al. Rhythm control in heart failure patients with atrial fibrillation. J Am Coll Cardiol, 2014; 64: 710–721. doi: 10.1016/j.jacc.2014.06.1169.

24. Woods CE, Olgin J. Atrial fibrillation therapy now and in the future: drugs, biologicals, and ablation. Circ Res, 2014; 14: 1532–1546.

25. European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Eur Heart J, 2010; 19: 2369–2429.

26. Whitbeck MG, Charnigo RJ, Khairy P et al. Increased mortality among patients taking digoxin: analysis from the AFFIRM study. Eur Heart J, 2013; 34: 1481–1488. doi: 10.1093/eurheartj/ehs348.

27. Pastori D, Farcomeni A, Bucci T et al. Digoxin treatment is associated with increased total and cardiovascular mortality in anticoagulated patients with atrial fibrillation. J Cardiol, 2014; 180: 1–5. doi: org/10.106.I.jcard.2014.11.112.

28. Vamos M, Erath JW, Hohnloser SH. Meta-analysis: Digoxin linked to elevated mortality risk in AF, congestive HF. Eur Heart J, 2015; 36: 1831–1838. doi: 10.1093/eurheartj/ehv143.

29. Packer M, Gheorghiade M, Young JB et al. Withdrawal of digoxin therapy from patients treated with angiotensin-converting enzyme inhibitors. N Engl J Med, 1993; 329: 1–7.

30. Ward RE, Gheorghiade M, Young JB. Economic outcomes of withdrawal of digoxin therapy in adult patients with stable congestive heart failure. J Am Coll Cardiol, 1995; 26: 93–101.

31. Ahmed A, Rich MW, Love TE et al. Digoxin and reduction in mortality and hospitalisation in heart failure: A comprehension *post hoc* analysis of the DIG trial. Eur Heart J, 2006; 27: 178–186. doi: 10.1093/eurheartj/ehi687.

32. Brophy JM. Rehabilitating digoxin. Eur Heart J, 2006; 27: 127–129. doi: 10.1093/eurheartj/ehi686.

33. Murpy SA. When 'digoxin use' is not the same as 'digoxin use': Lesson from the AFFIRM trial. Eur Heart J, 2013; 34: 1465–1467. doi: 10.1093/eurheartj/eht087.

34. Ciolino JD, Carter RE. Reanalysis or redefinition of the hypothesis? Eur Heart J, 2015; 36: 340–341. doi: 10.1093/eurheratj/ehu311.

35. Yusuf S, Negassa A. Choice of clinical outcomes in randomized trials of heart failure therapies: Disease-specific or overall outcomes? Am Heart J, 2002; 143: 22–28.

36. Cox J, Schuessler R, D'Agostino H et al. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. J Thorac Cardiovasc Surg, 1991; 101: 569–583.

37. Starck CT, Steffel J, Holubec T, Falk V. Current aspects of atrial fibrillation surgery. Cardiovasc Med, 2015; 18: 181–185.

38. Jia Chen J, Lin Y, Chen L et al. A decade of complex fractionated electrograms catheter-based ablation for atrial fibrillation: Literature analysis, meta-analysis and systematic review. Int J Cardiology Heart Vess, 2014; 4: 63–72. doi: 10.1016/j.ijchv.2014.06.013.

39. Mont L. Atrial fibrillation ablation: Less is more? Eur Heart J, 2015; 36: 1792–1793. doi: 10.1093/eurheartj/ehv224.

40. Abed HS, Wittert GA, Leong DP et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: A randomized clinical trial. JAMA, 2013; 310: 2050–2060. doi: 10.1001/jama.2013.280521.

41. Krijthe BP, Heering J, Hofman A et al. Non-steroidal anti-inflammatory drugs and the risk of atrial fibrillation: A population-based follow-up study. BMJ Open, 2014; 4: e004059. doi: 10.1136/bmjopen-2013-004059.