

Management of atrial fibrillation in specific patient populations

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INTRODUCTION

Treatment of atrial fibrillation (AF) is often demanding because of various comorbidities highly prevalent in AF patients. A holistic approach to AF management must include:

- anticoagulation with regard to the thromboembolic and bleeding risk;
- choosing the rhythm control or rate control strategy;
- assessment and treatment of cardiovascular (CV) risk factors; and
- treatment of CV and non-CV comorbidities.

Therefore, modern, individually tailored AF treatment must be based on current studies and data from clinical trials that are summed up in the recommendations or guidelines from the various scientific societies. Unfortunately the current European AF guidelines do not fully explore the treatment algorithms, especially for specific populations including patients with asymptomatic and/or device-detected AF, obstructive sleep apnoea (OSA), or chronic kidney disease (CKD) [1, 2].

The current review aims to describe the most recent data on the management of AF in different clinical scenarios, focusing on the anticoagulation strategies and different aspects of AF management.

ASYMPTOMATIC AND DEVICE-DETECTED AF

The number of diagnosed AF cases is growing worldwide and is likely to double in the forthcoming years [3]. These changes are caused by the increasing lifespan of the population and improvements in heart rhythm monitoring techniques. Nevertheless, early recognition of AF is not always possible given the often 'silent' presentation of the arrhythmia. Indeed, 13% to 40% of patients with AF do not experience symptoms and have been categorised as 'asymptomatic AF' [2, 4, 5]. One study comparing clinical characteristics of patients with first-diagnosed symptomatic and asymptomatic AF showed that factors predictive of asymptomatic AF were persistent or permanent AF, slower ventricular rate during AF ($< 100/\text{min}$), CHA₂DS₂-VASc score of 0, history of diabetes mellitus, and male sex [4]. Other risk factors for asymptomatic AF include older age, previous myocardial infarction, and limited physical activity [6]. Nevertheless, a recent meta-analysis showed that only male sex was an independent risk factor for asymptomatic AF [7].

A large number of asymptomatic AF cases are detected due to prolonged heart rhythm monitoring strategies and data obtained from implantable electronic cardiac devices (IEDs). In patients with ischaemic stroke of unknown aetiology implantable cardiac monitors caused an over 7-fold improvement in the AF detection over 12 months of monitoring, while event recorder-detected AF was present in 16.1% of patients in the first month, compared to 3.2% in the routinely screened group [5, 6].

In the population of IECD recipients, the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial

(ASSERT) found that AF (defined as IECD detected episode of atrial rate > 190 bpm lasting more than 6 min) was present in 10% of patients and was associated with a 2.5-fold increase in the risk of stroke or systemic thromboembolism [8].

In the general population, the risk of all-cause death, CV death, stroke, or systemic thromboembolism is at least as high or even higher than in symptomatic patients [4, 7]. Nevertheless, asymptomatic patients rarely receive oral anticoagulation [9].

Current European guidelines do not address the issue of anticoagulation in this population [1, 2], and AF guidelines of the Canadian Cardiovascular Society (CCS) recommend anticoagulation in patients having > 1 point in the CHADS₂ score, with silent AF episodes lasting > 24 h and less in case of high risk (i.e. recent cryptogenic stroke) [10]. American Heart Association Guidelines also do not mention anticoagulation in asymptomatic patients, but include one recommendation for their treatment different from the symptomatic population, allowing a lenient rate-control strategy, with resting heart rate < 110 bpm for patients with preserved left ventricular systolic function [11].

Given the lack of prospective studies assessing the benefits and risk from anticoagulation in patients with asymptomatic and/or device-detected AF it is reasonable to recommend anticoagulation management similar to that for patients with symptomatic AF.

Key points

- *Asymptomatic AF is associated with thromboembolic risk similar to the general AF population.*
- *Anticoagulation in silent and IECD-detected AF is recommended in the same way as in symptomatic patients, based on the risk-factor profile.*

ATRIAL FIBRILLATION, ARTERIAL HYPERTENSION, AND OTHER CARDIOVASCULAR RISK FACTORS

Atrial fibrillation is the most common, sustained arrhythmia, and arterial hypertension is one of the most prevalent CV risk factors [12]. Therefore, AF and arterial hypertension often coexist, and hypertension is the most common comorbidity in AF patients. Even in relatively young AF patients, arterial hypertension is found in over 70% of cases and in recent trials such as the RE-LY study, hypertension was diagnosed in 90% of patients [13, 14].

Hypertension has a role in the development, course, and outcomes of AF. The Framingham study showed that the presence of hypertension increases the odds of developing AF by 40% to 50% [15]. Untreated or suboptimally treated arterial hypertension leads to left ventricular hypertrophy, reduction of left ventricular compliance, and an increase in its stiffness and filling pressure, with activation of the sympathetic nervous system and of the renin–angiotensin–aldosterone system.

These factors lead to enhanced connective tissue deposition and atrial fibrosis, which result in electrical, contractile, and structural remodelling [16]. The continuum of CV risk factors and their relation to AF is shown in Figure 1.

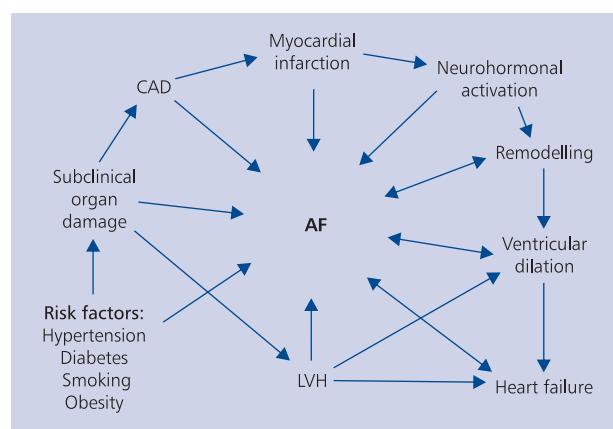


Figure 1. Association between atrial fibrillation (AF) and arterial hypertension. Modified from [16]; CAD — coronary artery disease; LVH — left ventricular hypertrophy

Treatment of hypertension in patients with sinus rhythm may lead to the reduction of AF. European hypertension guidelines list “prevention of AF” as one of the specific conditions in which angiotensin receptor blockers (ARB), angiotensin converting enzyme inhibitors (ACEI), beta-blockers, and mineralocorticoid receptor antagonists should be preferred [17]. At the same time, in the European document there is a class IIa recommendation for using ARBs and ACEI in patients with arterial hypertension for prevention of new-onset AF, especially in patients with left ventricular hypertrophy, and American guidelines recommend a similar algorithm [11]. Also, the guidelines of the Polish Society of Arterial Hypertension recommend using ACEIs, ARB, or (in concomitant heart failure [HF]) eplerenone for prevention of *de novo* or recurrence of AF [18].

In patients with established AF, guidelines recommend other classes of hypotensive agents, mainly due to their heart rate reducing properties. The choice of drug for rate control depends on lifestyle and concomitant diseases (Fig. 2). In hypertensive patients, the most appropriate drugs reducing heart rate in AF include beta-blockers and non-dihydropyridine calcium antagonists (Table 1) [1, 11, 18].

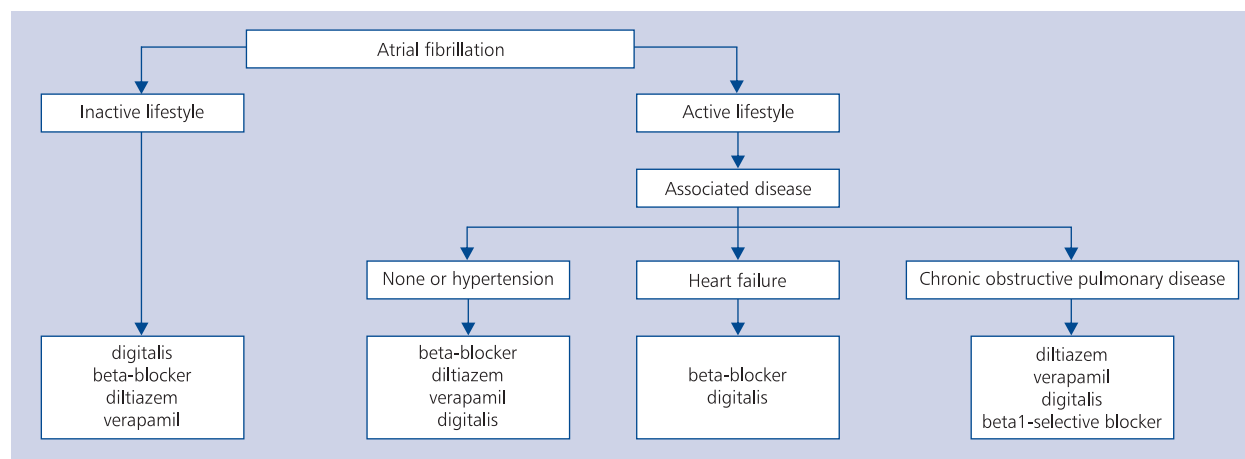


Figure 2. Choice of the appropriate heart rate control drug in atrial fibrillation patients [2].

Table 1. Role of hypotensive agents group in the treatment of atrial fibrillation (AF)

Drug groups	Additional role in AF patients
Angiotensin converting enzyme inhibitors	Prevention of AF development/re-occurrence
Angiotensin receptor blockers	Prevention of AF development/re-occurrence
Diuretics	None
Beta-blockers	Heart rate reduction in rate-control strategy
Dihydropyridine calcium antagonists	None
Non-dihydropyridine calcium antagonists	Heart rate reduction in rate-control strategy
Mineralocorticoid receptor antagonists (namely, eplerenone)	Prevention of AF development/re-occurrence in patients with concomitant heart failure

Oral anticoagulation treatment in hypertensive AF patients with no other risk factors is mandatory according to the European, Canadian, and Polish guidelines, while the American guidelines allow also aspirin or no treatment [3, 10, 18]. The 'hypertension' criterion in the CHA₂DS₂-VASc score refers to history of hypertension or uncontrolled blood pressure. History of hypertension emerges as a stroke risk factor given the likely vascular changes associated with prior hypertension (e.g. small vessel disease) that increase the propensity to stroke. Also, what is well-controlled hypertension today is not necessarily the case over time due to non-compliance with drugs, the rise of blood pressure with age, etc. An individualised approach may be needed in the patient where hypertension is the only evident risk factor.

Non-vitamin K oral anticoagulants (NOAC) are a feasible, effective treatment option in hypertensive AF patients, characterised by similar efficacy as in normotensive patients [19]. Nevertheless, some AF patients require vitamin K antagonists (VKA). Decision making between a VKA or NOAC can be helped by using the SAME-TT₂R₂ score [20]; this simple score tries to incorporate the common clinical features associated with good anticoagulation control (as reflected by time in therapeutic range [TTR]) [21–23], and a SAME-TT₂R₂ score of 0–2 is associated with a good TTR and lower propensity to thromboembolism, bleeding, and mortality [24].

Other CV risk factors highly prevalent in AF include dyslipidaemia. The guidelines do not address specifically this condition in AF patients, but focus on the utility of statins in AF patients. Statins are a part of so-called "upstream" therapy in AF patients [1]. This kind of treatment is focused on preventing onset, re-occurrence, or consequences (including remodelling) of AF. Positive consequences of statin treatment in AF include anti-inflammatory and antioxidant actions, reduction of endothelial dysfunction and neurohormonal activation, altered membrane fluidity, and ion channel conductance [25]. Nevertheless, this kind of treatment is recommended only in patients with underlying CV disease, HF, or in those undergoing coronary artery bypass grafting [2]. Statins may be associated with a lower risk of dementia in AF patients [26].

Recent studies show that erectile dysfunctions (a non-classical CV risk factor) are highly prevalent in AF patients, and are associated with a greater thromboembolic risk profile [27, 28]. Unfortunately, no data are available on the most appropriate mode of treating erectile dysfunction in AF patients.

Key points

- ACEI and ARB are a valid option for AF prevention in hypertensive patients.
- Beta-blockers and non-dihydropyridine calcium antagonists are useful in heart-rate reduction in hypertensive AF patients.
- Patients with AF and arterial hypertension should be considered for stroke prevention, oral anticoagulation.

- Statins are a valid option for AF prevention in patients with underlying CV disease, HF, or undergoing coronary artery bypass grafting.

ATRIAL FIBRILLATION AND CHRONIC KIDNEY DISEASE

Chronic kidney disease is a systemic disease associated with alterations in CV, endocrine and nervous system, haematopoiesis, and inflammatory response, which promote AF. Criteria for CKD are met by approximately 10% to 15% of AF patients [1]. The Chronic Renal Insufficiency Cohort (CRIC) study, which included patients with estimated glomerular filtration rate (eGFR) < 45 mL/min, showed the prevalence of AF to be 20.4% [29].

On one hand, CKD is not included in the CHADS₂ and CHA₂DS₂-VASc scores routinely used in thromboembolic risk assessment. Large studies have shown that CKD with a creatinine clearance < 60 mL/min was independently associated with elevated stroke risk [30, 31]. Furthermore, stroke risk is significantly higher in patients with CKD regardless of baseline CHA₂DS₂-VASc score, and the proportion of high-risk patients increases with eGFR category [32, 33]. However, various studies have shown that CKD does not independently add to stroke prediction in AF [34–36], but this is perhaps unsurprising since CKD is associated with the component risk factors of the CHA₂DS₂-VASc score.

Chronic kidney disease is also associated with elevated bleeding risk, included in the HAS-BLED score. Therefore, balancing expected benefit and potential harm of anticoagulation in AF patients with CKD requires caution. Many clinical trials concerning AF treatment put lowered eGFR as an exclusion criterion, and results have to be extrapolated from the population with normal kidney function. The lack of prospective studies concerns mostly dialysis patients and those with end-stage kidney disease [37].

Nevertheless, observational cohort studies show that, despite increased bleeding risk, anticoagulation in patients with CKD, AF, and high thromboembolic risk is associated with a net clinical benefit, represented by reduction in the risk of all-cause death, CV death, and composite end-point of fatal stroke/fatal bleeding [38].

No specific recommendations are available on the anticoagulation and choosing between NOAC and VKA in AF patients with mildly depressed renal function. All oral anticoagulants are metabolised in kidney (but to different extents), so they require dose modification according to kidney function (Table 2) [39]. Warfarin is metabolised in the kidney in 92% of the dose. This might be one of the reasons why warfarin causes a gradual decrease in kidney function [40]. Other reasons include renal microbleeds, and warfarin-induced calcification and apoptosis of renal cells [41, 42].

Limited data on the unfavourable effect on kidney function are available for NOAC. One interesting study reported that the

Table 2. Pharmacokinetics of oral anticoagulants depending on kidney function; estimated drug half lives and effect on area under the curve non-vitamin K oral anticoagulants plasma concentrations in different chronic kidney disease (CKD) stages

	dabigatran	apixaban	edoxaban	rivaroxaban
Percentage elimination in kidney	80%	27%	50%	35%
Creatinine clearance > 80 mL/min	12–17 h	12 h	10–14 h	5–9 h young 11–13 h elderly
Creatinine clearance 50–80 mL/min I–II stages CKD	~17 h (+50%)	~14.6 h (+16%)	~8.6 h (+32%)	~8.7 h (+44%)
Creatinine clearance 30–50 mL/min III stage CKD	~19 h (+320%)	~17.6 h (+29%)	~9.4 h (+74%)	~9 h (+52%)
Creatinine clearance 15–30 mL/min IV stage CKD	~28 h (+530%)	~17.3 h (+44%)	~16.9 h (+72%)	~9.5 h (+64%)
Creatinine clearance ≤ 15 mL/min V stage CKD	No data	– (+36%)	– (+93%)	– (+70%)

rate of renal function decline was lower in dabigatran-treated patients compared to those treated with warfarin, in the RELY trial [40]. This, along with lower risk of bleeding compared to warfarin, is a reason for recommending NOAC over warfarin for patients with mild to moderate CKD. Of course, dose adjustment is required according to kidney function, and NOAC treatment in patients with creatinine clearance < 15 mL/min (< 30 mL/min for dabigatran) is not recommended.

Key points

- AF patients with CKD have elevated thromboembolic and bleeding risk.
- NOACs are a valid anticoagulation option in this group of patients, as long as prescription label guidance is followed.

ATRIAL FIBRILLATION AND HEART FAILURE

Heart failure is one of the CV diseases associated with the worst prognosis and the highest mortality rate. It is often associated with heart muscle remodelling that causes myocardial stretch and fibrosis that promotes arrhythmia, including AF. The prevalence of AF in HF patients depends on the HF severity. In asymptomatic patients AF is found in 6% of cases, while it is between 15% and 30% in patients with higher New York Heart Association classes [43, 44].

During the progressive course of HF, methods focused on preserving sinus rhythm are less effective, and AF transforms to persistent/permanent form in most cases. Therefore, a rate control strategy is widely used in HF patients. Rapid ventricular rhythm is associated with worse prognosis. An increase in the heart rate by 10 bpm causes an increase of over 25% in the risk of all-cause death, CV death, or HF hospitalisation [45]. European and American guidelines recommend beta-blockers and digoxin for heart rate control in AF patients with HF [1, 11].

A recent meta-analysis compared the effects of digoxin on death from any cause in AF and chronic HF patients,

and found that in AF patients with HF, who were treated with digoxin, there was an overall 21% increase in the risk of death from any cause compared with patients who were not receiving this treatment [46]. Therefore, it is probably reasonable to recommend treatment with beta-blockers in patients with AF and HF for heart rhythm reduction. However, a study by Kotecha et al. [47] showed that in patients with HF and AF treatment with beta-blockers did not lead to a significant reduction in mortality observed in a population with sinus rhythm. Therefore, beta-blockers should not be used preferentially over other rate-control medications and should not be regarded as standard therapy to improve prognosis in patients with concomitant HF and AF.

As with anticoagulation, HF is an independent risk factor for thromboembolism, which is included in the most popular risk scores. In the first year from HF occurrence, 2% of patients are afflicted with stroke [48]. In the settings of concomitant AF and HF, blood stasis is caused by blood flow stasis in the atria and ventricles and worsening patient prognosis. Oral anticoagulation is essential in HF patients with AF. One recent meta-analysis showed that in this group of patients standard-dose NOAC regimens have a better efficacy and safety profile than warfarin, while low-dose regimens are similarly effective and safe as warfarin, and therefore should be preferred [49].

Key points

- HF is one of the most important thromboembolic risk factors in AF patients.
- In light of recent data, beta-blockers should be recommended for rate-control in AF, and digoxin should be prescribed with caution.
- The majority of patients with HF require oral anticoagulation, and (full-dose) NOACs seem to be a more efficient and safe treatment option.

ATRIAL FIBRILLATION AND OBSTRUCTIVE SLEEP APNOEA

Obstructive sleep apnoea is a disease highly prevalent in patients with CV disease, including patients with AF [50]. Recent studies concerning relatively young populations of AF patients show that OSA is found in approximately 40% of cases [51].

Obstructive sleep apnoea is independently associated with a risk of myocardial infarction, stroke, and death [52]. In AF patients it worsens the outcomes of cardioversion and ablation procedures [53, 54]. Whenever possible, upstream treatment of OSA should be considered prior to ablation or cardioversion. For example, continuous positive airway pressure (CPAP) therapy may be a feasible option for AF recurrence risk reduction and for improving the patient's general CV risk profile [52]. One recent meta-analysis showed that CPAP treatment is associated with a 42% decrease in the risk of AF [55].

Obstructive sleep apnoea is independently associated with higher thromboembolic risk, translated also to alterations in biomarkers [56]. It is advised to screen patients for OSA to improve identification of high stroke risk patients and choosing appropriate thromboprophylaxis [57].

Key points

- OSA is underdiagnosed and undertreated in the general population and in AF patients.
- OSA is associated with elevated thromboembolic risk in AF patients.
- OSA worsens the outcomes of rhythm control strategy in AF.
- Treatment of OSA may lower the thromboembolic risk and improve outcomes of procedures such as AF cardioversion and ablation.

CONCLUSIONS

Treatment of AF in the setting of underlying conditions is often difficult and demanding. Modern management strategies in specific patient groups with AF require knowledge on the recommendations included in guidelines from different scientific societies as well as the results of more recent studies.

Conflict of interest: none declared

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