Review Article

Hypertension and atrial fibrillation: diagnostic approach, prevention and treatment. Position paper of the Working Group 'Hypertension Arrhythmias and Thrombosis' of the European Society of Hypertension

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Hypertension is the most common cardiovascular disorder and atrial fibrillation is the most common clinically significant arrhythmia. Both these conditions frequently coexist and their prevalence increases rapidly with aging. There are different risk factors and clinical conditions predisposing to the development of atrial fibrillation, but due its high prevalence, hypertension is still the main risk factor for the development of atrial fibrillation. Several pathophysiologic mechanisms (such as structural changes, neurohormonal activation, fibrosis, atherosclerosis, etc.) have been advocated to explain the onset of atrial fibrillation. The presence of atrial fibrillation per se increases the risk of stroke but its coexistence with high blood pressure leads to an abrupt increase of cardiovascular complications. Different risk models are available for the risk stratification and the prevention of thromboembolism in patients with atrial fibrillation. In all of them hypertension is present and is an important risk factor. Antihypertensive treatment may contribute to reduce this risk, and it seems some classes are superior to others in the prevention of new-onset atrial fibrillation and prevention of stroke. Antithrombotic treatment with warfarin is effective in the prevention of thromboembolic events, although quite recently, new classes of anticoagulants that do not require international normalized ratio monitoring have been introduced with promising results.

Keywords: anticoagulants, antihypertensive treatment, atrial fibrillation, hypertension

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; b.i.d., bis in die (twice a day); CCB, calcium channel blockers; ESC, European Society of Cardiology; ESH, European Society of Hypertension; FDA, Federal Drug Association; hs-CRP, highly sensitive C-reactive protein; INR, international normalized ratio; LVH, left ventricular hypertrophy; RAS, renin–angiotensin system; VKA, vitamin K antagonist

INTRODUCTION

Hypertension is the most common cardiovascular disorder affecting 20–50% of the adult population in developed countries [1]. The prevalence of hypertension increases with age, rising steeply after the age of 50, and affecting more than 50% of this population. Atrial fibrillation is the most common clinically significant sustained cardiac arrhythmia, occurring in 1–2% of the general population. Over 6 million Europeans suffer from atrial fibrillation, and its prevalence is estimated to at least double in the next 50 years as the population ages [2].

In recognition of the burden of atrial fibrillation among hypertensive individuals the Working Group 'Hypertension arrhythmias and thrombosis' of the European Society of Hypertension (ESH), decided to write a position paper on the diagnostic approach, prevention and treatment of

Journal of Hypertension 2012, 30:239–252

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Received 29 June 2011 **Revised** 8 November 2011 **Accepted** 8 November 2011

DOI:10.1097/HJH.0b013e32834f03bf

hypertension in association with atrial fibrillation with a view to summarize 'best practice'.

The present document summarizes the available evidence, and puts forward consensus statements that may help to define evidence gaps and assists in everyday clinical practice. The ultimate judgement regarding care of a particular patient must be made by the healthcare provider in light of all of the circumstances presented by the patient.

EPIDEMIOLOGY

Different risk factors, clinical conditions and subclinical or clinical organ damage such as hypertension, diabetes mellitus, obesity, sleep apnoea, age, metabolic syndrome, left ventricular hypertrophy (LVH), coronary heart disease, heart failure and the like are important risk factors for the development of atrial fibrillation (Box 1). Hypertension *per se* increases the risk of atrial fibrillation by about two-fold [3]. However, due to the high prevalence of hypertension in the population, hypertension accounts for more cases of atrial fibrillation than any other risk factor. Hypertension commonly coexists with many conditions associated with atrial fibrillation, namely in 72% of stroke patients, 82% of chronic kidney disease, 77% of diabetics, 73% of coronary artery disease, 71% of heart failure patients and 62% of metabolic syndrome [4]. Long-standing hypertension, especially if sub-optimally controlled, leads to LVH, structural changes and enlargement of the left atrium, heterogeneity of atrial conduction and fibrosis [5], all of which may contribute to the development of atrial fibrillation [6–9].

Hypertension is frequently seen in patients with atrial fibrillation as those included in major clinical trials. In particular, it was found in 49–90% of individuals in atrial fibrillation trials [49% in Pharmacological Intervention in Atrial Fibrillation, 51% in Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), 51.8% in Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity, 55% in RAte Control Efficacy in permanent atrial fibrillation, 62.6% in Strategies of Treatment of Atrial Fibrillation, 63% in Heart Survey, 64.4% in How to Treat Chronic Atrial Fibrillation, 68% in Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation, 71% in AFFIRM overall, 86.3% in A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter, 86.6% in Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE), 80% in Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY), 90% in Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) and 86% in Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES)], showing the significant role of hypertension in the development of atrial fibrillation [10–22] (Fig. 1). Hypertension is a risk factor for chronic kidney disease, and recent studies have shown that the progression of renal dysfunction is a powerful predictor of new-onset atrial fibrillation in patients with hypertension, independently of LVH and left atrial dilatation [23].

Atrial fibrillation may occur in all stages of the cardiovascular disease continuum. In the early stages the presence of multiple risk factors (hypertension, diabetes, and obesity) predispose patients to atrial fibrillation, but the development of subclinical and clinical organ damage not only predisposes patients to atrial fibrillation, but the presence of atrial fibrillation may in turn increase the risk of cardiovascular disease (Fig. 2). In a subanalysis from the Action in Diabetes and Vascular Disease (ADVANCE) Study (75% were taking antihypertensive treatment), with 4.3 years of follow-up, patients with diabetes and atrial fibrillation were at 61% increased risk for all-cause mortality and had similarly higher risks for cardiovascular death, stroke and heart failure (61%), compared to patients who did not have atrial fibrillation [24].

Atrial fibrillation is the most common arrhythmia in patients with heart failure and it worsens prognosis in New York Heart Association classes III–IV [25]. A recent meta-analysis with more than 54 000 patients found that atrial fibrillation was significantly associated with all-cause mortality [26]. Not only the presence of atrial fibrillation but also the new onset of atrial fibrillation carries a higher risk in patients with heart failure. In the Euro Heart Failure Survey among patients hospitalized for heart failure, the rate of in-hospital mortality was significantly higher in those patients with new-onset atrial fibrillation than in those with no atrial fibrillation or those with prior documented atrial fibrillation [27]. Atrial fibrillation is the leading cause of hospitalizations for arrhythmias and accounts for approximately one third of hospitalizations for heart rhythm disturbances [28]. Indeed, atrial fibrillation hospitalizations have increased dramatically in recent years by two to three times [29].

Box 1 Epidemiology and consequences of hypertension and atrial fibrillation

1. Hypertension accounts for more cases of atrial fibrillation than any other risk factor, and has been found to affect up to 90% of the participants in atrial fibrillation trials.
2. Atrial fibrillation may occur in all stages of cardiovascular continuum, and the presence of atrial fibrillation at all stages increases the risk of cardiovascular morbidity and mortality.
3. Consequences of atrial fibrillation include increase in overall mortality, stroke, heart failure, hospitalization, it affects quality of life and results in impaired cognitive function.
4. At the very least, the coexistence of hypertension and atrial fibrillation will double the risk for all of the above.
5. More than 30% of patients have asymptomatic atrial fibrillation but the risk is the same as in symptomatic ones.

PATHOPHYSIOLOGY

Untreated or suboptimally treated hypertension leads to the development of LVH, which is one of the most important expressions of subclinical organ damage, and is an independent risk factor for cardiovascular events, including the development of atrial fibrillation. In the presence of LVH, left ventricular compliance is reduced, left ventricular stiffness and filling pressure increase, coronary flow reserve is decreased, wall stress is increased and there is activation of the sympathetic nervous system and of the renin–angiotensin–aldosterone system. In the atria, proliferation and differentiation of fibroblasts into myofibroblasts and

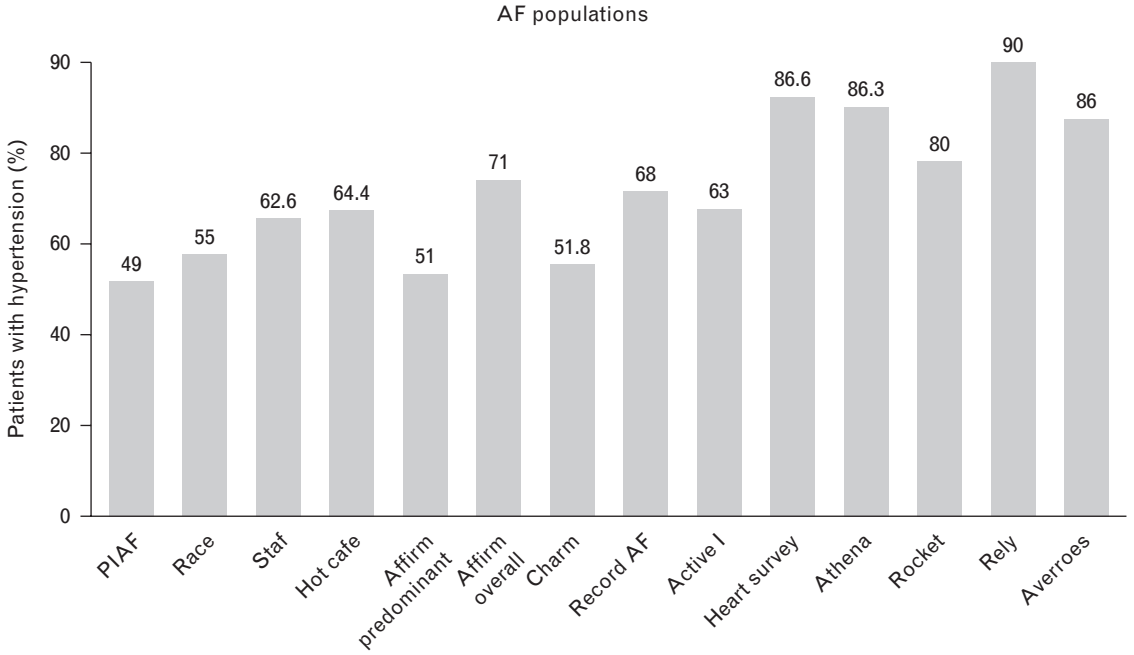

FIGURE 1 Prevalence of hypertension in atrial fibrillation trials.

enhanced connective tissue deposition and fibrosis are the hallmarks of this process. Structural remodelling results in electrical dissociation between muscle bundles and in local conduction heterogeneities facilitating the initiation and perpetuation of atrial fibrillation. This electroanatomical substrate permits multiple small re-entrant circuits that can stabilize the arrhythmia. Over time tissue remodelling promotes and maintains atrial fibrillation by changing the fundamental properties of the atria. Atrial remodelling consists of three components:

1. Electrical remodelling: where at rapid atrial rates, such as those observed during fibrillation paroxysms, intracellular changes in calcium handling lead to a reduction in the action potential duration. Even in the case of prolonged atrial fibrillation, electrical remodelling reverses quickly and completely once sinus rhythm is restored.
2. Contractile remodelling: occurs rapidly. The abnormal calcium handling at the high rates of contraction seen in atrial fibrillation may be responsible for loss of contractility. The contractile remodelling induced by atrial fibrillation may be responsible for its most devastating consequence, which is stroke. Impaired atrial contraction leading to stasis of blood, primarily in the left atrial appendage, is thought to be the major

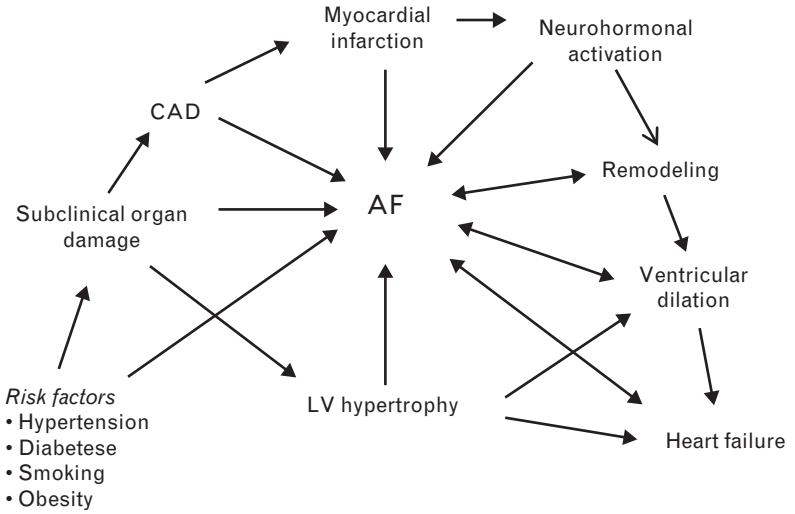

FIGURE 2 Presence of atrial fibrillation in different stages of cardiovascular continuum.

contributor to the development of blood clots, thus promoting thromboembolic events.

3. Structural tissue remodelling: occurs after periods of weeks or months and in this case we have macroscopic and microscopic changes in the myocardium, which contribute to contractile dysfunction and decreased cardiac output [30].

In the Framingham Heart Study the levels of SBP and duration of hypertension were predictive of adverse left atrial remodelling [31], whereas a wide pulse pressure is associated with increased incidence of atrial fibrillation [32]. A study of 1665 older individuals reported a 48% higher risk of atrial fibrillation in those with a 30% increase in left atrial volume [33]. The monitoring of trends and determinations in cardiovascular disease/cooperative research in the region of Augsburg study reported that both obesity and hypertension were independent predictors of left atrial enlargement [odds ratio (OR) 2.4 and 2.2, respectively, $P < 0.001$], but the coexistence of hypertension with obesity was associated with higher left atrial enlargement [34]. Both obesity and hypertension are risk factors for atrial fibrillation and both have been associated with birth weight [35]. A recent prospective study of 27 982 women reported a significant association between birth weight and atrial fibrillation [36]. According to another study in patients with hypertension, highly sensitive C-reactive protein (hs-CRP) and P wave dispersion are interrelated and associated with atrial fibrillation, suggesting an active role of inflammation in the atrial electrophysiological remodelling predisposing to atrial fibrillation [37].

CONSEQUENCES OF ATRIAL FIBRILLATION

Atrial fibrillation is an independent risk factor for death. Compared to individuals with normal sinus rhythm, those with atrial fibrillation have a 40–90% higher risk of overall mortality [38]. Atrial fibrillation complicates or is frequently associated with other cardiovascular disorders, and the two most important ones are stroke and heart failure (Table 1) [39–42]. It is well known that hypertension is a major risk factor for stroke, but many studies have shown that atrial fibrillation is an independent risk factor for stroke and thromboembolic events. Atrial fibrillation is responsible for 15–20% of all ischemic strokes [43], increases the risk of stroke four-fold to five-fold [42], and is an independent risk factor for ischemic stroke severity and recurrence [44]. Other consequences of atrial fibrillation include worsening of cognitive function, increased risk of hospitalization and cost, and impaired quality of life. In the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study, for example, patients with new-onset atrial fibrillation had approximately two-fold increased risk of cardiovascular events, about three-fold higher risk of fatal and nonfatal stroke, and five-fold increased rate of hospitalization for heart failure [9]. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial patients with new-onset atrial fibrillation had equally poor cardiovascular prognosis at the end of the follow-up period as those with atrial fibrillation at baseline, and new-onset atrial fibrillation was present in almost all patients who developed heart failure whether they had concomitant diabetes or not [45]. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, baseline atrial fibrillation or atrial flutter also increased cardiac morbidity and mortality [46].

The systematic review from the Stroke Risk in Atrial Fibrillation Working Group identified the following independent risk factors for stroke: prior stroke or transient ischemic attack, increasing age, history of hypertension, diabetes mellitus, structural heart disease and obesity [47]. In the presence of both hypertension and atrial fibrillation, data from the Atrial Fibrillation Investigators have shown that the risk of stroke doubled (10.4%) in patients with atrial fibrillation associated with hypertension or diabetes or prior stroke compared to those without these comorbidities (4.3%). In patients with atrial fibrillation and history of hypertension there was a three-fold increase in the annual incidence of stroke compared to those without a history of hypertension [48]. In at least 33% of atrial fibrillation patients, the arrhythmia could be asymptomatic [49]. Holter and transtelephonic monitoring studies have demonstrated that asymptomatic episodes of paroxysmal atrial fibrillation are 10–12 times more frequent than symptomatic episodes [50,51], but the consequences are the same. The Asymptomatic Stroke and Atrial Fibrillation Evaluation in Pacemaker Patients Trial followed 2600 patients who were at least 65 years old with history of hypertension but no history of atrial fibrillation who received a pacemaker or implantable cardioverter defibrillator, and found that over 36% had a device-detected atrial arrhythmia. According to the findings, those who had one episode within the first 3 months had more than doubled the risk of stroke or systemic embolism [52]. Paroxysmal atrial fibrillation has a significant

TABLE 1. Consequences of atrial fibrillation

Atrial fibrillation		Atrial fibrillation with comorbidities	
Stroke[a]	X 5	HTN[d]: CV events	X 3
Hospitalizations[a]	X 2–3	Stroke	X 3
Mortality[b]	X 2	Hospitalizations for HF	X 2
	CHF[e]: Mortality		X 2
Reduced quality of life[c]	Myocardial infarction[f]	In-hospital mortality	X 2
		Long-term mortality	X 1.8

[a]Wolf *et al.* [42].
[b]Benjamin *et al.* [38].
[c]Hammer *et al.* [39].
[d]Wachtell *et al.* [9].
[e]Wang *et al.* [40].
[f]Pizzetti *et al.* [41].

impact on patient quality of life independent of frequency or duration of symptoms and the impaired quality of life is similar to that in heart failure, myocardial infarction and angioplasty [39,53,54]. Recent data from the Intermountain Heart Collaborative Study showed that atrial fibrillation is independently associated with all forms of dementia and with an increased risk for Alzheimer's disease [55].

DIAGNOSTIC APPROACH AND RISK STRATIFICATION FOR ATRIAL FIBRILLATION

Atrial fibrillation may cause symptoms such as palpitations, dizziness, anxiety, generalized weakness, and mild shortness of breath. However, up to 90% of atrial fibrillation episodes may be asymptomatic. More serious signs and symptoms, such as chest pain, severe shortness of breath and hemodynamic instability, may be due to associated cardiac disease such as ischemic heart disease or heart failure. When atrial fibrillation is suspected, a 12-lead ECG is recommended as first step to establish the diagnosis. When arrhythmia or therapy related symptoms are suspected, monitoring using Holter recordings or external event recorders should be considered. In patients with hypertension an echocardiogram should be considered. Various cardiac diseases, including ischemic heart disease, valvular diseases, and heart failure, are associated with atrial fibrillation. Therefore, after the diagnosis of atrial fibrillation is confirmed with ECG or other cardiac tests, an evaluation of serum cardiac biomarkers and B-type natriuretic peptide should be considered.

However, there is still the need to improve clinicians' ability to diagnose atrial fibrillation. Data from the Screening for Atrial Fibrillation in the Elderly (SAFE) study showed that among general practitioners and nurse practitioners from 49 practices in Central UK, the majority of primary care providers were not able to reliably diagnose the presence or absence of atrial fibrillation on ECG; 20% of cases of atrial fibrillation were missed and the probability that a diagnosis of atrial fibrillation was correct only in 41% [56]. Atrial fibrillation is classified as first diagnosed (irrespective of the duration), paroxysmal (self-terminating usually within 48 h or in fewer that 7 days), persistent (lasts longer than 7 days or required termination by cardioversion) and permanent (exists for more than 1 year). A silent atrial fibrillation may be discovered from an atrial fibrillation-related complication as first manifestation or may be diagnosed by an opportunistic ECG [57]. There are two types of risk: risk for atrial fibrillation and risk from atrial fibrillation. There are different risk factors for the development of atrial fibrillation. The early recognition of the risk factors that can lead to the development of atrial fibrillation may help to develop risk prediction models to direct preventive efforts especially in asymptomatic atrial fibrillation. Several variables have been shown to increase the risk for atrial fibrillation, including clinical conditions, cardiovascular risk factors and subclinical markers (Table 2). Hypertension increases the risk for atrial fibrillation in men and women by 1.5-fold and 1.4-fold, respectively, and is the most common underlying risk factor for the development of atrial fibrillation [3]. Framingham researchers developed a risk prediction model to determine an individual's absolute risk of developing atrial fibrillation within the next 10 years based on a number of clinical factors identified to be predictive for atrial fibrillation. By multivariate analyses age, sex, BMI, SBP, treatment of hypertension, PR interval and heart failure accounted for up to 64% of the risk [58].

TABLE 2. Risk factors, clinical conditions and markers for the development of atrial fibrillation

Risk factors	Markers
Age	Increased arterial stiffness
Hypertension	Left atrial enlargement
Diabetes mellitus	Increased PR interval
Obesity	P wave dispersion
Metabolic syndrome	Birth weight
Alcohol consumption	hs-CRP
Smoking	Inflammatory markers
Clinical conditions	Neurohormones
Left ventricular hypertrophy	Genetic variants
Myocardial infarction	Pulse pressure
Heart failure	
Obstructive sleep apnoea	
Renal dysfunction	
Valvular heart disease	
Thyroid disease	

hs-CRP, highly sensitive C-reactive protein.

RISK STRATIFICATION AND PREVENTION OF THROMBOEMBOLISM FROM ATRIAL FIBRILLATION

Atrial fibrillation is associated with an increased risk of thromboembolism resulting in transient ischemic attack, stroke or peripheral embolization. A history of stroke or transient ischemic attack, increasing age, hypertension and structural heart disease (LVH or dysfunction) were identified as predictors of stroke in patients with atrial fibrillation. Numerous risk factors have been used to formulate various stroke risk stratification schemes and several predictive rules have been developed to determine the risk of complications from atrial fibrillation. Due to its simplicity and ease of use, the $CHADS_2$ (Congestive heart failure, Hypertension, Age, Diabetes, Stroke) score has become the most commonly used predictive rule in clinical practice [59]. The $CHADS_2$ index assigns 1 point each for a history of heart failure, hypertension, age more than 75 years and diabetes, and 2 points for a history of stroke or transient ischemic attack. Based on their score patients can be classified as having low risk (score 0), moderate risk (score 1) or moderate/high risk (score 2 or greater) for stroke. Aspirin (81–325 mg) is recommended for low risk, aspirin or anticoagulation (warfarin) for moderate risk and anticoagulation with warfarin for patients with $CHADS_2$ score at least 2, with an international normalized ratio (INR) of 2.0–3.0 (target 2.5) unless contraindicated. A refined version of the original $CHADS_2$ score using what was previously referred to as 'less well validated or weaker stroke risk factors' in the older guidelines, that is, female sex, age 65–74 years, and vascular disease, and known as the CHA_2DS_2-VASc score [60] was recently validated in several

	Risk factors	Score
C	Recent congestive heart failure	1
H	Hypertension	1
A_2	Age ≥ 75 years	2
D	Diabetes mellitus	1
S_2	History of stroke or transient ischemic attack	2
V	Vascular disease (prior MI, PAD, or aortic plaque)	1
A	Age 65-74	1
Sc	Sex category (female sex)	1

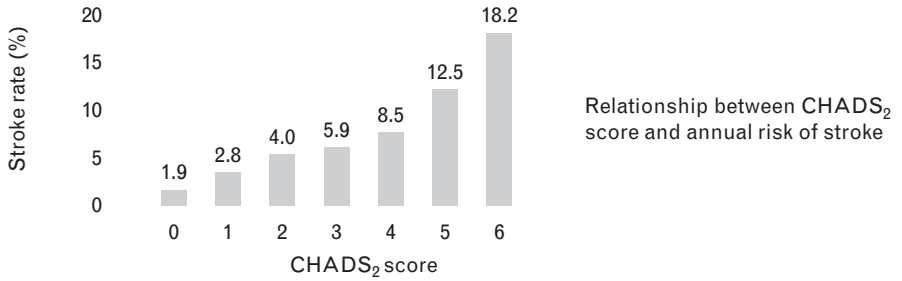

FIGURE 3 CHA_2DS_2-VaSc Score and annual risk of stroke.

independent cohorts. The CHA_2DS_2-VASc score outperformed the $CHADS_2$ score in identifying 'truly low-risk' individuals who do not need antithrombotic therapy, whereas those with at least one stroke risk factors should be considered for oral anticoagulation therapy, whether this is undertaken with well controlled warfarin or one of the new agents that do not require INR monitoring that have been introduced (see below). Figure 3 shows the CHA_2DS_2-VASc score and the relation between these risks scores and the annual risk of stroke.

MANAGEMENT OF ATRIAL FIBRILLATION

Management of patients with atrial fibrillation is aimed at preventing atrial fibrillation by controlling the risk factors for the development of atrial fibrillation, at reducing the symptoms, and at preventing severe complications associated with atrial fibrillation. In this position paper we will discuss the role of antihypertensive and antithrombotic therapy in patients with atrial fibrillation, but will not address other topics such as rate and rhythm control, ablation and so on, because they are covered by the recently published European Society of Cardiology (ESC) guidelines for the management of atrial fibrillation [57].

ATRIAL FIBRILLATION AND ANTIHYPERTENSIVE TREATMENT

Antihypertensive drugs reduce the risk for atrial fibrillation mainly by lowering high blood pressure. However, some antihypertensive drugs may also reduce the risk for atrial fibrillation through other mechanisms (Box 2). There have been few prospective studies on the development of atrial fibrillation in hypertensive individuals, but there are several secondary analyses of large randomized trials and some meta-analyses.

Renin–angiotensin system blockers (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers)

In an early meta-analysis of 11 randomized controlled clinical trials by Healey *et al.* [61], the authors found that renin–angiotensin system (RAS) blockers significantly reduced the relative risk (RR) of new-onset atrial fibrillation by 28% (15–40%), but this benefit was limited to patients with systolic left ventricular dysfunction or LVH. In another meta-analysis by Kalus *et al.* [62], the use of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) was associated with an average 49% (35–72%) relative reduction in new-onset atrial fibrillation, a 53% (24–92%) lower failure rate of electrical cardioversion of atrial fibrillation, and a 61% (20–75%)

Box 2 Atrial fibrillation and antihypertensive treatment

1. Our main goal in patients with hypertension and atrial fibrillation is blood pressure reduction per se.
2. Drugs blocking the renin–angiotensin–aldosterone system reduce the risk of new-onset atrial fibrillation. Nevertheless this effect has been mainly observed in high-risk patients particularly in those with left ventricular dysfunction, left ventricular hypertrophy and postmyocardial infarction patients. Most of the supportive data is from posthoc analyses
3. Beta-blockers are effective for rate control and possibly for maintaining sinus rhythm. There is not enough data regarding their use in the prevention of new-onset atrial fibrillation.
4. There is not enough data for the other drug classes.

lower rate of recurrence of atrial fibrillation after electrical cardioversion. In a meta-analysis by Schneider *et al.* [63], RAS-blockade reduced the OR for atrial fibrillation by 32% (0.22–0.43, $P < 0.00001$), with similar effects of ACEIs and ARBs. In primary prevention, RAS blockade was most effective in patients with LVH and/or heart failure. In secondary prevention, RAS blockade reduced the odds for atrial fibrillation recurrence after cardioversion by 45% (0.34–0.89, $P < 0.01$) and on medical therapy by 63% (0.27–0.49, $P < 0.00001$). However, we must remember that most of the trials included in these meta-analyses were not designed to investigate atrial fibrillation. In a prespecified analysis of the VALUE trial, the use of valsartan (vs. amlodipine) was associated with a 16% reduction ($P < 0.0455$) in the incidence of at least one documented occurrence of new-onset atrial fibrillation and reduced the incidence of persistent atrial fibrillation by 32% ($P < 0.0046$) [46]. Similar findings showing the benefit of ARBs in reducing the incidence of new-onset atrial fibrillation were also documented in prespecified analysis of data from the LIFE study, in which the incidence of new-onset atrial fibrillation was compared between patients treated with losartan vs. the beta-blocker, atenolol [9]. The 2007 ESH/ESC guidelines [64] summarize evidence from posthoc analyses of heart failure and hypertension trials showing a lower evidence of new-onset atrial fibrillation in patients receiving an ARB (in one trial an ACE inhibitor). Although warning against the possible bias of posthoc analyses, nonetheless the guidelines suggested ARBs and ACE inhibitors as preferred drugs in patients with hypertension at risk for developing atrial fibrillation. A plausible explanation for this was the association between atrial enlargement and LVH, the favourable effects of blockers of the RAS on both cardiac alterations, and the relationship between LVH regression and reduction in new-onset atrial fibrillation [65,66]. However, data accumulated since then do not consistently support in all of them this recommendation. Since then, new studies such as the ONgoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND), the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial and the Irbesartan in Heart Failure with Preserved Systolic Function trial were published. In ONTARGET [67] new atrial fibrillation was just slightly less frequent with the ARB (telmisartan) than with the ACE inhibitor (ramipril) treatment, indicating no difference between these two types of RAS blockade. The placebo comparisons in the TRANSCEND [68] and the PROFESS [69] trials, could not confirm a protective effect of ARBs against onset of atrial fibrillation, although the absolute numbers were low and the detection power of the analysis may have been insufficient. The Heart Outcomes Prevention Evaluation study included patients with high cardiovascular risk without heart failure and left ventricular systolic dysfunction and randomized the patients to treatment with an ACE inhibitor (ramipril) or placebo [70]. No statistically significant difference in the proportion of patients who developed atrial fibrillation was found between the ACE inhibitor and placebo, and treatment with ACE inhibition had no protective effect on development of atrial fibrillation with an OR of 0.92 (0.68–1.24, $P = 0.57$). In the TRANSCEND trial [68], patients intolerant to ACE inhibitors with cardiovascular disease or diabetes with end-organ damage, were randomized to treatment with an ARB (telmisartan) or placebo, and no significant effect on new-onset atrial fibrillation was found. Several relatively small prospective randomized controlled trials have demonstrated that therapy with ACE inhibitors or ARBs conferred an additional benefit on risk of recurrent atrial fibrillation after cardioversion when coadministered with antiarrhythmic drug therapy, usually amiodarone, compared with an antiarrhythmic drug alone [71,72]. Meta-analyses driven by these studies have reported a significant 45–50% reduction in RR of recurrent atrial fibrillation [73,74]. Conversely, a double-blind, placebo-controlled study – Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) – failed to demonstrate any benefit of therapy with candesartan for preservation of sinus rhythm after cardioversion in patients who did not receive antiarrhythmic drug therapy [75]. The largest secondary prevention study, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca atrial fibrillation (GISSI-AF), in 1442 patients with cardiovascular risk factors (mainly hypertension, 85%) and paroxysmal or recently cardioverted persistent atrial fibrillation, demonstrated no effect of valsartan added on top of optimal medical therapy (including antiarrhythmic drugs and ACE inhibitors) on the primary endpoint of time to first atrial fibrillation recurrence [heart rate (HR) 0.99; 95% confidence interval (CI) 0.85–1.15; $P = 0.84$] or the number of patients with more than one atrial fibrillation recurrence (26.9 vs. 27.9%) compared with placebo at 1-year follow-up [76]. There are different mechanisms explaining the beneficial effects of RAS blockers in patients with hypertension with atrial fibrillation. Blockade of the RAS may prevent left atrial dilatation, atrial fibrosis, dysfunction and slowing of conduction velocity, with some studies also indicating direct antiarrhythmic properties. Favourable effects of RAS blockers on cardiac alterations such as atrial enlargement and LVH may explain the reduction in new-onset atrial fibrillation [69,70].

Beta-blockers

The use of beta-blockers as first-line therapy for hypertension has lately been questioned, but beta-blockers are undoubtedly effective in atrial fibrillation rate-control during atrial fibrillation and possibly in maintaining sinus rhythm, especially in heart failure and in cardiac postoperative settings [77,78]. In a systematic review including almost 12 000 patients with systolic heart failure (about 90% received RAS-blockade), and therefore at high risk for atrial fibrillation, the incidence of new-onset atrial fibrillation was significantly lower in the patients treated with beta-blockers compared with those assigned to placebo with a RR reduction of 27% (14–38%, $P < 0.001$) [78]. A history of atrial fibrillation and systolic heart failure may be a specific indication for using beta-blockers. Treatment with sotalol, a nonselective beta-blocker with class III antiarrhythmic activity, is effective in maintaining sinus rhythm after cardioversion, but has proarrhythmic effects and is not recommended as antihypertensive treatment. In hypertension trials like the LIFE study, the ARB-based therapy (losartan)

was superior to beta-blocker (atenolol) in reducing the risk of new and recurrent atrial fibrillation. However, it is also difficult to draw conclusions from the results of trials comparing two or more active antihypertensive treatment regimens, due to uncertainty as to whether the observed effects may represent a detrimental effect of one regimen or a beneficial effect of the other. In the United Kingdom-based General Practice Research Database, with approximately 5 million patient records, it was found that ACE inhibitors, ARBs and beta-blockers were more effective than calcium channel blockers (CCBs) in reducing the risk of atrial fibrillation [79]. Possible mechanisms of action of beta-blockers to this effect may be prevention of adverse remodelling and ischemia reduced sympathetic drive or counteraction of the beta-adrenergic shortening of action potential, which otherwise could contribute to perpetuation of atrial fibrillation [77,78]. However, recurrence rate of atrial fibrillation is known to be high, even under beta-blocker prophylaxis.

Calcium channel blockers

CCBs are a heterogeneous group of drugs with antihypertensive properties. Nondihydropyridines such as diltiazem and verapamil are used to slow the ventricular response in atrial fibrillation, and verapamil has also been investigated for its effectiveness in maintaining sinus rhythm after cardioversion. Calcium lowering drugs could hypothetically attenuate the calcium overload in tachycardia-induced electrical remodelling of the atria [80]. In a study by De Simone *et al.* [81] additional treatment with verapamil significantly reduced the recurrence of atrial fibrillation within 3 months compared with propafenone alone. However, other studies have shown more disappointing results [80–82]. In the VALUE trial the ARB valsartan was more effective than the CCB amlodipine in preventing new-onset atrial fibrillation [46].

In a retrospective study using a national integrated medical and pharmacy claims database in the United States, almost 5500 patients treated for hypertension with an ACE inhibitor were compared to an equal number of matched patients treated with a CCB. At about 4 years of follow-up the incidence of new atrial fibrillation was significantly lower in the ACE inhibitor-treated patients with a HR of 0.85 (0.74–0.97) [83]. In a nested case–control analysis from the United Kingdom-based General Practice Research Database, similar results were found [79]. Four thousand six hundred and sixty-one patients with atrial fibrillation and 18 641 matched controls from a hypertension population were compared and the authors found that treatments with ACE inhibitors [OR 75 (0.65–0.87)], ARBs [OR 0.71 (0.57–0.89)] or beta-blockers (OR 0.78 (0.67–0.92)) were associated with a lower risk for atrial fibrillation than treatment with CCBs. However, in such observational studies, bias in treatment cannot be excluded and blood pressure control and changes cannot be evaluated.

Diuretics

Diuretics are often included in antihypertensive treatment regimens, but the effect on new-onset atrial fibrillation has to our knowledge not been thoroughly investigated. Caution to electrolyte balance changes during chronic antihypertensive therapy with K^+ wasting diuretics such as thiazides, chlortalidone and indapamide is recommended.

Aldosterone antagonists

Patients with primary hyperaldosteronism have a 12-fold higher risk of developing atrial fibrillation than their matched counterparts with essential hypertension. Increased aldosterone levels have been reported in patients with atrial fibrillation. Pretreatment with spironolactone in a dog atrial fibrillation model reduced the amount of atrial fibrosis and inducibility of atrial fibrillation. Several trials with spironolactone and eplerenone are ongoing.

ATRIAL FIBRILLATION AND ANTITHROMBOTIC TREATMENT

The decision to cover the topic of antithrombotic treatment was based on the fact that in all atrial fibrillation trials the prevalence of hypertension varies from 60 to 90%, showing the importance of hypertension as a risk factor for the development of atrial fibrillation [10–23] (Box 3). Hypertension is part of $CHADS_2$ [59] and CHA_2DS_2-VASc risk score [60] for stroke, and according to the guidelines patients with risk score 1 should receive oral anticoagulation treatment or aspirin; however, oral anticoagulation treatment is preferred rather than aspirin [63]. In daily practice a large proportion of patients with hypertension are older than 65, or are women, and since patients with hypertension have a risk score of at least 2, the majority should receive oral anticoagulation treatment, unless contraindicated. Indeed, anticoagulation treatment should be given not only to patients with persistent or permanent atrial fibrillation, but also to those with paroxysmal atrial fibrillation, who should be regarded as having the same risk.

For over half a century oral anticoagulation in atrial fibrillation was limited to the use of vitamin K antagonists (VKAs). Oral anticoagulation with VKA (with target INR 2–3) is the current guideline recommended standard of care for stroke prevention in atrial fibrillation in moderate- and high-risk patients (Fig. 1). VKA are highly effective when patients are maintained at an appropriate therapeutic range (INR 2–3) for the majority of time (60–70%). The target intensity of anticoagulation involves a balance between prevention of ischemic stroke and avoidance of hemorrhagic complications, and risk/benefit ratio should

Box 3 Atrial fibrillation and antithrombotic treatment

1. Patients with CHADS2-VASc score $\geq$1 should receive aspirin or oral anticoagulation treatment. However, in viewing that most patients with hypertension are over 65 years old, of which half of them are female and most of them have subclinical or clinical organ damage it is concluded that they will receive anticoagulation treatment.
2. VKAs have been proven effective for more than 50 years and are the standard anticoagulation treatment for atrial fibrillation. However, they have disadvantages that result in substantial morbidity and mortality as well as underutilization for different reasons.
3. New oral anticoagulants such as rivaroxaban, dabigatran and apixaban that do not require international normalized ratio monitoring, seems to be particularly promising according to recent studies. Rivaroxaban was approved by the Federal Drug Association in 2010 and by the European Medicines Evaluation Agency in 2011.

be estimated in each individual patient. Targeting the lowest adequate intensity of anticoagulation to minimize the risk of bleeding is particularly important for elderly atrial fibrillation patients. An assessment of bleeding risk should be part of the patient assessment before starting anticoagulation. The use of HAS-BLEED score should be used in order to assess the risk of bleeding in atrial fibrillation patients [84] and a risk score at least 3 indicates a risk of bleeding that requires caution and/or regular review, as well as consideration of correctable risk factors for bleeding (e.g. uncontrolled blood pressure, avoiding concomitant aspirin and/or NSAIDs, improving INR control to avoid 'labile INRs', etc.). A meta-analysis of 29 trials with more than 28 000 patients showed that adjusted-dose warfarin results in a reduction in ischemic stroke by 64% and in all-cause mortality by 26%. This reduction was similar for both primary and secondary prevention and for both disabling and nondisabling strokes. By on-treatment analysis, the prevention efficacy of oral anticoagulation exceeded 80%. Supported by the results of the trials, treatment with oral anticoagulation should be considered for atrial fibrillation patients with at least one stroke risk factors provided there are no contraindications. Aspirin offers only modest protection against stroke for patients with atrial fibrillation, and in the meta-analysis by Hart *et al.* [85] resulted in a nonsignificant 19% reduction in stroke and insignificant impact on mortality. Even this 19% reduction was driven by one single positive trial, the SPAF-I trial that used aspirin 325 mg daily, with significant internal heterogeneity between the warfarin eligible and ineligible groups, and since the trial was stopped early, the effect size of aspirin may have been exaggerated. In the other trials, the dose of aspirin also differed markedly, ranging from 50 to 1300 mg daily. Nine studies compared the effects of VKA with aspirin and found significant reduction of primary endpoint 39% in favour of treatment with VKA.

Recent studies have assessed the thienopyridine antiplatelet agent clopidogrel with aspirin for stroke prevention in atrial fibrillation. The atrial fibrillation Clopidogrel Trial with Irbesartan for the prevention of Vascular Events-Warfarin arm trial (ACTIVE-W), compared clopidogrel plus aspirin with oral anticoagulation therapy with warfarin for prevention of vascular events in atrial fibrillation with an average of two stroke risk factors. Anticoagulation therapy was superior to the combination of clopidogrel plus aspirin (RR reduction 40%) with no differences in bleeding events between treatment arms [86]. The aspirin arm (ACTIVE A) trial assessed whether the addition of clopidogrel to aspirin would reduce the risk of vascular events in atrial fibrillation patients who were considered unsuitable for therapy with oral anticoagulation with warfarin. It was found that major vascular events are reduced by 11% in patients receiving the combination aspirin–clopidogrel vs. aspirin alone, and the reduction was primarily due to a reduction in the rate of stroke with clopidogrel [87]. However, it was reported an increased risk of major haemorrhages in patients receiving aspirin plus clopidogrel vs. those receiving aspirin plus placebo.

Although millions of patients have benefited from drugs like warfarin, these agents come with a large list of disadvantages/problems that result in substantial mortality/morbidity as well as underutilization of anticoagulation, particularly in the elderly, for whom numerous concomitant medications are typically prescribed. Underuse of oral anticoagulants for high-risk atrial fibrillation patients was found in most of the 54 studies (1998–2008) reporting both patient stroke risk and patients treated. Over two-thirds of studies of atrial fibrillation patients with prior stroke or transient ischemic attack reported treatment levels of under 60% of eligible patients. Most studies based on $CHADS_2$ score reported oral anticoagulant treatment levels of high-risk individuals below 70% [88].

Aiming to avoid these problems, the pharmaceutical industry has recently succeeded in developing novel oral anticoagulants that are likely to change the approach to anticoagulation dramatically.

NEW AND INVESTIGATIONAL ANTITHROMBOTIC AGENTS

The new oral anticoagulants fall into two broad categories: the oral direct thrombin inhibitors (e.g. dabigatran, ximelagatran) and the oral factor Xa inhibitors (e.g. rivaroxaban, apixaban, edoxaban). Different trials were published or are under investigation in this new area such as RELY, the stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trial, ROCKET-AF, AVERROES, the Apixaban for Reduction In STroke and Other ThromboembboLic Events in atrial fibrillation (ARISTOTLE) trial, and the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 trial (Table 3).

RELY trial

Dabigatran was evaluated in a large, open-label, randomized trial (RELY) in which it was compared with warfarin (goal INR 2.0–3.0) in 18 113 patients with nonvalvular atrial fibrillation [20]. Eligible participants had at least one risk factor. Two doses of dabigatran (110 and 150 mg twice daily) were evaluated. The mean age of participants was 71 years, 63.6% were male, half had prior long-term therapy with VKAs, and the mean $CHADS_2$ risk prediction score was 2.1. The primary outcome was all stroke (ischemic or hemorrhagic) or systemic embolism. The 150 mg twice daily dabigatran treatment was superior to warfarin treatment. The primary outcome of stroke or systemic embolism occurred in 1.71% of patients per year in the warfarin group, in 1.54% of patients per year in the 110 mg twice daily dabigatran group ($P = 0.34$), and in 1.11% of patients per year in the 150 mg twice daily dabigatran group ($P < 0.001$), respectively. The rate of major bleeding was 3.57% per year in patients treated with warfarin, 2.87% per year in patients treated with 110 mg b.i.d. [bis in die (twice a day)] dabigatran ($P = 0.003$) and 3.32% in patients treated with 150 mg twice daily dabigatran ($P = 0.31$) [89]. The rate of haemorrhagic stroke was reduced with both doses of dabigatran compared to warfarin treatment (0.12% per year with 110 mg and 0.10% per year with 150 mg vs. 0.38% with warfarin, $P < 0.001$). Warfarin needs to be monitored by determining the INR, but dabigatran does not require monitoring. Recent group analysis of the RELY trial found

TABLE 3. Trials with new oral anticoagulants

Trial	RELY	ROCKET-AF	ARISTOTLE
Drug used	Dabigatran vs. warfarin	Rivaroxaban vs. warfarin	Apixaban vs. warfarin
Dose	150 or 110 mg b.i.d.	20 or 15 mg QD	5 mg b.i.d.
	vs warfarin (INR 2–3)	vs warfarin (INR 2–3)	Vs warfarin (INR 2–3)
Number of patients	18 113	14 000	18 201
Mean age (years)	71.5	73	70
Percentage of hypertension	80	90	85
Mean $CHADS_2$ Score	2.1	2.1	2.1
Conclusions	Dabigatran 110 mg noninferior to warfarin, with 20% less major bleedings	Rivaroxaban noninferior to warfarin on intention to treat analysis but superior in on treatment analysis	Apixaban was superior to warfarin in the risk of stroke or systemic embolism, bleeding and all-cause mortality
	Dabigatran 150 mg superior to warfarin with similar rate of major bleedings	Similar rate of major bleedings	
Approval	FDA	FDA-EMA: under consideration	
	Doses of 150 and 75 mg (if CrCl 15–30 ml/min) EMA: positive opinion		

b.i.d.bis in die (twice a day); CHADS, Congestive heart failure, Hypertension, Age, Diabetes, Stroke; FDA, Federal Drug Association; INR, international normalized ratio.

no significant interactions between the time within the therapeutic range with warfarin treatment and both doses of dabigatran, thereby confirming the benefit of the 150 mg twice daily dose of dabigatran at reducing stroke independent of the quality of warfarin treatment [90]. Another subgroup analysis of patients with prior stroke or transient ischaemic attack showed noninferiority of both doses of dabigatran compared with warfarin in preventing stroke but did not show superiority of dabigatran in this subgroup of patients with $CHADS_2$ score of at least 3 [91]. Myocardial infarction was numerically (but not statistically) more frequent with dabigatran and occurred at rates of 0.82% (RR 1.29; 95% CI 0.96–1.75; $P = 0.09$) and 0.81% (RR 1.27; 95% CI 0.94–1.71; $P = 0.12$) with dabigatran, 110 mg and 150 mg twice daily, respectively, and 0.64% with warfarin. There is no specific antidote for dabigatran, which has a half-life of 12–17 h. Supportive therapy for severe haemorrhage may include transfusions of fresh frozen plasma, packed red blood cells, haemodialysis or surgical intervention if appropriate. Dabigatran etexilate was approved by the Federal Drug Association (FDA) on 19 October 2010, for marketing in the United States for the prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation. A dose of 150 mg twice daily was approved for patients with a creatinine clearance higher than 30 ml/min, whereas in patients with severe renal insufficiency (creatinine clearance 15–30 ml/min) the approved dose is 75 mg twice daily, a dose currently marketed in the European Union but not evaluated in the RELY trial. Recently the European Medicines Evaluation Agency also approved dabigatran in Europe. Thus, dabigatran is the first new oral anticoagulant to become available for clinical use in more than 50 years.

SPORTIF trials

Two long-term phase III studies compared ximelagatran with warfarin in patients with atrial fibrillation [92,93]. Despite evidence of efficacy comparable to warfarin and some advantages in terms of bleeding risk, ximelagatran development was abandoned, mainly because of concerns about hepatic toxicity.

ROCKET-AF trial

A total of 14 264 patients with atrial fibrillation were randomized in a double-blind, double dummy manner to receive either the factor Xa inhibitor rivaroxaban 20 mg once daily (15 mg if creatinine clearance was between 30 and 49 ml/min) or dose-adjusted warfarin (INR 2.0–3.0). Inclusion criteria were documented atrial fibrillation within 6 months prior randomization and at least two risk factors [21]. Patients with $CHADS_2$ score of at least 2 were enrolled but only 13% of all patients had a $CHADS_2$ score of 2, whereas all other patients (87% of all) enrolled in ROCKET atrial fibrillation had a $CHADS_2$ score of at least 3. The primary endpoint of stroke and noncerebral embolism occurred in 2.12% per year of patients treated with rivaroxaban and in 2.42% of patients treated with warfarin ($P = 0.117$). Overall, rivaroxaban was noninferior to warfarin in terms of the primary end point, and as noted, was superior to warfarin in patients who remained on treatment over the course of the 40-month trial. Rivaroxaban was not superior to warfarin in the more conservative and conventional intention-to-treat analysis. Major bleeding occurred in 3.6% of patients in the rivaroxaban group vs. 3.45% in the warfarin-treated group ($P = 0.576$). The rate of intracranial haemorrhage was significantly lower with rivaroxaban treatment compared to warfarin treatment (0.49 vs. 0.74%, $P = 0.019$). In the ROCKET-AF trial there was no significant difference in myocardial infarction between rivaroxaban and warfarin.

AVERROES

The AVERROES trial was a double-blind, randomized comparison of the oral factor Xa inhibitor apixaban vs. aspirin for stroke prevention in patients with atrial fibrillation who were not suitable for oral anticoagulation with a VKA. Patients were randomized to receive either apixaban 5 mg twice daily or aspirin (81–324 mg daily). Five thousand and six hundred patients were enrolled in AVERROES, and the study was terminated early after an interim analysis revealed a more than 55% reduction in the primary endpoint of stroke or systemic embolism in patients treated with apixaban compared to patients receiving aspirin, over

a mean follow-up of 1.1 years. The AVERROES data demonstrated that 39.5% of randomized patients had received prior oral VKA and 60.5% had not. A total of 72% of all randomized patients had a $CHADS_2$ score of 2 or less and 28% had a score of at least 3. The primary endpoint of stroke and systemic embolism occurred in 3.9% per year of aspirin-treated patients vs. 1.7% per year of apixaban-treated patients ($P < 0.001$). The rate of major bleeding was 1.2% for aspirin and 1.4% for apixaban ($P = 0.33$). There was no significant difference in haemorrhagic stroke with a rate of 0.2% per year in both treatment groups. Also, aspirin was significantly less well tolerated compared to apixaban [22]. Thus, in patients who fail VKA or refuse VKA, aspirin is clearly an inferior drug for stroke prevention, it is not safer in terms of major haemorrhage or intracranial bleeding and is less well tolerated than the oral anticoagulant apixaban. The positive results with apixaban for atrial fibrillation in AVERROES come on the heels of disappointing recent top-line results of a Phase 3 trial testing this agent in high-risk patients with recent acute coronary syndrome. The APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events) study was stopped November 2010, when it became clear that the increase in bleeding risk in patients randomly assigned to apixaban would not be offset by a reduction in ischemic events. The ARISTOTLE trial randomized 18 201 atrial fibrillation patients to apixaban (5 mg orally twice daily) or warfarin (target INR 2.0–3.0). After a median follow-up of 1.8 years, results showed that apixaban was associated with a 21% reduction in the risk of stroke or systemic embolism, a 31% reduction in bleeding, and an 11% reduction in all-cause mortality. Apixaban was superior to warfarin in preventing stroke or systolic embolism (the primary end point) and was also associated with less bleeding and lower mortality than warfarin [94].

WHAT DO CURRENT GUIDELINES RECOMMEND FOR THE NEW ANTITHROMBOTIC DRUGS?

The ESC guidelines for the management of atrial fibrillation [57]: There was no formal recommendation for the use of dabigatran, because at the time of the publication there was no approval for the drug in Europe. However, the guidelines did include the results of the RELY trial and text on how to use dabigatran 110 and 150 mg b.i.d. in relation to stroke risk (CHA_2DS_2-VASc) and bleeding risk (HAS-BLED) [57].

An American Heart Association/American Stroke Association stroke guideline [95] did not include any formal recommendation for the use of new anticoagulants as approval was not available at the time of writing.

The Canadian Cardiovascular Society guidelines give a conditional recommendation of high quality of evidence suggesting that when oral anticoagulation is indicated most patients should receive dabigatran in preference to warfarin [96].

American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society focussed update [97,98] gave dabigatran a class I recommendation for atrial fibrillation patients as follows: 'dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent atrial fibrillation and risk factors for stroke or systemic embolization, who do not have a prosthetic heart valve or haemodynamically significant valve disease, severe renal failure (creatinine clearance < 15 ml/min) or advanced liver disease (impaired baseline clotting function)' (Level of Evidence B). However, the cost of the drug is an important issue, and it is also important to select the candidates for the use of the above new drugs in order for the therapy to be cost effective. Nevertheless, the cost of regular INR monitoring should also be taken into account.

Regarding some practical aspects on the use of dabigatran: When switching from warfarin to dabigatran, the latter has to be started when after stopping warfarin, INR falls below 2.0. When there is need to switch again to warfarin and renal and renal function is normal (i.e. CrCl > 50 ml/min), warfarin is started along with dabigatran and the latter is stopped after 3 days of concomitant administration. When renal function is impaired (CrCl = 30–50 ml/min) dabigatran should be stopped on day 0 and warfarin be started on day 1. In case of an elective surgical procedure and when renal function is normal (i.e. CrCl > 50 ml/min) the procedure can be undertaken after skipping 2 doses of dabigatran (i.e. 24 h). When renal function is impaired (CrCl = 30–50 ml/min) dabigatran has to be stopped 3–5 days before the elective procedure. Six hours after restarting dabigatran there is maximal anticoagulant effect of the drug.

Some patients on dabigatran have dyspeptic complaints. They should take the medicine with water or food. The use of proton pump inhibitors can be very helpful.

CONCLUSION

Patients with hypertension suffer from an increased risk of atrial fibrillation and hypertension is the most common disorder in atrial fibrillation trials. Awareness of the increased risk of atrial fibrillation in patients with hypertension may require closer follow-up as atrial fibrillation has a significant effect on cardiovascular outcome. Atrial fibrillation is usually a progressive disease that often worsens over time ('atrial fibrillation begets atrial fibrillation') and this worsening is driven by electrical, contractile and structural changes in the atria, known as atrial remodelling. Atrial fibrillation leads to reduced cardiac function and increased risk of thromboembolism. Prevention and new treatment regimens of atrial fibrillation are needed, considering the increasing elderly population, the high percentage of uncontrolled hypertension, the risk of stroke and the worsening of other comorbidities in the presence of atrial fibrillation.

Management of atrial fibrillation includes antihypertensive, antiarrhythmic and antithrombotic drugs. Prevention of atrial fibrillation with antihypertensive drugs such as ACE inhibitors, ARBs and beta-blockers has been shown to be more effective than other classes mainly in postmyocardial infarction and heart failure trials and in other high-risk patients with hypertension including those with LVH by ECG. Antithrombotic treatment is very effective in the prevention of stroke and new oral antithrombotics that do not require INR monitoring seem to be particularly

promising drugs according to recently published trials and guidelines.

ACKNOWLEDGEMENTS

Document Reviewers: Ettore Ambrosioni, Michel Burnier, Mark Caulfield, Anna F. Dominiczak, Guido Grassi, Stephane Laurent, Peter M. Nilsson, Michael Hecht Olsen, Harry A.J. Struijker Boudier, Leonidas Poulimenos, Andreas Pittaras, Margus Viigimaa, Massimo Volpe.

Conflicts of interest

There are no conflicts of interest.

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