

Risk Alteration for Atrial Fibrillation with Different Antihypertensive Drugs

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Abstract

A large percentage of patients with hypertension suffer from atrial fibrillation (AF). The concomitance of both conditions in the same patient markedly increases cardiovascular risk. Therefore, prevention of new-onset AF in hypertensive population should be a relevant target.

High blood pressure promotes structural and electrophysiological changes in the heart that promote the development of AF. Thus, the most important therapeutic approach to prevent incident AF in hypertensive population is to reduce blood pressure values to recommended goals. However, in specific conditions, some antihypertensive agents may provide additional benefits beyond blood pressure reduction, such as in hypertension with left ventricular hypertrophy with renin angiotensin system blockade. On the other hand, in patients with hypertension and permanent AF, beta blockers and nondihydropyridine calcium antagonists (verapamil and diltiazem) play an important role.

Antihypertensive agents may provide beneficial effects on incident AF, regardless of the presence of hypertension. Thus, renin angiotensin system inhibitors may reduce new-onset AF in patients with heart failure or after the cardioversion of persistent AF. On the other hand, the preoperative administration of beta blockers may reduce the incidence of postoperative AF in some patients.

In this manuscript, the available evidence about the effects of different antihypertensive agents on new-onset AF in different populations is reviewed.

Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia in clinical practice. The prevalence of AF increases with age, from 0.5% at 40–50 years, to 5–15% at 80 years. Overall, it

affects 1–2% of subjects. However, due to the continuous ageing of the population, it is very likely that these numbers will increase in the following 50 years.¹⁻³ Remarkably, the presence of AF doubles the mortality rates and is associated with a greater risk of stroke and heart failure.^{4,5}

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Hypertension is one of the main cardiovascular risk factors. However, hypertension does not only increase the risk of developing ischemic heart disease, heart failure, stroke or renal insufficiency, but also is a risk factor for incident AF and for AF-related complications such as stroke and systemic thrombo-embolism.⁶ In fact, hypertension is the most important risk factor for AF on a population basis. Thus, although diabetes conferred a 1.4- (men) and 1.6-(women) fold risk, and hypertension a 1.5- and 1.4-fold risk, respectively, because of its high prevalence in the population, hypertension was responsible for more AF in the population (14%) than any other risk factor.⁷

Hypertension and AF are closely related. A significant proportion of hypertensive patients will develop AF, and vice versa, hypertension is a very common condition in patients with AF. Hypertension causes structural and electrophysiological changes in the heart that promote the development of AF.⁸ This issue is very relevant, since the concomitance of both markedly increases the risk of cardiovascular outcomes.⁶ However, does anti-hypertensive treatment change the clinical

course and the prognosis of patients with hypertension and AF? In this review, the available evidence about the relationship between these conditions and the best therapeutic approach is analyzed.

Epidemiology, clinical profile of patients with hypertension and atrial fibrillation and risk factors for developing atrial fibrillation

The presence of hypertension increases the risk of development AF. Thus, in a recent study performed in primary care in 119,526 outpatients (mean age 52.9±15.2 years; 40.9% male), 7,260 subjects suffered from AF (6.1%). AF was more frequent in those patients with hypertension (14% vs 1.9%; $p<0.001$),⁹ and when other comorbidities are present in hypertensive population, the risk of AF markedly rises. In a study performed in 2,024 patients with chronic ischemic heart disease and hypertension, 338 (16.7%) exhibited AF.¹⁰ On the other hand, in patients with AF hypertension is very frequent, increasing these numbers with the presence of other comorbidities. In a cross-sectional study performed in 32,051 outpatients and attended by 1,159 physicians specialized in primary-care

Table 1

Clinical profile of patients with chronic ischemic heart disease and hypertension according to the presence of atrial fibrillation and clinical profile of patients with atrial fibrillation, according to the presence of hypertension (adapted from 9 and 13).

	Patients with chronic ischemic heart disease and hypertension attended by cardiologists		P	Patients with AF attended by General Practitioners		P
	Sinus Rhythm	Atrial Fibrillation		With Hypertension	With Hypertension	
Age (years)	65.9	71.3	<0.001	72.3	66.7	<0.0001
Gender (men, %)	71.0	54.7	<0.001	52.1	55.5	NS
Hypercholesterolemia (%)	79.5	72.2	0.02	71.0	66.0	0.048
Diabetes (%)	30.1	44.6	<0.001	35.6	10.4	<0.0001
Ischemic heart disease (%)	100	100	NS	22.0	5.6	<0.0001
Heart failure (%)	13.6	42.9	<0.001	22.5	6.1	<0.0001
Peripheral arterial disease (%)	14.6	22.2	0.001	10.0	5.1	<0.0001
Renal disease (%)	9.9	25.3	<0.001	12.3	4.1	<0.0001
Stroke (%)	6.9	16.3	<0.001	11.5	5.1	<0.0001

(79%) and cardiology (21%) in Spain, arterial hypertension was diagnosed in 25% of the patients with AF [11]. In a study performed in 756 patients with AF in France, cardiac disorders were present in 534 patients (70.6%), being hypertension (39.4%), coronary artery disease (16.6%), and myocardial diseases (15.3%), being the most common causes [12]. In another study developed in a Primary Care setting in Spain, 92.6% of patients with AF had history of hypertension [9].

But, does the clinical profile differ according to the presence of AF in patients with hypertension and vice versa according to the presence of hypertension in subjects with AF? Different studies have analyzed this issue. In patients with AF, the presence of hypertension was associated with a higher proportion of hypercholesterolemia, diabetes mellitus, metabolic syndrome, sedentary life style, as well as more vascular diseases (heart failure, ischemic heart disease, cardiac valve diseases, renal insufficiency, stroke, peripheral arterial disease and advanced retinopathy) [9]. Similarly, the presence of AF in patients with hypertension and chronic ischemic heart disease was associated with more diabetes and comorbidities (Table 1) [13]. This worse clinical profile found in patients with hypertension and AF may explain at least in part the increased mortality rates of this population [14]. Thus, not surprisingly, the death rates are doubled by AF, independently of other known predictors of mortality [5,15].

These data clearly show that AF is increased in patients with hypertension. But, which factors increase the likelihood of developing AF in patients with hypertension?

Blood pressure control is crucial to improve cardiovascular prognosis in hypertensive population. Even small elevations above optimal blood pressure values increase the probability of cardiovascular disease. In 1990, MacMahon et al. demonstrated that blood pressure reduction was critical to decrease the risk of cardiovascular outcomes and

preventing major coronary events [16]. However, although blood pressure control is necessary, clinical practice guidelines agree that the aim of therapeutic approach in hypertensive population should not only be to control blood pressure but to reduce cardiovascular risk. Thus, a multifactorial intervention is necessary to actually improve cardiovascular prognosis in this population, including the reduction of new-onset AF [17].

In a study that included 34,221 women participating in the Women's Health Study, after 12.4 years of follow-up, 644 incident AF events occurred. Blood pressure was strongly associated with incident AF, and systolic blood pressure was a better predictor than diastolic blood pressure. Even more, systolic blood pressure levels within the nonhypertensive range were independently associated with incident AF [18]. In light of these results, some authors have suggested that it should be investigated whether AF is a marker of risk or directly a cardiovascular risk factor by itself in hypertensive patients and that future hypertension guidelines should assign a more important role to AF for cardiovascular risk stratification in this population [19]. In another study aimed to determine whether the risk of incident AF among patients treated for hypertension differed by the degree of blood pressure control, uncontrolled elevated systolic blood pressure and systolic blood pressure <120 mm Hg, these variables were associated with an increased risk of incident AF [20].

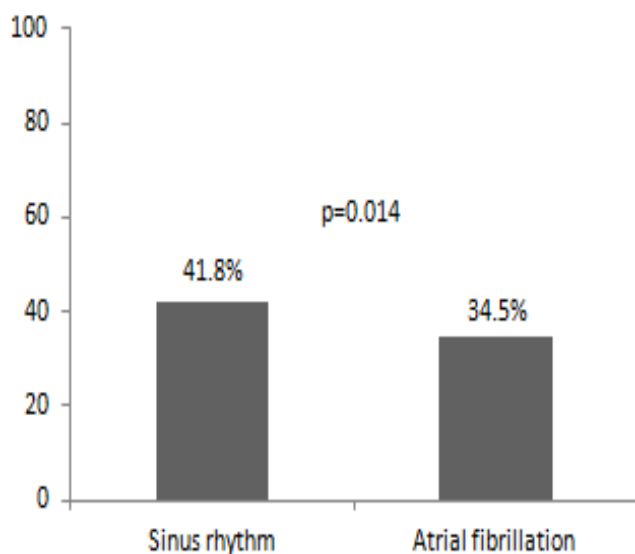
Unfortunately, the presence of AF is related with a worse blood pressure control (Figure 1) [13].

Chronic kidney disease is a powerful predictor of cardiovascular morbidity and mortality. Hypertension is one of the main causes of renal insufficiency [17]. In a study performed in 1,118 hypertensive patients, without previous paroxysmal AF, heart failure, myocardial infarction, or valvular disease, the complication of chronic kidney disease, especially progressed renal dysfunction, was a powerful predictor of new-onset AF, independently of left ventricular hypertrophy and

left atrial dilatation.²¹ Moreover, chronic kidney disease increases the risk of thromboembolism in patients with AF, particularly in patients with hypertension, which markedly increases morbidity and mortality in this population.²² As a result, to reduce the risk of new-onset AF in hypertensive patients, one of the goals should be to prevent or at least delay the development of renal dysfunction.

Left ventricular hypertrophy is the most important subclinical cardiac organ damage in hypertensive population.²³ Its early detection and treatment is essential in clinical practice, not only because LVH regression is associated with a marked improvement in cardiovascular prognosis, but also because it may reduce some potentially related complications, including AF.²⁴ In a study performed in 2,482 hypertensive subjects, after 16 years-period follow-up, a first episode of AF occurred in 61 subjects at a rate of 0.46 per 100 person-years. Age and left ventricular mass (both $P < 0.001$) were the sole independent predictors of AF. For every 1 standard deviation increase in left ventricular mass, the risk of AF was increased 1.20 times (95% CI, 1.07 to 1.34). AF became chronic in 33% of subjects, and age, left ventricular mass, and left atrial diameter (all $P < 0.01$) were independent predictors for the development of chronic AF.²⁵

Figure 1: Blood pressure control rates in patients with hypertension and chronic ischemic heart disease according to the presence of atrial fibrillation (adapted from 13).



This is very relevant, since in hypertensive patients with left ventricular hypertrophy, the development of AF is associated with a worse prognosis, with a significant increase of fatal and non-fatal strokes.²⁶ As previously commented, left ventricular hypertrophy is associated with an increased risk of AF and this association might be in part mediated via left atrial enlargement. Both, left ventricular hypertrophy and AF independently promote left atrial enlargement and left atrial enlargement facilitates the development of new episodes of AF or chronic AF. It has been reported that persistence or development of new electrocardiographic left ventricular hypertrophy during antihypertensive therapy was associated with an increased risk of left atrial enlargement after 3-year follow-up, and, importantly, regression of left ventricular hypertrophy was not associated with an increased risk of left atrial enlargement.²⁷ With these results, authors suggested that these findings provided insight into a potential mechanism by which changes in left ventricular hypertrophy were associated with changing risk of developing AF. Moreover, it has been demonstrated that left atrial diameter/height predicts risk of cardiovascular events independent of other clinical risk factors in hypertensive patients with left ventricular hypertrophy.²⁸

Finally, different neuro-hormonal systems, such as renin-angiotensin system and sympathetic systems have been implied in the development of AF^{29,30} Structural remodeling may be the main arrhythmogenic substrate perpetuating AF. Fibrosis, inflammation and oxidative stress appear strongly interconnected in the pathogenesis of remodeling-induced abnormalities in AF. Although drugs that block the renin-angiotensin system do not have a direct antiarrhythmic effect, it has been observed that atrial remodeling is at least partially induced by activation of the renin-angiotensin system.²⁹ As a result, the aim of the inhibition of the renin-angiotensin system is to limit the structural remodeling of the atrium in AF and secondarily, if possible, to have a preventive effect on the occurrence of AF in at-risk patients, such as those with hypertension, heart failure or ischemic heart disease.³¹⁻³³ AF occurs frequently after cardiac

surgery. In this context, the inhibition of sympathetic system may play an important role, as the use of beta blockers has been related with an amelioration of ischemia, an anti-inflammatory effect, and inhibition of sympathetic hypertonia in this context [34]. On the other hand, the sympathetic nerve density endocardially and epicardially is significantly higher in rheumatic heart disease patients with AF when compared with rheumatic heart disease patients without AF.³⁰

Therapeutic approach in hypertensive patients to prevent new-onset atrial fibrillation

Although attaining blood pressure goals should be the first target in the whole hypertensive population, and in this context diuretics, angiotensin-converting enzyme inhibitors, calcium antagonists, angiotensin receptor antagonists, and beta-blockers have been considered suitable for initiation of antihypertensive treatment, as well as for its maintenance, in specific situations, some antihypertensive agents could provide an extra benefit.³⁵ On the other hand, the effects of some of these drugs on the prevention of new-onset AF have been analyzed in different clinical scenarios, not only in hypertensive population.

Several studies have reported that the preoperative administration of beta blockers leads to an effective modulation of severe blood pressure fluctuations and a reduction in the incidence of postoperative AF. When an AF episode occurs, although pharmacological or electrical cardioversion is an option, the use of intravenous digoxin, diltiazem, or beta blockers may be helpful to slow the ventricular response. In this context, digitalis is the least effective and beta blockers are the most effective for controlling the ventricular response during AF. Moreover, the use of beta blockers has been shown to accelerate the conversion of postoperative supraventricular arrhythmias to sinus rhythm compared with diltiazem.³⁶⁻⁴⁰ However, not all the beta blockers equally reduce the risk of AF. Thus, the incidence of post-discharge AF after coronary artery bypass grafting in patients with decreased left ventricular function was lesser with bisoprolol when compared with

carvedilol.⁴¹ By contrast, other studies showed that carvedilol was superior to metoprolol in decreasing development of early postoperative AF after coronary artery bypass grafting.^{42,43} Moreover, in heart failure trials, carvedilol compared to metoprolol decreased the risk of progression to AF.⁴⁴

The effects of renin-angiotensin system inhibitors on prevention of new-onset AF have been specifically analyzed in patients with heart failure. Thus, in TRACE (Trandolapril Cardiac Evaluation), the effects of trandolapril on the incidence of AF in patients with reduced left ventricular function secondary to acute myocardial infarction was evaluated.⁴⁵ Of the 1,749 patients included in the TRACE study, 1,577 had sinus rhythm on the electrocardiogram recorded at randomization. During the 2- to 4-year follow-up period, significantly more patients developed AF in the placebo group than in the trandolapril group (5.3% versus 2.8%, respectively, $P < 0.05$). Trandolapril significantly reduced the risk of developing AF (RR 0.45; 95% CI, 0.26-0.76; $P < 0.01$) [45]. In a retrospective analysis of the patients from the Montreal Heart Institute (MHI) included in the Studies Of Left Ventricular Dysfunction (SOLVD), after a mean follow-up of 2.9 years, 5.4% in the enalapril group and 24% in the placebo group ($P < 0.0001$) developed AF (HR 0.22; 95% CI 0.11-0.44; $P < 0.0001$).⁴⁶ In Valsartan Heart Failure Trial (Val-HeFT), the occurrence of AF was evaluated based on adverse event reports in the patients with HF.⁴⁷ During the mean 23 months of follow-up, AF was reported in 5.12% of patients allocated to valsartan and in 7.95% of those allocated to placebo, $p = 0.0002$. Valsartan treatment was independently associated with AF occurrence (HR 0.63, 95% CI 0.49-0.81).⁴⁷ In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program, from 7,601 patients with symptomatic chronic heart failure and reduced or preserved left ventricular systolic function, 6446 patients (84.8%) did not have AF on their baseline electrocardiogram. Of these, 392 (6.08%) developed AF during follow-up, 177 (5.55%) in the candesartan group and 215 (6.74%) in the placebo group (OR 0.81, 95% CI 0.66-0.99, $P = 0.048$). After adjustment for baseline covari-

ates, the odds ratio was 0.80 (95% CI 0.65-0.99, $P = 0.039$). Remarkably, there was no heterogeneity of the effects of candesartan in preventing AF between the 3 component trials ($P = 0.57$).⁴⁸

Another clinical scenario is the prevention of new AF episodes and the maintenance of sinus rhythm after cardioversion. In a study that included patients with an episode of persistent AF for >7 days and scheduled for electrical cardioversion, two groups of patients were compared: Group I was treated with amiodarone, and Group II was treated with amiodarone plus irbesartan. The Kaplan-Meier analysis of time to first recurrence during the follow-up period (median time 254 days) showed that patients treated with irbesartan had a greater probability of remaining free of AF (79.52% versus 55.91%, $P=0.007$).⁴⁹ In another study aimed to assess whether enalapril could improve cardioversion outcome and facilitate sinus rhythm maintenance after conversion of chronic AF, patients were randomly allocated to receive amiodarone or amiodarone plus enalapril 4 weeks before scheduled external cardioversion. After a median follow-up of 270 days, those allocated to enalapril showed a higher probability of remaining in sinus rhythm (74.3% vs 57.3%, $P=0.021$).⁵⁰

What about hypertensive population? In patients with hypertension and permanent AF, beta blockers and nondihydropyridine calcium antagonists (verapamil and diltiazem) remain important classes of drugs in order to both control ventricular rate and reduce blood pressure values.¹⁷ In patients with hypertension at sinus rhythm, the first step to reduce the incidence of new-onset AF is to reduce blood pressure values to recommended targets. Several trials have tested different antihypertensive drugs in this setting. In CAPPP (Captopril Prevention Project), 10,985 patients aged 25-66 years with a measured diastolic blood pressure ≥ 100 mm Hg on two occasions were randomly assigned to captopril or conventional antihypertensive treatment (diuretics, beta-blockers). After a mean follow-up of 6.1 years, no significant differences were found between groups in the incidence of new-onset AF, a secondary endpoint

of the study [51]. The STOP-2 (Swedish Trial in Old Patients With Hypertension-2) trial was a prospective, randomized trial performed in 6,614 patients aged 70-84 years with hypertension (blood pressure ≥ 180 mm Hg systolic, ≥ 105 mm Hg diastolic, or both). Patients were randomly assigned to conventional antihypertensive therapy (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily) or “newer” drugs (enalapril 10 mg or lisinopril 10 mg, or felodipine 2.5 mg or isradipine 2-5 mg daily). As in STOP-2, no differences were found in the incidence of AF along the study.⁵²

L'Allier et al. performed a retrospective, longitudinal cohort study from a database of 8 million people in the U.S. Hypertensive patients age ≥ 18 years were included if they filled a prescription for either an angiotensin-converting enzyme inhibitor or a calcium channel blocker. A total of 10,926 patients were analyzed. The main results of this study showed that angiotensin-converting enzyme inhibition was associated with a reduced incidence of AF for patients with hypertension in usual care setting.⁵³ In the LIFE (Losartan Intervention For End Point Reduction in Hypertension) study, 9,193 hypertensive patients with electrocardiographic left ventricular hypertrophy were randomized to once-daily losartan- or atenolol-based antihypertensive therapy. A total of 8,851 patients without AF by electrocardiogram or history, were followed for 4.8 years. The main findings were that in this population, new-onset AF and associated stroke were significantly reduced by losartan- compared to atenolol-based antihypertensive treatment with similar blood pressure reduction.⁵⁴

Fogari et al. evaluated the effect of losartan compared with amlodipine, both associated with amiodarone, in preventing the recurrence of AF in hypertensive patients with a history of recent paroxysmal AF. After 12 months of follow-up, blood pressure values were significantly reduced by both losartan (from 151.4/95.6 to 135.5/83.7 mm Hg, $P < 0.001$ versus baseline) and amlodipine (from 152.3/96.5 to 135.2/83.4 mm Hg, $P < 0.001$ versus baseline), with no difference between both groups.

At least one ECG-documented episode of AF was reported in 13% of the patients treated with losartan and in 39% of the patients treated with amlodipine, $P < 0.008$ [55]. In the VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) trial, a total of 15,245 hypertensive patients at high cardiovascular risk received valsartan 80-160 mg/day or amlodipine 5-10 mg/day combined with additional antihypertensive agents. During antihypertensive treatment, the incidence of at least one documented occurrence of new-onset AF was 3.67% with valsartan and 4.34% with amlodipine (HR 0.843, 95% CI 0.713-0.997; $P = 0.0455$) [56]. In HOPE (Heart Outcomes Prevention Evaluation),

among 8,335 high-risk participants ≥ 55 years (47% with hypertension), without known heart failure or left ventricular systolic dysfunction and followed for a median period of 4.5 years, ramipril did not significantly reduce the rate of new AF compared with placebo (2.0% vs 2.2%; OR 0.92; 95% CI 0.68-1.24; $P = 0.57$) [57]. In the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) study, which included more than 25,000 patients who had vascular disease or high-risk diabetes without heart failure (69% with hypertension), the incidence of new-onset AF, a predefined secondary endpoint, was similar in patients treated with ramipril (6.9%) and telmisartan (6.7%) [58]. In the TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease) trial including patients with vascular disease or high-risk diabetes without heart failure, intolerant to angiotensin-converting enzyme inhibitors 76% of them with hypertension, no significant differences were found between telmisartan and placebo in the incidence of new-onset AF [59]. The GISSI-AF (Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico-Atrial Fibrillation) study was a large, randomized, prospective, placebo-controlled, multicenter trial aimed to test whether valsartan could reduce the recurrence of AF in patients with underlying cardiovascular disease, diabetes, or left atrial enlargement (85% had hypertension) and who were in sinus rhythm

but had had either ≥ 2 documented episodes of AF in the previous 6 months or successful cardioversion for AF in the previous 2 weeks. A total of 1,442 patients were enrolled in the study. AF recurred in 51.4% of patients treated with valsartan group and in 52.1% of patients treated with placebo (HR 0.97; 95% CI 0.83-1.14; $P = 0.73$) [60].

In another study aimed to determine the relative risk for incident AF among hypertensive patients who received antihypertensive drugs from different classes, 4,661 patients with AF and 18,642 matched control participants from a population of 682,993 patients treated for hypertension were included for the analysis. Patients with clinical risk factors for AF were excluded. Long-term therapy with angiotensin-converting enzyme inhibitors (OR 0.75; 95% CI 0.65-0.87), angiotensin II-receptor blockers (OR 0.71; 95% CI 0.57-0.89), or beta-blockers (OR 0.78; 95% CI 0.67-0.92) was associated with a lower risk for AF than current exclusive therapy with calcium channel blockers [61]. A population-based case-control study aimed to determine whether antihypertensive treatment with angiotensin-converting enzyme inhibitors/angiotensin II-receptor blockers or beta-blockers, compared with diuretics, was associated with the risk of incident AF in a community practice setting, showed that single-drug users of angiotensin-converting enzyme inhibitors/angiotensin II-receptor blockers had a lower risk of incident AF compared with single-drug users of a diuretic (OR 0.63; 95% CI 0.44-0.91), while single-drug use of beta-blockers was not significantly associated with lower AF risk (OR 1.05; 95% CI 0.73-1.52). Also, none of the most commonly used two-drug regimens was significantly associated with AF risk, in comparison with single-drug use of diuretic [62].

A number of meta-analyses have studied the effects of renin-angiotensin system inhibition on the prevention of new-onset AF [63-65]. Healey et al. analyzed a total of 11 studies, which included 56,308 patients: 4 in heart failure, 3 in hypertension, 2 in patients following cardioversion for AF, and 2 in patients following myocardial infarction. Overall, renin-angiotensin system inhibi-

tors reduced the relative risk of AF by 28% (95% CI 15%-40%, $p = 0.0002$). Reduction in AF was similar between angiotensin converting enzyme inhibitors and angiotensin receptor blockers and was greatest in patients with heart failure (relative risk reduction 44%, $p = 0.007$). Despite there was no significant reduction in AF in the overall hypertensive population (relative risk reduction 12%, $p = 0.4$), in patients with hypertension and left ventricular hypertrophy there was a significant reduction of 29%.⁶³ Schneider et al. analyzed a total of 23 randomized controlled trials with 87,048 patients. Overall, renin-angiotensin system inhibitors reduced AF by 33% ($p < 0.00001$), but there

was substantial heterogeneity among trials. In primary prevention, renin-angiotensin system inhibition was effective in patients with heart failure and those with hypertension and left ventricular hypertrophy but not in post-myocardial infarction patients. In secondary prevention, renin-angiotensin system inhibitors were often administered in addition to antiarrhythmic drugs, including amiodarone, further reducing the odds for AF recurrence after cardioversion by 45% ($p = 0.01$) and in patients on medical therapy by 63% ($p < 0.00001$) (Table 2).⁶⁴ More recently, Huang et al. analyzed 21 clinical trials including 91,381 patients and 5,730 AF events. Renin-angiotensin system inhibitors reduced the relative risk of AF by 25% (primary prevention by 24% and secondary prevention by 27%). Relative risk reduction was 0.71 in patients with hypertension (95%CI: 0.54-0.92), 0.58 in patients with chronic heart failure (95%CI: 0.39-0.87) and 0.71 in those with AF (95%CI: 0.52-0.96).⁶⁵

Aliskiren is the first oral direct renin inhibitor available, and its current licensed indication is essential hypertension. Although no clinical trials have specifically analyzed the effects of aliskiren on the prevention of new-onset AF, experimental data have reported that aliskiren may have anti-arrhythmic and anti-heart failure properties.⁶⁶ A cross-sectional survey has recently suggested that aliskiren might reduce the risk of developing permanent AF in patients

with par-oxysmal or persistent AF.⁹ On the other hand, it has been suggested that agents with anti-aldosterone properties should be the preferred diuretics for reducing hypertension related AF.⁶⁷

Conclusions

Hypertension and AF are closely related. Hypertension causes structural and electrophysiological changes in the heart that promote the development of AF. The development of AF increases cardiovascular risk in hypertensive population. As a result, all efforts performed to prevent or at least delay new-onset AF will result in an important beneficial effect on the prognosis of this population.

Therefore, to reduce the risk of new-onset AF in hypertensive population, the first and most important step is to reduce blood pressure levels to recommended targets. The next question to be answered is whether some antihypertensive agents when compared with others could provide additional beneficial effects beyond blood pressure control. The main problem of these studies is that the great majority of them are analyses post hoc. Moreover, as clinical trials include populations with different clinical profiles, it is difficult to establish clear recommendations in this context. For instance, there are striking differences on the reported incidences of AF between different studies (e.g. Fogari with 39% AF in the control group compared to VALUE and HOPE with 4 or

Table 2

Effects of renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists) on occurrence of AF (adapted from 64).

Clinical Situation	Odds Ratio	95%CI
Hypertension (overall)	0.89	0.75-1.05
Hypertension (LVH)	0.65	0.52-0.80
Heart Failure	0.52	0.31-0.87
Postmyocardial Infarction	0.72	0.41-1.27
Postcardioversion	0.55	0.34-0.89

2 %, respectively) .⁵⁵⁻⁵⁷ Despite that, the available evidence supports that in hypertensive patients with left ventricular hypertrophy, renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists), have been shown to reduce new-onset AF.

On the other hand, in patients with hypertension and permanent AF, beta blockers and non-dihydropyridine calcium antagonists (verapamil and diltiazem) remain important classes of drugs in this context in order to both control ventricular rate and reduce blood pressure values. Some antihypertensive agents have shown to be beneficial in the prevention of AF in some populations, regardless the history of hypertension. Thus, preoperative administration of beta blockers leads to an effective modulation of severe blood pressure fluctuations and a reduction in the incidence of postoperative AF in some patients. Similarly, different studies have reported that renin-angiotensin system inhibition provides substantial benefits in patients with heart failure and after the cardioversion of persistent AF, particularly when patients also received amiodarone.

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