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REVIEW ARTICLE

What do we actually know about the relationship between arterial hypertension and atrial fibrillation?

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Abstract

Arterial hypertension and atrial fibrillation (AF) are very prevalent cardiovascular diseases, commonly seen together. Considering the fact that frequency of these medical conditions is constantly increasing due to human life extension, AF will be one of the major risks of cardiovascular morbidity and mortality in the future. Several pathophysiological mechanisms have been proposed to explain the onset of AF in arterial hypertension, and there are numerous theories that explain the protective effect of renin–angiotensin–aldosterone system (RAAS) blockade on new-onset AF. However, the consensus on pathophysiology and the favorable effect of RAAS blockade on AF development is still missing. On the other hand, large clinical trials and meta-analyses demonstrated a positive effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on AF prevention, which is why these drugs are included in the current guidelines for arterial hypertension, and will probably be better positioned in the new guidelines, which will be published this year. The recent studies have also shown a preventive effect of other antihypertensive drugs on AF occurrence and demonstrated that aggressive approach to hypertensive patients with AF is very important not only for conversion into sinus rhythm, but also for sinus rhythm maintenance.

Key Words: *Antihypertensive treatment, arterial hypertension, atrial fibrillation*

Introduction

Atrial fibrillation (AF) is the most common clinically significant sustained cardiac arrhythmia, occurring in 1–2% of the general population (1,2). Over 2.3 million Americans and six million Europeans are affected by AF and its prevalence is estimated to at least double in the next 50 years as the population ages (3,4). The Framingham study reveals that the incidence of AF increases significantly with age, and that the AF incidence doubles with each decade after the age of 50 and reaches around 10% at the age of 80 (5). Arterial hypertension (HT) is the most prevalent cardiovascular disorder affecting 20–50% of the adult population in developed countries (6). The prevalence of HT increases with age, particularly after the age of 50, similarly like AF prevalence. Studies showed that HT is present in up to 60% of the patients with AF (7), whereas HT was the only cause of AF in about 15% (8). The importance of blood pressure (BP) in AF development was confirmed in a recently published investigation, which revealed that even subjects with sustained upper normal systolic BP had increased risk of AF occurrence (9).

In the present article, we discuss the epidemiology of HT and AF, the role of HT in the pathogenesis of AF, the impact of the renin–angiotensin–aldosterone system (RAAS) and autonomous nervous system in the development of AF, and the clinical evidence for treatment and prevention of AF.

Epidemiology

Many different risk factors such as HT, obesity, diabetes, age, sleep apnea syndrome, metabolic

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syndrome, coronary artery disease, valvular heart disease, left ventricular hypertrophy (LVH), atrial dilatation, heart and renal failure are associated with AF occurrence (10). However, HT is the most common, and what is more important, potentially modifiable risk factor of AF, which gives it the highest priority in the AF prevention. HT is seen in 50–90% of patients with AF (11,12), and increases the risk of AF by approximately two-fold, which only confirms its great importance in AF development (13). Comparing with heart failure (relative risk 6.1–17.5) or valvular heart disease (relative risk 2.2–8.3), the impact of HT on AF occurrence is modest, but bearing in mind the great prevalence of HT, it is not surprising that HT represents the most important risk factor of AF (1,2,8).

Pathophysiology of atrial fibrillation in arterial hypertension

Arterial HT causes the reduction of left ventricular compliance, diastolic dysfunction and LVH. All of these functional and structural changes could induce AF (14); however, LVH is the most important predictor because it increases LV stiffness, wall stress and filling pressure, decreases coronary flow reserve, and increases the activation of the sympathetic nervous system and of the RAAS, which are associated with AF occurrence. On the other hand, atrial structural remodeling is strongly connected with proliferation and differentiation of fibroblasts into myofibroblasts and enhanced connective tissue deposition and fibrosis, which subsequently cause disturbances in extracellular matrix. A recent study showed that the enzymes that are essential for the cardiac extracellular matrix remodeling were significantly changed in the hypertensive patients with AF (15). Thus, the levels of matrix metalloproteinases were higher, whereas the levels of their tissue inhibitors were lower, which promoted cardiac fibrosis (16).

Atrial structural remodeling furthers results in electrical dissociation among muscle bundles and in disturbance of local conduction, which facilitates the beginning and maintenance of AF. This electroanatomical substrate allows multiple small reentrant wavelets that could sustain the arrhythmia. Eventually, tissue remodeling induces and maintains AF by changing the essential characteristics of the atria. Atrial remodeling has three components: electrical, structural and contractile remodeling (16,17).

Electrical remodeling implies that the stretch impulses depolarize the myocyte membrane within milliseconds and induce afterpolarizations, which produce premature depolarizations. These afterdepolarizations are mediated by calcium influxes through stretch-activated calcium channels (18). However, electrical remodeling reverses promptly and completely once sinus rhythm is restored, even in the cases of prolonged AF.

Contractile remodeling happens quickly and it is a consequence of the abnormal calcium handling at the high rates observed in AF. Loss of contractility induced by AF leads to blood stasis, primarily in the left atrial appendage, and could be the most responsible for its dangerous consequence – stroke.

Structural tissue remodeling occurs after a few weeks or months and it is characterized by macroscopic and microscopic changes in the myocardium, which furthermore contribute to electrical and contractile dysfunction, as well as decreased cardiac output (19). Eventually, all these changes induce atrial enlargement and after reaching a critical mass, the remodeled atrium becomes a perfect place for the maintenance of AF (20).

Autonomic nervous system and atrial fibrillation

The sympathetic nervous system is very important for BP regulation, and BP elevation in essential HT is frequently initiated and maintained by its activation (21). Atrial electrophysiological characteristics are also significantly influenced by the autonomic nervous system (ANS), thus in patients with structural heart disease, AF is mainly sympathetically dependent, while in other patients AF is vagally mediated (22). Sympathetic activity predominance or increased vagal tone was reported before postoperative paroxysmal AF (23), previous to the paroxysmal AF during sleep (24), whereas vagal predominance was detected in young patients with lone AF and nocturnal episodes of paroxysmal AF (25).

Earlier investigations showed that the cardiac ANS had an important role in the dynamics of AF occurrence and maintenance (26). Hyperactivity of the intrinsic cardiac ANS induces the release of acetylcholine and catecholamines, which may consequently induce fast ectopic impulses from pulmonary veins or non-pulmonary vein locations (26). There is interdependence between the extrinsic and intrinsic cardiac ANS. Each system can change the activity of the other throughout efferent and afferent connections; however, each system could function independently of the other. Studies showed that intrinsic cardiac ANS (alone or together with extrinsic cardiac ANS) is a constant trigger of paroxysmal atrial tachyarrhythmias (27).

Renin–angiotensin–aldosterone system and atrial fibrillation

Atrial dilatation, myocytes stretching and AF had been revealed to cause up to a three-fold increase in the expression of tissue angiotensin-converting enzyme (ACE) in the atria (28), and consequently an increased concentration of angiotensin II, which

further activated mitogen-activated kinases. These enzymes stimulate transcription of proteins that promote cellular proliferation and differentiation, which results in myocyte hypertrophy, interstitial fibrosis and apoptosis (29). Additionally, angiotensin II promotes neutrophiles and monocytes infiltration, vasoconstriction, and increased platelet activity. The last part of this cascade is aldosterone, which also stimulates fibroblasts and promotes fibrosis, throughout its impact on mitogen-activated kinases (30). RAAS also increases matrix metalloproteinase activity, which contributes to general atrial remodeling and development of AF (31). On the other hand, angiotensin II changes cellular concentration of calcium and potassium, impairs atrial electrophysiology and promotes AF (32).

The relationship, interdependence and positive feedback between the sympathetic nervous system and RAAS characteristic of systemic HT (33) multiply the importance of these two biohumoral systems in the development of AF.

Blood pressure, blood pressure variability and atrial fibrillation

Mitchell et al. in the Framingham Heart Study showed that systolic BP and duration of HT were associated with left atrial remodeling, however, pulse pressure was the strongest predictor of AF (34), which was also confirmed in other studies (35,36). Recently has been reported that even high-normal BP represents a risk factor for development of AF (9). In a large cohort of 34,221 initially healthy women, Conen et al. showed that systolic BP was a better predictor of AF occurrence than diastolic BP (37). The BAFTA study, which included patients with AF older than 75 years of age, revealed that the mean diastolic BP was substantially higher in patients with AF compared with the general population of the same age (38).

A recently published study, which enrolled 1385 patients with newly diagnosed AF, showed that risk of permanent AF was similar for patients with and without HT and across BP levels which could possibly be a consequence of antihypertensive drugs (39). Interestingly, research showed that the lack of normal nocturnal BP reduction, known as non-dipping BP pattern, in hypertensive patients was associated with AF occurrence (40). On the other side, Webb & Rothwell, in a systematic review that included 125,878 treated hypertensive patients, did not find any connection between the effects on BP variability and AF (41). In Table I, there are studies concerning the relationship between systolic and diastolic BP, as well as BP variability.

Antihypertensive therapy and atrial fibrillation – analyses of clinical trials

Antihypertensive therapy decreases the risk of AF development mostly by lowering high BP. Nevertheless, some antihypertensive drugs could reduce the risk of AF through other mechanisms. There are few prospective studies on the AF development in

Table I. The impact of hypertension on atrial fibrillation (AF) occurrence.

Reference	Sample size and subjects included in the study	Main findings
Grundvold et al. (9)	2014 healthy men	Upper normal systolic BP was long-term predictor of incident AF in initially healthy middle-aged men
Framingham Heart Study (34)	5331 subjects older than 35 years without AF at the beginning of study	Systolic and pulse BP were risk factors for AF development
LIFE study (35)	8810 hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy	Systolic, diastolic and pulse BP were predictors of new-onset AF
ONTARGET–TRANSCEND study (36)	30,424 patients with complicated diabetes or vascular disease who were in sinus rhythm at entry	Systolic and pulse BP, left ventricular hypertrophy, and hypertension were associated with AF development
Women's Health Study (37)	34,221 healthy women	Systolic BP was a better predictor than diastolic BP for AF occurrence
BAFTA study (38)	106,258 participants older than 75 years	Hypertension is very common in older patients with AF. The mean systolic BP is slightly lower, but the mean diastolic BP is substantially higher in older patients in AF, compared with the general population
Thacker et al. (39)	1385 patients aged 30–84 with newly diagnosed AF	Risk of permanent AF was similar for patients with and without hypertension and across BP levels
Pierdomenico et al. (40)	1141 patients aged ≥ 40 years with sustained hypertension	Non-dipper sustained hypertensive patients have a two-fold greater risk of developing AF than dippers
Webb & Rothwell (41)	125,878 treated hypertensive patients	Variability in BP was not related with risk of new-onset AF

BP, blood pressure; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant subjects with Cardiovascular Disease; BAFTA, Birmingham Atrial Fibrillation in the Aged.

hypertensive patients, but there are several secondary analyses of large randomized trials and some meta-analyses.

Renin–angiotensin-aldosterone system blockers

Pedersen et al. first reported the clinical evidence of the favorable effect of the RAAS antagonist, which was detected in a *post hoc* analysis of the TRACE study, which included patients after myocardial infarction who had been treated with trandolapril (42). This study was followed by several secondary analyses (meta-analyses and systematic reviews) of large clinical trials, which demonstrated the positive effect of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in the prevention of AF in various patient populations. Tables II and III summarized the studies of ACEIs and ARBs for prevention of AF in hypertensive patients and meta-analyses in different patient populations (43–62).

Earlier clinical trials and studies which involved hypertensive patients treated with various ACEIs showed that RAAS blockade significantly decreased AF onset, but these investigations were inconsistent when compared ACEIs with other antihypertensive drugs (43–45). Thus, STOP-H2 study showed that there was no difference in AF occurrence between different ACEIs and calcium channel blockers (CCBs) (43); the CAPP study revealed no difference between ACE and beta-blockers (BBs) with or without diuretics in efficacy in AF preventing (44); whereas L'Allier et al. demonstrated the superiority of ACEIs over CCBs (45).

More recent trials showed the efficacy of ARBs (losartan, valsartan and telmisartan) in primary and secondary prevention of AF in the hypertensive patients (46–49,51–53). The PRoFESS study showed that telmisartan significantly decreased a risk of AF in comparison with placebo (48), whereas the GISSI – AF study did not confirm this finding with valsartan-based antihypertensive therapy (50). The investigations showed superiority of ARBs over the other group of BP lowering drugs. Therefore, the LIFE study (46) and Galzerano et al. (53) showed that ARBs were more effective than BBs in the prevention of the new onset of AF or recurrent episodes of arrhythmia, whereas the VALUE study and Fogari et al. revealed higher efficacy of ARBs in comparison with CCBs in the prevention of AF development (47,52). Interestingly, the ONTARGET study, which included 25,620 patients randomized into telmisartan-based and ramipril-based therapy, found that despite similar BP lowering, telmisartan was slightly more effective than ramipril in preventing new episodes of AF (49). Similar results were obtained by Fogari et al., who studied valsartan versus ramipril

Table II. The studies of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) for prevention of atrial fibrillation (AF) in hypertensive patients for prevention of AF in different patient populations.

Reference	Treatment	No. of patients	Age (years)	Main findings
STOP-H2 (43)	Enalapril and lisinopril vs CCB	6616	76	There is no difference in AF occurrence between different ACEIs, or in comparison with CCBs.
CAPPP (44)	Captopril vs BB± diuretics	10,985	52.6 ± 8.4	Captopril and conventional treatment (BBs ± diuretics) did not differ in efficacy in AF preventing.
L'Allier et al. (45)	ACEI vs CCB	10,926	65	ACEIs significantly more reduced risk of AF development.
LIFE (46)	Losartan vs atenolol	9193	66.9 ± 7	New-onset AF was significantly reduced by losartan- compared with atenolol-based antihypertensive treatment with similar blood pressure reduction.
VALUE (47)	Valsartan vs amlodipine	15,245	70.5 ± 7.4	Valsartan-based treatment reduced the risk of new-onset AF compared with amlodipine-based therapy.
PRoFESS (48)	Telmisartan vs placebo	20,332	66.1 ± 8.6	Telmisartan reduced the risk of AF development in comparison with placebo.
ONTARGET (49)	Telmisartan vs ramipril	25,620	66.4 ± 7.2	New-onset of AF was slightly less frequent with the telmisartan-based than with the ramipril-based treatment.
GISSI – AF (50)	Valsartan vs placebo	1442	67.8 ± 9.2	Treatment with valsartan was not associated with a reduction in the incidence of recurrent AF.
Fogari et al. (51)	Valsartan vs ramipril	369	64 ± 7	Despite similar BP lowering, valsartan and ramipril were more effective than amlodipine in preventing new episodes of AF, but valsartan was more effective than ramipril.
Fogari et al. (52)	Losartan vs amlodipine	213	63.4 ± 7.9	Losartan in combination with amiodarone was more effective than amlodipine/amiodarone combination in preventing new episodes of AF.
Galzerano et al. (53)	Telmisartan vs carvedilol	132	55.8	Telmisartan was significantly more effective than carvedilol in preventing recurrent AF episodes.

CCB, calcium channel blocker; BB, beta-blocker; STOP-Hypertension 2, Swedish Trial in Old Patients with Hypertension 2; CAPP, Captopril Prevention Project; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; ProFESS, Prevention Regimen for Effectively Avoiding Second Strokes; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; GISSI-AF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation.

Table III. The studies meta-analyses of renin–angiotensin–aldosterone system (RAAS) blockade for prevention of atrial fibrillation (AF) in different patient populations.

Reference	No. of patients	Main findings
Disertori et al. (54)	4395	ARBs in secondary prevention of AF are not effective, whereas there are no strong enough data for a conclusion about ACEIs effectiveness.
Huang et al. (55)	91,381	ACEIs and ARBs are effective for primary and secondary prevention of AF, especially in patients with hypertension.
Lally et al. (56)	59,828	Blockade of RAAS reduced AF occurrence.
Healey et al. (58)	56,308	ACEIs and ARBs were effective in the prevention of AF, especially in patients with LVH or systolic left ventricular dysfunction.
Kalus et al. (59)	15,616	RAAS blockers were associated with a reduction in new-onset atrial fibrillation, a lower failure rate of electrical cardioversion of AF, and a lower rate of AF recurrence after electrical cardioversion.
Schneider et al. (60)	87,048	RAAS inhibition was effective for the primary and secondary prevention of AF.
Bhuriya et al. (61)	2323	ACEs and ARBs were associated with a significant reduction in recurrent AF.
Zhang et al. (62)	67,329	The preventive effect was similar between ACEIs and ARBs, but preventive effects was greater regarding recurrent AF than new-onset AF.

ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; LVH, left ventricular hypertrophy.

in AF prevention (51). Such a small difference between ARBs and ACEIs effects in prevention of AF indicates that there is no difference between these two types of RAAS blockade.

The majority of systematic reviews and meta-analyses showed primary and secondary preventive effect of ACEIs and ARBs in the development of AF (55–62). The authors who disagree are in the minority (54). On the other hand, most authors claimed that the results that connected ACEIs or ARBs with decreased risk of new-onset of AF were actually *post hoc* analyses of heart failure and HT trials. Even though the possible bias of *post hoc* analyses exists, the latest guidelines recommended ARBs and ACEIs as preferred drugs in the patients with HT at risk of developing AF (63). A reasonable explanation could lie in the fact that these drugs not only significantly decrease BP level, as do other antihypertensives, but also are related to the reduction of atrial volume (64) and LV mass (65), and reverse atrial and cardiac remodeling, which initially induced AF (66).

Aldosterone antagonists are a powerful therapeutic measure improving neuroendocrine blockade and providing inverse remodeling effects. Although they are not a common choice in the treatment of arterial HT, the EMPHASIS-HF trial, which included 2737 patients with NYHA class II heart failure who received eplerenone or placebo, revealed that patients without baseline AF who were treated with eplerenone developed new AF in 2.7%, compared with 4.5% of the controls ($p = 0.034$) (67).

There is still no evidence about the protective effect of the direct renin inhibitor (aliskiren) on AF onset. However, studies showed that aliskiren was as effective as losartan in promoting LV mass regression (68). Moreover, the reduction in LV mass with the combination of aliskiren and losartan was not significantly different from that with losartan monotherapy. These results suggest that aliskiren is as successful as ARB in reducing myocardial damage in hypertensive patients and probably has a similar preventive effect on AF development, like ARB.

Beta-blockers as antihypertensive drugs and atrial fibrillation

Despite the fact that the ANS, especially the sympathetic nervous system, has an important role in pathophysiology of HT, the usage of BBs as first-line therapy for HT has been questioned lately. However, BBs are certainly very successful in AF rate-control and probably in sinus rhythm maintaining, especially in heart failure and in cardiac perioperative management.

The CAPPP study showed that BBs were similarly effective in AF prevention to ACEI (captopril) in the hypertensive patients (44). In a systematic review, which included almost 12,000 patients with systolic heart failure (about 90% received RAS-blockade) and consequently at high risk of AF, the incidence of new-onset AF was significantly lower in the patients treated with BBs compared with those who received placebo with a relative risk reduction of 27% ($p < 0.001$) (69). Schaer et al. claimed that ACEIs, ARBs and BBs were more effective than CCBs in reducing the risk of AF in the UK (70). Possible mechanisms of BBs protective action could be the prevention of adverse cardiac remodeling and ischemia, induced by sympathetic overactivity, which could also provoke the shortening of action potential, which contributes to maintenance of AF. On the other side, there are investigations that favored ARBs over BBs in primary and secondary AF prevention (46,53).

Calcium channel antagonists as antihypertensive drugs and atrial fibrillation

Non-dihydropyridines such as diltiazem and verapamil are often used to slow the ventricular response

in AF, and verapamil has also been examined for its efficacy in sustaining sinus rhythm after cardioversion. De Simone et al. demonstrated that additional therapy with verapamil significantly decreased the AF recurrence within 3 months compared with propafenone alone (71). However, not all the studies agreed with this finding (72).

Dihydropyridines are much more used in therapy of HT, but their role in prevention of AF is more disappointing. The VALUE trial showed that valsartan was more effective than amlodipine in the prevention of new-onset of AF (47). Fogari et al. confirmed the favorable effect of losartan over amlodipine on AF prevention in hypertensive patients (52). The nested case–control study conducted in the UK on 23,302 hypertensive patients also did not have any encouraging results (70). Namely, Schaer et al. found that treatments with ACEIs, ARBs or BBs were associated with a lower risk of AF than treatment with CCBs. However, in such types of studies (observational studies), treatment bias cannot be eliminated, and BP control and variations cannot be estimated.

Diuretics as antihypertensive treatment and atrial fibrillation

Diuretics are a frequent part of antihypertensive therapy, but the effect of this drug group on AF new-onset has not been sufficiently investigated so far. Special concern should be the electrolyte balance alterations during chronic antihypertensive therapy with potassium wasting diuretics such as thiazides, chlortalidone and indapamide.

Recently Bandeali et al. published a large study that included 12,593 patients undergoing cardiac surgery, which showed that preoperative diuretic usage increased the incidence of postoperative major adverse events, renal failure and AF (73). The unfavorable effect of diuretics on AF occurrence could be explained by hypokalemia and hypomagnesemia, often seen in these patients, which could result in an increased incidence of cardiac arrhythmias in the postoperative period (74). Furthermore, higher dosage of diuretics could induce hypotension and hypovolemia, which lead to a catecholamine surge, which was shown to be a risk factor for postoperative AF (75).

On the other hand, the studies showed that hydrochlorothiazide was associated with greater reduction in the left atrial size than the other antihypertensive drugs, and with a significant reduction in LV mass (76,77), which could possibly be associated with lower risk of AF occurrence. However, the reduction of LV mass with diuretics was mostly the result of decreased ventricular diameter and volume, and not reduction of LV wall thickness, which was not investigated in this study (77).

Conclusion

The incidence of AF increases with age, and since human life is becoming longer, AF will be one of a major cardiovascular diseases responsible for significant morbidity and mortality in the future. Primary prevention of AF is a relatively new concept; however, aggressive BP reduction (78), especially by ACEIs and ARBs, seems very promising, which is why the authors of the current guidelines for HT included these drugs as a prevention in patients at risk of AF development.

Potential conflict of interest: None.

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