

# Hypertension and Atrial Fibrillation

## Doubts and Certainties From Basic and Clinical Studies

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**Abstract:** Hypertension and atrial fibrillation (AF) are 2 important public health priorities. Their prevalence is increasing worldwide, and the 2 conditions often coexist in the same patient. Hypertension and AF are strikingly related to an excess risk of cardiovascular disease and death. Hypertension ultimately increases the risk of AF, and because of its high prevalence in the population, it accounts for more cases of AF than other risk factors. Among patients with established AF, hypertension is present in about 60% to 80% of individuals. Despite the well-known association between hypertension and AF, several pathogenetic mechanisms underlying the higher risk of AF in hypertensive patients are still incompletely known. From an epidemiological standpoint, it is unclear whether the increasing risk of AF with blood pressure (BP) is linear or threshold. It is uncertain whether an intensive control of BP or the use of specific antihypertensive drugs, such as those inhibiting the renin–angiotensin–aldosterone system, reduces the risk of subsequent AF in hypertensive patients in sinus rhythm. Finally, in spite of the observational evidence suggesting a progressive relation between BP levels and the risk of thromboembolism and bleeding in patients with hypertension and AF, the extent to which BP should be lowered in these patients, including those who undergo catheter ablation, remains uncertain. This article summarizes the main basic mechanisms through which hypertension is believed to promote AF. It also explores epidemiological data supporting an evolutionary pathway from hypertension to AF, including the emerging evidence favoring an intensive BP control or the use of drugs, which inhibit the renin–angiotensin–aldosterone system to reduce the risk of AF. Finally, it examines the impact of non–vitamin K antagonist oral anticoagulants compared with warfarin in relation to hypertension. (*Circ Res.* 2018;122:352-368. DOI: 10.1161/CIRCRESAHA.117.311402.)

**Key Words:** atrial fibrillation ■ coronary artery disease ■ hypertension ■ myocardial infarction ■ stroke

Hypertension and atrial fibrillation (AF) are 2 important public health priorities. Hypertension is the most powerful predictor of mortality in high- and low-income countries.<sup>1</sup> It progressed from rank No. 4 in year 1990 to rank No. 1 in year 2010 as a global risk factor for death, disability-adjusted life-years, and years of life lost.<sup>2</sup> The prevalence of hypertension is growing, being currently around 20% to 50% in the adult population worldwide.<sup>3,4</sup> Although coronary heart disease and stroke mortality increase with usual blood pressure (BP) levels,<sup>5</sup> specific cardiovascular events differ in their relation with BP. In a cohort of 1.25 million patients, the association between each 20-mmHg increase in systolic BP and outcome was strongest for intracerebral hemorrhage, subarachnoid hemorrhage, stable angina and ischemic stroke, and weaker for abdominal aortic aneurism and transient ischemic attack.<sup>6</sup>

AF—the most frequent cardiac arrhythmia—is becoming a growing burden to healthcare systems for several reasons. AF is associated with a 5-fold increase in the risk of stroke, a 3-fold increase in the risk of heart failure (HF), and a 2-fold increase in the risk of mortality.<sup>7,8</sup> The prevalence of AF in United States is rising markedly, with 2.7 million

of affected individuals in 2010 and 5.6 million of expected people in 2050.<sup>9</sup> In Europe, the number of adults with AF was 9 million in 2010, and it is expected to grow to 17 million in 2050, mostly because of the contribution of individuals aged  $\geq 75$  years.<sup>10</sup> From 1980 to 2010, there has been an impressive rise in the prevalence and incidence of AF worldwide, with an alarming impact on morbidity and mortality.<sup>11</sup> About 1% to 2% of the total population is affected by AF, but the prevalence of this condition rises to  $\approx 10\%$  in individuals aged  $>75$  years.<sup>8–10,12</sup> The true prevalence of AF is probably higher than that indicated by current statistics because prolonged electrocardiographic monitoring may detect clinically silent AF in a variable proportion of subjects who present in sinus rhythm.<sup>13–15</sup>

Hypertension and AF often coexist. In the Framingham study, hypertension portended an excess risk for AF by 50% in men and 40% in women, ranking No. 4 after HF, aging, and valvular heart disease.<sup>16</sup> However, because of its higher prevalence in the population, hypertension accounts for more cases of AF than other risk factors.<sup>17,18</sup> In the ARIC study (Atherosclerosis Risk in Communities), hypertension was the main contributor to the burden of AF, explaining  $\approx 20\%$  of new

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*Circulation Research* is available at <http://circres.ahajournals.org>

DOI: 10.1161/CIRCRESAHA.117.311402

Nonstandard Abbreviations and Acronyms	
ACE	angiotensin-converting enzyme
AF	atrial fibrillation
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ARB	angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
AVERROES	Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment
BP	blood pressure
CAPPP	Captopril Prevention Project
Cardio-Sis	Studio Italiano Sugli Effetti Cardiovascolari Del Controllo Della Pressione Arteriosa Sistolica
CI	confidence interval
EF	ejection fraction
ENGAGE-AF TIMI 48	Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48
HAS-BLED	hypertension (uncontrolled, >160 mmHg systolic), abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (ie, therapeutic time in range <60%), elderly (>65 years), drugs/alcohol concomitantly (antiplatelet agents, nonsteroidal anti-inflammatory drugs)
HEMORR <sub>2</sub> HAGES	hepatic or renal disease, ethanol abuse, malignancy, older (aged >75 years), reduced platelet count, rebleeding risk, uncontrolled hypertension, anemia, genetic factors, excessive fall risk, previous stroke/transient ischemic attack
HF	heart failure
HR	hazard ratio
LA	left atrium
LIFE	Losartan Intervention for Endpoint Reduction
LV	left ventricular
MESA	Multi-Ethnic Study of Atherosclerosis
NOAC	non-vitamin K antagonist oral anticoagulant
ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial
RAAS	renin-angiotensin-aldosterone system
RCA	radiofrequency catheter ablation
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
ROCKET AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
RSD	renal sympathetic denervation
SAMEe-TT2R2	Sex (female), age (60 years), medical history (2 of the following: hypertension, diabetes mellitus, MI, peripheral artery disease, congestive HF, history of stroke, pulmonary disease, hepatic, or renal disease), treatment (interacting medications; eg, amiodarone), tobacco use (within 2 years; scores double), race (nonwhite; scores double)
SHR	spontaneously hypertensive rat

(Continued)

Nonstandard Abbreviations and Acronyms Continued	
SOLVD	Study of Left Ventricular Dysfunction
SPAF	Stroke Prevention in Atrial Fibrillation
SPORTIF	Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation
SPRINT	Systolic Blood Pressure Intervention Trial
STOP-2	Second Swedish Trial in Old Patients With Hypertension
TRACE	Trandolapril Cardiac Evaluation
TRANSCEND	Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation

cases.<sup>18</sup> Among patients with established AF, hypertension is present in ≈60% to 80% of individuals.<sup>19</sup>

Despite the well-established epidemiological association between hypertension and AF, the pathogenetic mechanisms explaining the higher propensity of hypertensive patients to develop AF are still incompletely known. From a clinical standpoint, several attempts have been made to estimate the risk of AF in individual patients.<sup>20,21</sup> It is not clear whether the risk of AF increases linearly with BP or whether there is a BP threshold above which the risk of this condition definitely increases.<sup>22,23</sup> Furthermore, it is not clear whether an intensive control of BP or the use of specific antihypertensive drugs reduces the risk of subsequent AF in hypertensive patients in sinus rhythm. Finally, although it is generally valued that an adequate BP control is important in patients with anticoagulated AF to prevent thromboembolic and hemorrhagic complications,<sup>24</sup> the most effective BP target in these patients is unknown.

The purpose of this article is to review (1) the mechanistic links of the relation between hypertension and AF; (2) the epidemiological association between high BP and AF, including the emerging data on the possibility of AF prevention through an intensive BP control or the use of drugs which inhibit the renin-angiotensin-aldosterone system (RAAS); (3) the impact of BP control on the major thrombotic and hemorrhagic complications in patients with established AF, including those with catheter ablation of AF. This article is specifically focused on the relations between hypertension and AF. Previous reviews have extensively discussed the complex relations between AF and its several pathogenetic factors.<sup>25–28</sup>

## Mechanisms Underlying AF in Hypertension

### Animal Models of Hypertension

Several animal models have been developed to investigate the pathophysiological mechanisms underlying the greater propensity of hearts of animals or humans with hypertension to develop AF. Some relevant features of these studies are shown in Table 1. Experimental models of hypertension included the partial stenosis of ascending aorta,<sup>29</sup> renal artery stenosis,<sup>30,31</sup> or prenatal exposure to corticosteroids.<sup>32</sup> Other studies used SHR (spontaneously hypertensive rats) matched with control rats.<sup>33–37</sup> Some of these studies focused their interest on the

**Table 1. Main Features of Studies Investigating the Pathophysiological Mechanisms Underlying the Greater Propensity of Hearts of Animals or Humans With Hypertension to Develop Atrial Fibrillation**

Author	Species	Model	Measures	Results
Choisy et al <sup>33</sup>	Male SHR. Age-matched Wistar-Kyoto rats	Burst pacing	LA tachyarrhythmias induced by bursts of rapid pacing and interstitial fibrosis at 3 and 11 mo	Incidence and duration of LA arrhythmias induced by burst pacing were greater in 11-mo-old SHR than in 3-mo-old SHR or controls. Greater interstitial fibrosis in 11-mo-old SHR than in 3-mo-old SHR or controls
Dunn et al <sup>34</sup>	SHR. Age-matched Wistar-Kyoto rats	ECG	Electrocardiographic markers of atrial and ventricular hypertrophy	Increased duration of P wave, with biphasic P-wave notching in SHR. Increased QRS voltage in SHR
Hohl et al <sup>38</sup>	Obese SHR. Lean normotensive control rats	Left atrial emptying function and electrophysiological parameters	LA emptying function, LA activation time, conduction heterogeneity, inducibility of AF, fibrosis	Compared with lean control rats, obese SHR showed impaired LA function, increased activation time, prolonged duration of inducible AF, and greater fibrosis, with upregulation of the profibrotic protein osteopontin
Kim et al <sup>29</sup>	Male Wistar rats	Hypertension mimicked by partial stenosis of ascending aorta. Sham-operated controls	LA hypertrophy and fibrosis. Pacing-induced AF	Increase of fibrosis, conduction heterogeneity, P-wave duration, LA dilatation, incidence and duration of pacing-induced AF, and reduced connexin 43 (gap junction protein) in rats with aortic stenosis
Kistler et al <sup>32</sup>	Sheep	Hypertension induced by prenatal exposure to corticosteroids. Control sheep.	Conduction velocity, AF inducibility, myocyte hypertrophy, fibrosis	Conduction abnormalities, shortening of LA wavelength, and increased AF inducibility in hypertensive sheep
Lau et al <sup>31</sup>	Sheep	Short-term 1-kidney, 1-clip hypertension. Control sheep.	LA remodeling (conduction velocity, LA ejection fraction, AF inducibility, AF duration, fibrosis)	Slower conduction velocity reduced LA ejection fraction, greater AF inducibility and duration, greater interstitial fibrosis in hypertensive sheep
Lau et al <sup>30</sup>	Sheep	1-kidney, 1-clip hypertension. Control sheep.	LA remodeling (LA hypertrophy and function, AF inducibility, conduction velocity, fibrosis) at 5, 10, and 15 wk of hypertension	Progressive changes in LA remodeling in hypertensive sheep: compared with early hypertension ( $\leq 5$ wk), prolonged hypertension ( $\geq 10$ wk) was associated with increased LA fibrosis, increased conduction heterogeneity, and more sustained AF
Lau et al <sup>35</sup>	SHR. Age-matched Wistar-Kyoto rats	Electrophysiologic study	LA remodeling (LA hypertrophy, LA refractoriness and conduction velocity, AF inducibility by rapid decremental pacing, macrophages infiltration, fibrosis) at 12 and 15 mo of age	Progressive changes in LA remodeling in SHR: increased LA fibrosis and macrophage infiltration, higher AF inducibility, and longer AF episodes in 15-mo-old SHR
Noresson et al <sup>36</sup>	SHR. Normotensive control rats.	Chronically implanted catheter	LA pressure at end expiration, intrapleural pressure	LA pressure at end expiration was $>2\times$ higher in SHR compared with normotensive rats
Okazaki et al <sup>39</sup>	Wistar-Kyoto rats	Hypertension induced by chronic inhibition of NO synthesis through L-NAME	LA thrombomodulin expression, LA fibrosis, mRNA levels of collagen type and TGF- $\beta$	Candesartan prevented the progression of LA fibrosis, the increase in collagen type 1 and TGF- $\beta$ , and the reduction of thrombomodulin expression induced by L-NAME
Pluteanu et al <sup>37</sup>	SHR. Age-matched Wistar-Kyoto rats	Isolation of LA myocytes	Ca <sup>2+</sup> handling by LA myocytes	At 7 mo, alterations of LA Ca <sup>2+</sup> handling in SHR, with frequency-induced arrhythmogenic Ca <sup>2+</sup> alternans

AF indicates atrial fibrillation; LA, left atrium; L-NAME, N-nitro-L-arginine methyl ester; SHR, spontaneously hypertensive rat; and TGF- $\beta$ , transforming growth factor- $\beta$ .

detection of some structural and functional abnormalities of the left atrium (LA) considered as potential triggers of AF. Other investigations included electrophysiological studies of the LA, generally with assessment of conduction velocity and inducibility of AF through several techniques.

In general, experimental hypertension rapidly induced hypertrophy, fibrosis, and inflammation of the LA.<sup>33–37</sup> The main

electrophysiological changes in the LA included an enhanced heterogeneity of conduction with shortening of atrial wavelength and greater AF inducibility and duration.<sup>29–33,35</sup> These electrophysiological abnormalities developed rapidly, being detectable just a few weeks after the induction of hypertension through either banding of ascending aorta<sup>29</sup> or renal artery stenosis.<sup>30</sup>

Duration of hypertension showed an association with the amount of LA remodeling. In SHR, incidence and duration of LA tachyarrhythmias induced by burst pacing were greater in older (11 months old) SHR than either in age-matched normotensive control rats or in younger (3 months old) SHR.<sup>33</sup> In this model, age may have interacted with hypertension in influencing the increased propensity to LA tachyarrhythmias. However, an increased inducibility of AF after partial aortic stenosis was not apparent before the 20th week after aortic banding.<sup>29</sup> Similarly, increased fibrosis with slowing of conduction and enhanced inducibility of AF were not evident before the 10th week after renal artery stenosis.

An altered  $Ca^{2+}$  handling by the atrial myocytes has been identified as a mechanism potentially able to trigger AF. Pluteanu et al<sup>37</sup> demonstrated the existence of subcellular alterations in  $Ca^{2+}$  handling in SHR, which were associated with an increased propensity of atrial myocytes to develop frequency-dependent, arrhythmogenic  $Ca^{2+}$  alternans. Other arrhythmogenic mechanisms seem to be involved. In SHR, ultrastructure observation of myocytes showed enhanced neoformation of side-to-side gap junctions, with reduction of end-to-end type junctions.<sup>40</sup> These changes, which can increase the propensity to tachyarrhythmias,<sup>41</sup> are overexpressed in rats with hypertension induced by stenosis of ascending aorta.<sup>29</sup>

Propensity to AF may increase when hypertension and obesity coexist. When compared with lean SHR, obese SHR showed enhanced extracellular matrix formation, increased diameter of myocytes, impaired LA emptying, and increased susceptibility to AF, with longer episodes of inducible AF.<sup>38</sup> Osteopontin—a profibrotic extracellular matrix protein, which independently predicts AF recurrence after ablation<sup>42</sup>—was highly upregulated in obese SHR, not in lean SHR.<sup>38</sup>

Overall, these experimental models suggest that hypertension may induce early and progressive changes in LA anatomy and function, which may promote AF through a variety of electrophysiological mechanisms, some of which are unclear. Although the application of basic research studies to humans should be made with caution, a reasonable implication of these findings could be the importance of an early control of

BP in hypertensive patients to prevent the progression of LA remodeling and enhanced AF inducibility.

### Translation of Experimental Findings to Humans

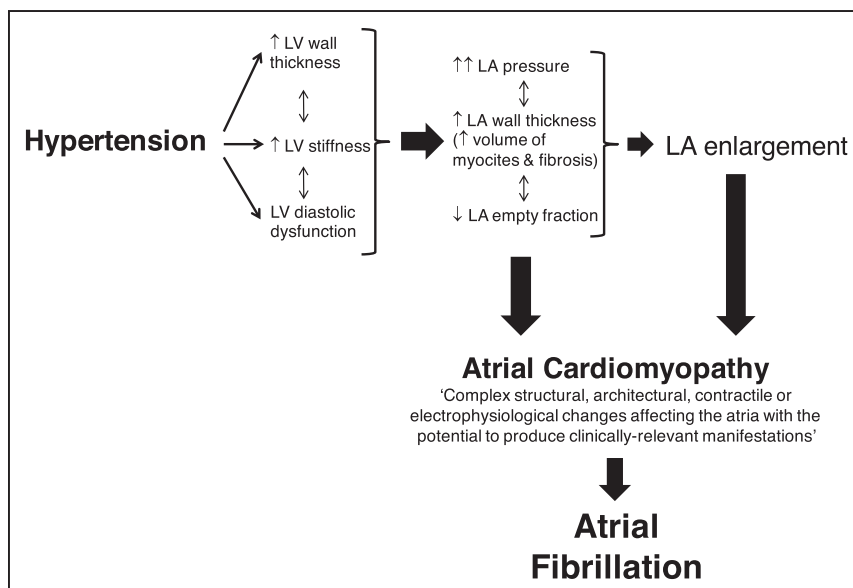
Several different mechanisms may be involved in the genesis of AF in hypertensive patients. A central role is expressed by the so called atrial cardiomyopathy, defined as a complex of structural, architectural, contractile, and electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations,<sup>43</sup> which may be induced by predominantly hemodynamic and nonhemodynamic mechanisms. The predominantly hemodynamic mechanisms (Figure 1) include the increase in left ventricular (LV) wall thickness, the rise in LV stiffness, and the impairment in LV diastolic function associated with hypertension. These processes may lead to a rise in LA stretch and pressure, with subsequent remodeling and dysfunction of the LA, ultimately predisposing to AF.

Several experiences in animals and humans supported the role of histological changes in the atria as potential triggers of AF.<sup>28</sup> The most important atrial changes include proliferation of fibroblasts, alterations of extracellular matrix, and hypertrophy of myocytes.<sup>28</sup> The resulting disorders of interconnections between muscle bundles may lead to shortening of LA refractoriness, unidirectional blocks, and reentry phenomena. These processes may initiate AF eventually triggered by ectopic stimuli originating from pulmonary veins or other sites. A European Consensus Document provided a detailed review of the complex interplay between hypertension and cardiac arrhythmias.<sup>44</sup>

### Cardiac Antecedents of AF in Humans

The atria of hypertensive patients may show subtle electrophysiological alterations predisposing to AF. In an elegant electrophysiological study conducted in hypertensive patients and normotensive controls, the former group showed slowing of global and regional conduction, an increase in areas of low voltage and, most notably, an easier inducibility of sustained AF.<sup>45</sup>

The Framingham study was the first to demonstrate a relationship between BP and LA dilatation, and the impact of systolic BP on the LA outweighed that of diastolic BP.<sup>46</sup> In



**Figure 1.** Potential mechanisms by which hypertension may favor the onset of atrial fibrillation. LA indicates left atrium; and LV, left ventricle.



another report from Framingham, the risk of AF increased with LA diameter and LV wall thickness and was inversely related to shortening fraction.<sup>47</sup>

In a study conducted in a large cohort of initially untreated hypertensive subjects, baseline LV hypertrophy almost doubled the risk of new-onset AF (Figure 2, left), and for each 1-SD increase in LV mass, the risk of AF increased by 20% (95% confidence interval [CI], 7%–34%). At any level of LV mass, the 5-year risk of permanent AF increased with LA diameter (Figure 2, right).<sup>48</sup> Thus, the risk of new-onset AF increased with age and LV mass in hypertensive patients in sinus rhythm at entry and no other major predisposing conditions, whereas increased LA size was more closely associated to the development of permanent AF. LV hypertrophy diagnosed by electrocardiography is also a significant predictor of AF in the general population<sup>49</sup> and in hypertensive patients.<sup>50</sup> In other studies, LA dilatation associated with atrial pump function<sup>51</sup> and LV diastolic dysfunction<sup>52</sup> identified patients at higher risk of AF.

Obstructive sleep apnea is another condition potentially involved in the pathogenesis of AF in hypertensive patients. Clinical studies showed that obstructive sleep apnea, which is present in ≈50% of patients with hypertension,<sup>53</sup> is associated with LA dilatation<sup>54</sup> and a higher risk of AF both in the presence and absence of LV dysfunction.<sup>55–57</sup>

The atria of patients with AF may present a greater amount of fibrosis and scarring. In a clinical study by Frustaci et al,<sup>58</sup> 12 patients with AF refractory to antiarrhythmic treatment underwent myocardial biopsy. The authors noted a marked rise in the content of collagen in the atria in all 12 patients, whereas these changes were present also in the ventricles in only 3 patients.<sup>58</sup> The possible involvement of ventricles in patients with AF has been hypothesized. A recent study with magnetic resonance imaging in patients with apparently lone AF found a subtle but significant impairment of LV function and myocardial energetics, which persisted after catheter ablation.<sup>59</sup> It should be noted that patients with controlled

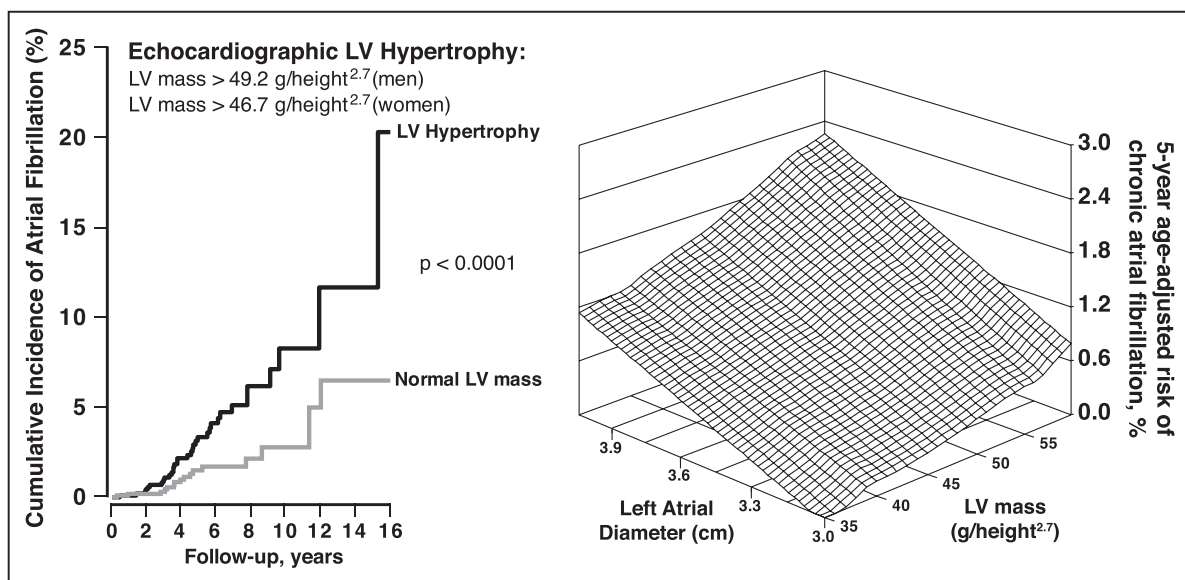
hypertension were not excluded from the study (only uncontrolled patients were excluded).<sup>59</sup> Thus, the provocative suggestion by the authors that AF may be the consequence, rather the cause, of an occult cardiomyopathy<sup>59</sup> should be verified after complete exclusion of hypertension as a potential determinant of LV dysfunction.

### Role of the RAAS

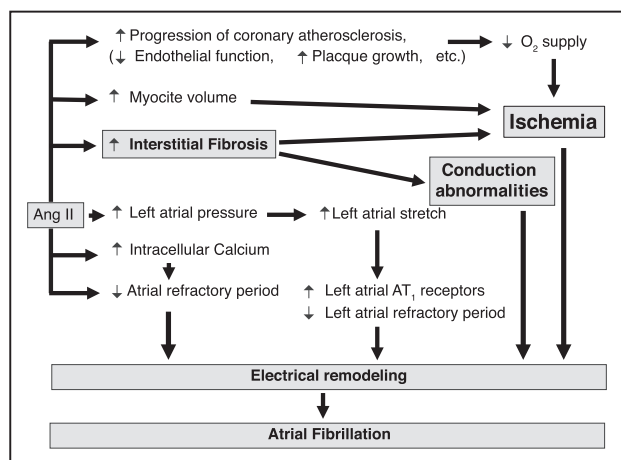
The RAAS may be involved in the pathogenesis of AF through several mechanisms (Figure 3). These include proliferation of fibroblasts and extracellular matrix and hypertrophy of myocytes, with potentially detrimental electrophysiological changes.<sup>60</sup> Angiotensin II may also modulate some ion currents in myocytes, including the L and T type inward  $Ca^{2+}$  current<sup>61,62</sup> and the potassium current,<sup>63</sup> although evidence from literature is not univocal.<sup>64</sup> In a study on isolated cardiac Purkinje fibers, angiotensin II increased the strength of contraction in association with a greater duration of the plateau phase of the action potential.<sup>65</sup> These effects were inhibited by a calcium antagonist.<sup>65</sup> In isolated cardiac myocytes from rats and mice, angiotensin II activated cAMP-dependent protein kinase A and Ca/calmodulin kinase II—a well-established proarrhythmic pathway in the setting of increased angiotensin II stimulation.<sup>66</sup>

Myocardial fibrosis induced by RAAS seems to be BP independent. In an animal study by Sun et al,<sup>67</sup> low doses of angiotensin II and aldosterone infused through a mini pump induced a marked increase of interstitial collagen after only 2 to 6 weeks of administration in the absence of any rise in BP. Anyway, angiotensin II does not exert any direct effects on atrial electrophysiological parameters in humans.<sup>68</sup>

The complex relations between aldosterone and AF in hypertension have been recently reviewed.<sup>69</sup> In particular, an impressive 12-fold higher risk of AF has been reported in patients with primary hyperaldosteronism when compared with patients with essential hypertension,<sup>70</sup> which is in line with the



**Figure 2.** Incidence of new-onset atrial fibrillation in hypertensive patients sorted by absence or presence of left ventricular (LV) hypertrophy at echocardiography (left), and 5-y risk of permanent atrial fibrillation in relation to LV mass and left atrial diameter. Adapted from Verdecchia et al<sup>48</sup> with permission. Copyright © 2003, the American Heart Association. Reported values are the division points for quartiles.



**Figure 3. Potential mechanisms by which the renin-angiotensin-aldosterone system may be involved in the onset of atrial fibrillation.** Ang II indicates angiotensin II; and AT<sub>1</sub>, angiotensin II type I.

known effect of aldosterone on cardiac inflammation, fibrosis, and hypertrophy.<sup>69,71,72</sup>

Several experimental studies support the protective role of pharmacological RAAS inhibition on the risk of AF. In a dog model of experimental congestive HF because of ventricular tachypacing, interstitial fibrosis, and atrial angiotensin II concentrations were increased by pacing. In these animals, enalapril significantly reduced tachypacing-induced changes in atrial angiotensin II concentrations and fibrosis.<sup>73</sup> In another dog model, sustained AF was induced in 20 animals by rapid pacing of the right atrium for 5 weeks.<sup>74</sup> Candesartan was administered orally (10 mg·kg<sup>-1</sup>·d<sup>-1</sup>) for 1 week before rapid pacing and was continued for 5 weeks. There was a marked reduction in the amount of fibrosis in the candesartan group.<sup>74</sup> In another study in SHR, sustained inhibition of NO synthesis obtained through N-nitro-L-arginine methyl ester increased the extent of fibrosis in atrial tissue, and both of these effects were prevented by candesartan but not by hydralazine.<sup>39</sup>

## Hypertension and the Risk of AF

### BP Levels and AF

In the general population, hypertension increases the risk for AF in both sexes.<sup>16</sup> In the Framingham Heart study, pulse pressure was superior to systolic and diastolic BP for prediction of AF even after adjustment for LA dimension, LV mass, and shortening fraction.<sup>75</sup> Pulse pressure emerged as a significant independent risk factor for AF also in another population study<sup>76</sup> and in a study restricted to patients with type 2 diabetes mellitus.<sup>77</sup> Overall, these data suggest that arterial stiffness, reflected by pulse pressure, is an important and modifiable risk factor for AF.<sup>75,77</sup>

It is unclear whether the relation between BP and the risk of AF is linear or whether there is a threshold BP value above which the risk definitely increases.<sup>22</sup> In a case-control population study, the risk of AF doubled in individuals with systolic BP of ≥150 mmHg, as compared with patients with systolic BP levels of 120 to 129 mmHg. However, this excess risk was not significant in participants with systolic BP 140 to 149 mmHg, whereas there was an increased risk of AF in those with a systolic BP <120 mmHg, consistent with a J-curve

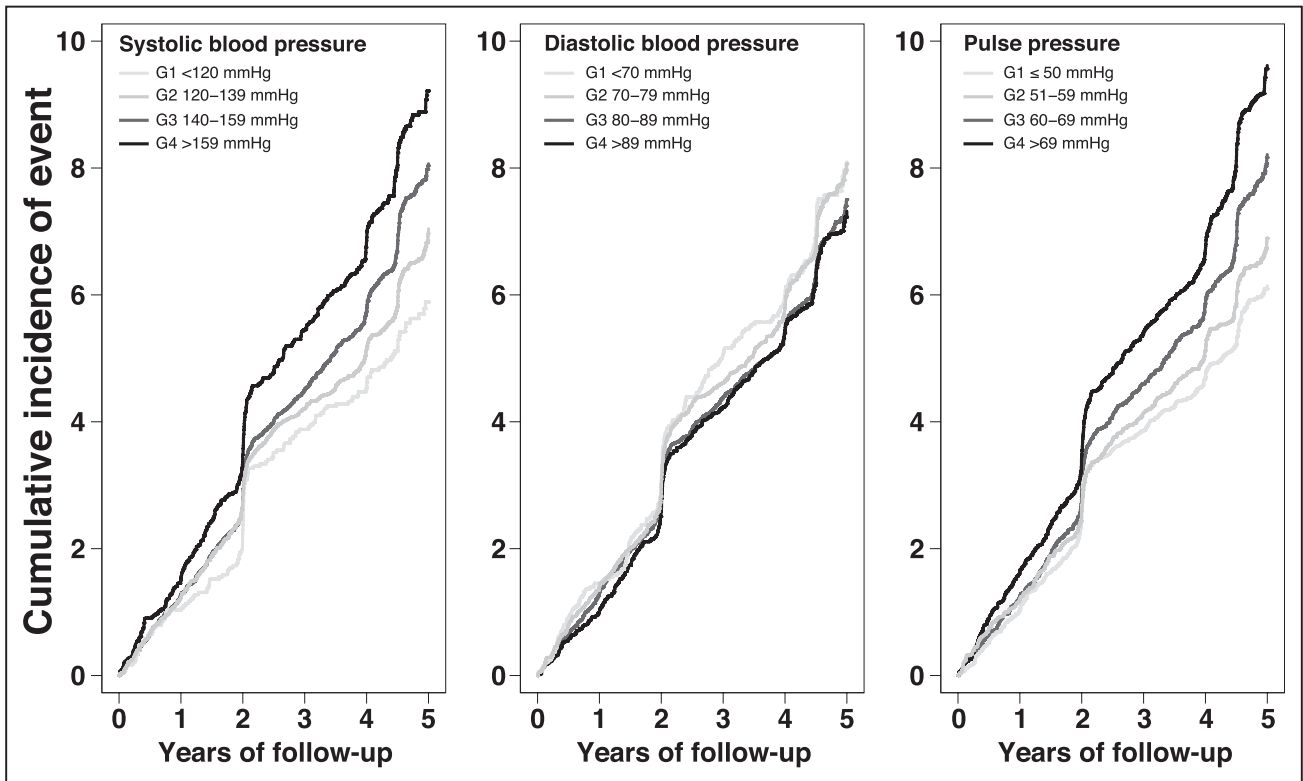
phenomenon.<sup>78</sup> This J phenomenon was not confirmed in a large cohort of women enrolled in the Women's Health Study, which showed a continuous relation between BP, even in the normal range, and the risk of incident AF during a median follow-up period of 14 years.<sup>79</sup> Notably, patients with BP in the so called high-normal range according to the European guidelines (130–139/85–89 mmHg) showed a 28% to 53% higher risk of incident AF when compared with women with BP <120/65 mmHg.<sup>79</sup>

The excess risk of AF in normotensive individuals with high-normal BP was confirmed in an analysis of the MESA (Multi-Ethnic Study of Atherosclerosis), which showed that prehypertension (120–139/80–89 mmHg) was associated with a significant 80% higher risk of AF even after multivariate adjustment for several potential confounders.<sup>80</sup> A continuous and direct relation between BP and AF emerged also in a study from Norway, in which a group of 2014 healthy men first scrutinized in years 1972 to 1975 were followed for a median of 30 years.<sup>81</sup> The risk of AF was significantly lower in individuals with BP at entry <128/80 mmHg (bottom quartile) than in those with higher BP levels. Notably, this finding remained significant even after adjustment for several adverse conditions, which emerged during follow-up and put these patients at increased risk for AF (myocardial infarction, HF, coronary artery bypass, and diabetes mellitus).<sup>81</sup> At variance with the above findings, the REGARDS study (Reasons for Geographic and Racial Differences in Stroke) did not show any significant differences in the prevalence of AF in relation to BP levels or response to antihypertensive treatment in a large mixed population of normotensive and hypertensive individuals.<sup>82</sup> Furthermore, a meta-analysis of 14 trials did not show any association between the variability in BP among different visits and the risk of new-onset AF.<sup>83</sup>

Thus, the majority of clinical studies showed a direct and linear relation between BP levels and the risk of AF. However, the shape of this relation in the growing segment of high-risk vascular patients with coronary artery disease, cerebrovascular disease, peripheral artery disease, or complicated diabetes mellitus remains unclear. This aspect was investigated in a post hoc analysis of the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial)/TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease).<sup>84</sup> The risk of AF significantly increased with systolic BP, pulse pressure, age, LV hypertrophy, body mass index, serum creatinine and history of hypertension, and coronary and cerebrovascular disease (Figure 4).<sup>84</sup> The impact of diastolic BP was not significant.

### Tachycardia and AF

Tachycardia could be an additional factor facilitating the onset of AF in hypertensive patients. In a post hoc analysis of the LIFE study (Losartan Intervention for Endpoint Reduction), a 10-beats per minute higher heart rate at follow-up was associated with a 19% higher risk of new-onset AF even after adjustment for randomized treatment (losartan versus atenolol), BP, and LV hypertrophy regression.<sup>85</sup> Several potential mechanisms, including increased sympathetic activity, subclinical reduction in LV function, and changes in the atrial



**Figure 4.** Relation between baseline blood pressure and later occurrence of atrial fibrillation in patients with sinus rhythm at entry enrolled in the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial)/TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease). Adapted from Verdecchia et al<sup>84</sup> with permission. Copyright © 2012, Lippincott Williams & Wilkins, Inc.

effective refractory period, could explain the higher risk of AF in association with tachycardia.<sup>85</sup> Ivabradine—an inhibitor of the pacemaker current ( $I_p$ ), which reduces tachycardia in the absence of negative inotropic effects—reduced inducibility of AF in a rat model of isolated heart.<sup>86</sup>

**Blunted Day–Night BP Fall and AF**

A blunted day–night fall in BP (non dipping or reverse dipping pattern) is an independent predictor of major cardiovascular events in hypertensive patients.<sup>87,88</sup> In clinical studies, a nondipping pattern has been associated with supraventricular<sup>89</sup> and ventricular<sup>90</sup> arrhythmias. In a study, hypertensive patients with a nondipping pattern had a 2-fold higher risk of developing AF when compared with those with a normal diurnal BP rhythm.<sup>91</sup>

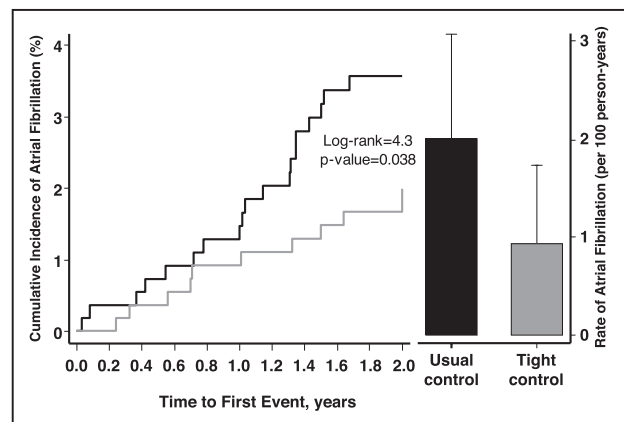
**Hypertension and AF in HF**

There is abundant evidence that hypertension is a major modifiable risk factor for HF (HF) with both preserved and reduced ejection fraction (EF),<sup>92</sup> although patients with HF with reduced EF often present low BP values because of the reduced pump function (decapitated hypertension).<sup>92</sup> The prevalence of AF in patients with HF is ≈53% in those with HF with reduced EF and 65% in those with HF with preserved EF.<sup>93</sup> In patients with HF, hypertension is a strong and independent predictor of AF, particularly when EF is <50%.<sup>93</sup> In the Women’s Health Study, participants with AF and systolic BP levels >120 mmHg were at higher risk of incident HF.<sup>94</sup> New-onset AF may be a particularly awful occurrence in hypertensive

patients with HF because the sudden loss of atrial pump function, possibly associated with tachycardia, LV dysfunction, and increased afterload, may rapidly trigger episodes of acute pulmonary edema.<sup>95</sup> HF remains the most common cause of death in patients with AF.<sup>96</sup>

**Intensive BP Control and the Risk of AF**

The direct relation between BP and AF observed in epidemiological studies raises the possibility that nonpharmacological



**Figure 5.** Incidence of new-onset atrial fibrillation in hypertensive patients randomized to a more-tight or less-tight blood pressure control (target systolic blood pressure, <140 vs <130 mmHg) in the Cardio-Sis study (Studio Italiano Sugli Effetti Cardiovascolari Del Controllo Della Pressione Arteriosa Sistolica).

and pharmacological interventions, which retard the progression from prehypertension to hypertension, may prevent the occurrence of new-onset AF. Similarly, an intensive control of BP in hypertensive patients could decrease the risk of new-onset AF. A meta-analysis of 18 randomized trials, which compared a more-intensive with a less-intensive BP target, showed that the more-intensive target significantly reduced stroke by 20%, myocardial infarction by 15%, HF by 25%, and cardiovascular death by 18%.<sup>97</sup> However, the impact of intensive BP reduction on the risk of AF is still undefined because of the paucity of published data.<sup>97</sup>

In the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), patients randomly assigned to doxazosin had a mean in-trial systolic BP by 3 mmHg higher than that of patients randomly assigned to chlorthalidone.<sup>98</sup> The incidence of new AF or flutter was significantly higher in the doxazosin group than in the chlorthalidone group (odds ratio, 1.35;  $P=0.02$ ).<sup>99</sup>

Comparative studies between different BP targets may be particularly useful in this setting. In the Cardio-Sis trial (Studio Italiano Sugli Effetti Cardiovascolari Del Controllo Della Pressione Arteriosa Sistolica), treated hypertensive patients in sinus rhythm at entry were randomly assigned to a target systolic BP <140 mmHg (usual control) or <130 mmHg (tight control), and new AF was a prespecified secondary outcome of the study. At the end of a median follow-up period of 2 years, new AF occurred in 3.8% of patients in the usual control group and 1.8% of patients in the tight control group (hazard ratio [HR], 0.46; 95% CI, 0.22–0.98;  $P=0.044$ ; Figure 5).<sup>100</sup> Because of the relatively small sample size of the Cardio-Sis study, the hypothesis that a tight BP control is protective from new-onset AF should be confirmed in larger trials. The SPRINT trial (Systolic Blood Pressure Intervention Trial),<sup>101</sup> funded by the National Institutes of Health, which gathered electrocardiographic tracings from thousands of hypertensive patients randomized to a more-intensive or less-intensive BP target (120 versus 140 mmHg), has the potential to answer this question.

### Inhibition of RAAS and the Risk of AF

The evidence from animal studies (see above) that the RAAS induces structural and functional changes in the LA potentially able to trigger AF stimulated a careful scrutiny of existing human studies conducted with ACE (angiotensin-converting enzyme) inhibitors or angiotensin receptor blockers (ARBs) to investigate the impact of these drugs on new-onset AF. In the SOLVD (Study of Left Ventricular Dysfunction), conducted in patients with asymptomatic or mildly symptomatic LV systolic dysfunction (EF,  $\leq 35\%$ ), enalapril significantly reduced the risk of new-onset AF, and this effect was independent of several potential confounders.<sup>102</sup>

In other studies conducted in patients with severe congestive HF, candesartan (HR, 0.80; 95% CI, 0.65–0.99;  $P=0.039$ )<sup>103</sup> and valsartan (HR, 0.63; 95% CI, 0.49–0.81;  $P=0.0003$ )<sup>104</sup> were more effective than placebo in reducing new-onset AF. Also in the TRACE study (Trandolapril Cardiac Evaluation)—a comparison of trandolapril versus placebo in postmyocardial infarction patients with low EF—trandolapril significantly reduced the risk of new-onset AF by 55%.<sup>105</sup> There was some hope that the dual blockade of the

RAAS with ACE inhibitors and ARBs could be particularly effective in preventing AF. However, in the ONTARGET/TRANSCEND trial, the incidence of new-onset AF was only marginally, and not significantly, lower in the patients randomized to ramipril+telmisartan (6.8%) as compared with telmisartan (6.9%) and ramipril (7.2%) alone.<sup>84</sup>

Obviously, a key target to pursue is the prevention of AF in hypertensive patients without HF or clinically overt coronary artery disease. A list of clinical studies that investigated the impact of RAAS inhibition on the risk of AF in hypertensive patients is reported in Table 2. In one of the largest studies—the LIFE study—the incidence of new-onset AF was 6.8 versus 10.1 per 1000 person-years of follow-up with losartan and atenolol, respectively (adjusted HR, 0.67; 95% CI, 0.55–0.83;  $P<0.001$ ).<sup>106</sup> In the VALUE study (Valsartan Antihypertensive Long-Term Use Evaluation), valsartan reduced the incidence of new-onset AF in hypertensive patients when compared with amlodipine-based therapy.<sup>107</sup> In a small study from Spain, irbesartan associated with amiodarone was more effective than amiodarone alone in preventing AF recurrence after cardioversion.<sup>108</sup>

Schneider et al<sup>117</sup> published a meta-analysis of 23 randomized controlled trials that compared ACE inhibitors, or ARBs, with placebo or an active control in several clinical settings. This meta-analysis provided mixed results. First, there was a significant heterogeneity across the studies, which means an analysis of different populations, different drugs, and different designs, which could have flawed the results. A significant reduction in the risk of AF for effect of ACE inhibitors or ARBs versus controls was observed in the analysis of HF trials and postcardioversion trials, whereas there were no significant differences between ACE inhibitors/ARBs versus controls in the analysis of hypertension studies and post-MI studies.<sup>117</sup>

After the publication of the above meta-analysis, other studies reported a comparison between different treatments with new-onset AF as outcome measure. Schaer et al<sup>115</sup> published a nested case-control analysis from a large UK database with >4000 hypertensive patients with AF and 18000 hypertensive controls in sinus rhythm. The control group was composed by patients treated with a calcium channel blocker, and the experimental groups were patients treated with ACE inhibitors, ARBs, or  $\beta$ -blockers.<sup>115</sup> These were mutually exclusive groups because patients treated with combinations of these drugs were excluded. When compared with patients receiving a calcium channel blocker, those receiving an ACE inhibitor, and ARB or a  $\beta$ -blocker, had a significant 25%, 29%, and 22% reduction, respectively, in the risk of subsequent AF.<sup>115</sup> In the ALLHAT study mentioned above,<sup>98</sup> the incidence of new-onset AF did not differ significantly between the chlorthalidone (20.9 per 1000 patient-years), amlodipine (22.4 per 1000 patient-years) and lisinopril (20.6 per 1000 patient-years) groups, whereas it was higher in the doxazosin group.<sup>98</sup> In a study from China, in which 149 hypertensive patients with paroxysmal AF were randomized to receive nifedipine or telmisartan, the rate of overall AF recurrence was similar in the 2 groups (59% with nifedipine and 55% with telmisartan), but the incidence of persistent AF was lower with telmisartan group than with nifedipine (5.4% versus 16.0%;  $P=0.035$ ).<sup>109</sup>



**Table 2. Clinical Studies Investigating the Impact of Renin–Angiotensin–Aldosterone System Inhibition on the Risk of Atrial Fibrillation in Hypertensive Patients**

Author	Design	No. of Patients	Antihypertensive Treatment	Mean Duration of Follow-Up, y	Results
Du et al <sup>109</sup>	Open-label RCT	149	Telmisartan vs nifedipine	2	Recurrence of AF not significantly different between telmisartan (58.7%) and nifedipine (55.4%). Persistent AF lower ( $P=0.035$ ) with telmisartan (5.4%) than with nifedipine (16.0%)
Fogari et al <sup>110</sup>	Double-blind RCT	250	Losartan vs amlodipine	1	New-onset AF lower ( $P=0.008$ ) with valsartan (11.7%) than with amlodipine (35.1%)
Fogari et al <sup>111</sup>	Double-blind RCT	296	Valsartan+amlodipine vs atenolol+amlodipine	1	New-onset AF lower ( $P=0.010$ ) with valsartan+amlodipine (18.9%) than with atenolol+amlodipine (31.8%)
Hansson et al <sup>112</sup>	CAPPP	10 985	Captopril vs $\beta$ -blockers or diuretics	5.5	New-onset AF not significantly different between captopril (2.13%) and $\beta$ -blockers or diuretics (2.45%)
Hansson et al <sup>113</sup>	STOP-2	6614	Enalapril (or lisinopril) vs various diuretics (or $\beta$ -blockers) vs various calcium antagonists	6	New-onset AF not significantly different between enalapril or lisinopril (19.0%) vs various diuretics or $\beta$ -blockers (16.4%) vs various calcium antagonists (17.1%)
Haywood et al <sup>99</sup>	Post hoc analysis of ALLHAT	31 724	Lisinopril vs amlodipine vs chlorthalidone	4.9	New-onset AF not significantly different between lisinopril, amlodipine, and chlorthalidone
Salehian et al <sup>114</sup>	Post hoc analysis of HOPE	8335	Ramipril vs placebo	4.5	New-onset AF not significantly different between ramipril (2.1%) and placebo (2.0%)
Schaer et al <sup>115</sup>	Nested case–control study	23 303	Various ACEis vs various ARBs vs various $\beta$ -blockers vs various CCBs	$\geq 1$	Current exclusive long-term therapy with ACEis, ARBs, or $\beta$ -blockers was associated with a lower risk for AF than current exclusive therapy with CCBs
Schmieder et al <sup>107</sup>	Post hoc analysis of VALUE study	15 245	Valsartan vs amlodipine	4.2	New-onset AF lower ( $P=0.0455$ ) with valsartan (3.67%) than with amlodipine (4.34%). Persistent AF lower ( $P=0.0046$ ) with valsartan (1.35%) than with amlodipine (1.97%)
Verdecchia et al <sup>84</sup>	Post hoc analysis of ONTARGET/TRANSCEND study	30 424	Telmisartan+ramipril vs telmisartan vs ramipril	4.7	New-onset AF not significantly lower with telmisartan+ramipril (6.8%) vs telmisartan (6.9%) vs ramipril (7.2%)
Wachtell et al <sup>106</sup>	Post hoc analysis of LIFE	9193	Losartan vs atenolol	4.8	New-onset AF lower ( $P<0.001$ ) with losartan (6.8%) than with atenolol (10.1%)
Yamashita et al <sup>116</sup>	Open-label RCT	318	Candesartan vs amlodipine	1	Development of persistent AF slightly but not significantly lower ( $P=0.008$ ) with candesartan (8.2%) than with amlodipine (15.0%)

ACEi indicates angiotensin-converting enzyme inhibitor; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB, angiotensin receptor blocker; CAPPP, Captopril Prevention Project; CCB, calcium channel blocker; HOPE, Heart Outcome Prevention Evaluation; LIFE, Losartan Intervention for Endpoint Reduction; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; RCT, randomized clinical trial; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease; and VALUE, Valsartan Antihypertensive Long-Term Use Evaluation.

Overall, these studies suggest that inhibition of RAAS with ACE inhibitors or ARBs might be considered for prevention of AF in hypertensive patients in sinus rhythm, although evidence is not yet conclusive. The recently released American guidelines for the management of patients with hypertension suggest that ARBs can be useful for prevention of recurrence of AF, with class of recommendation 2A and level of evidence B-R (moderate-quality evidence from  $\geq 1$  randomized trial or moderate-quality meta-analyses of randomized trials).<sup>118</sup>

### Impact of BP Control in Patients With AF

#### Prevalence of Hypertension in Patients With AF

Hypertension is frequent in patients with AF. A Position Paper of the Working Group ‘Hypertension Arrhythmias and

Thrombosis’ of the European Society of Hypertension explored the prevalence of patients with hypertension among those enrolled in the main AF trials.<sup>24</sup> Prevalence values ranged between 49% and 90%.<sup>24</sup> In recent trials that addressed the non–vitamin K antagonist oral anticoagulants (NOACs), prevalence of hypertension was 78.9% in the RE-LY study (Randomized Evaluation of Long-Term Anticoagulation Therapy),<sup>119</sup> 90.5% in the ROCKET AF study (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation),<sup>120</sup> 87.4% in the ARISTOTLE study (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation),<sup>121</sup> 86% in the AVERROES study (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients

Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment),<sup>122</sup> and 93.6% in the ENGAGE-AF TIMI 48 study (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48).<sup>123</sup> However, it should be noted that the above trials defined hypertension on the basis of current antihypertensive drug treatment, or based on BP values persistently >140/90 mmHg, and excluded patients with BP  $\geq$ 170 to 180 mmHg systolic or  $\geq$ 90 mmHg diastolic.

### Prognostic Impact of Hypertension in Patients With AF

Hypertension is a potent and independent risk factor for ischemic and hemorrhagic stroke.<sup>6,124,125</sup> A large systematic review showed a linear relation at any age between usual BP and mortality from stroke, starting from values of 115/75 mmHg.<sup>5</sup> However, because the above studies have been conducted in a mixed population of individuals with and without AF,<sup>5</sup> the independent contribution of AF to the risk of cerebrovascular complications associated with high BP remains unclear.

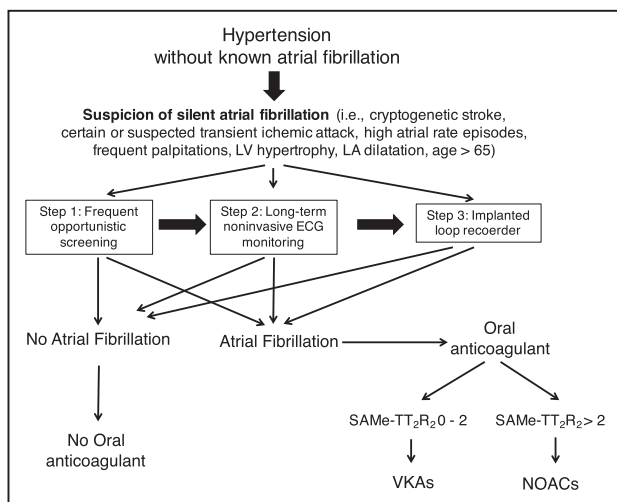
From a clinical standpoint, individual hypertensive patients who present with sinus rhythm, an uncertain history of AF, and a clear evidence of prior cerebrovascular events should be studied accurately to differentiate strokes of cardioembolic origin from lacunar infarcts or strokes resulting from complicated atherosclerotic plaques or cerebral hemorrhages.<sup>23</sup> In these cases, remote ECG monitoring would be helpful to identify the patients with silent AF,<sup>13,14</sup> who might benefit from anticoagulation. An AF burden of at least 5 to 6 minutes is generally considered sufficient to start anticoagulation.<sup>44,126</sup> A European Consensus Document suggests commencing appropriate therapy (anticoagulation, ablation, etc) in hypertensive patients with arrhythmia confirmed either by (1) standard 12-lead ECG or (2) 24- to 48-hour Holter (in patients with standard ECG not diagnostic) or (3) 30-day event monitoring (in those with diagnosis still uncertain but highly symptomatic or at high risk for stroke).<sup>44</sup> Figure 6, modified from Dzashka et al,<sup>127</sup> suggests a strategy in patients with hypertension and suspicion of silent

AF. Suspicion may be based on  $\geq$ 1 factors, which include a prior cryptogenic stroke, certain or suspected transient ischemic attack, high atrial rate episodes on interrogation of implanted device, frequent palpitations, LV hypertrophy, LA dilatation, and elderly. Depending of the clinical characteristics of patients and the importance of making diagnosis of silent AF, a progressive strategy may include frequent opportunistic screenings as first step, followed by extended noninvasive ECG monitoring and implanted loop recorded. Should AF be detected, the CHA<sub>2</sub>DS<sub>2</sub>VASc (congestive HF, hypertension, age  $\geq$ 75 [doubled], diabetes mellitus, stroke [doubled], vascular disease, age 65–74, and female sex) score<sup>128</sup> would be at least 2 in women and at least 1 in men. Therefore, oral anticoagulants should be considered according to European guidelines.<sup>8</sup> NOACs may be preferred over vitamin K antagonists<sup>8,127</sup> in patients with predicted poor control of international normalized ratio with vitamin K antagonists, according to the SAME-TT<sub>2</sub>R<sub>2</sub> score (Sex [female], age [60 years], medical history [2 of the following: hypertension, diabetes mellitus, MI, peripheral artery disease, congestive HF, history of stroke, pulmonary disease, hepatic, or renal disease], treatment [interacting medications; eg, amiodarone], tobacco use [within 2 years; scores double], race [non-white; scores double]).<sup>129</sup> Conversely, the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines suggest that in patients with nonvalvular AF and a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 1, no antithrombotic therapy or treatment with oral anticoagulant or aspirin may be considered.<sup>7</sup>

In patients with documented AF, hypertension increases the risk of thromboembolism and bleedings<sup>130–132</sup> and facilitates the progression from paroxysmal to persistent or permanent AF.<sup>133–135</sup> Prevalence of hypertension seems to be similar in patients with asymptomatic and symptomatic AF.<sup>135,136</sup>

The potential mechanisms linking hypertension with thromboembolism in patients with established AF are elusive. Because prior stroke, aging, hypertension, and diabetes mellitus are the main independent risk factors for stroke in patients with<sup>137</sup> and without<sup>5,124,125</sup> AF, it is unlikely that cardioembolism is the dominant mechanism of stroke in the former.<sup>137</sup> However, clinical studies suggest that hypertension could directly promote LA thrombosis. For example, in a study by Zabalgoitia et al,<sup>138</sup> hypertensive patients showed a lower flow velocity and a higher risk of thrombosis in the LA appendix. These results have been confirmed by Goldman et al<sup>139</sup> in a subanalysis of the SPAF-III study (Stroke Prevention in Atrial Fibrillation), which demonstrated a significant inverse association between systolic BP and the flow velocity of the LA appendix. These results raise the hypothesis, to be tested in specifically designed trials, that a strict BP control in hypertensive patients with AF might be useful also for prevention of cardioembolic stroke.

Large population studies in anticoagulated patients with AF have confirmed the importance of hypertension as a predictor of both thrombotic and hemorrhagic complications. Friberg et al<sup>140</sup> analyzed a large Swedish registry of 182 678 anticoagulated patients with AF and found that hypertension was an independent predictor not only of thromboembolic complications but also of intracranial hemorrhage and major bleeding. Unfortunately, diagnosis of hypertension was based on certificates at hospital discharge, without specific standardization of BP measurement. In this setting, it is important to



**Figure 6. Proposed strategy in hypertensive patients in sinus rhythm and suspicion of atrial fibrillation.** LA indicates left atrium; LV, left ventricle; NOAC, non-vitamin K antagonist oral anticoagulant; and VKA, vitamin K antagonist.

remark that the available automated BP monitors that have been validated in subjects in sinus rhythm may not be accurate in patients with AF.<sup>141</sup> It is believed that multiple BP measurements are needed in patients with AF<sup>142</sup> and that validation studies performed on specific monitors cannot be extrapolated to different machines.<sup>143</sup>

In a retrospective study from China, conducted in anticoagulated hypertensive patients with AF, those who achieved a target BP <130/80 mm Hg showed a lower incidence of ischemic stroke (0.9% versus 3.1% per year;  $P=0.01$ ) but a similar risk of major bleeding ( $P=0.61$ ) and intracranial bleeding ( $P=1.00$ ) when compared with patients with higher BP values.<sup>131</sup> Conversely, in a post hoc analysis of the SPORTIF III and V trials (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation), conducted in patients with anticoagulated AF randomized to ximelagatran or warfarin, BP showed a significant association with the risk of hemorrhagic stroke but not with that of major or minor bleedings.<sup>144</sup>

The recent guidelines of the European Society of Cardiology for the management of AF assigned to a class IIa and level of evidence C the recommendation that BP control in anticoagulated patients with AF should be considered to reduce the risk of bleeding.<sup>8</sup>

For the estimate of individual risk of stroke, a history of hypertension contributes with 1 point to the CHADS<sub>2</sub> score (congestive HF, hypertension, age  $\geq 75$ , diabetes mellitus, stroke [doubled]).<sup>145</sup> Also the CHA<sub>2</sub>DS<sub>2</sub>VASc score,<sup>128</sup> which outperforms the CHADS<sub>2</sub> score for identification of patients at low risk of stroke (CHA<sub>2</sub>DS<sub>2</sub>VASc score=0),<sup>8,146,147</sup> assigns 1 point to a resting BP >140 mm Hg systolic or >90 mm Hg diastolic on at least 2 occasions or current antihypertensive pharmacological treatment. The definition of hypertension in the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scores pertains to office BP not home or ambulatory BP. Guidelines suggest that male patients with AF with a CHA<sub>2</sub>DS<sub>2</sub>VASc score=1 solely because of coexistent office hypertension should be anticoagulated (class IIa, level of evidence B).<sup>8</sup> However, because the risk of stroke related to hypertension strikingly differs according to BP levels,<sup>5</sup> the impact of hypertension in the above scores should be probably refined. A further consideration, raised by Rabkin et al,<sup>23</sup> is that hypertension alone has not been included as the only criterion for entry in the AF trials with anticoagulants, including the NOACs.

Hypertension is also a modifiable risk factor included in scores aimed to estimate the individual risk of bleeding. For example, the HEMORR<sub>2</sub>HAGES score (hepatic or renal disease, ethanol abuse, malignancy, older [aged >75 years], reduced platelet count, rebleeding risk, uncontrolled hypertension, anemia, genetic factors, excessive fall risk, previous stroke/transient ischemic attack)<sup>148</sup> assigns 1 point to uncontrolled hypertension (systolic BP, >160 mm Hg). Similarly, the HAS-BLED score (hypertension [uncontrolled, >160 mm Hg systolic], abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [ie, therapeutic time in range <60%], elderly [>65 years], drugs/alcohol concomitantly [antiplatelet agents, nonsteroidal anti-inflammatory drugs])<sup>149</sup> also assigns 1 point to uncontrolled hypertension.

In a study conducted in a large cohort of Chinese patients with AF, the HAS-BLED score was superior to predict bleeding events compared with a European score.<sup>150</sup> Unfortunately, the most appropriate BP target to curtail the risk of thrombotic and hemorrhagic complications in anticoagulated hypertensive patients with AF is still undefined. Some authorities suggest that an intensive BP lowering below the target recommended by guidelines might be harmful in patients with AF because of the frequent coexistence with coronary artery disease, with potential risks of coronary hypoperfusion.<sup>151</sup> Because of the increasing number of these patients worldwide, controlled trials comparing different BP targets in patients with AF are urgently needed.

### Control of Hypertension in Patients Undergoing Catheter Ablation

Because of the growing number of patients with AF who undergo radiofrequency catheter ablation (RCA), the hypothesis that an intensive control of BP may prevent recurrence of AF after RCA is timely and important. Such hypothesis has been addressed in systematic reviews and meta-analyses, with discordant results.<sup>152,153</sup> In a randomized study, Parkash et al<sup>154</sup> randomized 184 patients with AF to a standard or intensive BP target (<140/90 mm Hg or <120/80 mm Hg, respectively) between 0 and 6 months before RCA and 3 months after ablation. The trial was negative because the primary end point—a composite of symptomatic AF, atrial flutter, or tachycardia lasting at least 30 seconds at >3 months after ablation—occurred in 61% of patients in both groups. However, a prespecified subgroup analysis showed a significant interaction with age ( $P=0.013$ ).<sup>154</sup> Patients >61 years of age showed a significant 42% reduction in the primary outcome in the more-intensive versus less-intensive group.<sup>154</sup> Obviously, because of the lack of differences between the 2 groups on the primary end point, these findings need to be verified in future studies.

It is possible that a more comprehensive approach to risk factors, not limited to BP, may be helpful in limiting the recurrence of AF after RCA. In a nonrandomized study of 165 patients with  $\geq 1$  cardiovascular risk factors who underwent AF ablation, the authors offered a structured and physician-directed program of risk factor management which included, in addition to BP control, weight and lipid management, glycemic control, smoking and alcohol control, and sleep-disordered breathing control.<sup>155</sup> Overall, 69 of these patients accepted the program and 96 refused. At the end of a 2-year follow-up, there was no evidence of recurrent AF, detected by periodical 7-day monitoring, in 32.9% of patients in the former group, versus 9.7% of patients in the latter group ( $P<0.001$ ).<sup>155</sup>

### Renal Sympathetic Denervation and AF Recurrence

The enthusiasm surrounding early experiences with renal sympathetic denervation (RSD) in the treatment of hypertension has been tempered after the publication of the Symplicity HTN-3 study, conducted in patients with resistant hypertension randomized to RSD or sham procedure.<sup>156</sup> Reinnervation of renal arteries, which may occur within 1 year after RSD,<sup>157</sup> has been advocated as 1 possible reason of the neutral results of this study.



Some investigations suggest that an additional potential benefit of RSD might be the limitation of AF recurrences.<sup>158</sup> Indeed, stimulation of renal sympathetic nerves may trigger AF by upregulating cardiac autonomic nervous activity and increasing dispersion of effective refractory period.<sup>158</sup> Nammias et al<sup>159</sup> reviewed several studies that demonstrated a reduced inducibility of AF for effect of RSD in animal models. Recently, in a study conducted in rabbits with HF induced by ventricular pacing, Yamada et al<sup>160</sup> showed a reduced amount of atrial fibrosis and a shortening of effective refractory period in the group of rabbits exposed to RSD compared with the rats not exposed to the procedure.

Despite promising data from animal studies, there is still limited clinical evidence to support the hypothesis that RCA combined with RSD is superior to RCA alone to prevent recurrence of AF in hypertensive patients. Two small randomized studies,<sup>161,162</sup> recently reviewed in a patient-level analysis,<sup>163</sup> showed a  $\approx 60\%$  lower risk of AF recurrence, during a 12-month follow-up, for effect of combined RCA and RSD versus catheter ablation alone (39% versus 59%) in patients with AF and resistant hypertension.<sup>163</sup> In a study conducted in patients with chronic kidney disease, the incidence of AF recurrence was 86% higher ( $P=0.025$ ) in patients exposed to RCA alone (61.5% of patients) than in those exposed to RCA combined with RSD (38.5%).<sup>164</sup>

Summing up the above studies, current evidence seems to be insufficient to recommend RCA as an additional procedure to limit recurrences of AF. Only a well-designed randomized study will provide a conclusive answer in this area.

### Impact of Hypertension on the Effects of NOACs

Because of the growing use of the NOACs in patients with AF, it is important to understand whether hypertension interferes with the effects of these drugs versus warfarin. In the RE-LY study, the benefits of dabigatran versus warfarin were not dissimilar in patients with and without hypertension.<sup>119</sup> The benefit of the lower dose of dabigatran (110 mg BID) versus warfarin on the risk of the primary RE-LY outcome bordered statistical significance in hypertensive patients (HR, 0.81; 95% CI, 0.65–1.02;  $P$  for interaction, 0.0547), whereas the benefit of the higher dose (150 mg) was statistically significant in patients with and without hypertension ( $P$  for interaction, 0.6207).<sup>165</sup> In another post hoc analysis of RE-LY, the lower dose of dabigatran was superior to warfarin in reducing the primary RE-LY outcome in AF patients with LV hypertrophy at ECG (80% of whom had coexistent hypertension), whereas the higher dose of dabigatran remained superior to warfarin regardless of LV hypertrophy.<sup>166</sup> These data suggest that the lower dose of dabigatran is superior to warfarin in reducing the risk of stroke or thromboembolism in hypertensive patients with AF and LV hypertrophy at ECG.<sup>166</sup> In the ROCKET AF study, in which about one third of patients had uncontrolled hypertension, the rate of primary outcome increased with systolic BP levels at entry, but the relative effectiveness and safety of rivaroxaban versus warfarin did not show any significant interaction with BP.<sup>167</sup> Even in this analysis, the adjusted risk of stroke and systemic embolism increased significantly with systolic BP.<sup>167</sup> In the ARISTOTLE study, where 87.5% of patients had a history of hypertension at entry, the risk of

primary outcome was higher in patients with a history of hypertension, elevated BP at entry, or elevated BP at any time point during follow-up. History of hypertension and elevated BP at entry or follow-up were associated with higher relative risk for hemorrhagic stroke. However, the relative benefit of apixaban versus warfarin was consistent in patients with and without a history of hypertension ( $P$  for interaction, 0.27) and high BP at entry ( $P$  for interaction, 0.43) or at follow-up ( $P$  for interaction, 0.97).<sup>168</sup> Also in the ENGAGE-AF study, the relative benefits of the higher (60/30 mg OD) and lower (30/15 mg OD) doses of edoxaban versus warfarin did not show any significant interactions with the hypertensive status.<sup>123</sup>

### Conclusions

Hypertension is the most important modifiable risk factor for AF. In patients with AF, management of hypertension is considered part of the holistic approach to these patients.<sup>169</sup> Although the role of hypertension as a determinant of AF and its major ischemic and hemorrhagic complications is well established, several unanswered questions remain. One, evidence is still limited from intervention studies that an intensive management of hypertension may reduce the risk of AF in subjects in sinus rhythm. Two, it is unknown whether lower BP targets may be associated with a lower risk of cerebrovascular, cardiac, and hemorrhagic complications in patients with established AF. Three, current hypertension guidelines, including the recently released American guidelines,<sup>118</sup> do not recommend more aggressive BP targets for prevention of AF, as well as in patients with established AF, although such suggestion may sound reasonable on the basis of epidemiological evidence. Four, antihypertensive drugs that inhibit the RAAS might be preferred to reduce the risk of AF, but evidence is not yet conclusive. Thus, an immense area is open to research. In a recent European Consensus Document, Lip et al<sup>44</sup> highlighted numerous settings for future studies. One, it would be important to refine the individual prediction of AF in hypertensive patients in sinus rhythm. For example, studies in large cohorts should investigate the impact of a blunted day–night BP rhythm as potential predictor of AF. Two, it is becoming increasingly important to identify, through remote ECG monitoring, the patients with silent AF who might benefit from an anticoagulant therapy because of their higher risk of stroke and death.<sup>170–172</sup> In this context, the role of hypertension as a single independent predictor of cerebrovascular events in patients with apparently lone AF should be clarified. Ad hoc designed intervention trials should also define an optimal BP target, which may balance the risk of thrombotic and hemorrhagic complications in anticoagulated patients with AF, as well as the risk of AF recurrence after catheter ablation.

### Disclosures

P. Verdecchia has received lecture fees and research funding from Boehringer-Ingelheim, Bayer, BMS-Pfizer, and Daiichi-Sankyo. The other authors report no conflicts.

### Sources of Funding

Supported, in part, by the Fondazione Umbria Cuore e Ipertensione-ONLUS, Perugia, Italy.



## Acknowledgments

We express our sincere thanks to Adolfo Aita, MD, Claudia Bartolini, MD, Marta Garofoli, MD, and Dario Turturiello, MD, for clinical data management.

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