

## Atrial Fibrillation and Hypertension

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Hypertension has a major impact on the pathogenesis, management, and prognosis of atrial fibrillation (AF; Figure).<sup>1</sup> Common consequences of hypertension, such as left ventricular (LV) hypertrophy, kidney dysfunction, cardiovascular, and cerebrovascular disorders, are recognized risk factors for AF occurrence and development of its complications.

Hypertension is very common in AF patients (Figure S1 in the [online-only Data Supplement](#)), and evidence points toward a significant contribution of high blood pressure (BP) to AF incidence<sup>2</sup> (Table S1). Patients with hypertension have 1.7-fold higher risk of developing AF than normotensive individuals, and 1 in 6 cases of AF has been attributed to hypertension.<sup>3,4</sup> Given the high incidence of AF in hypertension, one may even argue that AF is yet another manifestation of the hypertensive target organ damage.

Adequate management of hypertension is important for AF prevention, rhythm control, heart failure, and stroke prevention. The management of cardiac arrhythmias in patients with hypertension has been the topic of a recent consensus produced by the European Heart Rhythm Society and European Society of Cardiology Council on Hypertension and endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society.<sup>4,5</sup> The objective of this narrative review is to summarize current data on the epidemiology and pathophysiology of hypertension in relation to AF, their management, and ongoing research in the field.

### New BP Targets

Currently, the Eighth Joint National Committee recommends a target BP of <140/90 mmHg for people younger than 60 years.<sup>6</sup> More relaxed BP control (ie, <150/90 mmHg) can be adopted in older patients, unless they had diabetes mellitus or chronic kidney disease. The European Society of Cardiology/European Society of Hypertension guidelines recommend achieving BP <140/90 mmHg in the general population, whereas in those older than 80 years, a systolic BP (SBP) between 140 and 150 mmHg should be maintained.<sup>7</sup>

Despite evidence that pharmacological BP reduction is associated with less target organ damage, lower rates of cardiovascular disease, and improved survival, the optimal

targets for BP control are far from being certain. The question of what is the optimal target BP has been addressed in numerous studies, and a J-shaped relationship between BP reduction and outcomes remains controversial. For example, the optimal BP for high-risk populations, such as the elderly or those with chronic kidney disease, requires further research.<sup>8</sup> Although AF patients were not specifically studied, they would be high risk from the cardiovascular perspective, and some insights from recent trials may be of interest.

There were enthusiasm and criticism<sup>9</sup> with respect to the recent SPRINT trial (Systolic Blood Pressure Intervention Trial).<sup>10</sup> This trial included high-risk patients determined by the preexisting cardiovascular disease, chronic kidney disease, aged >75 years, or a Framingham 10-year cardiovascular risk score of  $\geq 15\%$ .<sup>10</sup> The lower rate of primary end point in the intensive treatment arm was largely driven by a reduction of heart failure–related hospitalizations, and no myocardial infarction and stroke reduction was observed.

The SPRINT findings differed from trials performed earlier, for example, SPS3 (Secondary Prevention of Small Subcortical Strokes)<sup>11</sup> and HOT (Hypertension Optimal Treatment Randomized Trial),<sup>12</sup> which did not find intensive BP treatment to be beneficial compared with standard therapy, except for a few prespecified subgroups, such as diabetic patients in the HOT trial. The recent HOPE-3 trial (Heart Outcomes Prevention Evaluation) included untreated intermediate-risk patients and found reductions in major cardiovascular events in patients with baseline SBP >143 mmHg as a result of an average 6/3 (systolic/diastolic) mmHg reduction in BP, but no further reduction in risk was achieved with lower BP.<sup>13</sup>

Nonetheless, intensive treatment (SBP target <120 mmHg) in SPRINT showed 25% reduction in the risk of the primary composite outcome of nonfatal myocardial infarction, stroke, acute decompensated heart failure, and death from cardiovascular causes. Importantly, there was a significant reduction in cardiovascular mortality (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.38–0.85) compared with the standard treatment.<sup>10</sup> Moreover, the SPRINT-Senior substudy with participants aged 75 years or older showed consistent efficacy for both the primary (HR, 0.66; 95% CI, 0.51–0.85) and

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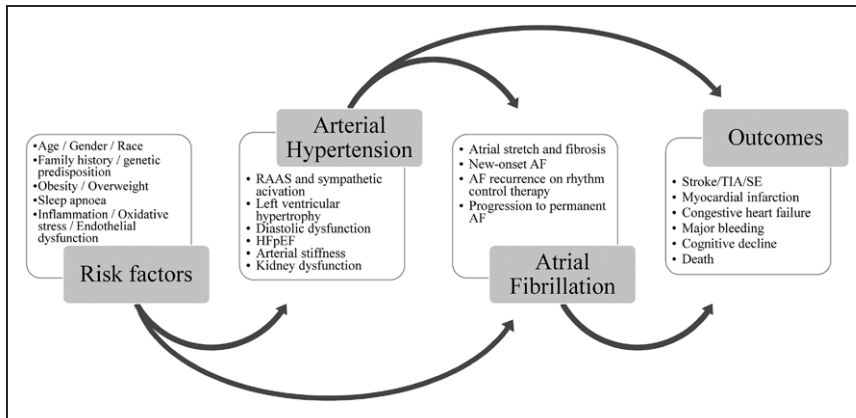
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**Figure.** Hypertension and atrial fibrillation (AF) axis in the cardiovascular disease continuum. HFpEF indicates heart failure with preserved ejection fraction; RAAS, renin-angiotensin-aldosterone system; SE, systemic embolism; and TIA, transient ischemic attack.

secondary (HR, 0.67; 95% CI, 0.49–0.91) end points without a significant increase in rate of therapy-related adverse events, even though one third of the studied population was considered as frail at study entry.<sup>14</sup>

### Implications of Low BP Targets in AF

Pathophysiologically lower BPs results in less strain on the LV, and, thus, more aggressive BP control may have benefits in terms of LV hypertrophy, myocardial fibrosis, diastolic dysfunction and retrograde atrial stretching and structural remodeling. The latter serves as substrate for AF development and persistence, and it progresses as a result of interaction of inflammation, oxidative stress, and renin-angiotensin-aldosterone activation, as well as with aging.<sup>1,15</sup>

Better BP control improved survival in AF patients. In the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy), there was no significant difference in vascular and all-cause death between patients with or without hypertension.<sup>16</sup> In the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) cohort, a diagnosis of hypertension was associated with lower risk of all-cause death (HR, 0.73; 95% CI, 0.61–0.88) and a nonsignificant trend toward lower cardiovascular mortality (HR, 0.81; 95% CI, 0.63–1.05).<sup>17</sup> In the ROCKET AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), lower screening SBP was associated with a higher risk of vascular death (HR, 0.95; 95% CI, 0.90–0.99).<sup>18</sup> All-cause mortality increased with decreasing screening SBP levels among patients with SBP <115 mmHg, whereas in those with SBP of ≥115 mmHg there was no difference in mortality risk.<sup>18</sup> Of note, higher diastolic BP was associated with lower all-cause mortality (HR, 0.92; 95% CI, 0.87–0.98).<sup>19</sup>

Thus, the available data do not advocate lowering of BP in AF patients below the recommended targets. Furthermore, both AF and hypertension are often accompanied by coronary heart disease,<sup>20</sup> and excessive BP reduction may result in clinically relevant coronary underperfusion. In the CLARIFY registry (Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease), SBP <120 mmHg (HR, 1.56; 95% CI, 1.36–1.81) and diastolic BP <70 mmHg (HR, 1.41; 95% CI, 1.24–1.61) were associated with a

higher risk of primary outcome of the composite of cardiovascular death, myocardial infarction, or stroke.<sup>21</sup>

### Subclinical Target Organ Damage and Risk of AF

Development of target organ damage in patients with poorly controlled hypertension puts them at higher risk of development of AF. Hypertension not only results in LV hypertrophy but also in arterial stiffening. Increased pressure pulsatility and pulse wave velocity further promote LV hypertrophy, diastolic dysfunction, and increased LV filling pressure, and, ultimately, left atrial (LA) stretch.<sup>22,23</sup>

The presence of LV hypertrophy and increased arterial stiffness in hypertensive patients have been associated with higher incidence of AF.<sup>24</sup> The Cardiovascular Health Study reported a 50% increase in risk of new-onset AF in individuals with electrocardiographic signs of LV hypertrophy and a 39% increase in those with LV hypertrophy confirmed by echocardiography, independently of other risk factors for AF.<sup>25</sup>

In the Framingham Heart Study, abnormal arterial stiffness and endothelial function were independently associated with increased risk of AF, for increased augmentation index (HR, 1.15; 95% CI, 1.02–1.29), for elevated central pulse pressure (HR, 1.14; 95% CI, 1.02–1.28), and for impaired flow-mediated arterial dilation (HR, 0.79; 95% CI, 0.66–0.94).<sup>26</sup> In the pooled AF cohort of 25767 participants from the Atherosclerosis Risk in Communities Study, MESA (Multi-Ethnic Study of Atherosclerosis), and the Rotterdam Study, higher pulse wave velocity was associated with increased AF incidence (HR, 1.18; 95% CI, 1.06–1.32 per quintile increase), although the association was reflective of poor BP control in patients with high arterial stiffness.<sup>27</sup>

The presence of the target organ damage in hypertensive people with AF has a prognostic implication. For example, in AF patients with hypertension and coronary heart disease, high pulse wave velocity independently predicted future cardiovascular events.<sup>28</sup>

Once the hypertension occurred, it predisposes to AF, even if BP control improves later. In the Framingham Heart Study, over 15-year follow-up, more effective pharmacological reduction of BP has not translated into a noticeable reduction in AF occurrence in hypertensive patients (AF risk in hypertensive versus nonhypertensive patients; HR, 2.05; 95% CI, 1.24–3.37 if BP reduced and HR, 1.95; 95% CI, 1.08–3.49

if BP increased).<sup>29</sup> Among all patterns, patients with baseline hypertension had 2-fold higher risk of AF development, irrespectively whether SBP increased or decreased during follow-up.<sup>29</sup> No association with AF incidence was found in relation to diastolic BP.<sup>29</sup> The data indicate that prompt BP control before remodeling occurs may be essential to prevent hypertension-related AF.

There is growing evidence that even high normal BP (ie, prehypertension) confers an increased risk of incident AF. In one study, both SBP  $\geq 140$  mmHg and SBP ranging between 128 and 138 mmHg were associated with new-onset AF, independent of cardiovascular disease (HR, 1.84; 95% CI, 1.07–3.19) and diabetes mellitus (HR, 1.98; 95% CI, 1.22–3.27).<sup>30</sup> In the LIFE study (Losartan Intervention for End Point Reduction in Hypertension), there was a lower risk of incident AF in patients with baseline on-treatment SBP  $\leq 130$  mmHg (HR, 0.60; 95% CI, 0.45–0.82) and SBP 131 to 141 mmHg (HR, 0.76; 95% CI, 0.62–0.93), than in those with SBP  $\geq 141$  mmHg.<sup>31</sup>

These data on the close relationship between hypertension and incident AF led to incorporation of hypertension as a risk factor into various clinical scores to assess the probability of incident AF. Hypertension is also a risk factor for AF recurrence, and where rhythm control is the chosen strategy for paroxysmal or persistent AF, effective hypertension management prolongs the AF-free period.<sup>1</sup>

### Effect of Antihypertensive Treatment on Diastolic Dysfunction and Arterial Stiffness

Good BP control reduces the progression of arterial stiffness and LV overload and hypertrophy, irrespectively of class of antihypertensive agents used.<sup>32</sup> LV hypertrophy contributes to diastolic dysfunction, another independent risk factor for incident AF. Diastolic dysfunction leads to heart failure with preserved ejection fraction commonly observed in AF. Thus, antihypertensive treatment to improve diastolic function is deemed appropriate; however, diastolic dysfunction can only partly reversed by reduction in cardiomyocyte hypertrophy, whereas the interstitial fibrosis remains an irreversible factor of diastolic dysfunction with an impact on LA and LV filling pressures.

Antihypertensive treatment in the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) resulted in regression of LV hypertrophy; however, early mitral inflow velocity and mitral annular early diastolic velocity ( $E/e'$ ) ratio did not change.<sup>33</sup> In a post hoc analysis of the ASCOT trial, a 1 mmHg increase in SBP was associated with 2% higher baseline NT-proBNP (N-terminal pro-B-type natriuretic peptide), and this predicted adverse cardiovascular events with a 22% net reclassification improvement of cardiovascular risk.<sup>34</sup> Indeed, biomarkers, such as natriuretic peptides, allow identification of conditions related to LV volume overload, including those related to hypertension (eg, LV hypertrophy, diastolic dysfunction, and heart failure with preserved ejection fraction).

From this perspective, early and perhaps more aggressive BP control is anticipated to be better tolerated by younger patients, being essential to prevent structural remodeling and substrate formation for AF development.

Activation of the renin–angiotensin system (RAS) is closely related to cardiovascular remodeling in both

hypertension and AF. These undesirable effects are mediated by oxidative stress, inflammation, tissue hypoxia, endothelial dysfunction, associated with RAS activation, and implicated in cardiac hypertrophy and fibrosis.<sup>15</sup> In theory, inhibition of RAS (eg, via angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists) should be helpful in for prevention and management of AF (so-called upstream therapy), and particularly so in those with hypertension. However, data to support this mainly comes from post hoc analyses, and they failed to provide consistent evidence for AF prevention by such treatments.<sup>35,36</sup> Accordingly, current guidelines only consider RAS inhibitors in patients with LV hypertrophy and LV dysfunction. More detailed discussion of perspective of aldosterone as a therapeutic target is discussed below.

### Balancing Stroke and Bleeding Risk in Hypertension and AF

Hypertension is an independent risk factor for stroke, increasing the risk  $\leq 3$ -fold.<sup>37</sup> In the systematic review by the Stroke Risk in AF Group, history of hypertension doubled the risk of stroke (relative risk, 2.0; 95% CI, 1.6–2.5).<sup>38</sup> In fact, hypertension was the strongest risk factor for recurrent stroke. More recent large observational studies, such as the Swedish Atrial Fibrillation cohort analysis (n=182678), have confirmed the major independent role of hypertension in prognosis in AF.<sup>39</sup> The findings are consistent with data from clinical trial cohorts, such as the SPORTIF trial (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation) that shows increased stroke rates in patients with SBP  $> 140$  mmHg.<sup>40</sup>

In a recent meta-analysis of hypertensive patients, antihypertensive treatment reduced the risk of recurrent stroke by 27%, disabling or fatal stroke by 29%, and cardiovascular death by 15%.<sup>41</sup> When meta-regression was applied, SBP reduction was significantly related to the lower risk of recurrent stroke, myocardial infarction, all-cause, and cardiovascular death.<sup>41</sup> Although better-controlled BP reduces the stroke risk, a prolong history of prior uncontrolled hypertension may lead to severe cerebral vascular changes, which may increased the stroke risk in case of excessive BP reduction. Of note, specific data in regard to patients with both hypertension and AF are lacking.

High BP also predisposes to bleeding, especially intracranial hemorrhage, in AF.<sup>42,43</sup> In the BAT study (Bleeding With Antithrombotic Therapy) of 4009 patients with cardiovascular or cerebrovascular diseases, both high SBP and diastolic BP were related to a higher incidence of intracranial hemorrhage.<sup>44</sup> Of interest, in the study, the cutoff BP for prediction of intracranial hemorrhage was  $\geq 130/81$  mmHg, the level often considered as high normal. Hypertensive patients also have more bleeding complications after percutaneous coronary intervention.<sup>45</sup> Even in hypertensives without AF or any antithrombotic therapy, for example, in survivors of intracranial hemorrhage of any cause, inadequate BP control was strongly associated with about 4-fold higher risk of the hemorrhage recurrence.<sup>46</sup>

Important data on the role of hypertension in AF have been provided by recent clinical trials. In the RE-LY trial (dabigatran versus warfarin), more major bleeds (but not intracranial hemorrhage) were seen in hypertensive patients

(3.39% versus 2.76% in those without hypertension). No impact of hypertension history on stroke and systemic embolism outcomes was observed, perhaps explained by a higher prevalence of stage I hypertension and high-quality BP control during the trial follow-up period.<sup>16</sup> When BP was analyzed as a continuous variable, increasing SBP and mean BP were associated with higher risk of stroke observed with every 10 mmHg BP increase.<sup>16</sup> Similarly, in an ancillary study from the ROCKET AF trial (rivaroxaban versus warfarin), the risk of stroke or systemic embolism increased by 7% for every 10 mmHg increase in screening SBP.<sup>2,18</sup> The ARISTOTLE trial (apixaban versus warfarin) also confirmed the importance of good BP control in AF. Elevated BP at any time during the trial increased risk of stroke and systemic embolism (HR, 1.53; 95% CI, 1.25–1.86), hemorrhagic stroke (HR, 1.85; 95% CI, 1.26–2.72), and ischemic stroke (HR, 1.50; 95% CI, 1.18–1.90).<sup>17</sup> The trial also highlighted the high frequency of suboptimal BP control.<sup>17</sup>

Hypertension is included into risk stratification scores in AF, for stroke (eg, CHA<sub>2</sub>DS<sub>2</sub>-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or systemic embolism, vascular disease, age 65–74 years, and female sex) and bleeding (eg, HAS-BLED: hypertension, abnormal renal or liver function, stroke, bleeding tendency or predisposition, labile international normalized ratio, age >65 years or frailty, drugs concomitantly or alcohol excess) assessment tools.<sup>1,42</sup>

When AF is diagnosed, the first step in patient management should be to define low stroke risk patients who do not need antithrombotic treatment, following which stroke prevention should be considered for those with ≥1 stroke risk factor—and effective stroke prevention means oral anticoagulation therapy.<sup>47</sup> Because hypertension scores 1 point as a stroke risk factor on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, such patients merit consideration of stroke prevention with anticoagulation, as well as good BP control.

However, many patients with AF are asymptomatic, and stroke can be the first manifestation of the arrhythmia. As many as 10% of cases of strokes present with previously unknown AF, and the frequency of AF detection in cryptogenic stroke increases with longer duration of ECG monitoring.<sup>48,49</sup> Patients with asymptomatic or atypical AF clinical presentation are more likely to have higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score that results in 3-fold higher risk of cerebrovascular events and increased cardiovascular and all-cause mortality.<sup>50</sup> Another large cohort of incidentally detected AF found an adjusted cumulative stroke incidence of 3.9% in nonanticoagulated patients versus 1.3% in those receiving warfarin.<sup>51</sup> The adjusted mortality rate in these untreated patients was also higher than in anticoagulated AF patients (7.2% versus 4.2%, respectively).<sup>51</sup>

The above data underscore the importance of timely detection of AF, but the frequency, setting, and target population for screening are debatable. Thus far, opportunistic screening for AF by pulse taking or ECG rhythm strips is recommended in patients older than 65 years, but more frequent (systematic) ECG screening may be considered in selected patients, for example, those aged >75 years or at high stroke risk.<sup>52</sup> Given that hypertension is a major stroke risk factor, opportunistic

screening should be done in hypertensive patients. Indeed, AF detection may be improved using oscillometric BP monitors with AF detection algorithms.<sup>48</sup>

Despite the clear association between hypertension and increases risks of stroke and bleeding in AF, there have been no randomized trials specifically designed to establish optimal BP targets and treatment strategies in hypertensive patients with AF.

### BP Variability

Excessive BP variability predisposes to stroke beyond the average BP. For example, in the population of the LIFE study, high on-treatment visit-to-visit BP variability predicted the composite end point of cardiovascular death, nonfatal myocardial infarction, or stroke at 24 months, but not the occurrence of myocardial infarction alone or development of target organ damage.<sup>53</sup>

The excess in strokes related to high BP variability is thought to be partly attributable to increased AF burden. A systematic review of 14 large randomized controlled trials reporting new-onset AF, excluding studies in heart failure and acute myocardial infarction, did not find any significant link between visit-to-visit BP variability and risk of new-onset AF.<sup>54</sup> However, detection of AF remains a problem and a possibility of silent AF contributing to strokes in people with high BP variability cannot be excluded.

### Aldosterone in Hypertension and AF

Activation of RAS results in increased synthesis of aldosterone, an established treatment target for hypertension and a promising target for management of heart failure with preserved ejection fraction and AF. Adverse effects of aldosterone are particularly apparent in primary hyperaldosteronism, but high normal levels persistent for long time promote myocardial fibrosis and vascular stiffening.<sup>15</sup>

Excessive aldosterone release results in arterial stiffening, impairment of endothelium-dependent vasodilation, smooth muscle cells contraction, enhanced accumulation of connective tissue fibers in the vascular wall, and promotion of vascular inflammation and oxidative stress. In contrast, downregulation of mineralocorticoid signaling prevents diastolic dysfunction, profibrotic, and proinflammatory effects to the cardiovascular system. Well-recognized detrimental cardiovascular effects of angiotensin II are partly dependent on signaling via mineralocorticoid receptors.<sup>55,56</sup> Also aldosterone signaling requires functional angiotensin II receptors, thus providing synergistic effects. Apart from structural effects, increased exposure to aldosterone also disturbs electric properties of myocardium via upregulation of calcium currents and induction of sarcoplasmic reticulum calcium overload.<sup>57,58</sup>

In the general population, increased plasma aldosterone levels have been associated with hypertension, AF occurrence, obesity, concentric LV hypertrophy, and diastolic dysfunction.<sup>59,60</sup> Although aldosterone promotes myocardial remodeling, predisposing to AF, the development of AF further increases aldosterone levels.<sup>58</sup> Cardiac expression of mineralocorticoid receptors is increased in AF, and their density correlates with AF duration and aldosterone levels.<sup>58</sup>

## Mineralocorticoid Receptor Antagonists in Hypertension and AF

Accumulating evidence encourages wider incorporation of mineralocorticoid receptor antagonists (MRA) into the management of hypertension. In the randomized PATHWAY2 trial (Optimum Treatment for Drug-Resistant Hypertension, NCT02369081), addition of spironolactone to the ACE inhibitor/angiotensin receptor blocker, calcium channel blocker, and thiazide-like diuretic resulted in a significantly greater reduction in SBP compared with addition of bisoprolol, doxazosin, or placebo.<sup>61</sup> Home and office SBPs were reduced by mean 12.8 and 20.7 mm Hg, respectively.<sup>61</sup>

Several trials have tested the effectiveness of spironolactone in heart failure with preserved ejection fraction. Treatment with spironolactone significantly improved diastolic function in the Aldo-DHF trial (Aldosterone Receptor Blockade in Diastolic Heart Failure, ISRCTN94726526), although this has not translated into significant changes in exercise tolerance or quality of life.<sup>62</sup> In the TOPCAT trial (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function, NCT00094302), there was no significant effect of spironolactone on the composite primary outcome of cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure in the overall population. However, there were significant regional differences in the trial outcomes, and American patients showed significant reductions in the primary outcome (HR, 0.82; 95% CI, 0.69–0.98).<sup>63,64</sup> Overall, the data on use of spironolactone in heart failure with preserved ejection fraction are inconclusive. Of note, the Aldo-DHF and TOPCAT trials mostly included patients with background hypertensive with relatively few AF patients included.

What are implications of therapy with MRA in AF? Aldosterone promotes both atrial and ventricular fibrosis and LV remodeling leading to elevation of LV filling pressure, atrial stretching and further fibrosis. This vicious circle results in AF and heart failure with preserved ejection fraction.<sup>15</sup> In a meta-analysis of 5 randomized controlled trials and 9 observational cohorts (included 5332 patients), use of MRA reduced AF occurrence: 8.5% versus 18.6%, driven by a reduction in both new-onset and recurrent AF.<sup>65</sup> The conclusions are consistent with another meta-analysis, which also where benefits of MRAs were evident in heart failure settings.<sup>66</sup>

The capacity of an MRA, spironolactone to improve exercise tolerance, quality of life, and diastolic function specifically in patients with AF is being tested the ongoing randomized controlled IMPRESS-AF trial (Improved Exercise Tolerance in Heart Failure With Preserved Ejection Fraction by Spironolactone on Myocardial Fibrosis in Atrial Fibrillation, NCT02673463).<sup>67</sup> The study has randomized 250 patients with permanent AF and preserved ejection fraction to receive spironolactone with placebo for 2 years.

### Renal Sympathetic Denervation: For Hypertension, AF, or Both?

Results from the Symplicity HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension)<sup>68</sup> and PATHWAY2 trials results<sup>61</sup> would limit use of renal denervation in hypertension management. In the placebo arms of hypertension, trials

revealed  $\approx$ 6 mm Hg fall in nonresistant patients and 9 mm Hg in patients with resistant hypertension.<sup>69</sup> Animal experiments show profound inhibition of renal sympathetic nerve activity and no response to electric stimulation immediately after a complete ablation, but reinnervation was already evident at 5.5 months after the procedure.<sup>70</sup> Reinnervation may explain lack of long-term effectiveness of renal denervation, although other still poorly understood mechanisms may be involved.<sup>70</sup>

Is renal denervation of importance with respect to AF? Fluctuations in both sympathetic and parasympathetic discharge contribute to electric remodeling in AF via a network of sympathetic and parasympathetic fibers. Sympathetic activation leads to cellular calcium overload and delayed afterdepolarizations.<sup>1</sup> Data from small animal experiments and human studies are conflicting but suggest beneficial electrophysiological changes in the LA, as well as lower rate of AF recurrence after catheter-based renal denervation.<sup>71,72</sup> The clinical use in individuals with hypertension and AF is yet to be established.

### Impact of Physical Activity and Obesity

Multiple studies have addressed effect of physical activity on the risk of hypertension. A meta-analysis of these studies showed benefits of both high intensity (relative risk, 0.81; 95% CI, 0.76–0.85) and moderate intensity (relative risk, 0.89; 95% CI, 0.85–0.94) recreational physical activity compared with low activity; however, benefits were not observed for occupational physical activity.<sup>73</sup>

Despite obvious beneficial effect of physical activity on hypertension, the relationship between physical activity and AF risk is more complex. High occupational physical activity confers an increased risk of AF compared with recreational activities.<sup>74</sup> For recreational activity, the association appears to be J shaped, that is, moderate physical activity reduces risk of AF development, but the benefits are lost at high activity.<sup>75</sup> In the MESA cohort, no association was found between vigorous physical activity or total intentional exercise and incident AF, but in a subgroup of patients who reported no vigorous activity, total intentional exercise was associated with a lower AF incidence.<sup>76</sup>

When organized in the form of exercise program tailored for age and physical ability, as was done in the CARDIO-FIT study (Impact of Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation), patients who achieved higher cardiorespiratory fitness were less likely to develop recurrent AF, although low cardiorespiratory fitness was an independent predictor of AF recurrence (HR, 2.75; 95% CI, 1.61–4.68).<sup>77</sup> Physical activity not only improved rhythm control but also reduced rates of cardiovascular death, all-cause mortality, and thromboembolic events.<sup>78</sup> In contrast, a sedentary lifestyle is linked to weight gain and obesity. Obesity is strongly linked to cardiometabolic comorbidities including hypertension, diabetes mellitus, and obstructive sleep apnea.<sup>79,80</sup> Similarly, increasing body mass index is related to increased risk of AF.<sup>2</sup>

Interventions to reduce body weight have numerous positive health effects in AF patients, including BP reduction, decrease in glucose, total cholesterol, low-density cholesterol, and triglycerides, inhibition of inflammation (eg, reduction in C-reactive protein levels), attenuation of pathological LA

remodeling (ie, decrease in LA volume) and LV remodeling (reduction of LV hypertrophy and E/e' ratio). The most prominent effects were seen in patients with  $\geq 10\%$  weight reduction. In the population of 1415 consecutive AF patients from the LEGACY (Long-Term Follow-Up Study), sustained weight loss translated into lower AF recurrence rates.<sup>81</sup>

## Conclusions

Epidemiological evidence links arterial hypertension with incident AF, and increased BP is common in AF patients. Apart from the epidemiological similarities, hypertension and AF share many mechanisms of pathogenesis. Hypertension is a modifiable risk factor and, therefore, carries a potential for AF prevention, lowering AF recurrence rates when rhythm control strategy is applied, and avoiding the debilitating complications, such as stroke. In the absence of new antihypertensive and antiarrhythmic drugs in recent years, efforts have been made to identify new mechanisms, improve management of risk factors, and tailor treatment in particular clinical scenarios. Nonetheless, many questions still need to be answered, like as optimal thresholds for BP, effectiveness of the renal denervation in patients who receive ablation for AF, impact of BP lowering on diastolic dysfunction, heart failure with preserved ejection fraction in people with AF. The recent shifts in hypertension management have been driven by hard end points rather than close attention to risk of AF in people with high BP. Nonetheless, it is uncertain whether recent evidence will lead to changes in BP targets for AF patients, and if this will affect the course of the arrhythmia.

## Disclosures

G.Y.H. Lip is a consultant for Bayer/Janssen, BMS (Bristol-Myers Squibb)/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo; and is a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. No personal fees received. The other authors report no conflicts.

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## Atrial Fibrillation and Hypertension

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**Recent Advances: Atrial Fibrillation and Hypertension**

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Supplemental References

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Supplemental Figure S1

## Supplemental References:

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**Supplemental Table S1.** Overview of recent studies on risk of incident AF in hypertension

Reference	Data source	Number of patients without AF	New-onset AF (%)	Hypertension or antihypertensive treatment (%)	Follow-up (yrs)	Risk for incident AF*
Prospective cohort studies						
Alonso et al, 2013 <sup>1</sup>	CHARGE-AF Consortium (ARIC, CHS, and FHS)	18556	6.4	FHS 29.6 CHS whites 43.8 CHS AA 61.5 ARIC whites 29.6 ARIC AA 58.4	Different between cohorts	1.20 (1.13-1.29) per 20 mmHg increase in SBP 0.91 (0.85-0.97) per 10 mmHg increase in DBP 1.41 (1.24-1.59) for AHT
Chamberlain et al, 2011 <sup>2</sup>	ARIC	14546	3.5	30.6	10	Reference SBP 100-<120 mmHg 1.42 (1.15–1.76) for SBP 120-<140 mmHg 2.16 (1.67–2.79) for SBP 140-<160 mmHg 2.63 (1.83–3.78) for SBP ≥160 mmHg Reference DBP 70-<80 mmHg 1.53 (1.06–2.22) for DBP 90-<100 mmHg 2.02 (1.20–3.41) for DBP ≥100 mmHg 2.55 (2.13–3.04) for AHT
Conen et al, 2009 <sup>3</sup>	WHS	34221	1.9	16.8 with SBP ≥140 mmHg 4.8 with DBP ≥90 mmHg	12.4 (median)	Reference SBP <120 mmHg 1.43 (1.09–1.87) for SBP 130-139 mmHg 1.78 (1.34–2.38) for SBP 140-159 mmHg 2.29 (1.45–3.63) for SBP ≥160
Emdin et al, 2017 <sup>4</sup>	Primary care database, United Kingdom (CPRD)	4269194	3.0	10.1 at baseline 29.0 during follow-up	6.9 (median)	1.21 (1.19-1.22) per 20 mmHg increase in SBP

Grundvold et al, 2012 <sup>5</sup>	Norwegian cardiovascular health survey	2014	5.1 per 1000 PY	Upper normal range of BP	30 (median)	1.22 (1.10–1.42) per SD (18 mmHg) increase in SBP 1.25 (1.11–1.43) per SD (10 mmHg) increase in DBP
Kokubo et al, 2015 <sup>6</sup>	Suita study	6906	3.7	HTN 29.1	12.8	1.24 (1.06–1.47) per 20 mmHg increase in SBP
Marcus et al, 2010 <sup>7</sup>	ARIC CHS	CHS 5220 ARIC 14386	CHS 22.5 ARIC 7.4	CHS 58.5 ARIC 33.7	CHS 10 ARIC 16 (median)	CHS 1.50 (1.33–1.70) for HTN ARIC 2.11 (1.87–2.38) for HTN
Mitchell et al, 2007 <sup>8</sup>	FHS	5331	13.1	22.6	16 (mean)	1.14 (1.04-1.25) per 20 mmHg increase in SBP 1.26 (1.12-1.43) per 20 mmHg increase in PP
Nyrnes et al, 2012 <sup>9</sup>	Tromso Study	22815	3.6	HTN 28.4 AHT 5.4	11.1 (mean)	1.98 (1.46-2.69) for HTN in females 1.40 (1.13-1.74) for HTN in males
O'Neal et al, 2015 <sup>10</sup>	MESA	5311	3.4	49	5.3 (median)	1.8 (1.004-3.2) for pre-HTN 2.6 (1.6-4.4) for HTN
Roetker, et al, 2014 <sup>11</sup>	MESA	6630	5.9 per 1000 PY	No incident AF group: 36 Incident AF: 56	7.8 (mean)	1.21 (1.09-1.36) per 21.5 mmHg increase in SBP 1.03 (0.91-1.16) per 10.3 mmHg increase in DBP 1.13 (1.01-1.27) per 12.6 mmHg increase in MAP 1.28 (1.14-1.44) per 17.2 mmHg increase in PP
Rosengren et al, 2009 <sup>12</sup>	PPS, intervention group	6903	18.2	5.0-5.9 in various study subgroups	2 (median)	Reference SBP <133 mmHg 1.40 (1.19–1.64) for SBP 146-161 mmHg 1.73 (1.48–2.03) for SBP >161 mmHg
Schnabel et al, 2009 <sup>13</sup>	FHS	4764	9.6	24	10 (max.)	1.21 (1.11–1.33) per SD increase in SBP 1.25 (1.14–1.36) per SD increase in PP 1.80 (1.48–2.18) for AHT
Smith et al, 2009 <sup>14</sup>	Malmo Diet and Cancer study (MDCS)	30129	4.7	HTN 68.1 in males, 56.3 in females	11.2 (mean)	1.78 (1.48–2.14) for HTN in males 1.74 (1.42–2.13) for HTN in females

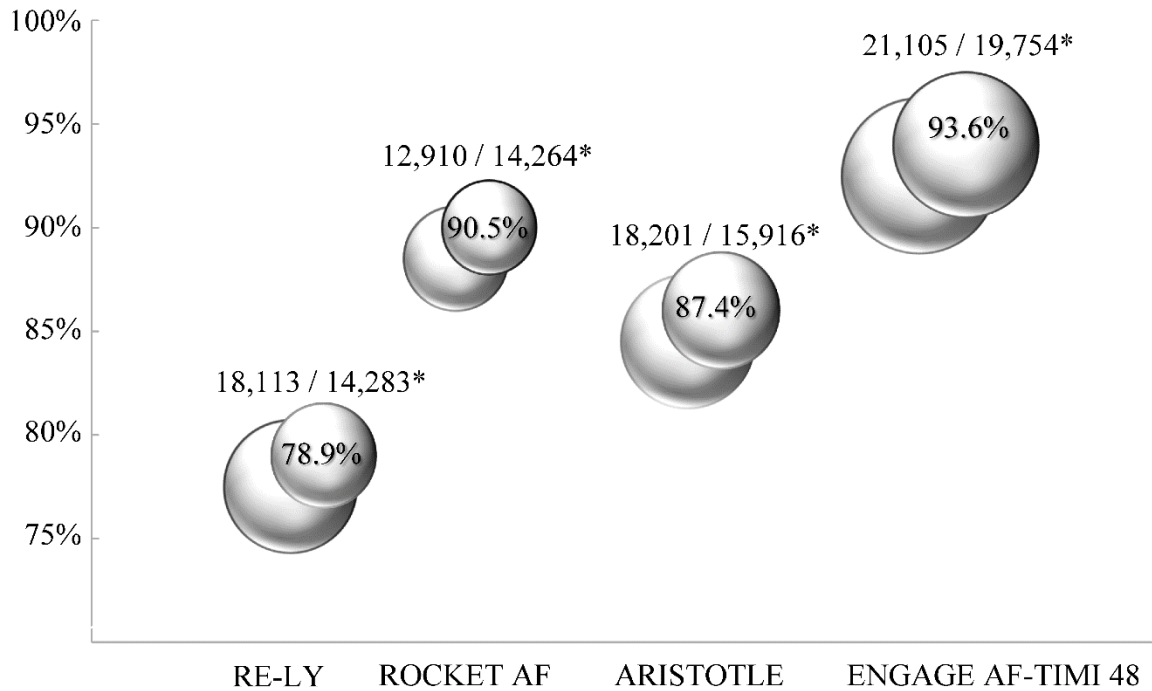
				AHT 17.3		
Son et al, 2016 <sup>15</sup>	National Health Insurance Service database, South Korea	206013	2.87 per 1000 PY	21.2	6	1.67 (1.54-1.81) for HTN
Vermond et al, 2015 <sup>16</sup>	PREVEND	8265	3.2	54 in Incident AF group 26 in AF-free group	9.7 (mean)	1.11 (1.01–1.22) per 10 mmHg increase in SBP 2.14 (1.43–3.20) for AHT
Post-hoc analysis of RCT cohorts						
Okin et al, 2015 <sup>17</sup>	LIFE	8831	7.9	100	4.6 (mean)	Reference SBP $\geq$ 142 mmHg 0.60 (0.45–0.82) for SBP $\leq$ 130 mmHg 0.76 (0.62–0.93) for SBP 131-141 mmHg 0.87 (0.83–0.91) per 10 mmHg decrease in SBP
Verdecchia et al, 2012 <sup>18</sup>	ONTARGET TRANSCEND	30424	15.1 per 1000 PY	70	4.7 (median)	1.34 (1.21–1.49) for HTN

\* expressed as hazard ratio and 95% confidence interval from multivariate models fully adjusted for possible confounders

AA, African-Americans; AGES, Age, Gene and Environment Susceptibility - Reykjavik study; AHT, antihypertensive treatment; ARIC, Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; CPRD, Clinical Practice Research Datalink; DBP, diastolic blood pressure; FHS, Framingham Heart Study; HTN, hypertension; MAP, mean arterial pressure; MESA, Multi-Ethnic Study of Atherosclerosis; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; PP, pulse pressure; PPS, Primary Prevention

Study; PREVEND, Prevention of Renal and Vascular End-stage Disease; PY, person-years; SBP, systolic blood pressure; SD, standard deviation; TRANSCEND, Telmisartan Randomized Assessment Study in ACE intolerant subjects with cardiovascular Disease; WHS, Women's Health Study





**Supplemental Figure S1.** Prevalence of hypertension in phase III clinical trials with the non-vitamin K oral anticoagulants versus warfarin for stroke prevention in AF<sup>19-22</sup>

\* total number of patients / number of patients with hypertension according to trial inclusion criteria

ARISTOTLE, Apixaban for Reduction In SStroke and Other ThromboemboLic Events in atrial fibrillation; ENGAGE AF – TIMI 48 Effective aNticoaGulation with factor Xa next GEneration in Atrial Fibrillation – Thrombolysis In Myocardial Infarction 48; 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