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## Why is atrial fibrillation so frequent in hypertensive patients?

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**Key words:** atrial fibrillation; hypertension; epidemiology; atrial cardiomyopathy

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Atrial fibrillation (AF) and hypertension have a close relationship, where the bidirectional link is complex and encompasses both epidemiological and pathophysiological aspects.

Hypertension is the most common, independent, and potentially modifiable cardiovascular risk factor in AF patients, being present in more than 70% of individuals analyzed in large epidemiological studies, AF clinical trials and in the most recent AF real-world registries<sup>1,2</sup>.

First of all, from an epidemiological point of view, the incidence and prevalence of these two clinical conditions increase with age. Indeed, given the shift of population's average age structure, analysis of future trends clearly has shown that both AF and hypertension can be considered an epidemic global health problems<sup>1,3</sup>. However, it should be highlighted that other epidemiological links are also present. Hypertension and AF are similarly associated with several clinical conditions or risk factors such as coronary artery disease, obstructive sleep apnea, chronic kidney disease, diabetes, obesity, excess alcohol consumption, physical inactivity and many others<sup>3</sup>.

In patients with hypertension, the risk of developing new-onset AF is almost doubled and notably, this risk is increased from high-normal blood pressure (BP) values (130-139/80-89 mmHg)<sup>4</sup>.

Despite several studies that described a direct and linear relation between BP levels and the risk of AF, some uncertainties still remain. It has not been completely clarified if in the high-risk population (patients with coronary artery disease, previous stroke, extensive peripheral artery disease, etc.), the shape of this relationship persists linear or if there is a threshold level above which the risk of incidence AF increases dramatically. Therefore, one practical question naturally arises: What are the optimal targets for BP control aimed at reducing the risk of new-onset AF? There is a general consensus that a strict BP control can reduce the risk of AF, but this goal is not always easily achieved in clinical practice. Nevertheless, in a population-based, case-control study, it has been observed that among hypertensive patients, both very low (systolic BP <120 mmHg) and uncontrolled elevated systolic BP (but not a systolic BP ranging from 130 to 149 mmHg) were associated with an increased risk of incident AF resulting in a J-shaped relationship between the achieved BP values and the presence of AF.<sup>5</sup>

Besides the well-known epidemiological links, AF and hypertension share numerous risk factors and pathophysiological mechanisms that can explain their intimate interplay (Figure).

For several years, the study of the pathophysiology of cardiomyopathies has mostly focused on the alterations of the ventricles downplaying the importance of the atria in the cardiac function. There is growing evidence now, that the atria play an active role in the pathophysiology of cardiomyopathies and any atrial pathologies have a considerable impact on cardiac performance.

This has led to the recently proposed concept of atrial cardiomyopathy, defined as “any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations”.<sup>6</sup> From a strict hemodynamic standpoint, long-term exposure to elevated BP levels induces arterial stiffness, left ventricular (LV) hypertrophy and increases LV stiffness resulting in an impairment of LV diastolic function<sup>6</sup>. As a consequence, there is an increase in the left atrial (LA) pressure, which causes atrial overload, LA stretch and finally LA remodeling and dysfunction. In this sense, AF could be considered as a manifestation of hypertensive heart disease<sup>6</sup>. Also screening for primary aldosteronism is now recommended in patients with hypertension who develop AF in the absence of obvious structural heart changes or other risk factors.<sup>7</sup> The resulting structural and functional modifications greatly change the electrophysiologic properties of the atria acting as a favorable substrate for the development, maintenance and progression of AF. It should be also noted that hypertension can directly affect the structure of the atria. Hypertension indeed has a central role in the structural remodeling process in enlarging the LA and promoting the inflammatory process which increases LA histological changes (i.e. interstitial fibrosis, alteration of extracellular matrix and hypertrophy of myocytes)<sup>3</sup>.

The relationship between hypertension and AF also has relevant prognostic and therapeutic implications. Hypertension not only frequently coexists in AF patients, but is an independent risk factor for thromboembolic and bleeding events<sup>1</sup>. If we consider that AF patients have a fivefold increase risk of stroke and high BP is a stroke risk factor per se, the prevention of thromboembolic events in patients with both coexisting diseases is of paramount importance.

Several studies confirmed that a history of hypertension almost doubles the risk of stroke in AF patients and optimal BP control is thus crucial in order to reduce this risk<sup>1</sup>. Such AF patients receiving antihypertensive treatment had the lowest rates of stroke when systolic BP was between 120 -130 mmHg with either higher or lower values associated with the increased risk.<sup>8</sup>

Furthermore, strict BP control in AF patients taking oral anticoagulants is also necessary to avoid bleeding complications. The precise BP threshold that ensures the most favorable risk/benefit ratio of oral anticoagulation therapy in AF patients is not well defined and available data are quite heterogenous. However, large observational studies and data from randomized clinical trials agree that systolic BP values above 140 mmHg and diastolic BP above 90 increased the risk of both thromboembolic and bleeding complications in AF patients<sup>1,4</sup>.

What do the guidelines say? The recent 2020 European Society of Cardiology guidelines on AF management state that in AF patients, a strict BP control (i.e. BP  $\leq$  130/80 mmHg) is mandatory in order to reduce AF recurrence, and risk of stroke and bleeding<sup>9</sup>.

In conclusion, the interplay between hypertension and AF is complex and includes epidemiological, pathophysiological, and clinical links. Hypertension and AF are naturally connected and frequently act in parallel, feeding one another. Moreover, in up to 35% of the patients, especially in those with fewer comorbidities (e.g. with hypertension only), AF runs completely asymptomatic or with atypical symptoms<sup>1</sup>. Therefore, in our clinical practice, opportunistic AF screening in hypertensive individuals aged 50 years and older should be encouraged and routinely performed. Given the high prevalence of AF among hypertensive patients and more importantly the higher risk of stroke which these two disorders confer when coexist, our clinical efforts should be focused on proactive management of both conditions. It is thus clear that hypertension should not be considered as a simple risk factor associated with AF and a clinical holistic approach aimed at treating patients rather than diseases is needed to achieve better outcomes.

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**FIGURE. The complex interplay between hypertension and atrial fibrillation**

*Legend: AF, atrial fibrillation, LA, left atrium; LV, left ventricle; OSAS, obstructive sleep apnea syndrome; RAAS, renin–angiotensin–aldosterone system; TE, thromboembolism*

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Figure 1

