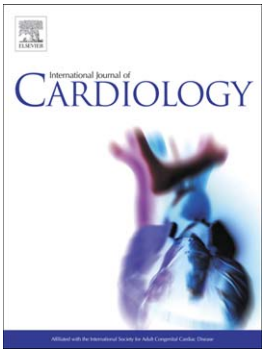

Atrial Fibrillation and Arterial Hypertension: *A Common Duet with Dangerous Consequences Where The Renin Angiotensin-Aldosterone System Plays An Important Role*

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Atrial Fibrillation and Arterial Hypertension: *A Common Duet with Dangerous Consequences Where The Renin Angiotensin-Aldosterone System Plays An Important Role*

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Abstract

Atrial fibrillation (AF), as it represents the most common sustained cardiac arrhythmia, affects 1%–2% of the general population and up to 15% of people over 80 years. High blood pressure, due to its high prevalence in the general population, is by far the most common condition associated with AF, although a variety of diseases, including valvular, coronary heart and metabolic diseases, are held to create the substrate favouring AF. Due to the concomitance of these conditions, it is quite often challenging to dissect the precise role of high blood pressure in triggering/causing AF.

Hence, even though the intimate association between high blood pressure and AF has been known for decades, the underlying mechanisms remain partially unknown. Accumulating evidences point to a major role of the renin-angiotensin-aldosterone system in inducing cardiac inflammation and fibrosis, and therefore electric and structural left atrial and ventricular remodelling, with changes in ions and cell junctions leading to AF development. These evidences are herein reviewed with a particular emphasis to the role of the renin-angiotensin-system aldosterone system.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an estimated prevalence of 1%–2% in the general population and up to 15% of people over 80 years [1-5]. These rates likely entail a marked underestimation because AF can be totally asymptomatic (silent AF). Moreover, due to aging of the population, a doubling of the prevalence of AF is expected to occur in the next 50 years thus leading an epidemic of AF worldwide.

AF doubles the risk of death independently of other known predictors of mortality [6] and represents the major cause of cardio-embolic stroke with ensuing long-term disability [1]. It also worsens the quality of life [7,8] and can lead to cognitive dysfunction and dementia by causing silent and recurring strokes [9].

As AF mandates long-term treatment for heart rate control and anticoagulation and, moreover, accounts for one third of all hospitalizations for arrhythmias, it imposes an enormous burden on the community [1].

Due to the high prevalence of high blood pressure (HBP) in the general population the vast majority of the cases of AF occurs in hypertensive patients, even though many other factors, as valvular and coronary artery diseases, heart failure, metabolic disorders as hyperthyroidism, obesity, and diabetes mellitus, often concur to create the stage favouring and maintaining AF. As HBP involves multiple hormonal and biochemical changes, it has been challenging to disentangle the role of HBP in triggering/causing AF from that of these other factors, and therefore the relative weight of different putative mechanisms underlying the association between AF and HBP still remain poorly understood [10]. Nonetheless, there is little doubt that a better identification of the mechanisms and predictors of AF in HBP is key for developing more effective prevention strategies and intervention programs. The aim of this review is meant to provide updated information on prevalence, predictors, and putative mechanisms of AF in the hypertensive heart disease.

1. Incidence of AF in HT patients. After anecdotal reports of an association between AF and HBP [11],

unambiguous evidence that HBP contributes to AF came from the Framingham Heart Study in 1994 [12]. During 38 years of follow-up of 2,090 men and 2,641 women 562 new cases of AF were observed, with a doubling AF incidence after 50 years of age with each successive decade, leading to almost 10% rate of AF in people who reached age 80 years of age.

The age-dependency of AF was emphasized by a more recent analysis of a cohort of the Framingham Heart Study: this showed increased age-adjusted AF prevalence rates from 1958-1967 to 1998-2007, which can be explained by the improved medical care leading to increased survival in general and after the onset of AF [13]. Of note, in the most recently examined decade of the Framingham Study, i.e. 1998–2007, notwithstanding the reduction over time of the prevalence of most modifiable risk factors for AF [13], HBP and anti-hypertensive treatment carried the greatest population-attributable risk. After age-adjustment, the only predictors of AF were HBP and ECG evidence of hypertensive left ventricular (LVH), besides diabetes mellitus and cigarette smoking (in women). Moreover, hypertensive men and women had 80% and 70% greater risk for AF, respectively, than normotensive subjects; ECG evidence of LVH increased risk of AF by almost a 3- and 4-fold, respectively (Table I)[12].

Other studies thereafter confirmed the role of HBP in causing AF: for example, in the 30,424 high CV risk participants of the Ontarget study (mean age 66 years), who were in sinus rhythm at enrolment, new AF occurred in 6.8% of the patients during a median follow-up period of 4.7 years. Age, history of HBP, and coronary or cerebrovascular disease, systolic BP, pulse pressure, LVH, body mass index, and serum creatinine predicted incident AF [14], which, in turn, implied an increased risk of congestive heart failure and cardiovascular death. In the PIUMA Study that prospectively examined the determinants of AF in 2,482 untreated essential hypertensive patients without valvular or rhythm diseases at baseline, LVMI predicted new onset AF and, alongside left atrial diameter, also chronic AF [15]. BP, EKG evidence of LVH, age, and male gender predicted AF in the hypertensive patients with echocardiographically determined

LVH of the LIFE study [16]; moreover, regression of LVH with treatment was associated with a lower incidence of AF as compared to persistent LVH [17;18], thus confirming the causative role of HBP-induced LVH in triggering AF. More recent studies showed that the increased risk of AF in hypertensive patients is not confined to those at high CV risk, like the ONTARGET or LIFE Studies patients, but would be shared also by those with BP in the upper normal range [19,20]. Of note, the observation that night-time ambulatory BP correlated with the left atrial size and the plasma levels of natriuretic peptides even in normotensive subjects with AF supported the causative role of BP in AF [21].

Finally, in summarizing the studies reporting an association of AF with HBP the *2012 Position paper of the Working Group on 'Hypertension Arrhythmias and Thrombosis' of the European Society of Hypertension (ESH)*[22] overall indicated that from 49% to 90% of AF patients have HBP [23-27].

2. Pathophysiology of AF associated with HT

The major mechanisms underlying AF in HT, although often concomitant, are herein reviewed separately for the sake of clarity.

2.1 Genetic factors. Rare gene mutations predisposing to AF were identified, but they were limited to isolated families without traditional risk factors; their interaction with HBP can be only speculated at this time [28,29]. In 2003 Chen et al. described a gain-of-function mutation in KCNQ1 gene responsible for AF in a Chinese family [30]. This gene encodes the α subunit of the slow component of the delayed rectifier K^+ current (IKs). The variant, as well as others thereafter identified, increases IKs during the action potential (AP) in the atria, thus shortening the atrial AP duration and/or atrial refractoriness [31,32]. Gain of function mutations in other K^+ channels (KCNE2, KCNE5 or KCNJ2), and loss-of-function mutation in the KCNA5 gene, which codes the atrial-specific K^+ voltage gated channel Kv1.5, were also reported to promote AF by inducing early atrial repolarisation [33-37]. Increased susceptibility to AF was also found in

patients with mutations in Na^+ or Ca^{2+} channel genes that control ion currents across cell or sarcoplasmic membranes in atrial myocytes [38-40]. Evidence that some mutations specifically increase the susceptibility to AF in hypertensive cardiac disease is, however, lacking. It is however, conceivable that, in the carriers of gene variants predisposing to HBP and AF, an interaction with additional risk factors, particularly in the presence of hypertensive cardiac remodelling, can more easily lead to AF with aging (Fig. 1)[41,42].

2.2 Channels and cell junctions. Mechanic overload, due to HBP or ischemic injury, were found to induce an abnormal expression of ion channels and/or junctional complexes, as connexin 40 and connexin 43, which can enhance myocardium vulnerability by triggering focal ectopic and re-entry activity [43,44]. Whether these alterations play a major role in AF in hypertensive patients has not been specifically investigated and, therefore, is unknown. Undoubtedly, HBP, by causing LVH and impaired LV filling, stretches the atria, thus favouring AF [45]. Moreover, in patients with HBP atrial remodelling and fibrosis can in turn affect channels and/or junctions in atrial cardiomyocytes [43].

2.3 Renin-angiotensin-aldosterone system (RAAS). Activation of RAAS, not only is a feature of high renin essential hypertension, renovascular hypertension and renin secreting tumours, but also represents a common consequence of treatment with diuretics and direct vasodilatators. It has electrophysiological effects that can trigger arrhythmias and ultimately induce structural remodelling of the atria, favouring the onset and the perpetuation of AF. For example, angiotensin (Ang) II activates profibrotic pathways via AT1 receptor in myofibroblasts [16,29], thus promoting transformation of resident atrial fibroblasts into myofibroblasts, as well as synthesis of TGFβ1, a major profibrotic cytokine in the atria and the ventricles. Myofibroblasts may in turn release TGFβ1, and other paracrine factors as PDGF, connective tissue growth factor (CTGF), fibroblast growth factor (FGF)-2, and interleukines of the IL-6 family that also affect myocyte electrical function [46,47]. Of note, TGFβ1 released by myofibroblasts differentially regulates the

transcription and function of the Na^+ channels [47], while CTGF affects the connexin expression pattern, leading to atrial remodelling and fibrosis (Fig. 2)[46]. Accordingly, some studies reported a lower incident AF in hypertensive patients treated with RAS inhibitors compared to controls [16,48].

Even though atrial wall stretch would be expected to lower aldosterone via enhanced ANP release, plasma aldosterone was found to be elevated in AF patients; conversely, restoration of sinus rhythm lowered its levels [49]. Interestingly, a causative role of aldosterone in the development of AF is supported by the finding of a 12-fold increase of the risk of AF in a large retrospective study of patients with primary aldosteronism, as compared to matched essential hypertensive patients (OR 12, 95% CI: 3.2-45.2, p <.0001)[50]. This increased risk of AF could be due to several mechanisms favouring left atrium dilatation, collagen deposition and development of cardiac fibrosis, including hypokalaemia, aldosterone-induced LV remodelling, hypertrophy, and diastolic dysfunction [51,52]. Aldosterone-induced oxidative stress and inflammation could further favour atrial structural and electrical remodelling [53,54]. The aforementioned reduced incidence of AF with AT1 receptor blockers (ARBs) in the LIFE and VALUE studies, compared to atenolol or amlodipine, respectively [16,48], also indirectly support a role of hyperaldosteronism in the onset of AF as ARBs may confer a protective effect not only by antagonizing Ang II on the AT1 receptors, but also by blunting AT1-mediated Ang II-dependent aldosterone secretion.

3. Diagnostic approach and treatment of AF in the hypertensive patient. Despite the well-known role of both HBP and AF as major causes of stroke, both conditions as well as their association remain markedly under-diagnosed. The Screening for Atrial Fibrillation in the Elderly (SAFE) Study showed that many UK primary care providers were unable to diagnose AF with EKG, with overlooking of as many as 20% of the cases [55]. This has ominous consequences, as undiagnosed AF patients cannot receive anti-coagulation and therefore are exposed to the risk of stroke. In 2012 acknowledging this burden and the under-diagnosis of AF in hypertensive patients, the Working Group on 'Hypertension arrhythmias and

thrombosis' of the European Society of Hypertension (ESH) published a position paper on the diagnostic approach, prevention and treatment of HBP associated with AF [22]. The recommendation of performing an EKG whenever AF is suspected and to perform 24-hours EKG Holter monitoring, or external event recorders for longer periods, when EKG does not show AF, but silent AF is probable, were reinforced. According to the AHA/ACC 2014 AF Guidelines all hypertensive patients with AF should also have a transthoracic echocardiogram to detect underlying structural disease, assess cardiac function, and measure atrial size [56].

In the ARAPACIS study (Atrial Fibrillation Registry for Ankle-brachial Index Prevalence Assessment: *C*ollaborative Italian Study) a 52% prevalence of echocardiographic LVH was found in patients with non valvular AF. Compared to those without LVH, the LVH patients were older and had a higher prevalence of HBP, besides diabetes, previous myocardial infarction and arterial wall stiffening, as evidenced by an ankle-brachial index > 0.90 [57].

New devices have been developed to automatically detect silent AF, including the MyDiagnostick (https://www.mydiagnostick.com)[58,59] and the MicrolifeWatchBP Home A (http://www.microlife.com), an oscillometric blood pressure monitor with an embedded algorithm that automatically detects pulse irregularity, and advices the user to transmit his/her pulse data to the general practitioner. The National Institute for Health and Care Excellence (NICE) supports the WatchBP device to detect asymptomatic AF and reduce the incidence of thromboembolic stroke (https://www.nice.org.uk).

4. Hypertension and thrombo-embolic risk stratification. Alongside a history of stroke or transient ischemic attack, increasing age, and structural heart disease (LVH or LV dysfunction), HBP entails an established predictor of stroke in patients with AF. The CHA2DS2 VASC score (http://www.mdcalc.com) has become the most popular tool in clinical practice to determine the cardioembolic risk in non valvular AF [60]. The HAS-BLED score (http://www.mdcalc.com) was also introduced in clinical practice to

estimate the risk of bleeding with anticoagulation and therefore to assist physician in the challenging task to decide whether to anticoagulate or not. Of importance, HBP enters in the calculation of both the CHA2DS2 VASC and the HAS-BLED score, but the BP threshold at which the benefit of stroke prevention with anticoagulation exceeds the risk of cerebral haemorrhage is unknown. Thus, even though a strict control of BP is recommended before starting the anticoagulant treatment, the level of BP associated with the minimal risk of stroke is unknown.

5. Rate and sinus rhythm control. Besides prevention of cardioembolism, goals of AF management include rate control, and restoration and maintenance of sinus rhythm. Rate control impacts on the quality of life, reduces morbidity, and decreases the potential for developing tachycardia-induced cardiomyopathy. The choice among beta blockers, non-dihydropyridine calcium channel blockers, digoxin, and antiarrhythmic drugs as sotalol, strictly depends on the patient's symptoms, hemodynamic status, presence/absence of heart failure, and potential triggers of AF [56].

In randomized clinical trials (RCTs) long-term AF management to restore and maintain sinus rhythm failed to show superiority over rhythm control in terms of death-free survival [23,43,61]. However, when applied to patients who are candidates to either rhythm or rate control strategy, the former resulted in more hospitalizations [62], suggesting that it is not the optimal choice for each patient. Whether control of BP affects duration of sinus rhythm maintenance or rate control remains to be established.

6. Treatment of hypertension and prevention of AF. The tight relationship between HBP and AF found in clinical studies [1,13,16] would imply that a good control of BP prevents atrial fibrillation. In the aforementioned LIFE study, the hypertensive patients who achieved in-treatment systolic BP lower than 130 mmHg showed a reduced risk of new-onset AF as compared to those who remained with systolic BP $\geq$ 142 mmHg [18]. Moreover, an effective antihypertensive therapy was associated with reduction of stroke rates, irrespectively of the drugs employed [63,64]. Nevertheless, BP remained remarkably unappreciated

in AF trials notwithstanding the fact that the prevalence of HT ranged from 79% (RE-LY) to 90% (ROCKET)(for a review see Ref [22]). The RE-LY, ROCKET, ARISTOTLE, AVERROES and ENGAGE AF TIMI 48 Studies, which examined the effectiveness of the oral non vitamin K anticoagulants (NVKACs) dabigatran, rivaroxaban, apixaban, and edoxaban in stroke prevention in AF, provided only limited data on BP values and BP control during the study, and on concomitant antihypertensive medication. A post-hoc analysis of data from AF trials considering the BP-adjusted outcomes could provide more accurate information on the effectiveness of NVKACs in preventing stroke or systemic embolism [22].

Theoretically, by preventing diastolic dysfunction and, thereby atrial stretch and dilation, all antihypertensive agents might be effective in reducing the risk of incident AF. However, no RCTs comparing head-to-head different agents have been performed specifically to this aim. Some studies suggest that RAS inhibitors can be more efficacious than other agents in preventing AF [16]: by meta-analysing 11 studies entailing a total of 56,308 patients Healey et al. found that ACE-I and ARBs overall reduced the relative risk of AF by 28% (95% CI: 15%-40%, p=.0002), without significant differences between these classes [29]. However, in this meta-analysis only three studies, which entailed 26,403 patients, were hypertension trials [16,65]. When only these trials were examined the relative risk reduction furnished by RAS blockade was two-fold smaller (12% (p= .04), possibly reflecting the smaller benefits of the RAS inhibitors when an effective antihypertensive therapy was used in the control arm. Moreover, these hypertension trials were heterogeneous for inclusion criteria, with Captopril prevention Project (CAPP) and Swedish Trial in Old Patients with Hypertension-2 (STOP-H2) enrolling hypertensive patients from the general population [65,66], and the LIFE Study recruiting high-risk patients with left ventricular hypertrophy [16]. Of interest, only the LIFE Study reported a reduction in AF with losartan over atenolol, whilst CAPP and STOP-H-2 showed no advantages. These results overall indicate that prevention of AF is more effective in the hypertensive patients with most severe hemodynamic

abnormalities.

Another meta-analysis also showed AF prevention of the hypertensive patients with ACEI or ARBs [67], while two others failed to show superiority of ACEI or ARBs over active therapy of the control groups [68,69]. Hence, it is not possible at present to draw solid conclusions about the superiority of the RAAS blockade over not RAAS blocker-based antihypertensive treatment (Table II). Nonetheless, some issues deserve consideration: *1)* incident AF could have been under-detected in the oldest trials CAPP and STOP-2H as it was not a pre-specified endpoint; *2)* patients included in the HOPE and TRASCEND study were high cardiovascular risk patients with HBP being only one of their risk factors. Therefore, these trials are not comparable to the trials including *'pure'* hypertensive patients; *3)* the follow-up largely differed across trials; *4)* only in the LIFE and VALUE studies, which showed the beneficial effects of ARBs on AF prevention, EKG was recorded yearly. Overall, these results suggested that AF could have been missed in many studies and that a proper search for AF is key for ascertainment of the antihypertensive effect of drug.

Finally, since AF develops more frequently in the hypertrophied dysfunctional hearts of patients with severe or resistant HBP, whether novel strategies such as baroreceptor stimulation therapy (BAT) and renal sympathetic denervation can be helpful for AF prevention and/or regression remains to be investigated.

7. Conclusions

In summary, since AF is common in the adult population and even more so in patients with HBP, in which it worsen prognosis and quality of life, there is an urgent need for a better understanding of its underlying mechanisms. As in many other fields of Medicine, better knowledge will translate into more effective prevention and treatment strategies of this arrhythmia that imposes an enormous burden on public health and will do even more so in the next decades.

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Table I. Risk factors for the development of AF in 38-years follow-up of the Framingham Study.

	Age-adjusted OR		Multiple risk Factor-adjusted OR	
Risk Factors	***Men***	***Women***	***Men***	***Women***
Smoking	1.0	1.4*	1.1	1.4
Diabetes	1.7**	2.1***	1.4*	1.6**
EKG-LVH	3.0***	3.8***	1.4	1.3
HT	1.8***	1.7***	1.5**	1.4*
BMI	1.03	1.02	--	--
Alcohol	1.01	0.95	--	--

BMI: body mass index; EKG–LVH: echocardiographic left ventricular hypertrophy; OR: odds ratio.
Analysis performed using 2-year pooled logistic regression; *p <.05; **p <.01; ***p <0.001.
Mod. From Kannel W.B. [12]

Table II. Randomized clinical trials on the effects of ACE-inhibitors or ARBs in HT patients with AF and inclusion in the meta-analyses.

Author ***Study acronym, year***	**Pure HT study (yes/no)**	**Additional Inclusion criteria**	**Population (n)**	**Follow-up (mo)**	**Active group treatment ACEI/ARB**	**Control group treatment**	**Meta-analysis inclusion (yes/no)**			
							Healey, 2005	**Anand, 2006**	**Schneider, 2010**	**Huang, 2011**
Hansson, ***CAPP, 1999*** [65]	yes		10,915	73	Captopril	Diuretic β-blocker	yes	yes	yes	yes
Hansson, ***STOP-H2, 1999*** [66]	yes		6,303	60	Enalapril/Lisinopril	Diuretic β-blocker CCB	yes	yes	yes	yes
Wachtell, ***LIFE, 2005*** [16]	yes	LVH	8,480	57	Losartan	Atenolol	yes	yes	yes	yes
Schmieder, ***VALUE, 2008*** [48]	no	HIgh CV risk	13,760	50	Valsartan	Amlodipine	no	yes	yes	yes
Salehlan, ***HOPE, 2007*** [70]	no	HIgh CV risk	8,335	54	Ramipril	Placebo	no	no	yes	no
Yusuf, ***TRASCEND, 2008*** [71]	no	HIgh CV risk	5,701	56	Telmisartan	Placebo	no	no	yes	no
Fogari, ***2006*** [72]	no	Paroxysmal AF	222	12	Losartan + Amiodarone	Amlodipine + Amiodarone	no	no	no	yes
Fogari, ***2008*** [73]	no	AF	369	12	Ramipril Valsartan	Amlodipine	no	no	no	yes

Abbreviations. AF: atrial fibrillation; ARB: Angiotensin AT1 receptors blockers; CCB: calcium channel blockers; CV: cardiovascular; HT: arterial hypertension; mo: months.
Pure HT study indicates that HT was the only inclusion criteria.
'*Additional inclusion criteria*' indicates that, besides HT, the inclusion criteria entailed high cardiovascular risk (coronary, peripheral, or cerebrovascular disease, or diabetes with end-organ damage) or AF.

Legends to Figures

Figure 1. Factors predisposing to atrial fibrillation (AF). A: AF prevalence increases with aging in the general population. B: In the normotensive subjects atrial vulnerability is mostly caused by genetic (*yellow*) and age-related remodelling (purple). Both factors contribute to onset of AF, which first presents as paroxysmal, then permanent, and finally as persistent (*petrol blue*). C. Remodelling induced by high blood pressure is the major factor predisposing to AF in the hypertensive patients, leading to an anticipation of the age of onset of paroxysmal AF and to a swifter transition to permanent AF. *(Modified from Wolf P.A.* [1]*and Hejiman J.* [41]*).*

Figure 2. Mechanisms underlying the development of atrial fibrillation (AF) in hypertensive patients. Left ventricular hypertrophy (LVH), by inducing electrical and structural remodelling not only of the ventricular, but also of the left atrial chamber, is the major determinant of AF onset. Activation of the sympathetic and renin-angiotensin systems contributes lo LVH mostly through inflammation and fibrosis. Aldosterone, the final effector of the RAAS, potently concurs to fibrosis and LVH development. The genetic background, by inducing changes in ion channels or cellular junctions and therefore leading to electrical and/or structural abnormalities, crucially affects the predisposition not only to AF but also to hypertension.

Figure 1

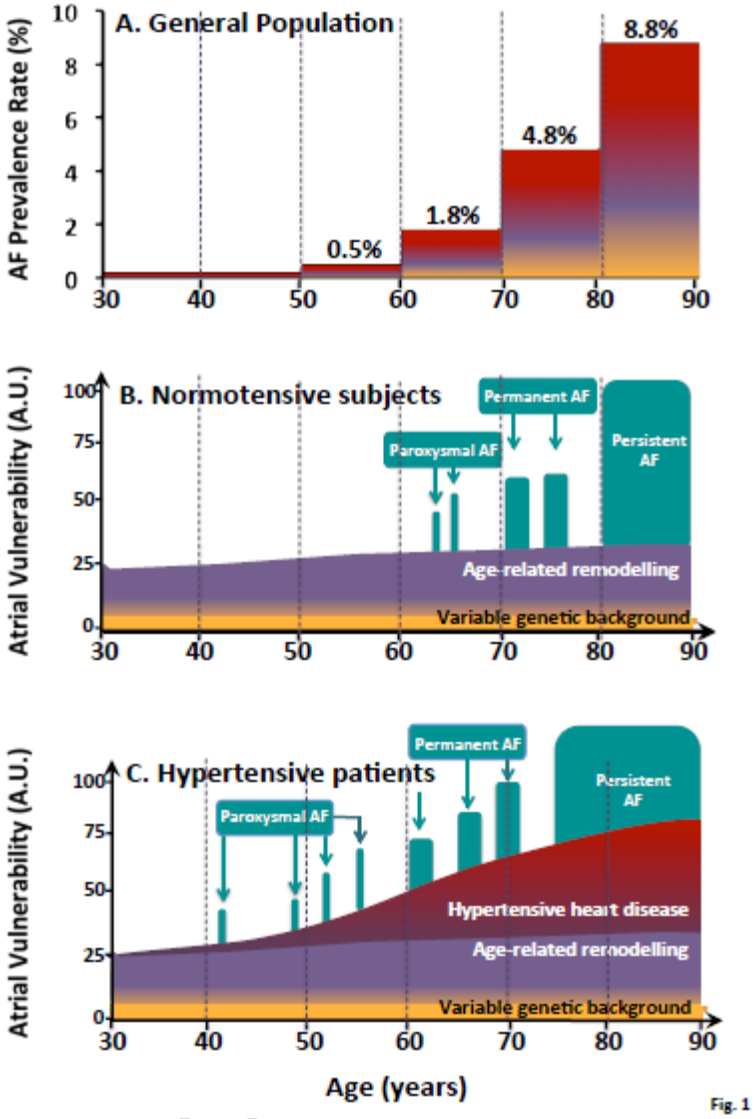

Fig. 1

Figure 2

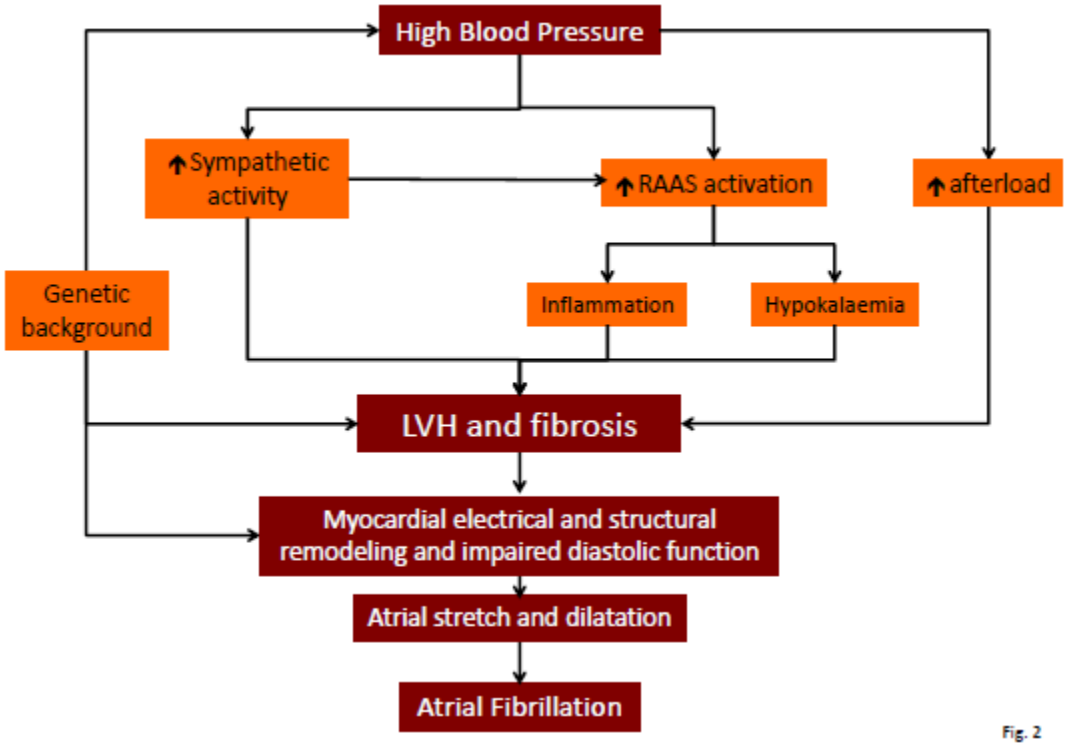

Fig. 2