REVIEW

Hypertension and Atrial Fibrillation: An Intimate Association of Epidemiology, Pathophysiology, and Outcomes

Mikhail S. Dzeshka,[1,2] Farhan Shahid,[1] Alena Shantsila,[1] and Gregory Y.H. Lip[1,3]

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia found in clinical practice. AF rarely exists as a single entity but rather as part of a diverse clinical spectrum of cardiovascular diseases, related to structural and electrical remodeling within the left atrium, leading to AF onset, perpetuation, and progression. Due to the high overall prevalence within the AF population arterial hypertension plays a significant role in the pathogenesis of AF and its complications. Fibroblast proliferation, apoptosis of cardiomyocytes, gap junction remodeling, accumulation of collagen both in atrial and ventricular myocardium all accompany ageing-related structural remodeling with impact on electrical activity. The presence of hypertension also stimulates oxidative stress, systemic inflammation, rennin–angiotensin–aldosterone and sympathetic activation, which further drives the remodeling process in AF. Importantly, both hypertension and AF independently increase the risk of cardiovascular and cerebrovascular events, e.g., stroke and myocardial infarction. Given that both AF and hypertension often present with limited on patient wellbeing, treatment may be delayed resulting in development of complications as the first clinical manifestation of the disease. Antithrombotic prevention in AF combined with strict blood pressure control is of primary importance, since stroke risk and bleeding risk are both greater with underlying hypertension.

Keywords: aging; atrial fibrillation; bleeding; blood pressure; epidemiology; fibrosis; hypertension; inflammation; oxidative stress; prevention; stroke.

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Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. It is associated with a significant increase in thromboembolic complications, for example, stroke and thromboembolism. Loss of synchrony between atria and ventricles leads to continuous atrial and ventricular mechanical dysfunction followed by the development of heart failure and decreased functional capacity. Patients with AF also report impaired quality of life as well as decline in cognitive function, and increased mortality when compared to patients in sinus rhythm.[1]

Lone AF, defined as AF in younger adults (age below 60 years) with no clinical history or echocardiographic evidence of concomitant cardiovascular or pulmonary conditions or an acute trigger, represents only a minority of cases of arrhythmia. Also given that more and more emerging risk factors for AF development have been recognized (e.g., obesity, obstructive sleep apnea, strenuous physical activity, inflammation, and so on), "lone AF" has essentially become a diagnosis of exclusion.[2,3] Even in such cases, the risk of adverse outcomes appeared to be higher compared to patients without AF.[4]

The vast majority of AF cases develop as a consequence of pre-existing cardiovascular diseases as well as noncardiac conditions, which are associated with structural and electrical changes that precipitate the development and persistence of AF. Arterial hypertension is highly prevalent within the general population and is therefore often present concomitantly with AF, as well as sharing a range of risk factors.[5,6]

Despite the availability of diagnostic methods and the availability of various antihypertensive drugs, further improved awareness of high blood pressure, adherence to treatment, and hypertension control is highly relevant for many patients.[7] Hypertension almost inevitably leads to cardiovascular diseases (as is the case for coronary artery disease and heart failure), which strengthens the link between hypertension and AF even more.[8]

In the current review article, we provide an overview of the epidemiological parallels between hypertension and AF, common pathophysiological pathways, and the implications of high blood pressure on outcomes in AF patients in various clinical scenarios.

EPIDEMIOLOGY OF HYPERTENSION AND AF: A 1-WAY PATH?

A retrospective analysis of 80 million adults in the United States found that the prevalence of hypertension was estimated to be 32.6% between 2009 and 2012.[7] There were more males suffering from hypertension aged <45 years whilst for those ≥65 years of age, the opposite gender relationship was observed. Between age 45 and 64 years, prevalence of

Correspondence: Gregory Y.H. Lip (g.y.h.lip@bham.ac.uk).

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[1]University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, UK; [2] Grodno State Medical University, Grodno, Belarus; [3]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

hypertension in males and females remains approximately similar.[7]

The National Health and Nutrition Examination Survey in 2011–2012 found that 17.2% of adults in the United States are unaware they have high blood pressure; also, over 10% of hypertensive patients failed to reach target blood pressure despite use of ≥4 drugs from 3 different drug classes, i.e., resistant hypertension.[7] The prevalence of hypertension demonstrates an increasing trend over past decades, and projections showed further anticipated increases up to 41.4%.[7] In the elderly, its prevalence is even higher (65.0% among US adults 60 years of age or older) with a higher percentage receiving treatment (86.1%) but a lower proportion of patients achieve blood pressure control (50.5%).[7]

The rising prevalence of hypertension is associated with increases in overall mortality. Life expectancy of normotensive individuals is approximately 5 years higher than in their hypertensive counterparts. Indeed, there were over 70,000 deaths attributable to hypertension that equated to a death rate of 19.9 in 2013. Amongst cardiovascular risk factors hypertension is the leading cause of death in females and only second after smoking as the cause of death in males. Of note, cardiovascular diseases are likely to occur 7 years later on a background of normal blood pressure.[7]

Unfortunately, reliable data from the developing as well as low- and middle-income countries are more scarce compared to developed high-income countries, and variability in studies design, population selection, methodology, and so on make direct comparison of the data hard to interpret.[9] Overall, there have been global disparities in hypertension prevalence and control.[9,10] Reported prevalence is higher in low- and middle-income countries than in high-income countries, while hypertension awareness, treatment, and control were much lower in low- and middle-income than in high-income countries.[10] Furthermore, the larger growing populations in developing countries make a greater impact upon the global burden of hypertension.[9] One of reasons for the increasing hypertension prevalence is major achievements in prevention and treatment of cardiovascular diseases leading to improved survival, increased life expectancy, and therefore an ageing population.[11]

Such trends are evident for AF epidemiology. In the Framingham Heart Study of over 200 thousand person-years, age-adjusted AF prevalence increased 4-fold from 20.4 to 96.2 cases and 13.7 to 49.4 cases per 1,000 person-years in males and females, respectively.[12] A similar trend was apparent for the age-adjusted AF incidence that increased from 3.7 to 13.4 cases per 1,000 person-years and 2.5 to 8.6 cases in males and females, respectively.[12] Furthermore, AF prevalence and incidence also show age-dependency. In the Rotterdam Study, for example, the prevalence of AF was 1.3% in men and 1.7% in women in patients aged of 55 to 59 years, but reached 24.2% and 16.1%, respectively, in those who were older than 85 years of age.[13] Lifetime risks for development of AF were approximately 1 in 4 in both the Framingham Heart Study (age of 40 years and older) and Rotterdam Study (age of 55 years and older).[14,15]

According to the global burden of disease study published in 2014, over 20 million males and 12 million females were estimated to suffer from AF worldwide, and close to 5 million new AF cases were added to AF burden annually.[16] During the 2 past decades AF-associated health burden evaluated with the disability adjusted life-years, increased by approximately 19%.[16] The estimated age-adjusted AF prevalence and incidence rates increased by 26.7 and 16.8 per 100,000 person-years in males as well as 13.2 and 15.7 per 100,000 person-years in females, respectively.[16] Western developed countries, i.e., United States and European Union, are major contributor to the global burden of AF, with approximately 8 and 9 million AF cases estimated.[13,16] The prevalence and incidence of AF in developing countries is likely to be lower, and also varies between developed countries.[17,18]

When current trends in the incidence and prevalence of AF (derived in the Olmsted County cohort) were applied, the projected number of AF cases by the year of 2050 is likely to increase 2–3 fold with 35% of new patients with AF attributed to growing AF incidence while another 65%—due to increase in population size, largely explained by increased survival accompanied by shift in age distribution (less due to population expansion itself).[19,20] In European countries, if the trends from the Rotterdam study remain, the numbers of individuals with AF is projected to double by 2060.[13]

Accurate assessment of AF epidemiology is subject to bias because of the absence of population-based data in many countries and peculiarities with regards to the clinical course of AF, for example, asymptomatic (silent) AF or those presenting with very short intermittent episodes.

Single time-point screening for AF *via* pulse palpation or short-term electrocardiogram recording was capable of identifying AF in as much as 1% of the screened population with previously unknown AF. This increased when subgroup of elder patients (e.g., 65 years of age or older) was chosen.[21,22] The probability of catching the episode of paroxysmal AF correlates with the duration of electrocardiogram monitoring. This was shown in patients with cryptogenic stroke who underwent electrocardiogram monitoring with implantable cardiac monitors. Cumulative detection rates of AF increased with continued monitoring, increasing from 3.7% at 1 month, to 12.4% at 1 year and reaching 30% at 3 years.[23]

Thus, the burden of AF reaching epidemic levels in the 21st century is an ever increasing reality.[24] Given that population ageing is at least in part attributable to improved survival due to implications of evidence-based treatment into routine clinical practice, the prevalence of comorbidities such as hypertension, coronary artery disease, diabetes mellitus, chronic kidney disease, heart failure, is also increasing alongside with aging, contributing to the growing AF burden. These conditions are intimately linked to each other, and the rate of their coexistence is high.

Hypertension is now the leading cardiovascular risk factor to predispose to AF globally. Mechanisms by which hypertension predisposes to AF development are summarized in the Figure 1. The evidence from multiple cohorts has confirmed a strong association between 2 conditions (see Table 1) leading to the inclusion of blood pressure indices into clinical risk scores for AF prediction (Table 2).

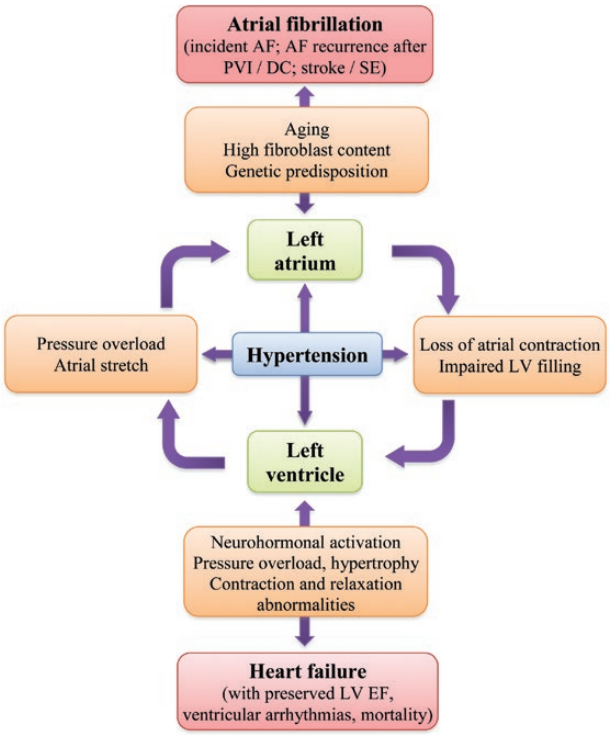

Figure 1. Association between hypertension and AF, and impact on outcomes. Abbreviations: AF, atrial fibrillation; DC, direct current cardioversion; LV EF, left ventricular ejection fraction; PVI, pulmonary vein isolation; SE systemic embolism.

MECHANISMS OF AF: FROM HYPERTENSION TO ARRHYTHMIA?

Risk factors and pathophysiology of AF have been studied extensively but definite mechanisms have not yet been fully elucidated and those that have are poorly understood. AF has a complex origin with multiple pathways of excitation. Notwithstanding epidemiological parallels between hypertension and AF, their coexistence is a common clinical scenario, but other cardiovascular and noncardiovascular conditions can also be causative of arrhythmia.[6] Irrespective of the underlying condition, a combination of diverse (but often interplaying) pathways lead to structural and functional changes followed by electrophysiological, contractile, and architectural disturbances within the left atrium, commonly defined as atrial cardiomyopathy and serve together as an arrhythmogenic substrate for AF initiation and persistence.[25]

To be responsible for arrhythmia development, there needs to be focal ectopic firing occurring from the triggered activity (early or, more frequently, delayed after depolarizations) and re-entry cycles formation, maintained by shortened atrial refractoriness, slowed conduction, and unidirectional blocks. These include structural remodeling, particularly left atrial fibrosis; dysfunction of autonomic nervous system; ion channel dysfunction; and calcium handling abnormalities.[6]

Structural remodeling

Structural remodeling is essential for arrhythmia initiation and perpetuation in the majority of AF cases. The mechanisms of structural remodeling both in the left atrium and left ventricles have been reviewed recently.[26] Diffuse accumulation of fibrotic tissue, e.g., collagen fibers and fibroblasts, in the extracellular matrix of atrial myocardium, is the hallmark of structural remodeling. Moreover cardiac fibroblasts and other cellular populations (e.g., progenitor cells, endothelial cells, etc.) *via* epithelial to mesenchymal transitions, can switch to a more profibrotic phenotype, the myofibroblast, with a higher capacity to proliferate and synthesize components of extracellular matrix.[26]

Apart from being the major source of collagen synthesis in the heart, the myofibroblasts also play roles in the release of a range of signalling molecules (including the upregulation of proinflammatory cytokines). Furthermore, there is direct involvement of cardiac fibroblasts/myofibroblasts in atrial arrhythmogenesis due to electrical coupling with cardiomyocytes, by interference with impulse propagation and slow conduction. Subsequently, myofibroblasts may cause reduction in cardiomyocytes resting membrane potential due to leakage of cardiomyocyte electrical current, fluctuations in action potential duration, appearance of delayed after depolarisations, leading to ectopic activity.[6,27]

Overall, turnover of extracellular matrix (like collagen synthesis) and degradation, as well as cardiac fibroblast proliferation and dedifferentiation are subject to multiple external influences, for example, inflammatory cytokines, reactive oxygen species, and hemodynamic load (Figure 2). However, the main effector for structural remodeling is the rennin–angiotensin axis activation, specifically angiotensin II.[5,26] Profibrotic effects of angiotensin II are largely mediated by the transforming growth factor beta 1 that *via* Smad pathway upregulates expression of particular genes, as well as increased aldosterone production, activation of nicotinamide adenine dinucleotide phosphate oxidase, increased inflammatory responses, and apoptosis.[26,28] Interestingly, transforming growth factor beta 1 is associated with a minor but significant increase in the risk of incident AF (standard mean difference 0.67; 95% confidence interval [CI] 0.29–1.05 when assessed as continuous variable; odds ratio 1.01, 95% CI 1.01–1.02, when assessed as categorical variable).[29]

Recently, thrombin *via* protease-activated receptors promotes fibrotic, hypertrophic, and inflammatory responses in atrial fibroblasts, for example, the expression of transforming growth factor beta 1 and monocyte chemoattractant protein-1 expression are upregulated as well as incorporation of 3-hydroxyproline was increased suggesting enhanced collagen synthesis by fibroblasts.[30] The latter changes translate into higher AF inducibility and complexity of the AF substrate. Of note, thrombin inhibition with dabigatran resulted in reduced alpha-smooth muscle actin expression (marker of transition of cardiac fibroblasts to myofibroblasts) and endomysial fibrosis.[30] Given that AF is associated with activation of coagulation and represents hypercoagulable state, these experimental findings are intriguing.

Finally, the atrial myocardium is more prone to develop fibrosis compared to ventricles.[31,32] Also, AF itself augments structural remodeling in the left atrium closing the vicious cycle and promoting arrhythmia progression to persistent and chronic presentation.[5,33]

Table 1. Association between hypertension and risk of incident AF

Ref.	Data source	Design	No of patients (AF free at baseline)	Incident AF	Population	Follow-up	Risk for incident AF[a]	Comments
Alonso *et al.*, 2013[86]	CHARGE-AF Consortium	Pooled cohort from ARIC, CHS, and FHS (Offspring cohort, the 6th examination) prospective cohort studies	18,556 (derivation cohort)	1,186 (derivation cohort)	Aged 46 to 94 yrs., from 60 ± 8 yrs. in FHS to 73 ± 5 yrs. in CHS Males form 34.1% in CHS AA to 45.5% in FHS and ARIC whites Antihypertensive Tx from 29.6% in FHS to 61.5% in CHS AA	Varies across the studies Up to 7 yrs. for pooled derivation cohort	SBP 1.22 (1.14–1.30) in simple model; 1.20 (1.13–1.29) in augmented model per 20 mm Hg increase DBP 0.90 (0.85–0.96) in simple model; 0.91 (0.85–0.97) in augmented model per 10 mm Hg Antihypertensive Tx 1.42 (1.25–1.60) in simple model; 1.41 (1.24–1.59) in augmented model	Simple model included age, race, height, weight, SBP, DBP, current smoking, antihypertensive Tx, DM, history of MI and HF. Augmented model included variables from simple model plus PR interval, ECG-based LVH.
Aviles *et al.*, 2003[87]	CHS	Prospective cohort study	5,491 (longitudinal study)	897 (16.3%)	Aged 73 ± 5 yrs. 42% males	Mean of 6.9 ± 1.6 yrs. (Me 7.8 yrs.)	SBP 1.14 (1.05–1.25) per SD increase DBP 0.92 (0.85–0.99) per SD increase HTN 1.28 (1.08–1.51)	Model included age, gender, race, LV dysfunction, BMI, CRP, CHD, CHF, DM, HTN, SBP and DBP, cerebrovascular disease, and smoking.
Chamberlain *et al.*, 2011[88]	ARIC	Prospective cohort study	14,546	515 (3.5%)	Aged 45 to 64 yrs. 44.7% males 30.6% antihypertensive Tx	10 yrs.	SBP 1.42 (1.15–1.76) for 120-<140 mm Hg 2.16 (1.67–2.79) for 140–<160 mm Hg 2.63 (1.83–3.78) for ≥160 mm Hg vs. 100–<120 mm Hg DBP 1.53 (1.06–2.22) for 90–<100 mm Hg 2.02 (1.20–3.41) for ≥100 mm Hg vs. 70–<80 mm Hg Antihypertensive Tx 2.55 (2.13–3.04)	HRs adjusted for age, gender, and race. 10-year risk estimation
Conen *et al.*, 2009[89]	WHS	Prospective cohort study	34,221	644 (1.9%)	Aged 55 ± 7 yrs. 100% females 16.8% SBP ≥140 mm Hg 4.8% DBP ≥90 mm Hg	Me 12.4 yrs.	SBP 1.43 (1.09–1.87) 130–139 mm Hg 1.78 (1.34–2.38) 140–159 mm Hg 2.29 (1.45–3.63) ≥160 vs. <120 mm Hg	Models including both SBP and DBP adjusted for age, BMI, DM, smoking, hypercholesterolemia, exercise, alcohol consumption, education, and randomized Tx assignment with BP changes over time being accounted. Other models addressed association with baseline BP levels, SBP and DBP separately, and adjusted for age only. No significant association for SBP of 120–129 mm Hg vs. <120 mm Hg

Table 1. *Continued*

Ref.	Data source	Design	No of patients (AF free at baseline)	Incident AF	Population	Follow-up	Risk for incident AF[a]	Comments
								DBP was associated with incident AF only when analysed separately from SBP in models with DBP updated overtime (HR 1.50, 95% CI 1.01–1.88 for 90–94 mm Hg vs. DBP <65 mm Hg), and models with baseline DBP (HR 1.53, 95% CI 1.05–2.23, and HR 2.15, 95% CI 1.21–3.84 for 85–89 mm Hg and ≥95 mm Hg, respectively, vs. <65 mm Hg)
Emdin *et al.*, 2016[48]	Primary care database, United Kingdom (CPRD)	Prospective cohort study	4,269,194	128,468 (3.0%)	Aged 30–90 yrs. Me 46 (IQR 36–59) yrs. 44.4% males 10.1% at baseline; 29.0% during follow up took antihypertensive Tx	Me 6.9 (IQR 3.0–11.2) yrs.	SBP 1.21 (1.19–1.22) per 20 mm Hg increase	The strength of the association declined with increasing age, from an HR of 1.91 (95% CI 1.75–2.09) at age 30–40 yrs. to an HR of 1.01 (95% CI 0.97–1.04) at age 80–90 yrs.
Grundvold *et al.*, 2012[90]	Norwegian cardiovascular health survey	Prospective cohort study	2,014	270 (5.1 per 1000 PY)	Aged 50 yrs. 100% males	Me 30 yrs.	SBP 1.22 (1.10–1.42) per SD increase (18 mm Hg) DBP 1.25 (1.11–1.43) per SD increase (10 mm Hg)	Adjusted for age, BMI, LVH, maximum exercise heart rate, and physical fitness. BP components were analysed separately in models.
Marcus *et al.*, 2010[91]	ARIC CHS	Pooled analysis of prospective cohort studies	CHS 5,220 ARIC 14,386	CHS 1,172 (22.5%) ARIC 1,068 (7.4%)	CHS Aged 73 ± 6 yrs. 42.8% males 58.5% HTN ARIC Age 54 ± 6 4854/14419 HTN 6429/14419 males	CHS Me 10 (6–13) yrs. ARIC Me 16 (15–17) yrs.	HTN 1.50 (1.33–1.70) in CHS cohort 2.11 (1.87–2.38) in ARIC cohort	HR from univariate analysis. HTN was defined as a BP ≥140/90 mm Hg or a physician diagnosis of HTN in the CHS. HTN was defined as a BP ≥140/90 mm Hg or current antihypertensive Tx in the ARIC.
Mitchell *et al.*, 2007[92]	FHS (the 16th examination of the original cohort and the 2nd examination of the offspring cohort)	Prospective cohort study	5,331	698 (13.1%)	Males aged 35–90 yrs. (Me 56 yrs.) Females aged 35–91 yrs. (Me 58 yrs.) 45% males	Mean 16 yrs.	SBP 1.14 (1.04–1.25) per 20 mm Hg increase PP 1.26 (1.12–1.43) per 20 mm Hg increase	There was no significant association with MAP, as well as change in SBP and PP assessed over time. HRs adjusted for age, gender, and time-dependent BMI, smoking, valvular disease, MI, HF, DM, ECG-based LVH, and HTN Tx.
Nyrnes *et al.*, 2012[93]	Tromso study	Prospective cohort study	22,815	822 (3.6%)	Aged 25 to 96 yrs., mean 46 yrs.	Mean 11.1 yrs.	HTN (univariate???) 1.98 (1.46–2.69) in females and 1.40 (1.13–1.74) in males	HTN was defined as BP >140/90 mm Hg or antihypertensive Tx.

Table 1. *Continued*

Ref.	Data source	Design	No of patients (AF free at baseline)	Incident AF	Population	Follow-up	Risk for incident AF[a]	Comments
O'Neal *et al.*, 2015[94]	MESA	Prospective cohort study	5,311	182 (3.4%)	Aged 62 ± 10 yrs. 47% males 21% pre-HTN 49% HTN	Me 5.3 (IQR 4.8–5.5) yrs.	Pre-HTN 1.8 (1.004–3.2) HTN 2.6 (1.6–4.4)	HRs adjusted for age, gender, race/ethnicity, income, education, smoking, DM, BMI, TC, HDL–cholesterol, lipid–lowering Tx, aspirin, and LVH Prehypertension was defined as BP between 120–139/80–89 mm Hg and no antihypertensive Tx. HTN was defined as BP ≥140/90 mm Hg or a history of at least 2 consecutive visits in which antihypertensive Tx use was reported.
Okin *et al.*, 2015[95]	LIFE	Prospective, double-blind randomized clinical trial	8,831	701 (7.9%)	Aged 67 ± 7 yrs. 45.5% males	Mean 4.6 ± 1.1 yrs.	SBP 0.60 (0.45–0.82) ≤130 mm Hg SBP 0.76 (0.62–0.93) 131–141 mm Hg vs. ≥142 mm Hg SBP 0.87 (0.83–0.91) per 10 mm Hg decrease	Adjusted for randomized Tx allocation, age, gender, race, DM, CHD, MI, HF, previous antihypertensive Tx, baseline glucose and creatinine, urine albumin/creatinine ratio, Sokolow–Lyon voltage and QRS duration (standard covariates), incident MI, HF, in-treatment DBP, Cornell product LVH, heart rate, HDL, and non-HDL cholesterol (time-varying covariates)
Roetker, *et al.*, 2014[96]	MESA	Prospective cohort study	6,630	307 (4.6%) 5.9 per 1,000 PY	No incident AF Aged 62 ± 10 yrs. 47% males 36% antihypertensive Tx Incident AF Aged 70 ± 8 yrs. 61% males 56% antihypertensiveTx	Mean 7.8 ± 1.7 yrs.	SBP 1.21 (1.09–1.36) per 21.5 mm Hg increase DBP 1.03 (0.91–1.16) per 10.3 mm Hg increase MAP 1.13 (1.01–1.27) per 12.6 mm Hg increase PP 1.28 (1.14–1.44) per 17.2 mm Hg increase	HRs adjusted for age, gender, race/ethnicity, and site. Various models were developed. PP remained significant when modelled jointly with MAP after additional adjustment for education, height, BMI, smoking status, antihypertensive Tx, DM, PR interval, heart rate, MRI-based LV mass, interim MI and HF events (HR 1.26, 95% CI 1.02–1.55 per 17.2 mm Hg increase)
Rosengren *et al.*, 2009[97]	PPS, intervention group	Prospective cohort study	6,903	1,253 (18.2%)	Aged 51.5 ± 2.3 yrs. 100% males HTN Tx 5.0–5.9 across study subgroups	Me 25.0 (IQR 20.1–28.7) months	SBP 1.40 (1.19–1.64) for 146–161 mm Hg 1.73 (1.48–2.03) for >161 mm Hg vs. <133 mm Hg	HRs adjusted for age. No significant association for SBP of 133–145 mm Hg vs. <133 mm Hg

Table 1. *Continued*

Ref.	Data source	Design	No of patients (AF free at baseline)	Incident AF	Population	Follow-up	Risk for incident AF[a]	Comments
Schnabel, *et al.*, 2009[98]	FHS (the 11th and the 17th examinations of original cohort; the 1st and the 3rd examinations of offspring cohort)	Prospective cohort study	4,764 (derivation cohort)	457 (9.6%)	Aged 45 to 95 yrs. (60.9 ± 9.9 yrs. on average) 45% males	Varies for different examination cycles; max. of 10 yrs. from the beginning of each follow-up period for the first AF event	SBP 1.21 (1.11–1.33) per SD increase PP 1.25 (1.14–1.36) per SD increase Treatment for HTN 1.80 (1.48–2.18)	No significant association with DBP. HRs adjusted for age and gender. 10-year risk estimation
Schnabel, *et al.*, 2010[99]	AGES CHS FHS (the 11th and the 17th examinations of original cohort; the 1st and the 3rd examinations of off spring cohort)	Validation of FHS algorithm to predict AF in two prospective cohort studies	14,412 AGES 4,238 CHS 5,410 FHS 4,764	1,359 (9.4%) AGES 12.8 per 1,000 PY CHS whites 22.7 per 1,000 PY FHS 4.5 per 1,000 PY CHS AA 18.4 per 1,000 PY	Aged from 60.9 ± 9.9 yrs. (FHS) to 76.3 ± 5.5 yrs. (AGES) Males from 35.8% (CHS AA) to 44.6% (FHS) Antihypertensive Tx from 24% (FHS) to 59.8% (AGES)	5 yrs.	SBP 1.14 (1.01–1.28) in AGES, 1.14 (1.07–1.22) in CHS white, 1.17 (1.01–1.36) in CHS AA, and 1.18 (1.03–1.35) in FHS per 20 mm Hg increase Antihypertensive Tx 1.89 (1.40–2.46) in AGES, 1.48 (1.29–1.69) in CHS white, 1.58 (1.09–2.31) in CHS AA, and 1.75 (1.28–2.37) in FHS	HRs adjusted for age and gender. 5-year risk estimation
Smith *et al.*, 2009[100]	Malmo Diet and Cancer study (MDCS)	Prospective cohort study	30,129	1,430 (4.7%)	Aged 44 to 73 yrs. (58.0 ± 7.6 on average) 39.8% males HTN 68.1% in males, 56.3% in females 17.3% antihypertensive Tx	Mean 11.2 yrs.	HTN 1.78 (1.48–2.14) in males 1.74 (1.42–2.13) in females	HRs adjusted for age HTN was defined as BP ≥140/90 mm Hg or antihypertensive Tx. For HTN defined as BP ≥160/95 HR 1.85 (95% CI 1.60–2.13) in males and HR 1.69 (95% CI 1.43–1.99) in females
Son *et al.*, 2016[101]	National Health Insurance Service database, South Korea	Prospective cohort study	206,013	3,517 (1.7%) 2.87 per 1000 PY	Aged ≥30 yrs. 58.8% males 21.2% HTN	6 yrs.	HTN 1.667 (1.537–1.807)	HR adjusted for age, gender, BMI and other comorbidities. HTN presence according to ICD-10 codes.
Thomas *et al.*, 2008[102]	Group Health (GH), US	Case–control study	899 controls, 433 incident AF	NA	AF pts aged 72 ± 9 yrs. 46.4% males Controls aged 67 ± 10 yrs. 57.3% males	NA	SBP 1.33 (1.16–1.52) per 14 mm Hg increase[b] PP 1.26 (1.10–1.44) per 14 mm Hg increase[b]	ORs adjusted for age, gender, and index year. BP levels achieved as a result of antihypertensive Tx were used. No significant association for achieved DBP per SD (9 mm Hg) increase.

Table 1. *Continued*

Ref.	Data source	Design	No of patients (AF free at baseline)	Incident AF	Population	Follow-up	Risk for incident AF[a]	Comments
Verdecchia *et al.*, 2003[103]	PIUMA	Prospective cohort study	2,482	61 (2.5%)	Aged 51 ± 12 yrs. 53.2% males No HTN Tx at study entry	Mean 5.3 yrs.	No association between ambulatory or office BP and AF risk	LV mass 1.73 (1.34–2.24) for acute AF 1.70 (1.19–2.43) for chronic AF per SD (14 g/height$^{2.7}$) increase were independent predictors of paroxysmal AF (age-adjusted) and chronic AF (age and LAD adjusted), respectively
Verdecchia *et al.*, 2012[104]	ONTARGET TRANSCEND	Pooled analysis of 2 parallel, prospective, randomized, double-blind clinical trials	30,424	2,092 pts (15.1 per 1,000 PY)	Aged 66.4 ± 7.0 yrs. 70.2% males	Me 4.7 yrs.	HTN 1.34 (1.21–1.49)	There was no significant association with baseline SBP since pts. with SBP 160-mm Hg or DBP 100-mm Hg at randomization were excluded.
Vermond *et al.*, 2015[105]	PREVEND LIFE	Prospective cohort study	8,265	265 (3.2%)	Aged 49 ± 13 yrs. 49.8% males Incident AF group Age 62 ± 9 yrs. 70% males 54% HTN No AF group 49 ± 13 yrs. 49% males 26% HTN	Mean 9.7 ± 2.3 yrs.	SBP 1.11 (1.01–1.22) per 10 mm Hg increase Antihypertensive Tx 2.14 (1.43–3.20)	HRs adjusted for age and gender. HTN was defined as SBP >140 mm Hg, DBP >90 mm Hg, or antihypertensive Tx.
Wachtell *et al.*, 2005[106]		Prospective, double-blind randomized clinical trial	8,851	371 (4.2%)	Age range 55–80 yrs.	Mean 4.8 yrs.	SBP 1.09 (1.01–1.18) per 10 mm Hg increase	Adjusted for age, male gender, Cornell voltage-duration

Abbreviations: AA, African Americans; AGES, Age, Gene and Environment Susceptibility - Reykjavik study; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CHD, coronary heart disease; CHS, Cardiovascular Health Study; CPRD, Clinical Practice Research Datalink; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; FHS, Framingham Heart Study; HF, heart failure; HTN, hypertension; ICD, international classification of diseases; IQR, interquartile range; LAD, left atrial diameter; LIFE, Losartan Intervention For Endpoint reduction in hypertension study; LVH, left ventricular hypertrophy; M, mean; MAP, mean arterial pressure; Me, median; MESA, Multi–Ethnic Study of Atherosclerosis; MI, myocardial infarction; NA, not applicable; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; PIUMA, Progetto Ipertensione Umbria Monitoraggio Ambulatoriale; PP, pulse pressure; PPS, Primary Prevention Study; PREVEND, Prevention of Renal and Vascular End-stage Disease; pts, patients; PY, person-years; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TRANSCEND, Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease; Tx, treatment; WHS, Women's Health Study; Yrs., years.

[a]Expressed as hazard ratio and 95% confidence interval.

[b]Odds ratio and 95% confidence interval.

Table 2. Clinical scores to assess risk of AF development

CHARGE-AF[86]	FHS AF risk score[98]	ARIC AF risk score[88]
Age (5-year increment)	Age (5-year increment, range 45–≥85)	Age (5-year increment, range 45–64)
Race (White vs. African Americans)	Body mass index (≥30 vs. <30 kg/m^2)	Race (Black vs. White)
Height (10 cm increment)	Systolic blood pressure (≥160 vs. <160 mm Hg)	Height (164–<173 cm or ≥164 cm vs.<164 cm)
Weight (15 kg increment)	Treatment for hypertension (Yes vs. No)	Systolic BP (20 mm Hg increment, range <100–≥160)
Systolic BP (20 mm Hg increment)	PR interval (160–199 or ≥200 ms vs. <160 ms)	Hypertension medication use (Yes vs. No)
Diastolic BP (10 mm Hg increment)	Significant cardiac murmur by years of age[a] (5-year increment, range 45–≥85)	Smoking status (Former or Current vs. Never)
Smoking (current)	Heart failure by years of age (5-year increment, range 45–84)	Precordial murmur (Yes vs. No)
Antihypertensive medication use (Yes vs. No)		Left atrial enlargement (ECG based, Yes vs. No)
Diabetes (Yes vs. No)		Left ventricular hypertrophy (ECG based, Yes vs. No for White race)
Heart failure (Yes vs. No)		Diabetes mellitus by years of age (5-year increment, range 45–64)
Myocardial infarction (Yes vs. No)		Heart failure (Yes vs. No)
Left ventricular hypertrophy (ECG based, Yes vs. No)		Coronary heart disease by years of age (5-year increment, range 45–64)
PR Interval (<120 or >199 vs. 120–199)		

Abbreviations: ARIC, Atherosclerosis Risk In Communities; BP, blood pressure; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; ECG, electrocardiogram; FHS, Framingham Heart Study.
[a]Grade 3/6 systolic, any diastolic.

Autonomic dysregulation

Dysregulation in the autonomic nervous system also contributes to the development of substrate for AF, the onset of arrhythmia and its maintenance. The left atrium has an extensive neural network of sympathetic and parasympathetic fibers, which form nerves, ganglia, and plexi, accumulating data from the baroreceptors, chemoreceptors, and mechanical stress receptors, located in the kidneys, major arteries (e.g., aorta, carotid bodies), and heart itself.[34] Indeed, arrhythmia onset was shown to be triggered by the synchronous increased sympathovagal discharge or fluctuations in autonomic tone[35,36]; when driven by strenuous physical activity or in patients with structural heart disease sympathetic flow contributes,[37] while vagal influences may be amenable for AF in patients with no evidence of structural heart disease, i.e., lone AF.[34]

What are the effects of sympathetic and parasympathetic system on atrial electrophysiology? Sympathetic activation *via* β1-adrenergic receptors leads to cellular calcium overload due to increased calcium influx *via* L-type calcium channels as well as release of calcium from the sarcoplasmic reticulum *via* ryanodine receptors during diastole. Excess of calcium is removed *via* sodium–calcium exchanger with a 3 (Na^+) to 1 (Ca^{2+}) ratio, generating electrical current sufficient for occurrence of delayed after depolarisations. With respect to action potential, the influence of sympathetic flow may vary with the plateau phase remaining unchanged or reduced. This is due to synergistic effect of increased L-type calcium current and potassium currents (ultra-rapid delayed rectified current, slow delayed rectified current, and acetylcholine-dependent current).[34]

Effects of parasympathetic system are mediated *via* muscarinic receptors and in contrast to effects of sympathetic system are associated with definite shortening of action potential duration and hence, decreased refractoriness due to inhibition of L-type calcium current and activation of acetylcholine-dependent potassium current.[34,38] With the onset of arrhythmia further shortening of action potential occurs because of autoprotective limitation of calcium entry to cells, that is activated as a result of calcium overload due to the high atrial activation rate. Ectopic activation is further supported with the spontaneous calcium release from the sarcoplasmic reticulum.[34]

Effect of hypertension on AF substrate

Are there similarities between the pathogenesis of AF and hypertension? A close relationship is apparent with respect to atrial fibrosis, given that hypertension may cause substantial structural changes in the left atrium.[25] Persistent hyperactivation of the rennin–angiotensin–aldosterone axis is one of the key mechanisms in the development of arterial hypertension with changes observed both in vascular beds and myocardium as well as other target organs, including vasoconstriction, cellular proliferation and hypertrophy, cells uncoupling, apoptosis, and fibrosis.[39] Moreover, renin–angiotensin–aldosterone system activation is associated with increased sympathetic flow and *vice versa*, sympathetic activation enhances renin synthesis in the juxtaglomerular cells.[40]

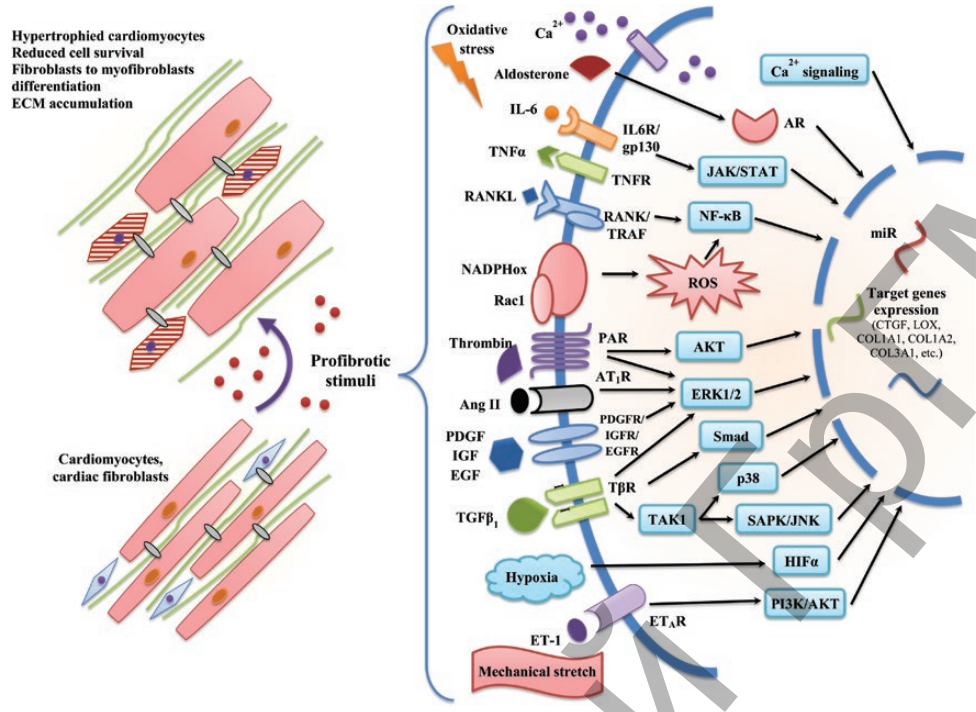

Figure 2. Simplified scheme of the profibrotic pathways at the tissue and cellular levels. Abbreviations: AKT, protein kinase B; AngII, angiotensin II; AT1R, AngII type 1 receptor; AR, aldosterone receptor; Ca^2+, calcium; COL1A1, gene encoding α1 type I collagen; COL1A2, gene encoding α2 type I collagen; COL3A1, gene encoding α1 type III collagen; CTGF, connective tissue growth factor; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, EGF receptor; ERK, extracellular signal-regulated kinase; ET-1, endothelin-1; ETAR, type A ET-1 receptor; gp130, glycoprotein 130; HIF-α, hypoxia inducible factor α; JAK, Janus kinase; JNK, c-jun N-terminal kinase; IGF, insulin-like growth factor; IGFR, IGF receptor; IL6, interleukin 6; IL-6R, IL-6 receptor; LOX, lysyl oxidase; MAPK, mitogen-activated protein kinase; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NADPHox, nicotinamide adenine dinucleotide phosphate oxidase; NFκB, nuclear factor kappa B; p38, protein 38 (member of MAPK, mitogen-activated protein kinases); PAR, protease-activated receptor; PDGFR, platelet derived growth factor; PDGFR, PDGF receptor; PI3K, phosphoinositide 3-kinase; Rac1, Ras-related C3 botulinum toxin substrate 1; RANK, receptor activator of NFκB; RANKL, RANK ligand; ROS, reactive oxygen species; SAPK, stress-activated protein kinase; Smad, transcriptional factor, named by fusion of C. elegans Sma protein and Drosophila Mad (mothers against decapentaplegic) protein; STAT, signal transducer and activator of transcription; TAK1, TGF-β1 activated kinase 1; TβR, TGF-β1 receptor (type I and type II); TGF-β1, transforming growth factor β1; TNFα, tumor necrosis factor α; TNFR, TNFα receptor; TRAF, TNF receptor associated factor.

Substantial data linking electrical, structural, and autonomic remodeling in hypertension and AF have been derived from studies on renal sympathetic denervation in animal experiments (Table 3) and human studies (Table 4). Early data obtained in the first human studies and animal experiments show an overall favorable effect of renal sympathetic denervation on electrophysiological parameters, which might affect AF inducibility and sustainability that translated into decreased recurrence rate in AF patients (Tables 3 and 4). However, there is still inconsistency between studies and criticisms due to study design and small number of patients involved. Thus, clinical trials that address renal sympathetic denervation as an complementary procedure to pulmonary vein isolation have started.[41]

When switching from the systemic effects of sympathetic and rennin–angiotensin–aldosterone system activation to simple hemodynamic fluctuations as a link between hypertension and AF, it is apparent that left ventricular diastolic dysfunction (associated with myocardial hypertrophy caused by hypertension) as well as arterial stiffening due to aging, hypertension, and other risk factors all lead to increased left ventricular filling pressures, and retrograde mechanical overload and stretching of left atrium (Figure 1). This is supported with both experimental and clinical data. In various hypertension models, Lau *et al.* observed progressive biatrial hypertrophy, left atrial dysfunction, and greater AF inducibility along with significant conduction slowing. This coupled with inflammatory cell infiltration and increased interstitial fibrosis resulted in longer and more fractionated AF episodes. Some electrical and structural changes became apparent as early as in 5 weeks after the onset of hypertension, some appeared later, but progressive atrial remodeling at a background of hypertension is indisputable.[42,43]

Examination of large cohort data from the Framingham Heart Study show higher augmentation index (hazard ratio [HR] 1.16; 95% CI 1.02–1.32), central pulse pressure (HR 1.14; 95% CI 1.02–1.28), and lower flow-mediated dilation (HR 1.27; 95% CI 0.63–0.99) to be associated with increased risk of incident AF.[44] Echocardiographic Doppler indices of left ventricular diastolic dysfunction are predictive of AF onset too.[45,46]

PROGNOSTIC IMPACT OF HYPERTENSION IN AF

AF may have a variety of implications with respect to patient prognosis. Participants from the Cardiovascular Health Study had poorer outcomes when AF was present at baseline or developed during follow-up, for example,

Table 3. Overview of studies addressing effect of renal sympathetic denervation on AF substrate and arrhythmia inducibility in animal experiments

Ref.	Model[a]	Autonomic and electrical remodeling[b]	Structural remodeling[b]	AF inducibility
Hou *et al.*, 2013[107]	Canines LSG stimulation RAP	↓ AERP shortening and dispersion ↓ Plasma NE	NA	↓
Liang *et al.*, 2015[108]	Canine Unilateral kidney injury (renal artery microembolisation)	↓ AERP shortening ↓ P-wave duration ↓ Antegrade Wenckbach point ↓ Plasma NE	↓ Plasma renin and aldosterone ↓ Angiotensin II, aldosterone, hs-CRP, and IL-6 in atrial myocardium ↓ Interstitial fibrosis in atrial myocardium	↓
Linz *et al.*, 2013[109]	Porcine RAP	↑ PQ-interval ↔ P-wave duration ↔ AERP shortening ↑ AV node effective refractory period ↓ Antegrade Wenckebach point	NA	↔ (but shorter duration)
Linz *et al.*, 2013[110]	Porcine OSA (repetitive NTP maneuvers)	↓ Spontaneous APC	↓ Plasma renin activity and aldosterone ↔ Angiotensin II, aldosterone, 11β-HSD2, and MR protein expression in atrial myocardium. ↔ NADPH oxidase activity, Prx-SO3 level, redox state of GSH ↔ CTGF mRNA or protein expression	↓
Linz *et al.*, 2015[111]	Goats RAP	↓ TH-positive sympathetic nerve staining ↓ Transcardiac NE levels ↓ NGF expression ↓ AF cycle length ↓ AF complexity. ↑ Conduction velocity ↔ Expression of β1 and β2-adrenergic receptors in the atrium	↓ Atrial interstitial fibrosis ↓ Myocyte diameter	↔
Wang *et al.*, 2013[112]	Canine RAP	↓ TH- and GAP43- positive nerves ↓ AERP shortening	↓ Plasma Angiotensin II and aldosterone ↓ ANP, TNF-α, and IL-6 in atrial myocardium ↓ Upregulation of caspase-3, bax, and Cx40 ↔ Cx43 ↓ Downregulation of Bcl-2 ↓ TUNEL-positive cells	↓
Wang *et al.*, 2014[113]	Canine Heart failure (RV tachypacing)	↓ P-wave duration and dispersion	NA	↓
Wang *et al.*, 2015[114]	Canine RAP	↓ AERP shortening ↑ AF cycle length ↓ AERP dispersion ↓P-wave duration and dispersion	↓ Fibrosis and ultrastructural changes ↓ Heterogeneity of Cx43 distribution in atrial myocardium.	↓
Wei *et al.*, 2016[115]	Rabbits Abdominal aortic constriction	NA	↓ Collagen volume fraction ↓ Collagen I, CTGF and TGF-β1 protein and expression in atrial myocardium ↓ Angiotensin II and aldosterone plasma levels	↓
Zhao *et al.*, 2012[116]	Canines RAP	↔	↔ Plasma renin and aldosterone (trend towards ↓)	↓
Zhao *et al.*, 2013	Canines HF (RV tachypacing)	↓ AERP shortening	↓ Atrial interstitial fibrosis ↓ BNP, Angiotensin II, TNF-α, and TGF-β1 expression in atrial myocardium	↓

Table 3. *Continued*

Ref.	Model[a]	Autonomic and electrical remodeling[b]	Structural remodeling[b]	AF inducibility
Zhou *et al.*, 2016[117]	Canine Acute atrial ischemia / infarction (coronary occlusion)	↓ Sympathetic discharges ↓ NE and EPI in the atrial myocardium	NA	↓

↑ = increased; ↓ = reduced; ↔ = not different. Abbreviations: 11β-HSD2, 11-β-hydroxysteroid-dehydrogenase-2; AERP, atrial effective refractory period; APC, atrial premature contraction; AF, atrial fibrillation; BCL-2, B-cell lymphoma gene 2; CTGF, connective tissue growth factor; GAP43, growth-associated protein 43; GSH, glutathione; LSG, Left stellate ganglion; MR, mineralocorticoid receptor; NADPH, nicotinamide adenine dinucleotide phosphate; NGFβ, nerve growth factor beta; NTP, negative tracheal and thoracic pressure; OSA, obstructive sleep apnea; Prx, peroxiredoxin; RAP, rapid atrial pacing; RSD, renal sympathetic denervation; TH, tyrosine hydroxylase; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling.

[a]Regimens of pacing to induce AF varied between studies (e.g., burst, intermittent, short-term or long-term pacing).

[b]Changes in animals, which underwent RSD, compared to those, which did not undergo RSD.

Table 4. Overview of studies addressing effect of renal sympathetic denervation on AF substrate and clinical course in humans

Ref.	Study population and design	No of patients	Duration of follow-up	Main results
McLellan *et al.*, 2015[118]	Treatment-resistant HTN[a] 2 (14%) pts had AF history	14	6 months	↓ P-wave duration ↑ Atrial global conduction velocity ↓ Fractionated electrograms ↓ Diffuse ventricular fibrosis (MRI-based assessment) ↔ LA size ↔ Global tissue voltage ↔ Discrete sites of low voltage ↔ APC/SVT burden ↔ AF inducibility
Pokushalov *et al.*, 2012[119]	Severe treatment-resistant HTN[b] and symptomatic drug-refractory paroxysmal/ persistent AF	27	1 year	69.2% vs. 28.6% AF-free pts in PVI with RSD vs. PVI-only group, respectively (P = 0.033)
Pokushalov *et al.*, 2014[120]	Pooled analysis of 2 studies—moderate and severe treatment-resistant HTN[b] and symptomatic drug-refractory paroxysmal/ persistent AF	86	1 year	63.4% vs. 41.0% AF-free pts. in PVI with RSD vs. PVI-only group, respectively HR 0.45, 95% CI 0.23–0.86 (adjusted for study and AF type)
Schirmer *et al.*, 2015[121]	Treatment-resistant HTN[a] Pts with AF history excluded	66	6 months	↓ LAVI (independently of SBP) ↓ APC (independently of LA size)

↑ = increased; ↓ = reduced; ↔ = not different as a result of RSD. Abbreviations: APC, atrial premature contractions; AF, atrial fibrillation; BP, blood pressure; HTN, hypertension; LA, left atrium; LAVI, left atrial volume index; MRI, magnetic resonance imaging; pts, patients; PVI, pulmonary vein isolation; RSD, renal sympathetic denervation; SVT, supraventricular tachycardia.

[a]Treatment-resistant hypertension was broadly defined as BP greater than target despite concurrent use of diuretic and at least 2 antihypertensive drugs at adequate doses belonging to different classes.

[b]Moderate treatment-resistant hypertension was defined as poor control by antihypertensive drugs with a BP range ≥140/90 to <160/100 mm Hg; severe—BP ≥160/100 mm Hg.

ischemic stroke (HR 1.98, 95% CI 1.63–2.39), coronary heart disease (HR 1.76, 95% CI 1.54–2.03), myocardial infarction (HR 1.40, 95% CI 1.14–1.71), heart failure (HR 3.18, 95% CI 2.78–3.64).[47] Similar evidence comes from a large primary care database in the United Kingdom that included over 4 million adults aged 30–90 years, where AF was associated with ischemic heart disease (HR 2.52, 95% CI 2.23–2.84), heart failure (HR 3.80, 95% CI 3.50–4.12), ischemic stroke (HR 2.72, 95% CI 2.19–3.38), hemorrhagic stroke (HR 2.22, 95% CI 1.60–3.08), chronic kidney disease (HR 1.42, 95% CI 1.31–1.54), peripheral arterial disease (HR 2.09, 95% CI 1.73–2.53), and vascular dementia (HR 1.57, 95% CI 1.14–2.17).[48]

Despite advances in diagnosis and treatment mortality from causes associated with AF remains high and has been shown to increase over past decades with age-standardized mortality rates rising from 70.6 to 107.1 per 100,000 of population; also, there was a 2.0% annual percent increase in 1999–2009, and to 4.5% up to 2014 in the United States.[49] This rise in AF-associated mortality particularly affected younger subjects compared to the whole AF population that is represented by elderly people, e.g., 3.7% and 7.3% before and after year 2010, respectively.[49]

How we best manage AF patients co-presenting with hypertension to improve patient outcomes is subject to much discussion. Hypertension is known to be an independent risk factor for range of cardiovascular complications while blood pressure reduction is associated with lower risk of adverse events.[50–52] It is beyond the scope of current review to analyse

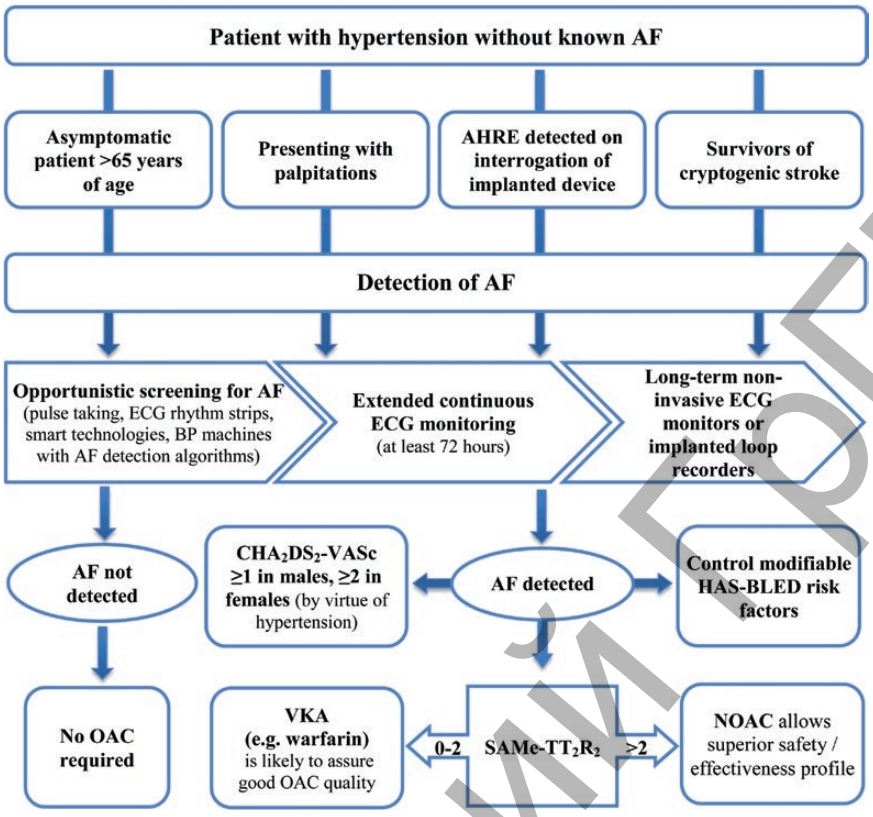

Figure 3. Decision pathway for stroke prevention in patient with hypertension and possible/newly diagnosed nonvalvular AF. For the CHA_2DS_2-VASc, HAS-BLED, and SAMe-TT_2R_2 see Table 5. Abbreviations: AF, atrial fibrillation; AHRE, atrial high rate episode (defined as episodes >5–6 minutes duration and heart rate of >180 bpm detected by an implanted device); BP, blood pressure; ECG, electrocardiogram; NOAC, nonvitamin K oral anticoagulant; OAC, oral anticoagulation; VKA, vitamin K antagonist.

Table 5. Stroke and bleeding risk stratification with the CHA_2DS_2-VASc and HAS-BLED scores, and choice of OAC with the SAMe-TT_2R_2 score

CHA_2DS_2-VASc[122]	Score	HAS-BLED[123]	Score	SAMe-TT_2R_2[69]	Score
CHF (moderate-to-severe LV systolic dysfunction with LV EF ≤40% or recent decompensated heart failure requiring hospitalization)	1	Hypertension (systolic blood pressure >160 mm Hg)	1	Sex category (i.e., female gender)	1
Hypertension	1	Abnormal renal or liver function	1 or 2	Age <60 years	1
Age ≥75 years	2	Stroke	1	Medical history (≥2 of the following: hypertension, diabetes mellitus, CAD/MI, PAD, CHF, previous stroke, pulmonary, hepatic or renal disease)	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1	Treatment with interacting drugs (e.g., amiodarone)	1
Stroke/TIA/SE	2	Labile INRs (if on warfarin)	1	Tobacco use (within 2 years)	2
Vascular disease (prior MI, PAD, or aortic plaque)	1	Age (e.g., >65, frail condition)	1	Race (i.e., non-Caucasian)	2
Aged 65–74 years	1	Drugs (e.g., concomitant antiplatelets or NSAIDs) or alcohol excess/abuse	1 or 2		
Sex category (i.e., female gender)	1				
Maximum score	9	Maximum score	9	Maximum score	8

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; INR, international normalized ratio; LV, left ventricular; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA/SE, transient ischemic attack/systemic embolism; PAD, peripheral artery disease.

Table 6. Effect of hypertension on PVI outcomes in AF

Ref.	Design	Recruitment	No of pts	Age (yrs.)	Males	AF history	AAD failed	Nonparoxysmal AF	LA diameter (mm)	HTN	Follow-up	AF recurrence	Effect of HTN on AF recurrence	Other independent predictors	General notes
Baek *et al.*, 2016[124]	Retrospective cohort study	2009–2015	1,825	57.9 ± 11.1	1354 (74.2%)	NR	NR	NR	NR	846 (46.4)	42 ± 19 mos.	523 (28.7%)	NS	Dyslipidemia, overweight	Cohort of pts. with metabolic syndrome
Bisbal *et al.*, 2013[125]	Prospective cohort study	NR	106	51.8 ± 11.4	80 (75.5%)	52 ± 62.5 mos.	NR	47 (44.3%)	41.9 ± 5.9	37 (34.9%)	Me 28.5 mos.	50.4% and 76.4% after single and repeated procedures	OR 3.69 (1.28–10.65)	LA sphericity	
Chen *et al.*, 2015[83]	Prospective cohort study	2008–2013	216	AF 65.8 ± 11.7 No AF 61.7 ± 9.7	AF 64 (75.3%) No AF 104 (79.4%)	NA	NR	NA	AF 41.5 ± 4.5 no AF 38.5 ± 4.6	AF 66 (77.6%) No AF 78 (59.5%)	29.1 ± 18.3 mos.	85 (39.4%)	2.52 (1.47–4.32) (univariate analysis), in multivariate analysis was included as component of the HATCH score)	HATCH score, LAD	Study addressed risk of AF onset after atrial flutter ablation
Efremidis *et al.*, 2014[126]	Prospective cohort study	NR	57	56.9 ± 12.2	34 (59.6%)	4.9 ± 4.7 yrs.	NR	0 (0%)	SR 40.4 ± 4.4 AF recurrence 40.3 ± 5.4	27 (47.4%)	8.0 ± 2.5 mos.	16 (28.1%)	NS	SF-36 Mental summary score, STAI-trait, BDI scores	Study addressed association QoI, depression and anxiety with AF recurrence
Heist *et al.*, 2012[127]	Prospective cohort study	2008–2010	143	62 ± 9	109 (76.2%)	5.7 ± 5.2 yrs.	NR	143 (100%)	45 ± 7.7	86 (60%)	>1000 days	74 (51.7%)	OR 2.83	Male gender, age, termination of AF during the procedure, ablation time	Cohort of pts. with NPAF
Hwang *et al.*, 2011[128]	Retrospective cohort study	2005–2009	105	58 ± 11	76 (72.4%)	35.0 ± 66.8 mos.	NR	49 (46.7%)	41.3 ± 6.9	41 (39.0%)	Mean 23 mos.	26 (24.8%)	NS	Aortic plaque thickness >4 mm	
Kim *et al.*, 2014[129]	Prospective cohort study	2008–2010	130	54.6 ± 9.3	114 (87.6%)	77.4 ± 66.2 mos.	NR	130 (100%)	LAVi SR maintenance 39.3 ± 12.0 ml/m^2 AF recurrence 35.0 ± 12.6 ml/m^2	22 (32.8%) 30 (49.2%)	2 yrs.	61 (46.9%)	NS	LAeF	Cohort of pts. with NPAF
Leong-sit *et al.*, 2013[130]	Prospective cohort study	2008–2009	144	60 (52–65)	114 (79.2%)	NR	NR	66 (45.8%)	46 ± 8	49 (34.0%)	1 year.	52 (36.1%)	4.15 (1.29–11.9) for postprocedural AF inducibility NS for AF recurrence	LAD >45 mm, persitent AF	
Letsas *et al.*, 2013[131]	Prospective cohort study	NR	226	55.9 ± 9.6	184 (81.4%)	NR	NR	92 (40.7%)	40.9 ± 5.3	103 (45.6%)	432.3 ± 306.1 days	95 (42.0%)	NS	Level of fibrinogen and uric acid	
Li *et al.*, 2013[132]	Prospective cohort study	2008–2011	1,768	58.8 ± 11.1	1218 (68.9%)	NR	NR	611 (34.6%)	39.6 ± 6.2	885 (50.2)	633 ± 415 days	703 (39.8%)	NS	LAD	Cohort of pts. with prior ischemic stroke
Lin *et al.*, 2014[133]	Prospective cohort study	NR	743	61.6 ± 10.1	0 (0%)	NR	NR	202 (27.2%)	38.8 ± 6.3	410 (55.2%)	43 (16–108) mos.	217 (29.2%)	NS	LAD	Cohort of pre-/post-menopausal women

Table 6. *Continued*

Ref.	Design	Recruitment	No of pts	Age (yrs.)	Males	AF history	AAD failed	Nonparoxysmal AF	LA diameter (mm)	HTN	Follow-up	AF recurrence	Effect of HTN on AF recurrence	Other independent predictors	General notes
Lioni *et al.*, 2014[134]	Prospective cohort study	NR	316	57.4 ± 11.6	178 (56.3%)	5.9 ± 5.1 in pts. ≥65 yrs. 4.7 ± 4.4 in pts. <65 yrs.	NR	NA	42.6 ± 4.5 in pts. ≥65 yrs. 39.1 ± 4.4 in pts. <65	114 (36.1%)	34.0 ± 15.1 mos.	112 (35.4%)	7.69 (2.35–25) in pts. ≥65 yrs. NR for pts. pts. <65 yrs.	LAD, dyslip-idaemia, CAD	Elderly pts.
Lodziński *et al.*, 2014[135]	Prospective cohort study	2003–2007	180	50.2 ± 11.2	123 (68.3%)	Me 60 mos.	5 ± 2	36 (20%)	42	83 (46.1%)	55 mos.	90 (65.7%)	OR 1.62 (1.19–2.53)	Persistent AF	
Machino-Ohtsuka *et al.*, 2013[136]	Prospective cohort study	2005–2011	75	65 ± 7	55 (73.3%)	7.3 ± 7.2 yrs.	3 ± 1	51 (68.0%)	LAVi 43 ± 14 ml/m^2	57 (77%)	34 ± 16 mos.	21 (28.0%)	2.04 (1.04–4.17)	AF type	
Miyazaki *et al.*, 2011[137]	Prospective cohort study	NR	474	61 ± 10	364 (76.8%)	55.6 ± 62.0 mos.	1.9 ± 1.5	0 (0%)	37.6 ± 5.1 mm	131 (28%)	30 ± 13 mos.	156 (32.9%)	NS	LAD	
Miyazaki *et al.*, 2012[138]	Prospective cohort study	NR	362	61.0 ± 9.8	274 (75.7%)	56.3 ± 58.8 mos.	From 1.4 ± 1.1 (yearly paroxysms) to 2.2 ± 1.5 (daily paroxysms)	0 (0%)	38.4 ± 5.4	111 (30.7%)	124 mos.	138 (38.1%)	NS	LAD	
Montserrat *et al.*, 2014[139]	Prospective cohort study	NR	154	53 ± 10	120 (77.9%)	After the first procedure 52 ± 34 mos. After repeated procedures 71 ± 54 mos.	NR	77 (50.0%)	43 ± 6	69 (44.8%)	6 mos.	47 (45.6%) after the first procedure 31 (60.8%) after repeated procedures	2.60 (1.11–6.12) after the first procedure NS after repeated procedures	After the first procedure LA expansion index After repeated procedures: age	
Neilan *et al.*, 2014[140]	Prospective cohort study	2009–2012	165	HTN 58 ± 12 Controls 57 ± 11	HTN 96 (66%) Controls 13 (65%)	37 (26–62) mos.	NR	NR	41 ± 5	145 (87.9%)	37 (26–62) mos.	45 (27.3%)	NS	ECV in ventricular myocardium	ECV correlated with LAV, LV mass, LV diastolic function
Park *et al.*, 2014[141]	Prospective cohort study	2009–2013	576	57.8 ± 11.6	435 (75.5%)	NR	NR	180 (31.3%)	From 40.5 ± 5.9 in pts. with PR<166 ms to 42.7 ± 6.1 in pts. with PR ≥202 ms	276 (47.9%)	13.1 ± 7.5mos.	80 (13.9%)	NS	Age, PR interval, mean LA voltage, and early recurrence (within 3 mos. blanking period)	
Parmar *et al.*, 2015[142]	Retrospective cohort study	2011–2012	94	66.5	63 (67.0%)	NR	NR	49 (52.1%)	146.8 ± 35.5 cm^2 [a]	56 (59.6)	Mean 336 days	26 (28.7%)	NS	Difference between EAM ablated area and LGE-MRI scar area	
Santoro *et al.*, 2015[143]	Prospective cohort study	NR	531	64.5 ± 9.6	370 (69.7%)	NR	NR	179 (33.7%)	44.1 ± 5.5 in uncontrolled HTN 42.7 ± 5.4 in controlled HTN mm 41.0 ± 6.1 in pts. without HTN	352 (66.3%), of which 160 (30.1%) uncon-trolled HTN	19 ± 7.7 mos.	65 (40.6%) in uncontrolled HTN 54 (28.1%) in controlled HTN 46 (25.7%) in pts. without HTN	2.59 (1.31–5.13) in pts. with uncon-trolled HTN and NPAF NS in PAF	non-PV triggers in pts. with uncontrolled HTN and NPAF	

Table 6. *Continued*

Ref.	Design	Recruitment	No of pts	Age (yrs.)	Males	AF history	AAD failed	Nonparoxysmal AF	LA diameter (mm)	HTN	Follow-up	AF recurrence	Effect of HTN on AF recurrence	Other independent predictors	General notes
Sotomi *et al.*, 2013[144]	Retrospective cohort study	2004–2010	392	61.7 ± 10.3	296 (75.5%)	51.9 ± 56.7 mos.	NR	113 (29%)	35.9 ± 5.3	173 (44%)	2.0 (1.5–3.2) yrs.	40 (10.0%)	NS	CRP>0.5 mg/dl	
Steinberg *et al.*, 2014[145]	Prospective cohort study	2001–2011	445	63.6 ± 10.7	327 (73.5%)	49.6 ± 46.7 mos.	NR	126 (28.3%)	41.0 ± 5.6	226 (50.8%)	66.0 ± 34.0 mos. (Me 62 mos.)	97 (21.8%)	1.88 (1.17–3.01)	Persistent AF	AF onset in pts. who were free from AF at least one year postablation
Takigawa *et al.*, 2012[146]	Retrospective cohort study	NR	292	61 ± 11	218 (74.7%)	4.43 ± 4.48 yrs.	1.6 ± 1.1	59 (20.2%)	38.2 ± 5.9	141 (48.3%)	18.9 ± 12.7 mos.	83 (28.4%)	2.86 (1.21–6.85) in pts. with nondilated LA NS in pts. with dilated LA	AF duration, RAS inhibitors use after procedure, LV EF in pts. with nondilated LA AF duration in pts. with dilated LA	
Teunissen *et al.*, 2016[147]	Prospective cohort study	2005–2011	509	57 ± 9.7	386 (75.8%)	6.9 ± 6.1 yrs.	NR	198 (38.9%)	43.1 ± 6.1	168 (33.0%)	After single procedure 66 ± 23 mos. Overall 55 ± 25 mos.	After sing le procedure 299 (58.7%) After last procedure 191 (37.5%)	NS after single procedure 1.57 (1.13–2.18) after last procedure	Persistent AF, long-standing persitent AF, AF duration (after single procedure) All above and female gender, DM	
Wang *et al.*, 2014[148]	Prospective cohort study	NR	213	58.3 ± 21.1 yrs.	112 (52.6%)	4–6 yrs.	NR	77 (36.2%)	From 36.6 ± 8.7 in normotensive PAF to 45.9 ± 12.8 in hypertensive NPAF	77 (36.2%)	up to 6 mos.	44 (20.6%)	16.2% in normo-tensive pts. vs. 28.6% in hyper-tensive pts.	HTN, size of the LA scar, LVA	
Winkle *et al.*, 2016[85]	Prospective cohort study	2003–2010	1,125 (derivation cohort)	62.3 ± 10.3	801 (71.2%)	6.4 ± 7.0 yrs.	1.30 ± 1.05	777 (69.1%)	43.0 ± 6.9	525 (46.7%)	2.5 ± 1.7 yrs.	302 (26.8%)	NS	Age, male gender, LAD, NPAF, CAD, No. of AAD failed	
Wójcik *et al.*, 2013[149]	Retrospective cohort study	NR	356	59 (51–65)	263 (73.9%)	4.99 (2.25–8.08) yrs.	At least one 356 (100) class I 144 (40.5%) class II 253 (71.1%) class III drugs 122 (34.3%) Amiodarone 90 (25.3%)	199 (55.9%)	21.9 (19.0–25.1) cm^2 [a]	266 (74.72)	5 yrs.	195 (54.8%)	1.37 (1.04 1.81) (univariate analysis) NS in multivariate analysis	NPAF, LA area, eGFR <68 ml/min	

Abbreviations: AAD, antiarrhythmic drugs; BDI, Beck Depression Inventory; CAD, coronary artery disease; CMR, cardiac magnetic resonance; DM, diabetes mellitus; EAM, electroanatomic map; ECV, extracellular volume; HTN, hypertension; LAEF, left atrial emptying fraction; LASP, left atrial sphericity; LAVi, left atrial volume index; LGE, late gadolinium enhancement; LVA, low voltage area; mos., months; MRI, magnetic resonance imaging; NPAF, nonparoxysmal AF; NR, not reported; NS, not significant; PAF, paroxysmal AF; PV, pulmonary veins; RAS, rennin–angiotensin system; SF-36, Short-Form Life Survey-36 items; STAI, State-Trait Anxiety Inventory; yrs., years.

[a]LA area.

all possible reciprocal relationships between AF, hypertension, and their respective complications. However, we focus on the impact of hypertension on stroke and systemic thromboembolism in AF and rhythm control management in AF.

Stroke prevention in AF

Prevention of stroke and other thromboembolic events is the principal component of AF management given that AF is associated with 5-fold elevated risk of stroke overall. Albeit AF confers procoagulant state itself stroke risk is largely determined by co-presenting stroke risk factors.[53] Oral anticoagulation with either vitamin K antagonists or nonvitamin K antagonists oral anticoagulant should therefore be considered in patients with at least 1 additional stroke risk factor[1,54] given that even a single stroke risk factor is associated with significantly increased risk.[55,56]

Hypertension is a well-established stroke risk factor not only in AF patients but also in patients with sinus rhythm.[57] In the large Swedish nation-wide AF cohort study presence of hypertension was shown to be associated with 19%; 95% CI 12–25% greater risk of ischemic stroke and 17%; 95% CI 11–22% greater risk of combination of ischemic stroke, transient ischemic attack, and systemic embolism.[58] Hypertension has been therefore incorporated into various stroke risk assessment schemes in line with other risk factors, including the guideline recommended CHA_2DS_2-VASc score (Table 5).[1,59]

Bleeding risk, along with AF-related stroke risk, must be evaluated in patients suitable for oral anticoagulant.[60] There are a range of factors which put patients at high risk of bleeding. Importantly, many risk factors confer both increased stroke and bleeding risk,[61] but many of them are also modifiable factors, hence a high bleeding risk score is not to rule out the use of oral anticoagulation but to highlight the importance of risk factor management. Indeed, uncontrolled hypertension is one of the independent risk factors for development of intracranial hemorrhage (HR 1.32, 95% CI 1.15–1.52) and major bleeding (HR 1.25, 95% CI 1.16–1.33).[58] Bleeding risk assessment using the HAS-BLED score (Table 5), includes uncontrolled hypertension (defined as blood pressure above 160 mm Hg) as one of the risk factors for bleeding.[1,53,59]

In the latest guidelines, nonvitamin K antagonists oral anticoagulants are recommended as first-line treatment in patients with AF requiring OAC.[62] Preference to nonvitamin K antagonists oral anticoagulants has been given in anticoagulation-naïve patient given their overall advantages over warfarin therapy as evidenced from trials and real-world data together with favorable pharmacokinetics and pharmacodynamics[63–67]; however, warfarin is a reasonable alternative, particularly when well managed and time in therapeutic range is high.[1,54,62,68] Many factors may interfere with the quality of anticoagulation control, including comorbidity and requirement to take many drugs.[69,70]

To avoid a trial period of vitamin K antagonists in the anticoagulation-naïve patients and aid decision making with respect to choice of oral anticoagulation the SAMe-TT_2R_2 score (Table 5) was developed and validated to distinguish patients who are capable of reaching the required time in therapeutic range with warfarin.[69,71]

Thus, AF and hypertension, stroke and bleeding risks, and even anticoagulation management are closely interlaced. Blood pressure control is an essential component of AF management. A schematic pathway for stroke prevention in the hypertensive patients with diagnosed or clinically suspected AF is shown in the Figure 3.

Rhythm control therapy in AF and hypertension

Rhythm and rate control strategies appeared to have similar effect in term of patients outcomes. The main advantage of a rhythm control strategy would be in symptomatic patients with AF where they are treated with the antiarrhythmic drugs or referred to either direct current cardioversion, catheter ablation of AF or both at different stages of the clinical course of this arrhythmia.[1] Given that hypertension contributes to structural and electrical remodeling in AF, it appeared to be predictive of AF recurrence after sinus rhythm restoration by either means. Recent studies on effect of hypertension on AF ablation outcome arrhythmia recurrence are summarized in Table 6.

However, approximately 30% of AF patients are asymptomatic and how best to treat this cohort of patients is of growing concern. A proportion of patients are fortunate enough to have AF detected by chance, often due to routine medical examinations for other reasons. The absence of symptoms does not remove or reduce the risk of associated

Table 7. Clinical scores for prediction of presence of AF substrate (DR-FLASH), onset of AF after atrial flutter ablation (HATCH), and freedom from AF after AF ablation (CAAP-AF)

DR-FLASH[84]	Score	HATCH[83]	Score	CAAP-AF[85]	Score
DM	1	Hypertension	1	Coronary artery disease	1
Renal dysfunction (eGFR <90 ml/min/1.73 m^2)	1	Age ≥75 years	1	Atrial diameter	0 to 4
Persistent AF	1	Transient ischemic attack or stroke	2	Age	0 to 3
LA diameter >45 mm	1	Chronic obstructive pulmonary disease	1	Persistent or long-standing AF	2
Age >45 years	1	Heart failure	2	Antiarrhythmics failed	0 to 2
Female sex	1			Female gender	1
Hypertension	1			Maximum score	13

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LA, left atrium.

stroke, with this cohort of patients often found to have a higher CHA_2DS_2VASc score than symptomatic patients.[22] Unfortunately, for the vast majority of patients with asymptomatic AF the first opportunity to detect this arrhythmia is in the context of an acute stroke.[72] One in 5 ischemic strokes are attributable to AF, of which greater than 20% AF are diagnosed after the stroke event.[73]

Overall the meta-analysis of Lin *et al.* that included 17 studies revealed a greater risk of postablation AF recurrence in hypertensive patients compared to those with normal blood pressure (relative risk 1.31, 95%CI 1.13–1.51); however, there was significant heterogeneity acknowledged.[74] An earlier meta-analysis did not demonstrate a significant association between hypertension presence and AF recurrence.[75]

Effectiveness of blood pressure management including control of other factors associated with blood pressure elevation has to be considered. Indeed, aggressive risk factor management that included blood pressure control along with weight reduction, blood lipids and glucose control, sleep-disordered breathing management, smoking and alcohol cessation resulted in greater reduction of LA volume index and LV hypertrophy compared to control subjects. This translates into a higher AF-free survival rate compared to conventional treatment.[76] Importance of early blood pressure control in slowing the rate of adverse remodeling seen in the myocardium of hypertensive patients is illustrated in the study by Fredersdorf *et al.*[77] They found lone AF to be a predictor of LA volume reduction after successful pulmonary vein isolation, while hypertension and LV hypertrophy interfered with the reverse remodeling.[77] Hypertension is one of independent predictors of overall procedural safety as evidenced from large real-world observational studies.[78]

Target organ damage in hypertension is also associated with AF recurrence. In the cohort of patients from the **A**trial **F**ibrillation **F**ollow up **I**nvestigation of **R**hythm **M**anagement (AFFIRM) trial those with normal left ventricular geometry experienced a 2-fold longer AF-free period while concentric left ventricular hypertrophy was associated with AF recurrence in the rhythm control arm (HR 1.49, 95% CI 1.10–2.01).[79] Significant left ventricular diastolic dysfunction that is commonly related to myocardial hypertrophy also places patients at higher risk of AF recurrence after catheter ablation.[80]

Subsequently, hypertension has been incorporated into several decision-making tools to aid rhythm control management (Table 7). Hypertension was found to be predictive of arrhythmia progression from paroxysmal to more sustained types (i.e., persistent or permanent). Among patients with paroxysmal AF participating in European Heart Survey hypertension was more common in those who developed persistent or permanent AF during 1-year follow-up (71% vs. 60%, HR 1.52, 95% CI 1.05–2.20).[81] This was further confirmed in a prospective survey on AF management, the RECORD-AF study (odds ratio 1.5, 95% CI 1.1–2.0).[82]

The **h**ypertension, **a**ge ≥75 years, **t**ransient ischemic attack or stroke, **c**hronic obstructive pulmonary disease, and **h**eart failure (HATCH) score was also applied to predict new-onset AF after successful ablation of typical atrial flutter. Chen *et al.*, 2015 observed 39% new-onset AF during 29.1 ± 18.3 months follow-up, and the HATCH score was predictive of AF development (HR 1.78, 95% CI 1.35–2.32). They also suggested the HATCH score of 2 as cut-off for high risk of AF onset (69% vs. 27%).[83] The **d**iabetes mellitus, **r**enal dysfunction, persistent **f**orm of AF, **L**A diameter >45 mm, **a**ge >65 years, female **s**ex, and **h**ypertension (DR-FLASH) score was developed to detect patients with high probability of the low voltage area presence, which reflects fibrotic areas in the left atrium, and are known to be predictors of AF recurrence after AF catheter ablation. Such patients are likely to benefit from additional substrate modification, and should be effectively detected therefore. The probability for the presence of LA substrate increased by a factor of 2.2 (95% CI 1.6–2.9) with each point scored (C statistic 0.767).[84] The risk of AF recurrence after pulmonary vein isolation increased by a factor of 1.3 (odds ratio 1.3, 95% CI 1.1–1.5) with every additional point and was almost 2 times higher in patients with a DR-FLASH score >3 (odds ratio 1.7, 95% CI 1.1–2.8).[84] The CAAP-AF score allows prediction of AF ablation outcome (freedom from AF after final ablation).[85] Thus, hypertension is an important risk factor that should be taken into account when managing AF with a rhythm control strategy.

CONCLUSION

Hypertension has a significant role as cardiovascular risk factor and has been shown to promote AF. Due to the growing prevalence of both conditions their co-presentation will be even more common in the future. Targeting blood pressure and optimizing its control should therefore be one of the major components of AF management to improve patient outcomes. The use of nonvitamin K antagonists oral anticoagulants where appropriate should be used in parallel in such patients as part of risk factor management as the prognosis of AF-related stroke is by far worse than that for non-AF related stroke.[72]

DISCLOSURES

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