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NOVEL TREATMENTS FOR HYPERTENSION (T UNGER, SECTION EDITOR)

# Blood Pressure Control versus Atrial Fibrillation Management in Stroke Prevention

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**Abstract** Hypertension is one of the major risk factors for atrial fibrillation which in turn is the most prevalent concomitant condition in hypertensive patients. While both these pathological conditions are independent risk factors for stroke, the association of hypertension and atrial fibrillation increases the incidence of disabling strokes. Moreover, documented or silent atrial fibrillation doubles the rate of cardiovascular death. Lowering blood pressure is strongly recommended, particularly for primary stroke prevention. However, a relatively small percentage of hypertensive patients still achieve the recommended blood pressure goals. The management of atrial fibrillation with respect to stroke prevention is changing. New oral anticoagulants represent a major advancement in long-term anticoagulation therapy in non valvular atrial fibrillation. They have several benefits over warfarin, including improved adherence to the anticoagulation therapy. This is an important issue since non-adherence to stroke prevention medications is a risk factor for first and recurrent strokes.

**Keywords** Blood pressure control · Antihypertensive drugs · ARBs · NOACs · Oral anticoagulants

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## Introduction

Stroke, a recurrent and, to a large degree, preventable disorder, represents the third-common cause of death worldwide. Despite evidence that the incidence of stroke has slightly declined in the western countries and the rate of in-hospital mortality has decreased in stroke patients over the past four decades [1], one-third of the stroke patients still die in the first year, and half of them become permanently disabled [1, 2]. It has been reported that the world-wide prevalence of stroke is about 15 million cases per year, and in the USA alone there are approximately 800,000 new patients per year suffering a stroke. The incidence of stroke in developing countries is increasing. Moreover, recurrent strokes still account for 25 % to 30 % of all strokes representing unsuccessful secondary prevention [3–5]. Therefore, both primary and secondary prevention is critical in limiting the burden of cerebrovascular disease worldwide. The purpose of primary stroke prevention is the management of the modifiable cardiovascular risk factors and the clinical conditions that predispose an individual to stroke occurrence, whereas secondary prevention is aimed to additionally target several different pathological conditions that predispose an individual to the occurrence of recurrent stroke.

In a large standardized case–control study performed in 22 countries worldwide over three years of follow-up, ten modifiable risk factors (including hypertension, smoking, abdominal obesity, diet, lack of physical activity, diabetes, alcohol intake, psychosocial stress, depression, cardiac causes, and lipid abnormalities) were associated with 90 % of all strokes. Among these risk factors, hypertension, smoking, waist-to-hip ratio, diet, and alcohol intake were significantly associated with intracerebral haemorrhagic stroke [6]. Evidence-based guidelines focused on primary and secondary prevention suggest that those modifiable risk factors should be targeted in clinical practice in order to reduce the health consequences

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and socio-economic burden of stroke [7]. For the secondary prevention of recurrent stroke risk-stratification according to the presence of diabetes, hyperlipidemia, atrial fibrillation, current tobacco smoking, and hypertension should be performed principally during the hospitalization for acute stroke. Therefore, any effort should be recommended to modify these risk factors in order to reduce the risk of recurrent stroke [7].

This is particularly true for hypertension which is responsible of about 50 % of strokes. Lowering blood pressure in hypertensive patients is strongly recommended, particularly for primary stroke prevention [7–9]. Furthermore, hypertension is also a distinct and major risk factor for the occurrence of atrial fibrillation (AF) [7–9]. In fact, it is a component of several prognostic scoring systems, including CHA2DS2 VASc scores in AF patients for stroke prevention.

AF is a serious risk factor for cardiovascular patients since it is associated with a high risk of cardiovascular complications, hospitalization, and death. Most importantly, AF increases five fold the risk of stroke and worsens the clinical outcome in patients who experienced stroke, in view of the fact that AF is associated with increased incidence of disabling strokes, particularly when associated to other cardiovascular risk factors, including hypertension [7, 9].

In this review we will focus on the current evidence of hypertension and AF management for stroke prevention.

## Hypertension and Stroke

Hypertension is one of the major and independent cardiovascular risk factors and contributes to the development of target organ damage and cardiovascular and cerebrovascular events. Both systolic and diastolic hypertension are associated with the occurrence of both primary and recurrent strokes [8, 9, 10, 11••], mainly when blood pressure remains poorly controlled [12, 13•]. Moreover, elevated systolic blood pressure upon hospital discharge after a stroke represents a strong predictor of early recurrence of further cerebrovascular events [14]. Notably, a correlation has been reported between the prevalence of hypertension and the mortality for stroke [15], which is significantly higher after a recurrent stroke compared to a primary stroke [16].

Over the past forty years, randomized controlled trials (most of them versus placebo) have provided evidence that lowering blood pressure with different classes of antihypertensive drugs results in risk reduction for major clinical cardiovascular outcomes, including fatal and nonfatal stroke in hypertensive individuals [8, 17]. This is strikingly evident for primary stroke prevention of any type [18]. In particular, a recent meta-analysis including more than 50,000 patients has shown that lowering blood pressure provided similar relative protection for all levels of baseline cardiovascular risk, although progressively greater absolute risk reductions for higher levels of baseline risk were observed [19••].

Post-hoc analysis of randomized data suggest that the reduction of fatal and non fatal cardiovascular outcomes are, in part, due to the regression of the alterations in the target organ damage, such as the structural alterations induced by hypertension in the cardiovascular system (i.e., left ventricular hypertrophy and remodelling, fibrosis, vascular remodelling, intima-media-thickness, and urinary protein excretion) [20, 21].

Undoubtedly, reducing blood pressure is the most important step in stroke prevention [22], even for patients at low-to-moderate cardiovascular risk and/or with baseline blood pressure in the range of grade 1 hypertension [23–25], although a large part of supporting evidence is provided by meta-analyses including a relatively small number of patients [23, 24]. However, less clear is the approach for lowering blood pressure in patients after a stroke. This is due to the paucity of published trials specifically focused on the management of hypertension for recurrent stroke prevention [11••, 12, 13•].

Nonetheless, as long as blood pressure is successfully reduced, all antihypertensive regimens are acceptable for stroke prevention [22], mainly in patients who had a previous stroke. Meta-analyses of randomized controlled trials have reported about a 40 % reduction in recurrent stroke risk with blood pressure lowering regimens [11••, 12, 26]. This has been shown without a clear J-curve effect, although this latter finding is not consistent in all the trials [27–31].

The ESH/ESC guidelines suggest treating hypertensive patients with a history of cerebrovascular events with a recommended therapeutic goal of <140 mmHg [8]. This target may be considered to be higher, to some extent, in elderly hypertensives with previous stroke or transient ischemic attack (TIA) [8]. Importantly, in high-risk patients, the antihypertensive regimen should be carefully monitored in order to avoid the variability of intra-individual blood pressure measurement at follow-up visits. Indeed, this is associated with the increased incidence of stroke [32]. The effects of antihypertensive drugs on blood pressure variability are dose-dependent and are more evident for a specific class of drugs such as calcium antagonists, mainly when used in combination with other antihypertensive drugs [33]. Interestingly, in a large-scale observational study, it has been shown that the recommended antihypertensive treatment achieved blood pressure control in a limited number of hypertensive patients seen by general practitioners (GPs) [34]. This highlights the discrepancies between clinical practice and guideline recommendations, suggesting that any effort should be provided in order to fill this gap in clinical practice. Indeed, an increased awareness of stroke risk factors by GPs is associated with improved blood pressure control in the ten-year estimated risk of stroke [35].

Meta-analyses and meta-regression analyses suggested that some differences in stroke prevention may exist among the

different antihypertensive classes of drugs. Beta-blockers may be inferior to calcium antagonists and renin-angiotensin system (RAS) blockers for stroke prevention [36, 37]. This is possibly due to the lesser effect of beta-blockers in reducing central systolic blood pressure and pulse pressure [38, 39]. Calcium antagonists may have a greater effectiveness on stroke prevention [40–42]. This may be due to more consistent blood pressure control obtained with this class of drugs although a less defined protective effect on the brain circulation could be also advocated [8].

Among RAS blockers, angiotenisn receptor blockers (ARBs) have shown greater cerebrovascular protective effects in clinical trials and meta-analyses compared to different classes of drugs [43, 44]. This is mainly due to the selective blockade of the RAS, which plays a central role in the development and maintenance of the structural and functional alterations in the cardiovascular system, typically associated with stroke occurrence [45–47]. In the MOSES trial (Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention), ARB did demonstrate the ability to reduce stroke recurrence compared to calcium channel blockers, though in a limited population sample [43]. ACE inhibitors did not show similar consistent protective effects; rather, in some trials, ACE inhibitors performed inferiorly to other classes of drugs in preventing stroke [40–42], unless they were used in combination therapy. In secondary stroke prevention in the PROGRESS trial (Perindopril Protection Against Recurrent Stroke Study), ACE inhibitors in combination with diuretics showed a significant reduction of cerebrovascular events [48]. However, this was apparently due mostly to the blood pressure lowering effect of the diuretic indapamide. In fact, combination therapy using a diuretic and another different class of drugs has shown to be successful in stroke prevention, particularly in the elderly and in higher cardiovascular risk patients [45, 49–51]. The use of combination therapy is quite common in clinical practice, since about 70–80 % of treated hypertensive patients may require combination therapy (at least two classes of drugs) in order to achieve the recommended blood pressure goals, particularly in high cardiovascular risk patients. Despite this evidence and the recommendations, a relatively small percentage of hypertensive patients (about 30–40 %) still achieve recommended blood pressure goals in clinical trials [52], and more than 50 % of patients still receive monotherapy.

## Atrial Fibrillation and Stroke

AF is one of the most common cardiac arrhythmias, with a relatively high prevalence in the general population (1–2 %) [53]. AF increases the risk of cardiovascular events, including stroke, since AF is present in about 15 % of patients who suffer cerebrovascular events. Interestingly, the risk of stroke is similar in both paroxysmal AF and permanent or persistent AF [54•]; as also, there is evidence that subclinical or silent AF might contribute to 25 % of unexplained strokes [54•, 55]. Documented AF or subclinical or silent AF doubles the rate of cardiovascular death [56].

Several cardiovascular risk factors are associated and predispose an individual to the occurrence of AF. Among those risk factors, age, hypertension, and diabetes correlate to the development of AF [6, 57–59]. These risk factors are also associated with thrombembolic complications of AF, mainly stroke. Several risk models are available for risk stratification and prevention of thromboembolism in patients with AF [7, 9]. In all of these models, hypertension is present and represents an important risk factor. The CHA2DS2-Vasc-score is a simple clinical approach to assess the individual risk for thromboembolic complications in patients with diagnosed AF. In those patients with a score >1, a net benefit from antithrombotic treatment in primary and secondary prevention has been shown [7, 9]. Nevertheless, AF may be silent and, therefore, unrecognized in about 40 % of AF patients [54•, 60•]. Time and duration of AF per day represent additional risk factors for cerebrovascular events, since it has been shown that one hour in daily AF time resulted in increased risk of stroke by about 3 % [61•]. Patients with silent AF are, indeed, at high risk for stroke which may occur in more than 30 % of patients [54•, 60•]. It is likely those patients do not receive anticoagulants, and this may increase the risk of stroke [62•], yet the benefits of antithrombotic treatment in patients with subclinical AF remain to be further studied [63]. Thus, monitoring AF episodes with electrocardiography (ECG) recording devices may become crucial and this approach should be considered in select patients [7, 9, 64].

In relation to the risk score, most patients with AF should receive anticoagulant therapy to reduce the risk of stroke. It has been shown that the relative risk of ischemic stroke was decreased by 67 %, and the risk of all-cause mortality was reduced by 27 % by using oral anticoagulants [65]. Antithrombotic treatment with the vitamin K antagonist (VKA) warfarin is effective in either primary or secondary prevention of thromboembolic events in AF patients. However, quite recently, novel oral anticoagulants (NOACs) that do not require international normalized ratio (INR) monitoring have been introduced with promising results in patients with non valvular AF [66]. NOACs include direct thrombin inhibitors, dabigatran, factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban; they have been shown to be noninferior and sometimes superior to warfarin [7, 9, 67], and have reduced all-cause mortality in different clinical trials [67]. The selection of an anticoagulant drug should be individualized based on renal and hepatic function, potential drug interaction, patient preference, tolerability, previous anticoagulation effectiveness and safety, as well as cost [66, 67]. Anticoagulants are associated with a risk of bleeding

complications. Therefore, the possibility of anticoagulation should be weighted against the bleeding risk of the patient. However, NOACs, compared with VKAs, are associated with less intracranial hemorrhage and are generally preferred over VKAs [66, 67].

It should be noted that, despite the evidence that long-term oral anticoagulation for secondary stroke prevention in AF is highly effective, it is frequently not started or discontinued in clinical practice. In a recent prospective cohort study the non-adherence to oral anticoagulation in stroke patients resulted from fear of potential complications (such as bleeding) or inconvenience of regular international normalized ratio measurements and physicians' concerns regarding functional status of patients [68•]. Nevertheless, there is evidence that persistence with therapy may be better with NOACs than with warfarin [67, 68•, 69]. It is important to note that in most studies addressing the efficacy of VKA or NOACs in patients with AF, blood pressure changes and the role of antihypertensive therapy are underreported or even not analyzed [70••].

## Hypertension and Atrial Fibrillation

High blood pressure is an established risk factor for AF which in turn is the most prevalent concomitant condition in hypertensive patients [7, 9]. AF greatly enhances the disability and mortality in hypertensive subjects [71–73]. Blood pressure values even in the high normal range are associated with the development of this arrhythmia [74]. AF may be associated with different functional and structural alterations induced by hypertension in the cardiovascular system, including structural changes in the heart (i.e., left atrium enlargement), fibrosis, heart failure, neurohormonal activation, and atherosclerosis [45–47]. In particular, a pooled analysis of data from AFFIRM (The Atrial Fibrillation Follow-up Investigation of Rhythm Management) and AF-CHF (Atrial Fibrillation and Congestive Heart Failure) patients with paroxysmal or persistent AF showed that systolic blood pressure is an important determinant of recurrent AF burden only in patients with left ventricular dysfunction (LVEF≤40 %) but not in those with preserved ventricular function [75•].

In hypertensive patients, AF is a common cause of cardiovascular complications, including stroke [76, 77]; thus, prevention of new episodes of AF is warranted, particularly in hypertensive patients [77]. Antihypertensive treatment may contribute to a reduction of risk, and it seems that some classes of drugs are superior to others in the prevention of new-onset AF and stroke prevention [67]. This is related to the concomitant clinical conditions and to the distinctive property of a specific drug in reversing structural cardiac damage caused by hypertension [78, 79].

In particular, ARBs seems to be more effective in preventing the first occurrence of AF than other drugs such as beta-blockers and calcium antagonists in hypertensive patients with structural heart disease (left ventricular hypertrophy or dysfunction) [80–84] and no history of AF [81, 85, 86]. However clinical trials have shown that ARBs were less able to prevent recurrences of paroxysmal or persistent AF [87, 88•, 89], and also did not improve survival in patients with established AF. Thus, the beneficial effects of ARBs may be limited to the prevention of incident AF in patients with hypertension and structural heart disease [88•] and no history of AF [8, 67]. This may be due to the beneficial effects on atrial stretch, interstitial fibrosis, inflammation, and structural remodelling. On the other hand, it should be noted that while ARBs may be helpful in prevention of AF in patients with early or reversible cardiac structural changes [45, 80], they may be much less effective in patients with more advanced or heterogeneous cardiac disease [87].

Nevertheless, a recent meta-analysis indicates that telmisartan seems to be more effective than other antihypertensive drugs in preventing AF recurrences among hypertensive patients with paroxysmal AF, beyond blood pressure reduction [90•]. Several mechanisms are postulated, including strong binding affinity to angiotensin II type 1 receptors, the specific property to block potassium channels involved in the ultra-rapid delayed rectifier currents in atrial myocytes [91] and an effect in facilitating parasympathetic activity as well as reducing QT dispersion [92]. These findings have not been confirmed in high-risk patients with established atherosclerotic disease [93, 94].

In patients with AF and a high ventricular rate, beta-blockers and non-dihydropyridine calcium antagonists are recommended [7, 9]; also, beta-blockers and mineralocorticoid antagonists may prevent atrial fibrillation, particularly in patients with heart failure [95, 96].

Hypertensive patients with AF should be assessed for the risk of thromboembolism by the above mentioned scores (i.e., CHA2DS2-Vasc-score) [7, 9]. Where indicated by the score, those patients should receive oral anticoagulation therapy [7, 9, 65]. In patients receiving anticoagulation therapy, effective blood pressure control should be warranted in order to reduce bleeding events [97••].

## Conclusion

Hypertension is the most common cardiovascular disorder and AF is the most common clinically relevant arrhythmia. Hypertension predisposes an individual to the development of AF and these conditions frequently coexist. Their prevalence increases rapidly with aging and is associated with the occurrence of both primary and recurrent cerebrovascular events. Stroke constitutes a clinical and socio-economic burden, due to the high prevalence of disability after the first year following an acute event. Stroke risk can be substantially reduced by

using the medical measures that have been proven in many randomized trials. Hence, prescription of evidenced-based stroke prevention medications in AF and/or hypertensisve patients is mandatory. However, it is still a challenge to translate the efficacy of the interventions reported in clinical trials into everyday clinical practice. Blood pressure control is extremely relevant for primary and secondary cardiovascular and cerebrovascular prevention, although only 30–40 % of patients with arterial hypertension achieve the recommended blood pressure goals in clinical trials [34, 35, 52]. Therefore, efforts should be made to improve blood pressure control, especially through the use of effective and well tolerated combination therapies in hypertensive patients, particularly those with high cardiovascular risk profiles.

The management of AF with respect to stroke prevention is changing. The antithrombotic therapy is challenging due to the overlap of ischemic stroke predictors such as the CHA2DS2 VASc score and major bleeding scores (i.e., HAS BLED score) [7–9, 66]. Currently, NOACs represent a major advance in long-term anticoagulation therapy in non valvular AF and have many benefits over warfarin; not secondly, this class of drugs is characterized by improved adherence to anticoagulation therapy. This is an extremely important issue since non-adherence to stroke prevention medications is a risk factor for first and recurrent strokes [98•]. Finally, the future management of AF should combine prevention and personalised treatment of AF that results in an effective prediction of AF and mortality and morbidity prevention.

**Compliance with Ethics Guidelines**

**Conflict of Interest** Carmine Savoia and Massimo Volpe report personal fees from Daiichi-Sankyo Italia. Lidia Sada declares no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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