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Novel oral anticoagulant drugs in hypertensive patients with atrial fibrillation

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Abstract

Hypertension (HTN) and atrial fibrillation (AF) are two major conditions that co-exist in many cardiac patients. The Novel Oral Anticoagulants (NOACs) trials have largely focused on the reduction in stroke/ systemic embolic events (primary outcome) and the rate of intracranial hemorrhage/major bleeding/ clinically- relevant non-major (CRNM) bleeding (safety outcome), but did not account for the impact and treatment of HTN in the disease process. Subsequent studies have used the data in these large-scale trials to take a closer look at HTN and its effect on the outcome of NOACs versus warfarin. This review briefly explains the current understanding of the relationship between AF and HTN and their pathophysiology and presents the sub-trials stemming from the data in the large NOAC trials where HTN has been investigated. These trials have demonstrated non-inferiority/ superiority of NOACs in regards to warfarin is maintained, regardless of the hypertensive status of the patients and have largely shown hypertension to be a significant independent risk factor for ischemic/hemorrhagic stroke or systemic embolic events, as well as major or non-major bleeding. This is supported by the inclusion of hypertension as a risk factor in both the CHADS-VASC and the HAS-BLED score, therefore emphasizing strict control of hypertension in order to reduce cardioembolic and hemorrhagic events..

Keywords: hypertension, atrial fibrillation, NOAC, dabigatran, rivaroxaban, apixaban, oral anticoagulant

Introduction

Hypertension (HTN) and atrial fibrillation (AF) are two major conditions that co-exist in many cardiac patients.

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This review briefly explains the current understanding of the relationship between AF and HTN and their pathophysiology and presents the sub-trials stemming from the data in the large NOAC trials (SPORTIF III, SPORTIF V, ARTISTOLE, RELY, J-ROCKET) where HTN has been investigated.

Epidemiology

AF is the most common sustained cardiac arrhythmias with a prevalence of 1-2% of the general population and up to 15% in patients over 80 [1-6]. In Europe, the current data shows that there are over 6 million patients suffering from AF [6]. The prevalence is underestimated as a large proportion of AF can be present as silent AF with no symptoms. Furthermore, within 50 years, the prevalence of AF is expected to double due to the increase in the aging population [7].

In Romania, according to the SEPHAR II national-representative survey [8,9] AF prevalence in 2.9% in the general adult population and 7.1% among Romanian adult hypertensive patients.[10-13] More data regarding the prevalence of AF in Romanian adult population and its trend in the last five years will be revealed by recently conducted SEPHAR III national-representative survey's results [14].

AF is one of the leading causes of cardio-embolic stroke with subsequent long term disability and requires long term management with anticoagulation and rate control [1]. Furthermore, it represents a huge burden on health systems worldwide, as it accounts for one third of hospitalizations for arrhythmia [1,15] and the number of AF-related hospitalizations have been increasing by 2-3 times [16].

AF is an important predictor of mortality, doubling the rate of death independent of other predictors [6] with a known association between it and all-cause mortality in a 54000-patient trial [17]. Significant morbidity has also been associated with AF by causing silent and recurring strokes leading to cognitive dysfunction and dementia [16] and an overall worse quality of life [18,19].

It is important to have a deep understanding of the pathophysiology of AF, as new onset AF carries a higher risk than documented or no AF in in patients with heart failure [20] and worsens prognosis in NYHA III-IV [21].

Many other conditions co-exist with AF, such as a history of stroke (72%), chronic kidney disease (82%), diabetes mellitus (77%), coronary artery disease (73%), heart failure (71%) and metabolic syndrome (62%) [22].

HTN, the most common cardiovascular disease affecting 20-50% of the adult population [17] increased the risk of AF by 2-3 fold [23]. Sub-optimally treated, longstanding HTN is known to cause structural changes: left ventricular hypertrophy (LVH), left atrial (LA) enlargement and eventually fibrosis changes in atrial conduction [24], all of the above being shown to contribute to AF development [25-28]. However the understanding of the underlying mechanisms behind the association of AF and HTN-induced hemodynamic changes remains poorly understood [29]. A better identification of the predictors and mechanisms behind AF in HTN is thought to potentially lead to a more effective prevention strategy and intervention [7].

HTN and AF

Several studies have shown that HTN and AF are associated. In the Framingham Heart Study, levels of systolic blood pressure (SBP) and duration of HTN were both predicting factors for the development of AF [30]. A cohort sub-study of the Framingham Heart Study looking at AF prevalence in over 9500 patients across 50 years clearly identified HTN as a major risk factor for developing AF. The study concluded that HTN and antihypertensive treatment carried the greatest population-attributable risk [31].

There have been other studies which have confirmed the role of HTN in the development of AF. The ONTARGET STUDY looked at patients at high risk for cardiovascular events and the effect of antihypertensive treatment using Telmisartan and Ramipril or both. In the 30,424 participants who were in sinus rhythm at enrollment, the rate of incident AF was 6.8% during a 4.7 year median follow-up period. A history of HTN, systolic blood pressure (SBP) and pulse pressure were all risk factors linked to the development of incident AF [32].

The LIFE study further enforced this by showing that Angiotensin II receptor blockade (ARB) using Losartan reduced incidence of AF. Furthermore, blood pressure (BP), ECG evidence of LVH, age and male

gender were associated with development of AF in hypertensive patients [28]. Adding to the argument are recent studies that have shown a correlation between BP in the upper-normal range and development of AF [33,34]

The link between LVH and the development of AF has also been proven, as evidenced by lower rates of AF in patients showing LVH regression following antihypertensive treatment, as opposed to refractory LVH [35,36].

Lastly, in a review paper in 2012, the European Society of Hypertension indicated that 49-90% of AF patients have HTN [37].

Pathophysiology

With longstanding sub-optimally treated HTN, subacute organ damage can occur in the form of LVH. LVH results in the modification of hemodynamic parameters in the left ventricle, such as a reduction in compliance and thus a lower end-diastolic volume, along with an increase in ventricular stiffness and filling pressures. The hypertrophic muscle has increased oxygen requirements, which cannot be met by coronary arteries, especially in the context of reduced coronary flow. These changes are partly attributable to activation of the sympathetic nervous system and the Renin-Angiotensin-Aldosterone System (RAAS) in response to HTN.

The importance of RAAS in the pathophysiology of cardiac remodelling and consequent development of AF has already been highlighted by studies such as ONTARGET and LIFE. Other studies, such as the VALUE trial serve to confirm that ARB treatment lowers the incidence of new-onset AF in HTN patients [38]. The role of aldosterone in AF development has been further explored by looking at patients with primary aldosteronism matched with patients suffering from essential HTN. There was a 12-fold increase in the risk of developing AF in the patients with primary aldosteronism (OR 12, 95% CI: 3.2-45.2, P<0.001) [39]. Conn's syndrome was linked with LV remodelling [40,41] and it has subsequently been shown that mineralocorticoid receptor activation promotes adverse cardiac remodelling and AF [42]. The idea that aldosterone promotes structural and electrical remodelling in the heart is further supported by a study looking at effects of spironolactone in a canine model of AF [43]. Plasma aldosterone levels are paradoxically increased in AF patients despite atrial stretch triggering enhanced ANP release. Another study showed that restoration to sinus rhythm in AF patients leads to a reduction in plasma aldosterone levels [44]. However, angiotensin II itself has been directly linked with the release of profibrotic cytokines such as TGFbeta- 1 in cardiac myofibroblasts via AT1 receptor activation [28,45]. The release of such paracrine factors has been shown to affect regulation of connexin patterns and N-cadherin expression [46] and even alter transcription of Na+ channels [47]. Thus, the reduction in AF with RAAS inhibiton by ACEI or ARB is thought to act by the blocking the direct effect on Angiotensin II, as well as reducing plasma aldosterone levels.

The changes in HTN-induced LVH eventually lead to LA remodelling [48] by impaired left ventricular filling causing atrial stretch and favouring AF [49]. This has been described as a 3-component process, involving electrical remodelling, contractile remodelling and eventual structural tissue remodelling [37].

Electrical remodelling occurs due to AF paroxysms resulting in intracellular changes in Calcium handling and is reversible. The role of electrical remodelling is supported by the findings in rare gene mutations resulting in channelopathies and predisposing to AF. Mutations in K+ channels (KCNE2, KCNE5, KCNU2, KNCA5) promote AF by inducing early atrial repolarization [50-54], as do mutations In Na+ and Ca2+ genes that control currents across the sarcoplasm membranes in atrial cardiomyocytes [54-57].

Following electrical remodelling is contractile remodelling with the classical disorganized pattern of atrial contraction being responsible for most of the devastating consequences of the disease. Systemic embolic events are promoted by stasis of blood, particularly in the left atrial appendage.

Structural tissue modelling ensues which has been linked with increased incidence of AF in a study reporting a 48% higher risk of AF in individuals with a 30% increase in left atrial size [50]. The molecular mechanisms can be explained by proliferation and differentiation of fibroblasts into myofibroblasts with subsequent fibrosis, as well as by the mechanical overload triggering an altered expression of junction complexes like connexin 40/43 promoting re-entrant activity [58]

The structural remodelling results in alteration of the electromechanical properties of atrial myocytes with dissociation between local conduction heterogeneities and muscle contraction. This uncoupling promotes and maintains AF by allowing multiple small re-entrant circuits.

Novel Oral Anticoagulant Drugs (NOACs)

As explained above, the contractile changes in the atria are a major cause of cardioembolic events. Thus, patients with AF necessitate anticoagulation which has been classically achieved by vitamin K antagonists (warfarin). Recent studies have compared warfarin with NOACs in large phase 3, randomised trails, in which both efficacy and safety outcomes were reported. A large meta-analysis of these trails (n=42411+ 29272) reports that compared to warfarin, NOACs have a favourable risk-benefit profile, with significant reductions in stroke or systemic embolic events (RR 0.81, 95% CI 0.73-0.91, p<0.0001), mainly attributable to a reduction in hemorrhagic stroke (RR 0.49, 95% CI 0.38-0.64, p<0.0001). With NOACs, there an overall decrease in all-cause mortality (RR 0.90, 95% CI 0.85-0.95, p<0.0001) and intracranial haemorrhage (RR 0.48, 95% CI 0.39-0.59, p<0.0001), similar rates of major bleeding, but increased rate of gastrointestinal bleeding RR 1.25, 95% CI 1.01-1.55, p=0.04) as compared to warfarin [59].

However, as discussed above, existing evidence points toward a major role of HTN and antihypertensive treatment in AF development and disease course. HTN also carries an increased risk of ischemic and hemorrhagic stroke. Thus, blood pressure and its significance were largely unexplored in the large-scale NOAC trials [60] which determined several groups to perform subset analyses of the effect of NOACs compared to warfarin in HTN patients.

SPORTIF III and V (in relation to HTN)

These two studies comparted ximelagatran with warfarin in patients with AF but despite evidence for comparable efficacy to warfarin and and a reduction in bleeding risk, drug development was abandoned due to concerns of hepatic toxicity. SPORTIF III involved 3407 randomized patients across 23 countries. The protocol was identical to the SPORTIF V trial, except contrasted to the open-label design of SPORTIF III, SPORTIF V involved double-blind treatment in 3913 patients. In both of them, patients were randomized to receive warfarin at a dose sufficient to maintain the International Normalized Ratio (INR) between 2 and 3 based on monthly measurements of prothrombin time, or ximelagatran at a fixed dose of 36 mg twice daily [61].

A subgroup analysis has been performed to test the hypothesis that the effects of NOACs were related to blood pressure. The proportion of subjects with mean systolic BP ≥ 140 mmHg was 35.8% (1220/3407) in SPORTIF III and 20.6% (807/3922) in SPORTIF V (P < 0.0001).

When comparing the top quartile of SBP with the lowest one, the hazard ratio (HR) for stroke and systemic embolic events (SEE) was 1.83 (95% confidence intervals [CI]: 1.22– 2.74). The rates of stroke/SEE increase at SBP>140 and event rates were highest in participants with highest average SBP reading [62].

Interestingly, there was a higher average SBP>140 in SPORTIF III, which may account for higher even rates than in SPORTIF V, where HTN is better controlled/ Control of HTN to lower SBP could therefore be associated with a uniformly lower SEE/stroke risk [63].

Another intriguing finding is that the mortality was lower in the top quartile (HR 0.64; 95% CI: 0.49–0.83), which adds to the debate on a potential J-curve in relation to BP and mortality among the elderly.

Thus, in the SPORTIF III Versus SPORTIF, controlled HTN associated with a low stroke risk comparted with patients with poorly controlled HTN. SBP was shown to be a better predictor than Diastolic Blood Pressure (DBP) in determining stroke risk for AF patients.

Even though HTN is a known RF for bleeding complications, including intracranial hemorrhage (ICH), the authors were not able to confirm a relationship between the higher quartiles of SBP and increasing rates of major and CRNM bleeding. This was explained as due to the close monitoring associated with the setting of the clinical trial and optimization of risk factor management [62].

The study concludes that HTN is an important RF in stratification scheme used to identify AF patients

who require anticoagulation and can still be used as a reliable predicting factor for development of ischemic events even when patients receive anticoagulation treatment.

ARISTOTLE

In this randomized, double-blind trial, apixaban (at a dose of 5 mg twice daily) was compared with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke [64].

A subset analysis was performed to assess the relationship between BP and clinical outcome in the ARISTOTLE trial. A total of 15 916 (87.5%) patients had a history of hypertension requiring treatment. [65].

For patient with a history of HTN or high BP at entry, there was increased risk of stroke/SEE and an increased risk of hemorrhagic/ ischemic stroke, but the later not significant. Rates of major bleeding were significantly lower in patients with a history of hypertension (HR, 0.80; 95% CI, 0.66-0.98), but not significantly lower in patients with elevated SBP at enrollment (HR, 0.89; 95% CI, 0.77-1.03).

For patients with an elevated BP measurement at any point during the trial, there was an increased risk of stroke/SEE (HR, 1.53; 95% confidence interval [CI], 1.25-1.86) and an increased risk of hemorrhagic stroke (HR 1.85; 95% CI, 1.26-2.72). Therefore, there was a 50% increase in the risk of stroke/SEE if the patient had an elevated BP reading at any point during the trial.

Apixaban was shown to be superior warfarin in efficacy outcome (SEE/stroke), effect independent of a history of HTN (P interaction=0.27), BP control at baseline (P interaction=0.43), and BP control during the trial (P interaction=0.97).

Thus, there is a clear association between elevated BP and a risk of stroke, highlighting the importance of lowering BP, especially since 50% of all patients had elevated BP during trial.

RE-LY

In this noninferiority trial, 18,113 patients with AF were randomized to receive, in a blinded manner, fixed doses of dabigatran — 110 mg (D110) or 150 mg (D150) twice daily or, in an unblinded manner, INR adjusted-dose warfarin (W) [66].

A subsequent sub-analysis looking at the primary outcome in relation to HTN was performed. In RE-LY, 14,283 patients (78.9%) had hypertension. The mean blood pressure at baseline was 132.6 ± 17.6/77.7 ± 10.6 and 124.8 ± 16.7/74.6 ± 10.0 mm Hg for patients with and without hypertension, respectively [67].

A history of HTN had no impact on risk of stroke/SEE when looking at hypertensive patients receiving D110, D150 and W (1.47%, 1.20%, and 1.81%) and normotensive patients receiving D110, D150 and W (1.79%, 0.78%, and 1.36%).

There was however a greater risk of major bleeding in HTN patients vs normotensive patients (3.39% vs 2.76%; p = 0.007), with similar ICH rates (0.47% vs 0.31%; p = 0.12).

When looking at HTN as continuous variable, a remarkable increase in the risk of stroke/SEE by 6 to 7% for every 10 mm Hg increase in mean SBP was noted. No association with increases in DBP was noted.

Dabigatran vs warfarin showed similar benefits with no interaction between anticoagulation treatment and presence of HTN.

There was no difference in mean SBP in all 3 arms (D150, D110, W), suggesting good control of HTN. This is probably also the reason why no difference in stroke/SEE was noted across the 3 groups. HTN patients and non-HTN patients had greater CHADS2 and CHADS-VASC score, but similar HAS-BLED. The increased risk of major bleeding can be explained by other risk factors other than HTN contributing to CHADSs and CHADS-VASC scores.

The results of looking at HTN as a continuous variable advocate for close monitoring and optimum control of HTN during chronic anticoagulant therapy.

The possibility of dabigatran playing a role in blood pressure control has also been brought forward following a case study of a 83 year old man with nonvalvular AF and HTN [68].

The patient was on warfarin, 100mg losartan and 25mg hydrochlorothiazide. Despite treatment he had an irregular BP with SBP>140 in > 70% of measurements. Warfarin was subsequently stopped due to labile INR and dabigatran was started. Following NOAC introduction, SBP measurements have consistently been below 140.

The proposed mechanism by which this occurred is hepatic metabolism of warfarin versus dabigatran. CYP2C9 metabolizes warfarin and losartan, with losartan having an active metabolite, E-3174 as a consequene of CYP2C9 metabolism. E-3174 has higher potency than losartan for angiotensin II receptors. Ceasing treatment with warfarin is therefore expected to lead to an increased losartan clearance, a reduction in losartan plasma concentration, but an increase in E-3174 concentration. Thus vitamin K antagonism using warfarin can reduce efficacy of some anti-hypertensive drugs like losartan. Hydrochlorothiazide is not metabolized and is rapidly eliminated by the kidneys, so it thought to have no impact on results.

J-ROCKET

In the ROCKET-AF trial, patients were randomly assigned to receive fixed-dose rivaroxaban (20 mg daily or 15 mg daily in patients with a impaired creatinine clearance) or adjusted-dose warfarin (with a target INR of 2-3). Patients in each group also received a placebo tablet in order to maintain blinding [69].

The efficacy of rivaroxaban and warfarin in patients with and without HTN was further analysed in a sub-trial [70]. The baseline blood pressure (BP) measurements of patients with hypertension in the rivaroxaban and warfarin groups were 130/77 mm Hg and 131/77 mm Hg, respectively, whereas those of patients without hypertension were 123/74 mm Hg and 124/73 mm Hg, respectively.

The incidence rates of the stroke/SEE in the rivaroxaban group and the warfarin group were 0.54% per year and 2.24% per year, respectively, in patients without baseline HTN (HR: 0.25; 95% CI: 0.03–2.25), and 1.45% per year and 2.71% per year, respectively, in patients with baseline HTN (HR: 0.54; 95% CI: 0.25–1.16), indicating no significant interaction (P=0.509). Therefore, rivaroxaban and warfarin are just as efficient in reducing SEE/stroke in both HTN patients and non-HTN patients.

There was a similar rate of bleeding events in patients with HTN and without HTN in both rivaroxaban and warfarin. However, in the rivaroxaban group, there was increased major bleeding in HTN patients and 14/15 patients who experienced ICH had baseline HTN (5/5 in rivaroxaban and 9/10 in warfarin)

Rivaroxaban and warfarin were shown to be just as efficient in reducing SEE/stroke in both HTN patients and non-HTN patients and there was no significant difference in incidence rates of safety outcomes between warfarin and rivaroxaban groups.

The sub-study showed that rivaroxban reduces rate of stroke/SEE regardless of HTN status, but patients with HTN have thrice the incidence of stroke/SEE than those without. Patients without HTN show a non-significant reduced frequency of major bleeding compared to those with HTN, but all ICH patients had baseline HTN, except for one. All the pacients who had ICH had higher CHADS and HAS-BLED scores, and since HTN is a factor for both, this further enforces the need of stringent BP management for administration for anticoagulant therapy.

Conclusion

Antithrombotic therapy is essential in patients with atrial fibrillation. Many of these patients have hypertension as well, which has been further studied in subsets of the large-scale new oral anticoagulant trials. These trials have largely shown hypertension to be a significant independent risk factor for ischemic/hemorrhagic stroke or systemic embolic events, as well as major or non-major bleeding. This is supported by the inclusion of hypertension as a risk factor in both the CHADS-VASC and the HAS-BLED score, therefore emphasizing strict control of hypertension in order to reduce cardioembolic and hemorrhagic events. Significant differences in outcome between the hypertensive and non-hypertensive patients have been generally attributed to the absence or rigorous control of high blood pressure in the second group. The demonstrated non-inferiority/ superiority of NOACs in regards to warfarin was maintained, regardless of the hypertensive status of the patient. The validity of the large-scale trials is thus maintained, however it is worth mentioning that hypertension was not closely looked at and treatment was largely left at the discretion of the patients' own healthcare providers. It is therefore important to maintain very rigorous control of hypertension, especially in the setting of atrial fibrillation, given the pathogenesis of the disease and the significant differences in outcome that can occur.

Conflicts of interest:

The authors confirm that there are no conflicts of interest.

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