

ATRIAL FIBRILLATION, ANTICOAGULATION TREATMENT AND HYPERTENSION

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1.0 INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in hypertensive patients while arterial hypertension (HTN) represents the most common comorbidity in patients with AF. In recent clinical trials that assessed the effect of direct oral anticoagulants in patients with AF, 80–90% of included patients suffered from HTN⁽¹⁾. These two conditions frequently coexist because they share common risk factors (diabetes mellitus, obesity, metabolic syndrome, smoking, alcohol consumption) but also because HTN per se increases the hazard for the development of AF⁽²⁾. The presence of HTN increases the risk of AF by up to 73% (especially in the presence of left ventricular hypertrophy)⁽³⁾ while arterial blood pressure (BP) levels of 120–130/60–69 mmHg confer the lowest risk for AF⁽⁴⁾. In addition, there is a linear correlation between BP levels and the risk of ischemic or hemorrhagic stroke⁽⁵⁾ while in patients with AF, the presence of HTN multiplies the annual risk of stroke by up to three-fold⁽⁶⁾. In AF patients receiving anticoagulation optimal BP control is a major determinant for the prevention of haemorrhagic complications. On the other hand, AF increases the risk of stroke by up to five and seventeen fold in non-valvular and valvular heart disease respectively. Without preventive treatment, each year approximately 1 in 20 patients (5%) with AF will have a stroke^(2,7,8). Thus, the use of oral anticoagulants (OAC) is imperative since 2/3 of strokes due to AF are preventable with appropriate anticoagulant therapy⁽⁹⁾. Taking into consideration all the above, optimal blood pressure control might decrease not only the AF burden in hypertensive patients but also prevent hemorrhagic and bleeding complications of OAC therapy in AF patients.

2.0 ORAL ANTICOAGULATION IN HYPERTENSIVE PATIENTS WITH ATRIAL FIBRILLATION

The introduction of the CHA₂DS₂-VASc (Congestive Heart failure, hypertension, Age \geq 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female)) score has simplified the initial decision for OAC use in AF patients.

According current ESC guidelines for the management of AF, OAC therapy to prevent thromboembolism is recommended for all male AF patients with a CHA₂DS₂-VASc score of 2 or more (class of recommendation I level of evidence A) while in male patients with a CHA₂DS₂-VASc score of 1, OAC therapy should be considered (class of recommendation IIa level of evidence B)⁽¹⁰⁾. In current guidelines there is a sex distinction since female gender increases the thromboembolic risk according the CHA₂DS₂-VASc score however if the patient has only the sex as risk factor (female gender) then there is no need for OAC therapy. Finally, when OAC is initiated in a patient with AF who is eligible, a direct oral anticoagulant (DOAC) (apixaban,

dabigatran, edoxaban, or rivaroxaban), is recommended in preference to a vitamin K antagonist⁽¹⁰⁾.

In these guidelines, the presence of hypertension plays a crucial role not only in the determination of thromboembolic risk but also in the determination of hemorrhagic risk. Arterial hypertension (especially when systolic BP levels are $>$ 160 mmHg) represents a significant risk factor for bleeding in anticoagulated patients based on HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol) score. In the Bleeding with Antithrombotic Therapy (BAT) Study⁽¹¹⁾, a multicentre prospective observational cohort study, 4009 patients receiving oral antithrombotic agents for cardiovascular or cerebrovascular diseases were followed. The purpose of the study was to clarify the association between major bleeding events and BP levels preceding bleeding events in antithrombotic users. In this study, changes in systolic and diastolic BP between entry and the last clinic visit before intracranial hemorrhage (ICH) or extracranial hemorrhage were recorded. In this study, SBP levels during the follow-up period were a strong predictor with a 45% and a 47% increase in risk for 10mmHg higher blood pressure in the first and second 6-month follow up respectively. The optimal cut-off BP level to predict impending risk of ICH was \geq 130/81 mm Hg. Likewise, in the randomized Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial that enrolled patients with previous stroke or transient ischemic attack, 72% of the patients were under antiplatelet therapy and 10% under OAC⁽¹²⁾. In this study, a reduction of 9 mmHg in SBP reduced the relative risk for hemorrhagic stroke by up to 50% while a 12 mmHg decrease in SBP by up to 76%⁽¹²⁾.

The intensity of anticoagulation involves a balance between prevention of thromboembolism and haemorrhage. The HAS-BLED score should be used in order to assess the bleeding risk in AF patients and to consider correctable risk factors for bleeding just like uncontrolled BP. A high HAS-BLED score by itself though, is not a reason to withhold OAC. The score should be rather used to identify those 'high risk' patients (score $>$ 3) for more careful review and follow-up, and as an opportunity to address reversible bleeding risk factors.

3.0 ANTITHROMBOTIC AGENTS, ARTERIAL HYPERTENSION AND RANDOMIZED CONTROLLED TRIALS

Despite the fact that there is a linear correlation between BP levels and the risk of ischemic or haemorrhagic events, very limited data regarding BP levels and control (including in-study and final blood pressure levels) as well as antihypertensive medications are provided, not only in previous but also in recent atrial fibrillation trials.

3.1 RECENT RANDOMIZED CONTROLLED TRIALS WITH DIRECT ORAL ANTICOAGULANTS

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial⁽¹³⁾ that enrolled 18,113 patients with AF the investigators randomized patients into dabigatran 110 or 150mg twice daily or adjusted-dose warfarin. In this study, dabigatran active arms (in both doses) had less stroke or systemic embolic events with similar or lower haemorrhagic events for the higher and lower dabigatran dose respectively⁽¹³⁾. Nevertheless, no data were reported initially regarding the antihypertensive drugs used and the BP levels during the follow up period for the 79% participants with HTN. However, in a post hoc analysis of the RELY trial⁽¹⁴⁾, the investigators compared the baseline characteristics and outcomes in patients with and without hypertension and assessed the efficacy and safety of both doses of dabigatran compared to well controlled warfarin. In this study BP control was adequate and the authors affirmed that every 10 mm Hg increase in mean BP and SBP, the risk of stroke increase by 6–7% respectively⁽¹⁴⁾.

Likewise, in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET) trial⁽¹⁵⁾, 14,264 AF patients were treated with rivaroxaban 20mg once daily or adjusted-dose warfarin. Rivaroxaban was non inferior to warfarin for stroke and non-cerebral embolism with similar major bleeding events, but significant less intracranial hemorrhagic events. Once again, 90% of the patients were hypertensive but no data were published initially regarding BP levels and antihypertensive treatment during the follow up period. However, in a retrospective analysis of the ROCKET AF trial, the investigators found that for every 10–mm Hg increase in baseline SBP levels, the adjusted risk of stroke or systemic embolism increased by up to 7%⁽¹⁶⁾.

In the Apixaban for Reduction In Stroke and Other Thromboembolic Events in atrial fibrillation (ARISTOTLE) trial⁽¹⁷⁾, 18,201 AF patients were treated with apixaban 5mg twice daily or adjusted-dose warfarin. Apixaban was superior to warfarin in reducing stroke or systemic embolic events with significant lower rates of haemorrhagic stroke. Hypertension was present in 88% of the patients but there were no data were regarding BP levels and antihypertensive treatment during the follow up period. However, in a post hoc analysis of the ARISTOTLE trial, the investigators affirmed that BP levels >140/90

mmHg increased the risk of hemorrhagic and thromboembolic events at any point of the study⁽¹⁸⁾.

Finally, in the Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES; atrial fibrillation patients who have failed or are unsuitable for VKA treatment) study⁽¹⁹⁾, 5599 AF patients were randomized to apixaban (5mg twice daily) or aspirin. Apixaban presented fewer thromboembolic events and similar rates of Intracranial bleeding with aspirin. Hypertension was present in 86 and 87% of the apixaban and aspirin-treated patients and once again there were no data regarding BP levels and antihypertensive treatment during the follow up period.

3.2 RANDOMIZED CONTROLLED TRIALS WITH OLDER ANTICOAGULANTS

Unfortunately, a review of studies with older anticoagulants reveals the same phenomenon. In nine randomized studies that evaluated the efficacy and safety of warfarin versus aspirin or placebo in patients with AF, warfarin was superior to aspirin or placebo in reducing the stroke or systemic embolic events however no data exist regarding BP levels and antihypertensive treatment during the follow up period^(1,7,8,20).

Despite the fact that the assessment of BP levels as well as antihypertensive therapy during the follow up was originally neglected in previous and recent atrial fibrillation trials, there are two large clinical studies that practically assessed this issue. In the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and SPORTIF V studies that compared ximelagatran (36mg twice daily) to adjusted-dose warfarin in AF patients, BP levels during follow up were recorded. Although ximelagatran was withdrawn due to liver toxicity, in these studies the event rates (stroke and systemic emboli) significantly increased at SBP levels of ≥140 mmHg⁽²¹⁾.

CONCLUSIONS

Anticoagulation treatment of patients with AF and HTN is challenging since uncontrolled hypertension increase markedly the risk of thromboembolic and haemorrhagic events. There is no doubt that OAC therapy is mandatory in a patient with AF who is eligible, however physicians must always respect and control BP levels.

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