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Editorial
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The role of blood pressure control in hypertensive patients with atrial fibrillation

Reinhold Kreutz *

[1] Department of Clinical Pharmacology and Toxycology, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

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Hypertension is the most important risk factor for both ischaemic and hemorrhagic stroke [1]. Similarly, patients with atrial fibrillation (AF) also have a major risk of ischaemic thromboembolic stroke and hemorrhagic stroke [1, 2]. The risk for the latter is anticipated to be particularly high in patients taking oral anticoagulation, which is considered as the fundamental treatment for stroke prevention in AF patients at increased risk of stroke [2]. Since the development of direct oral anticoagulants (DOACs) and their introduction into clinical practice during the last decade, the implementation of anticoagulation has drawn much attention in the care of AF [3, 4]. However, it should not be dismissed that AF and hypertension often coexist, especially in the elderly population. Hence, in the four pivotal outcome trials with DOACs, the mean age of patients was 71.5 years, and the hypertension prevalence 88% [5]. Consequently, treatment of hypertension and blood pressure (BP) control should not be dismissed in patients with AF and hypertension. A recent post-hoc analysis of the Hypertension in the Very Elderly Trial (HYVET) highlighted the increased risk in older hypertensive patients with AF as their risk of mortality, cardiovascular events, all stroke, and all-heart failure was significantly increased (with hazard ratios [HR] of 2.49, 2.47, 2.47, and 2.33, respectively) compared to hypertensive patients without AF [6]. However, the optimal BP in patients with AF and hypertension is not known due to the lack of data from dedicated randomized controlled trials (RCTs) in this setting. Moreover, many clinical trials in hypertension have excluded AF patients because of uncertainty in measuring BP because of inherently increased beat-to-beat BP variability in these patients [7]. Observational data from a large national cohort of 298,374 patients in Korea indicated that in oral anticoagulant-naïve AF patients undergoing hypertension treatment, a systolic BP of 120 to 129 mmHg and diastolic BP <80 mmHg was the optimal BP treatment target [8]. Thus, the data confirmed the potential relevance of a J-shaped curve by showing that AF patients with BP values below 120/80 mmHg or ≥130/80 mmHg were at significantly higher risk of major cardiovascular events [8]. However, this study could not provide further information on the role of BP control in AF patients during anticoagulation since these patients were not included. In this regard, a recent meta-analysis by Kollias *et al.* is interesting because the authors conducted a systematic review and meta-analysis of studies addressing the prognostic value of office BP measurement in patients with AF on anticoagulation [9]. In six studies that included 61,055 patients, they found that elevated office BP or diagnosis of hypertension vs. normotension associated with increased risks of stroke and/or systemic embolism (HR 1.29; 95% confidence intervals [CI] 1.12 to 1.47). Their meta-analysis of three studies that included 29,233 patients showed that elevated follow-up office BP

* Correspondence to: Reinhold KREUTZ, Professor, Institute of Clinical Pharmacology and Toxicology Charitéplatz 1, D-10117, Berlin, Germany.
E-mail: reinhold.kreutz@charite.de

predicts a higher stroke/systemic embolism risk (HR 1.79, 95% CI 1.38 to 2.32). In contrast, office BP and hypertension diagnosis did not significantly predict major bleeding events (HR 1.10; 95% CI 0.97 to 1.25) or all-cause mortality (HR 0.96; 95% CI 0.89, 1.05) [9]. The lack of association between BP and hypertension with bleeding risk appears of interest and contrasts with the inclusion of hypertension – as defined by a systolic BP >160 mmHg – as an important modifiable risk factor predicting bleeding risk in the HAS-BLED score [10]. Nevertheless, the authors did not specifically consider the risk of intracerebral hemorrhage and/or hemorrhagic stroke, for which a high systolic BP value is considered a major risk factor. Thus, in one of the pivotal DOAC studies included in the meta-analysis, the risk of hemorrhagic stroke was significantly increased (HR 1.85; 95% CI 1.26 to 2.72) in patients with uncontrolled BP during follow-up [11]. This is in agreement with more previous data from an RCT showing a substantial increase in both ischaemic and hemorrhagic stroke risk at systolic BP values above 140 mmHg in AF patients taking warfarin [12].

Taken together, despite the limitations of the available studies, the reported data support the current recommendation of the European Hypertension Guidelines to aim for a target systolic BP of at least <140 mmHg and to consider lowering to <130 mmHg [1]. Oral anticoagulants should be used with caution in patients with marked BP elevation (systolic BP ≥180 mmHg and/or diastolic BP ≥100 mmHg). Finally, apart from one exception, all first-line BP-lowering drugs can be used in patients undergoing anticoagulation, including DOACs, without a significant risk for clinically relevant drug interactions. The exception applies to non-dihydropyridine calcium channel blockers (e.g., verapamil and diltiazem) because they are moderate inhibitors of the cytochrome P-450 isoenzyme 3A4 and P-glycoprotein and may thereby increase the plasma concentrations of all DOACs and thus the bleeding risk when concomitantly used with DOACs [2, 13].

Finally, dedicated RCTs in hypertensive patients with AF are needed to define the target BP better and secure the most favorable risk/benefit ratio of oral anticoagulation therapy in AF patients. Until such data become available, the use of standard BP measurement methods and targets as recommended in the current guidelines appear appropriate in the management of patients with hypertension and AF [1].

Conflict of interest

Reinhold Kreutz reports research support from Bayer, lectures honoraria from Bayer, Berlin-Chemie/Menarini, Daiichi Sankyo, Ferrer, Merck, Sanofi and Servier outside this work.

References

1. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V and Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European heart journal. 2018;39:3021–3104.
2. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP and Watkins CL. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European heart journal. 2020.
3. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ and Heidbuchel H. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. European heart journal. 2018;39:1330–1393.
4. Goto S, Angchaisuksiri P, Bassand JP, Camm AJ, Dominguez H, Illingworth L, Gibbs H, Goldhaber SZ, Goto S, Jing ZC, Haas S, Kayani G, Koretsune Y, Lim TW, Oh S, Sawhney JPS, Turpie AGG, van Eickels M, Verheugt FWA and Kakkar AK. Management and 1-Year Outcomes of Patients With Newly Diagnosed Atrial Fibrillation and Chronic Kidney Disease: Results From the Prospective GARFIELD – AF Registry. Journal of the American Heart Association. 2019;8:e010510.
5. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T and Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet (London, England). 2014;383:955–62.
6. Antikainen RL, Peters R, Beckett NS, Rajkumar C and Bulpitt CJ. Atrial fibrillation and the risk of cardiovascular disease and mortality in the Hypertension in the Very Elderly Trial. Journal of hypertension. 2020;38:839–844.
7. Kyriakoulis KG, Kollias A and Stergiou GS. Blood pressure and outcome in patients with atrial fibrillation: floating in uncharted waters. Journal of hypertension. 2021;39:592–593.
8. Kim D, Yang PS, Kim TH, Jang E, Shin H, Kim HY, Yu HT, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B and Lip GYH. Ideal Blood Pressure in Patients With Atrial Fibrillation. Journal of the American College of Cardiology. 2018;72:1233–1245.

9. Kollias A, Kyriakoulis KG, Stambolliu E and Stergiou GS. Prognostic value of office blood pressure measurement in patients with atrial fibrillation on anticoagulation therapy: systematic review and meta-analysis. Journal of hypertension. 2020;38:13–20.
10. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ and Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138:1093–100.
11. Rao MP, Halvorsen S, Wojdyla D, Thomas L, Alexander JH, Hylek EM, Hanna M, Bahit MC, Lopes RD, De Caterina R, Erol C, Goto S, Lanas F, Lewis BS, Husted S, Gersh BJ, Wallentin L and Granger CB. Blood Pressure Control and Risk of Stroke or Systemic Embolism in Patients With Atrial Fibrillation: Results From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Journal of the American Heart Association. 2015;4.
12. Lip GY, Frison L and Grind M. Effect of hypertension on anticoagulated patients with atrial fibrillation. European heart journal. 2007;28:752–9.
13. Hanigan S, Das J, Pogue K, Barnes GD and Dorsch MP. The real world use of combined P-glycoprotein and moderate CYP3A4 inhibitors with rivaroxaban or apixaban increases bleeding. Journal of thrombosis and thrombolysis. 2020;49:636–643.