Mineralocorticoid receptor antagonists and prevention of atrial fibrillation in patients with hypertension

To the editor In the March 2020 issue of *Kardiologia Polska (Kardiol Pol, Polish Heart Journal)*, 2 articles by Mujovic et al[1] "Risk factor modification for the primary and secondary prevention of atrial fibrillation" have been published. Because in my opinion the choice of cited studies is not entirely representative, I would like to draw attention to aldosterone pathway blockade to prevent atrial fibrillation (AF) and the role of mineralocorticoid receptor antagonists. Among patients with established AF, hypertension is present in 60% to 80% of individuals and remains the main cause of AF, also due to the widespread occurrence in the population. The authors in the context of the primary prevention of AF referred to the EMPHASIS (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) study, which is difficult to understand, because it was a trial conducted in patients with heart failure, and hypertension was not included in the inclusion criteria. The mean (SD) systolic pressure in the study cohort was 124 (17) mm Hg and diastolic, 75 (10) mm Hg, and 66.7% of patients had a history of hypertension. On the other hand, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the key first-line drugs to treat hypertension, but despite this, AF occurs with increasing prevalence, also due to the aging of the population. Over the past 10 years, increased attention has been paid to excessive aldosterone activity in patients with hypertension and AF, especially in the elderly. Subclinical forms of hyperaldosteronism are also common. It is of importance because, according to the current European Society of Cardiology and European Society of Hypertension recommendations (2018), spironolactone plays an important role in the treatment of resistant hypertension (step 3 of treatment), which the authors do not mention in the Secondary prevention section.

In addition to the known hypertensive effect of aldosterone, experimental studies have shown a number of adverse effects, including increased hypertrophy, fibrosis, and necrosis of the atrial and ventricular muscle cells and damage to the endothelium and vascular walls. Aldosterone stimulates the synthesis of collagen I and III and fibroblasts via the activation of local mineralocorticoid receptors. Indirectly, aldosterone can also induce cell proliferation and fibrosis through increased AT1 receptor concentration, local expression of angiotensin converting enzyme and endothelin. Aldosterone also promotes inflammatory responses and oxidative stress. The potentially arrhythmogenic mechanisms of aldosterone involve inhibition of noradrenaline reuptake, impairment of baroreceptors function, increase of their sensitivity to catecholamines, and the associated reduction of sinus rhythm variability. It results in additional stimulation of the sympathetic nervous system and a decrease in parasympathetic activity. The loss of potassium and magnesium caused by this hormone is also important.[2]

Aldosterone levels increase during AF episodes. Patients with primary aldosteronism have a 12-fold higher risk of having an AF episode based on age, sex, and blood pressure. Mineralocorticoid receptor antagonists (spironolactone, eplerenone) prevent these adverse mechanisms, inhibit fibrosis, reduce preload and afterload, increase potassium levels and have beneficial impact on the remodeling of atria and ventricles. They have greater antiarrhythmic potential and effectiveness in this respect than angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. These findings were confirmed in clinical studies and meta-analyses.[3-5] It is estimated that the wider use of mineralocorticoid receptor antagonists in patients with hypertension and AF in both primary and secondary prevention would help avoid up to 30% of recurrent AF episodes.

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REFERENCES

1 Mujovic N, Marinkovic M, Mihajlovic M, et al. Risk factor modification for the primary and secondary prevention of atrial fibrillation. Kardiol Pol. 2020; 78: 181-191.

2 Schmidt BM, Schmmieder RE. Aldosterone-induced cardiac damage: focus on blood pressure independent effects. Am J Hypertens 2003; 16: 80-86.

3 Dabrowski R, Borowiec A, Smolis-Bak E, et al. Effect of combined spironolactone-β-blocker ± enalapril treatment on occurrence of symptomatic atrial fibrillation episodes in patients with a history of paroxysmal atrial fibrillation (SPIR-AF study). Am J Cardiol. 2010; 11: 1609-1614.

4 Neefs J, van den Berg NW, Limpens J, et al. Aldosterone pathway blockade to prevent atrial fibrillation: a systematic review and meta-analysis. Int J Cardiol. 2017; 231: 155-161.

5 Alexandre J, Dolladille C, Douesnel L, et al. Effects of mineralocorticoid receptor antagonists on atrial fibrillation occurrence: a systematic review, meta-analysis, and meta-regression to identify modifying factors. J Am Heart Assoc. 2019; 22: e013267.

Authors' reply We thank Dr Dąbrowski[1] for his interest in our study entitled "Risk factor modification for the primary and secondary prevention of atrial fibrillation. Part 1." In his letter, Dr Dąbrowski discussed in detail the important role of the renin-angiotensin-aldosterone system (RAAS) in pathophysiological mechanisms of atrial fibrillation (AF) as the rationale for a wider clinical use of mineralocorticoid receptor antagonists (MRA) in the primary prevention of AF in patients with hypertension. Also, Dr Dąbrowski criticized our citation of the EMPHASIS (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) study in the context of MRA use among hypertensive patients for primary prevention of AF, because the inclusion criterion for the study was left ventricular (LV) systolic dysfunction and not hypertension.[2]

The main objective of our 2-part article was to systematically review all relevant clinical studies on the primary and secondary prevention of AF by treating modifiable cardiometabolic risk factors in order to emphasize the risk factors management as an evidence-based, guideline-recommended goal for practicing clinicians.[1] Possible pathophysiologic link(s) between the modifiable risk factors covered in our studies (eg, hypertension, diabetes mellitus, physical activity, and cigarette smoking in part 1 and obesity, obstructive sleep apnea, alcohol consumption, and dyslipidemia in part 2) and AF are detailed in Figure 2 of part 1, and further detailing of the pathophysiology of AF would be beyond the scope of our article.[1]

We fully agree with Dr Dąbrowski that the EMPHASIS study analyzed the effect of MRA on AF occurrence only in patients with advanced LV systolic dysfunction (baseline LV ejection fraction <30%–35%).[3] However, history of hypertension at inclusion was reported in a significant proportion of patients (64.5%). This large randomized study demonstrated that addition of eplerenone on top of optimal treatment for heart failure, including angiotensin-converting-enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and β-blockers significantly reduced incident AF rate by 42% during the 21-month follow-up.[3] Dr Dąbrowski argued that the baseline mean blood pressure in the EMPHASIS cohort was "normal," but we emphasized in our paper that, compared with other antihypertensive drugs, the RAAS blockers, such as ACEIs, ARBs, and MRAs probably yielded some additional, class-specific benefits beyond simple blood pressure control with respect to the prevention of AF among hypertensive patients, thus supporting the profound involvement of the RAAS in AF pathogenesis.[2,3]

Dr Dąbrowski suggested that the recent meta-analysis of 24 studies (n = 1714 patients) supports overall protective effects of MRA on new-onset and recurrent AF among hypertensive patients, with or without heart failure.[4] However, these conclusions should be interpreted with caution. The median proportion of patients with hypertension in this meta-analysis was 58.4%, which is even lower than in the EMPHASIS study (64.5%). In addition, a significant reduction in the occurrence of AF with MRA use in the meta-analysis was mostly driven by considerably higher prevalence of AF in the earlier and / or observational studies (n = 13), whereas a sensitivity analysis of 6 randomized placebo-controlled trials failed to demonstrate beneficial effects of MRA therapy for AF prevention (P = 0.11).[4] Moreover, the aforementioned meta-analysis reported a significant heterogeneity among the included studies (I^2 = 54%; P = 0.0008), a significant interaction between MRA effect and type of AF (the effect was higher for AF recurrence than new-onset AF, P = 0.01). Of note, contemporary more aggressive treatment of hypertension has been recently shown to be associated with a significant reduction of incident AF compared with older reports.[1] For these reasons, a routine use of MRA for AF prevention in hypertensive patients is still controversial.

Recently, the RACE 3 (Routine Versus Aggressive Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure) trial confirmed that targeted therapy of underlying conditions consisting of MRAs, ACEIs / ARBs,

statins and cardiac rehabilitation significantly reduced the recurrence of persistent AF among patients with mild-to-moderate heart failure.[5] We believe that additional data from large randomized studies are needed to support a wider use of MRA for the primary AF prevention in patients with hypertension and no structural heart disease. Currently, the use of MRA for the primary AF prevention should be restricted to hypertensive patients with history of heart failure and / or LV systolic dysfunction and in addition to full treatment with ACEI / ARBs and β-blockers.

ARTICLE INFORMATION

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REFERENCES

1 Mujović N, Marinković M, Mihajlović M, et al. Risk factor modification for the primary and secondary prevention of atrial fibrillation. Part 1. Kardiol Pol. 2020; 78: 181-191.

2 Dąbrowski R. Mineralocorticoid receptor antagonists and prevention of atrial fibrillation in patients with hypertension. Kardiol Pol. 2020; 78: 609-610.

3 Swedberg K, Zannad F, McMurray JJ, et al. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. J Am Coll Cardiol. 2012; 59: 1598-1603.

4 Alexandre J, Dolladille C, Douesnel L, et al. Effects of mineralocorticoid receptor antagonists on atrial fibrillation occurrence: a systematic review, meta-analysis, and meta-regression to identify modifying factors. J Am Heart Assoc. 2019; 8: e013267.

5 Rienstra M, Hobbelt AH, Alings M, et al. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. Eur Heart J. 2018; 39: 2987-2996.