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# COMMENTARY

# Aldosterone-receptor antagonism as a potential therapeutic option for atrial fibrillation

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Recent research provided important insights into the development of atrial fibrillation (AF)-maintaining substrate and suggested targeting of the underlying molecular mechanisms, 'upstream' of the electrical aspects of AF, as a novel strategy for AF treatment ('upstream' therapy). Upstream therapies for AF include drugs targeting the renin-angiotensin II-aldosterone system (angiotensin converting enzyme inhibitors and $AT_1$ receptor antagonists and aldosterone antagonists), statins, steroids and ω-3 fatty acids (fish oil). Aldosterone causes volume retention, cardiac hypertrophy and fibrosis, and systemic inflammation and coagulation that promote AF development and its complications and blockade of aldosterone receptors with spironolactone or eplerenone suppresses inducible AF. Although the clinical impact of spironolactone treatment requires validation in randomized clinical trials in AF patients, further understanding of the molecular mechanisms by which aldosterone causes atrial remodelling is likely to lead to development of novel therapeutic approaches to AF.
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**Keywords:** aldosterone; apoptosis; atrial remodelling; fibrillation; fibrosis; rapid pacing; renin-angiotensin-aldosterone system

**Abbreviations:** AF, atrial fibrillation; RAAS, renin-angiotensin-aldosterone system

Recent research provided important insights into the development of atrial fibrillation (AF)-maintaining substrate and suggested targeting of the underlying molecular mechanisms, 'upstream' of the electrical aspects of AF, as a novel strategy for AF treatment ('upstream' therapy). Upstream therapies for AF include drugs targeting the renin-angiotensin II-aldosterone system (RAAS), which include angiotensin converting enzyme (ACE) inhibitors and angiotensin $AT_1$ receptor antagonists and aldosterone antagonists, along with statins, steroids and ω-3 fatty acids (as in fish oil).

AF is associated with substantial structural changes in atrial tissue that, to a large extent, depend on increased activity of the RAAS. AF can activate the RAAS both in blood and in cardiac tissue, with increased expression/activity of ACE and elevated levels of angiotensin II (Ang II) being major promoters of functional and structural changes during AF. AF also profoundly modulates atrial and ventricular expression levels of both Ang II receptors ($AT_1$ and $AT_2$), but AF-related expression patterns differ between short-term (paroxysmal) and persistent AF (Goette *et al.*, 2000a, 2000b).

Aldosterone causes atrial fibrosis independent of changes in wall stress or hypertension and the aldosterone-receptor antagonist spironolactone prevents fibrosis (Sun *et al.*, 1997). Selective aldosterone-receptor blockade with eplerenone suppresses inducible AF in experimental heart failure (Shroff *et al.*, 2006). Plasma aldosterone levels are raised in AF patients (Goette *et al.*, 2001) and aldosterone-receptor expression is higher in atria of AF patients (Pei *et al.*, 2007). In addition, patients with primary aldosteronism have a 12-fold higher risk of developing AF when compared to blood pressure-matched controls further supporting a critical role of aldosterone in the atrial remodelling leading to AF (Milliez *et al.*, 2005).

In various experimental and clinical settings, Ang II and aldosterone synergize to produce deleterious cardiac effects (Milliez *et al.*, 2005; Min *et al.*, 2007; Lemarié *et al.*, 2009). Both Ang II and aldosterone increase volume retention, cardiac hypertrophy and fibrosis, and systemic inflammation and coagulation. However, the relative contribution of aldosterone to AF-dependent atrial fibrosis, hypertrophy, apoptosis, degradation of myofilaments, mitochondrial swelling and dysfunction has not been assessed previously. In this issue of

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the *BJP*, Zhao *et al*. (2010) show that spironolactone largely prevents AF-related changes in atrial structure and function in an *in vivo* canine model of persistent AF. Spironolactone reduced apoptotic cell death, myolysis, pro-fibrotic pathways and activity, and mitochondrial swelling, and maintained functional parameters such as left atrial ejection fraction. These findings strongly suggested that aldosterone-receptor blockade represents a powerful therapeutic option that, when combined with ACE inhibition or Ang II receptor blockade, may help to maintain atrial integrity and function during AF. Precise molecular mechanisms of how spironolactone prevents structural remodelling were not elucidated in the present study.

Recent evidence indicates that aldosterone has both rapid, non-genomic and slow, genomic effects (Lemarié *et al.*, 2009). Rapid signalling via classical mineralocorticoid receptors (MRs) potentiates the $AT_1$ receptor-mediated action of Ang II (Min *et al.*, 2007; Lemarié *et al.*, 2009), and non-canonical MRs, probably located on the plasmalemma, have also been implicated in Ang II/$AT_1$ receptor signalling. Aldosterone enhances the effects of Ang II in part, via increased transcription of $AT_1$ receptor and ACE, whereas Ang II may increase systemic and tissue levels of aldosterone, consistent with elevated plasma levels of both Ang II and aldosterone during AF (Goette *et al.*, 2001).

Aldosterone and Ang II activate ERK1/2, JNK and NF-κB-signalling pathways in a synergistic manner and these signal pathways are associated with hypertrophic, pro-fibrotic and oxidative stress-responses during AF (Goette *et al.*, 2000a, 2000b; Min *et al.*, 2007). Recent work directly demonstrated that the effects of aldosterone depend on the presence of $AT_1$ receptors. Aldosterone can also transactivate Ang II type 1a receptors, increasing phosphorylation of ERK1/2, JNK and NF-κB. Interestingly, Ang II stimulates nuclear localization of MRs, and spironolactone inhibits Ang II-mediated MR-dependent gene expression in VSMCs. Ang II-mediated MR activation is also inhibited by losartan, demonstrating a link between $AT_1$ receptor activation and MR transcriptional activation (Lemarié *et al.*, (2009); Min *et al.* (2007); Sun *et al.* 1997). Although aldosterone is produced in the failing human heart (Milliez *et al.*, 2005), it is unclear, whether AF *per se* induces cardiac synthesis of aldosterone. However, it is tempting to speculate that the increased atrial expression and activation of the Ang II system may enhance cardiac aldosterone synthesis, which could contribute to increased plasma aldosterone levels during AF (Goette *et al.*, 2001). Besides its profibrotic effects, aldosterone enhances potassium and magnesium excretion, decreases myocardial reuptake of catecholamines, and induces baroreceptor dysfunction. Aldosterone increases L-type calcium currents and prolongs action potential duration which may result in early afterdepolarizations. Diastolic calcium leak from the cardiac sarcoplasmic reticulum (SR) leads to delayed afterdepolarizations and AF and chronic stimulation of MRs reduces binding of ryanodine receptor-inhibitory FK506-binding protein, enhancing SR calcium leak (Gómez *et al.*, 2009). Thus, inhibition of aldosterone actions may produce beneficial effects during AF through a variety of mechanisms and further work is needed to dissect the specific pathways of aldosterone-induced atrial remodelling.

In conclusion, although spironolactone appears effective in reducing circulating levels of pro-collagen type III N-terminal amino peptide (a marker of collagen turnover), influencing heart rate variability and molecular atrial biology (Zhao *et al.*, 2010) the clinical impact of spironolactone treatment has not been elucidated in AF patients. In experimental studies, treatments can be administered before AF develops, but clinical AF has to be treated after its onset. There is presently no information about whether targeting MR receptors is effective after AF has become established. Nevertheless, further understanding of the molecular mechanisms by which aldosterone causes atrial remodelling may lead to development of novel therapeutic approaches to AF.

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## Conflicts of interest

No conflict of interest to disclose.

## References

Goette A, Arndt M, Röcken C, Spiess A, Staack T, Geller JC *et al.* (2000a). Regulation of angiotensin II receptor subtypes during atrial fibrillation in humans. *Circulation* **101**: 2678–2681.

Goette A, Staack T, Röcken C, Arndt M, Geller JC, Huth C *et al.* (2000b). Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. *J Am Coll Cardiol* **35**: 1669–1677.

Goette A, Hoffmanns P, Enayati W, Meltendorf U, Geller JC, Klein HU (2001). Effect of successful electrical cardioversion on serum aldosterone in patients with persistent atrial fibrillation. *Am J Cardiol* **88**: 906–909.

Gómez AM, Rueda A, Sainte-Marie Y, Pereira L, Zissimopoulos S, Zhu X *et al.* (2009). Mineralocorticoid modulation of cardiac ryanodine receptor activity is associated with downregulation of FK506-binding proteins. *Circulation* **119**: 2179–2187.

Lemarié CA, Simeone SMC, Nikonova A, Ebrahimian T, Deschênes M-E, Coffman TM *et al.* (2009). Aldosterone-induced activation of signaling pathways requires activity of angiotensin type 1a receptors. *Circ Res* **105**: 852–859.

Milliez P, Deangelis N, Rucker-Martin C, Leenhardt A, Vicaut E, Robidel E *et al.* (2005). Spironolactone reduces fibrosis of dilated atria during heart failure in rats with myocardial infarction. *Eur Heart J* **26**: 2193–2199.

Min LJ, Mogi M, Iwanami J, Li JM, Sakata A, Fujita T *et al.* (2007). Cross-talk between aldosterone and angiotensin II in vascular smooth muscle cell senescence. *Cardiovasc Res* **76**: 506–516.

Pei DA, Li L, Xu ZY, Zou LJ, Zhang BR, Huang SD *et al.* (2007). Expression of mineralocorticoid receptor and 11-beta-hydroxysteroid dehydrogenase type 2 in human atria during

chronic atrial fibrillation: study of 25 cases. *Zhonghua Yi Xue Za Zhi* **87**: 816–819.

Shroff SC, Ryu K, Martovitz NL, Hoit BD, Stambler BS (2006). Selective aldosterone blockade suppresses atrial tachyarrhythmias in heart failure. *J Cardiovasc Electrophysiol* **17**: 534–541.

Sun Y, Ramires FJ, Weber KT (1997). Fibrosis of atria and great vessels in response to angiotensin II or aldosterone infusion. *Cardiovasc Res* **35**: 138–147.

Zhao J, Li J, Li Y, Shan H, Gong Y, Yang B (2010). Effects of spironolactone on atrial structural remodeling in a canine model of atrial fibrillation produced by prolonged atrial pacing. *Br J Pharmacol* **159**: 1584–1594.