Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 9 Issue 8 August 2025

Short Communication

Fibrosis and Atrial Fibrillation: The Role of Antifibrotic Treatment in the Therapy of AF

Hazarapetyan LG, Zelveian PH and Grigoryan SV*

Yerevan State Medical University, National Medical Center 'Yerevan', 2 Koryun Street, Yerevan, Armenia

***Corresponding Author:** Grigoryan SV, Yerevan State Medical University, National Medical Center 'Yerevan', 2 Koryun Street, Yerevan, Armenia.

Received: June 25, 2025

Published: July 16, 2025

Atrial fibrillation (AF) is the most common arrhythmia with heterogeneous clinical manifestations and severe complications such as heart failure and stroke. Atrial fibrillation has a multi-factorial nature and complex pathogenesis. The process of atrial remodeling is the basis of the occurrence and recurrence of AF, which affects the electrical, contractile, structural function and also impact on autonomic nervous system dysfunction, which leads to their morphological changes in atrium [1].

Cardiac structural remodeling is characterized by atrial enlargement and tissue fibrosis, characterized by the excessive accumulation of collagenous material in the extracellular space [2,3]. Fibrosis is promoted by various risk factors as an aging, obesity, arterial hypertension, heart failure, diabetes, sleep disordered and nearly all type of heart disease, including different ischemic and non-ischemic etiologies [4].

Atrial fibrosis interferes with impulse propagation by forming barriers to electrical conduction and thus separating the associated syncytium. Increased extracellular collagen contributes to disruption of fiber continuity, causing local conduction disturbances. In addition, perivascular fibrosis around intracoronary vessels may impair oxygen availability, contributing to myocyte ischemia. The mechanisms underlying atrial fibrosis are multifaceted, involving stretch-induced fibroblast activation, oxidative stress, inflammation, and coagulation pathways. Atrial fibrosis is considered a critical prognostic factor for the development of atrial fibrillation and its associated complications, including stroke and infarction [5,6].

Experimental and clinical studies suggest a bidirectional relationship between AF and atrial fibrosis, whereby AF can induce fibrosis and fibrotic remodeling, in turn, exacerbates the risk and progression of AF [7]. The pathophysiology of atrial fibrosis involves several interrelated processes, including stretch-induced fibroblast activation, reactive oxygen species generation, local and systemic inflammatory responses, activation of coagulation pathways, and fibro-fatty infiltration [8,9].

Understanding the relationship between fibrosis and AF in patients is complicated by the presence of diverse underlying risk factors that often coexist. These factors not only contribute to fibrosis but also induce additional structural alterations that affect electrical conduction.

It was revealed that in patients with AF, hemodynamic overload of the atria is observed. Constantly increased intra-atrial pressure leads to thinning of the atrial wall, to decrease in the number of contractile myocardial cells and the development of diffuse atrial sclerosis. The specific gravity of the fibrous tissue of such atria is much higher than normal. It is believed that the development of fibrosis has several causes: 1) a consequence of the inflammatory process ("atrial myocarditis" as the cause of AF); 2) hyperactivation of the renin-angiotensin-aldosterone system with the negative effects of excessive formation of angiotensin and aldosterone; 3) an increase in other biologically active agents capable of inducing fibrosis, such as galectin-3 [12]. The process of fibrosis is characterized by the proliferation and differentiation of fibroblasts

and myofibroblasts, followed by an increase in collagen synthesis to form fibrous tissue. An increase of atrial fibrosis is observed at biopsy and autopsy in AF patients [13]. The relationship between the volume of fibrosis in the left atria and the number of cases of postoperative AF was revealed. With a fibrosis volume of up to 15%, AF developed in 16% of patients in the postoperative period; with a volume of fibrosis of 15–23% - in 21% of patients and with a volume of fibrosis of 23–32% [14]. This significantly increases the risk of recurrence of AF [15]. Atrial fibrosis is a multifactorial process resulting from complex interactions between neurohormonal and cellular mediators [16]. Fibrosis is understood as an increase in the level of the collagen fraction by 2-3 times, i.e. the predominance of collagen synthesis over its breakdown. It has been proven that the more collagen, the higher the rigidity of not only the vascular wall, but also the myocardial wall [17]. Several profibrotic signaling pathways are known to promote the transition of profibrotic molecules and mediators to atrial fibrosis. For example, angiotensin II, a well-known profibrotic molecule, plays a central role in collagen production. It acts by binding to 2 different subtypes of receptors: angiotensin type I receptor (AT1R) and type II (AT2R). AT1R realize the profibrogenic effects of angiotensin II by stimulating fibroblast proliferation, hypertrophy and apoptosis of cardiomyocytes [18]. Activation of type 1 AT II receptors stimulates the accumulation of extracellular matrix proteins and fibrosis. The influence of angiotensin II on the composition of the extracellular matrix and collagen expression is partially mediated by local synthesis of the cytokine transforming growth factor-beta-1TGF-β1. Which, being a profibrotic cytokine, controls the production and composition of the extracellular matrix. TGF-β1 is secreted by both cardiomyocytes and fibroblasts and is the main mediator of angiotensin II regulatory signals for autocrine (influence on the angiotensin II producing cell itself) and paracrine (influence on neighboring cells) regulation mechanisms [19]. The main cardiac effects of TGF-β1 are: hypertrophy, fibrosis and apoptosis. Excessive expression of TGF-β1 enhances the synthesis of the extracellular matrix and stimulates the progression of organ fibrosis. It is known that the level of TGF-β1 in patients with AF is higher than in patients with sinus rhythm. In addition, activation of TGF-β1 receptors also results in the expression of connective tissue growth factor, which is released locally, further stimulating extracellular matrix proteins and enhancing the progression of atrial fibrosis. As a result, the accumulation of fibrillar and non-fibrillar collagen leads to the progression of atrial fibrosis and the maintenance of AF, i.e. either to its recurrence, or to the transition to a permanent form of AF. The relationship between TGF-β1 and RAAS is quite interesting; angiotensin II stimulates the synthesis of TGF-β1, which is a potent stimulator of fibroblast activity. Conversely, TGF-β1 reciprocally enhances the production of angiotensin II and additional profibrogenic factors; thus, a positive feedback loop is formed [20]. It appears that fibrosis progresses despite compensatory changes in TGFβ1 signaling pathways, and high blood levels of TGFβ1 are a potential non-invasive predictor of atrial electrical and structural remodeling in AF.

Currently, some pharmacological agents can be used to prevent the progression of atrial fibrosis associated with underlying heart disease. Thus, it has been found that the use of ACE inhibitors, ARBs or mineralocorticoid receptor antagonists can prevent the onset of atrial fibrosis. Experimental studies show that inhibition of the RAAS system can mitigate the development of fibrosis and reduce the incidence of AF [21-23].

Recently, special attention has been paid to SGLT2 inhibitors, which affect atrial fibrosis through, attenuation of pro-fibrotic signaling pathways such as the TGF-β/SMAD axis. In addition, SGLT2 inhibitors have anti-inflammatory properties by reducing circulating levels of cytokines such as IL-6 and TNF-α, which are key factors in cardiac fibroblast activation and extracellular matrix remodeling [24,25]. Improved myocardial energy metabolism relieves cellular stress, while natriuretic and diuretic effects reduce atrial wall stretch, further reducing mechanical stress-induced fibrosis [26-28].

GLP-1RAs counteract atrial fibrosis by modulating cardiac fibroblast activity through activation of the GLP-1 receptor. This suppresses pro-fibrotic pathways including TGF-β and connective tissue growth factor. Moreover, they significantly reduce systemic and local inflammation and pro-inflammatory cytokine levels [29-31].

In directly, they alleviate cardiac hypertrophy by reducing mechanical stress on atrial tissue and further attenuating fibrosis [32]. Anti-inflammatory role of glucagon-like peptide 1 receptor SGLT2 inhibitors and GLP-1RAs may potentially synergistically attenuate atrial fibrosis via complement pathways.

In summary, atrial fibrosis is mediated by complex paracrine signaling networks regulating fibroblast proliferation, activation, and collagen synthesis. Therapeutic strategies target key pathways including the renin-angiotensin-aldosterone system, endothelin-1 signaling, protease-activated receptors, and mineralocorticoid receptor antagonists. Novel antidiabetic drugs, including sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, reduce oxidative stress and profibrotic signaling pathways.

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