

FOCUS ISSUE: ATRIAL FIBRILLATION

Atrial Fibrosis: Mechanisms and Clinical Relevance in Atrial Fibrillation

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Atrial fibrillation (AF) is the most common arrhythmia in the clinical setting, and traditional pharmacological approaches have proved to have important weaknesses. Structural remodeling has been observed in both clinical and experimental AF paradigms, and is an important feature of the AF substrate, producing fibrosis that alters atrial tissue composition and function. The precise mechanisms underlying atrial fibrosis are not fully elucidated, but recent experimental studies and clinical investigations have provided valuable insights. A variety of signaling systems, particularly involving angiotensin II and related mediators, seem to be centrally involved in the promotion of fibrosis. This paper reviews the current understanding of how atrial fibrosis creates a substrate for AF, summarizes what is known about the mechanisms underlying fibrosis and its progression, and highlights emerging therapeutic approaches aimed at attenuating structural remodeling to prevent AF. (J Am Coll Cardiol 2008; 51:802-9) © 2008 by the American College of Cardiology Foundation

In recent years, atrial fibrillation (AF) has increasingly become a focus of attention because it remains the most encountered arrhythmia in clinical practice (1) and a major cause of morbidity and mortality (2). The fundamental mechanisms underlying AF have long been debated, but electrical, contractile, and structural remodeling are each important synergistic contributors to the AF substrate (3-5). Fibrosis is a hallmark of arrhythmogenic structural remodeling (4,5). Tissue fibrosis results from an accumulation of fibrillar collagen deposits, occurring most commonly as a reparative process to replace degenerating myocardial parenchyma with concomitant reactive fibrosis, which causes interstitial expansion (6,7). Animal models indicate regional differences in fibrotic remodeling (8), with the atria seeming to be more sensitive than the ventricles (9). Atrial fibrosis occurs as a convergent pathological end point in a variety of settings, such as senescence (10,11), cardiac dysfunction (12), mitral valvular disease (13,14), and possibly myocardial ischemia (15). Atrial fibrosis involves multifactorial processes that result from complex interactions among neurohormonal and cellular mediators. Interventions that prevent atrial fibrosis may be useful in preventing AF occurrence (1). An understanding of the mechanisms underlying atrial fibrosis is relevant to designing

improved strategies for preventing AF-promoting structural remodeling.

Clinical Relationship Between Atrial Fibrosis and AF

Atrial fibrosis is a common feature of clinical AF (16). Atrial fibrillation is thought to be secondary to underlying organic heart disease in approximately 70% of patients, with lone AF occurring in the absence of any detectable etiology in approximately 30% of cases (17). Increased collagen deposition has been documented in lone-AF patients compared with sinus rhythm control subjects (18), and in patients with AF secondary to mitral valve disease versus those in sinus rhythm (19). Extracellular matrix (ECM) volume and composition correlate with AF persistence (20). These findings highlight the association between atrial fibrosis and AF, although determining the causal importance of tissue fibrosis in AF occurrence and persistence remains an important challenge. Experimental models have helped to develop an appreciation for the relationship between atrial fibrosis and AF (Table 1). Ventricular tachypacing (VTP) induces congestive heart failure (CHF) in dogs by causing a tachycardiomyopathy (21), and produces atrial interstitial fibrosis comparable to atrial pathology in many forms of clinical AF (4). In the dog model, atrial fibrosis causes localized regions of conduction slowing, increasing conduction heterogeneity and providing an AF substrate (4). Conduction abnormalities provide a basis for unidirectional conduction block and macro-re-entry (22,23); however, there is also evidence for focal atrial tachyarrhythmias (24). Extracellular matrix genes are in-

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duced early after VTP onset in the dog (25), with a time course paralleling the development of fibrosis and AF sustainability (26). Extracellular matrix gene expression changes in human AF patients show similar profibrotic patterns (27). Figure 1 illustrates the pathophysiology of AF associated with CHF. In addition to inducing fibrosis, CHF also affects atrial ionic current (28) and Ca²⁺ handling properties (29). Atrial tachycardia itself alters atrial electrical properties in a way that promotes AF induction and maintenance (“AF begets AF” [3]). Tachycardia-induced ionic remodeling in the presence of CHF, as occurs when AF develops in a CHF patient, differs from that of CHF or AF alone, and from simple additive effects (30). Atrial tachypacing with ventricular rate control produces ECM accumulation (31,32), suggesting that AF itself promotes atrial fibrosis.

Ultrastructural Alterations

Myocyte loss, either by apoptosis or necrosis (9,26), is observed in parallel with the onset of fibrosis. Reparative fibrosis replaces degenerating myocardial cells (33), whereas coexisting reactive fibrosis causes interstitial expansion between bundles of myocytes (7,34), as shown in Figure 2. Pathologically produced collagen differs from that in normal myocardium, with altered ratios of collagen subtypes (20,35). Dense and disorganized collagen weave fibrils physically separate remaining myocytes (36), and can create a barrier to impulse propagation.

Fibrosis interferes with conduction by impairing intermyocyte coupling. Myocardial electrical continuity is maintained by specialized proteins called connexins located in gap junctions, which form cell-to-cell connections that maintain low-resistance intercellular coupling. Alterations in ventricular expression and function of the major cardiac connexin, connexin 43, are observed in CHF and correlate with proarrhythmic conduction slowing (37). Hypophosphorylation of connexins and their redistribution to lateral cell borders are the salient features (37,38), with connexin disorganization correlating with fibrosis (39). Studies of gap-junctional remodeling in the atria have produced discrepant results (40), and changes may depend on the degree and/or type of underlying pathology (41). Atrial gap junc-

tion remodeling seems to reverse slowly (42), but it is still unclear how much connexin disruption is required to observe an effect on conduction.

Mechanisms of Atrial Fibrosis

Profibrotic signals. Atrial fibrosis results from a variety of cardiac insults that share common fibroproliferative signaling pathways. Several secreted factors that cause profibrotic responses often work in concert in the clinical setting (43). Angiotensin II (AngII) is a well-characterized profibrotic molecule, along with prominent downstream mediators like transforming growth factor (TGF)-beta 1. Other potential mediators such as platelet-derived growth factor (PDGF) and connective tissue growth factor have recently become of interest.

The renin-angiotensin-aldosterone system is involved in myocardial fibrosis in hypertensive heart disease, CHF, myocardial infarction, and cardiomyopathy (44). Patients with primary hyperaldosteronism have an increased incidence of AF (45), and locally produced AngII is associated with cardiomyocyte apoptosis and reactive interstitial fibrosis (46). Increased AngII production in transgenic mice with cardiac-restricted angiotensin-converting enzyme (ACE) overexpression causes marked atrial dilation with focal fibrosis and AF (47). Atrial AngII levels increase early in the course of VTP-induced CHF (26,48). Mitogen-activated protein kinases are important potential mediators of AngII effects on tissue structure (49-51), and overactivity of this pathway may also directly influence cardiomyocyte gap-junctional coupling and conduction properties (52).

Transforming growth factor-β₁ is central to signaling cascades implicated in the genesis of cardiac fibrosis (53), for example as a primary downstream mediator of AngII effects (54,55). AngII induces TGF-β₁ messenger ribonucleic acid

Abbreviations and Acronyms

- ACE** = angiotensin-converting enzyme
- AF** = atrial fibrillation
- AngII** = angiotensin II
- AT1** = angiotensin II type 1
- CHF** = congestive heart failure
- ECM** = extracellular matrix
- PDGF** = platelet-derived growth factor
- TGF** = transforming growth factor
- VTP** = ventricular tachypacing

Table 1 Animal Models With Selective Atrial Fibrosis Associated With AF

Animal	Model	Finding	Clinical Correlate	Ref. #
Dog	VTP	Atrial fibrosis, AF, conduction heterogeneity	CHF	4
Dog	Aging	Atrial fibrosis, AF	Ageing	10,11
Dog	Mitral regurgitation	Atrial fibrosis, AF	Mitral valve disease	14
Dog	Atrial tachypacing with ventricular rate control	Qualitative increase in atrial fibrosis	Atrial tachycardia remodeling	14
Pig	Atrial tachypacing with ventricular rate control	Atrial fibrosis, AF	Atrial tachycardia remodeling	31,32
Transgenic mouse	Cardiac overexpression:			
	ACE	Atrial fibrosis, AF, normal ventricular structure and function	Atrial pathology in CHF	47
	TGF-β ₁	Atrial fibrosis, AF, normal ventricular structure and function	Atrial pathology in CHF	63,64

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; CHF = congestive heart failure; TGF = transforming growth factor; VTP = ventricular tachypacing.

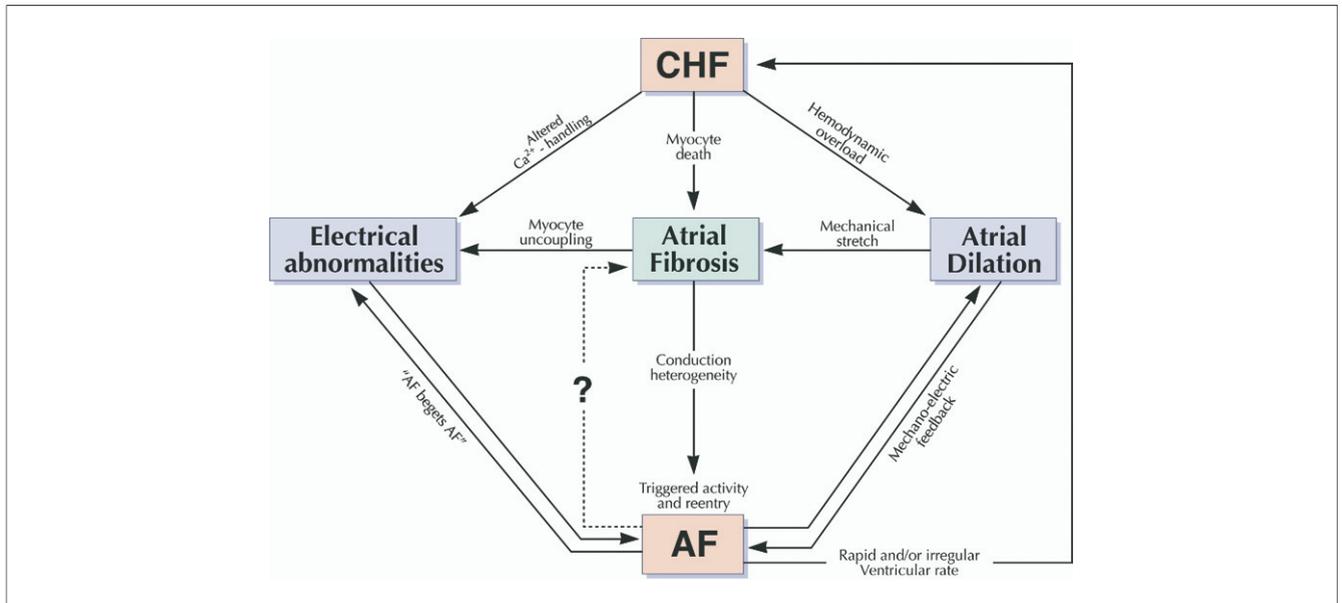


Figure 1 Mechanisms by Which CHF Leads to AF

In turn, AF causes changes that can impair cardiac function, leading to potentially deleterious positive-feedback systems. Figure illustration by Rob Flewell. AF = atrial fibrillation; CHF = congestive heart failure.

expression, protein elaboration and activity in vitro (56) and in vivo (57,58), and blockade of the angiotensin II type 1 (AT1) receptor suppresses TGF- β 1 upregulation (59-61). Primarily, TGF- β 1 acts through the SMAD signaling pathway to stimulate collagen production (60,62). As for tissue AngII, rapid increases in atrial expression of activated TGF- β 1 occur in VTP-induced CHF (9). Targeted cardiac overexpression of constitutively active TGF- β 1 causes se-

lective atrial fibrosis, conduction heterogeneity, and AF propensity (63,64). Normal ventricular structure and function in this model, despite equal overexpression, implies that: 1) TGF- β 1 may be a key mediator of atrial fibrosis, 2) fibrosis-related promotion of AF can occur in the absence of ventricular dysfunction, and 3) regional differences exist in structural remodeling vulnerability, with the atria particularly prone to fibrosis. The latter notion is consistent with

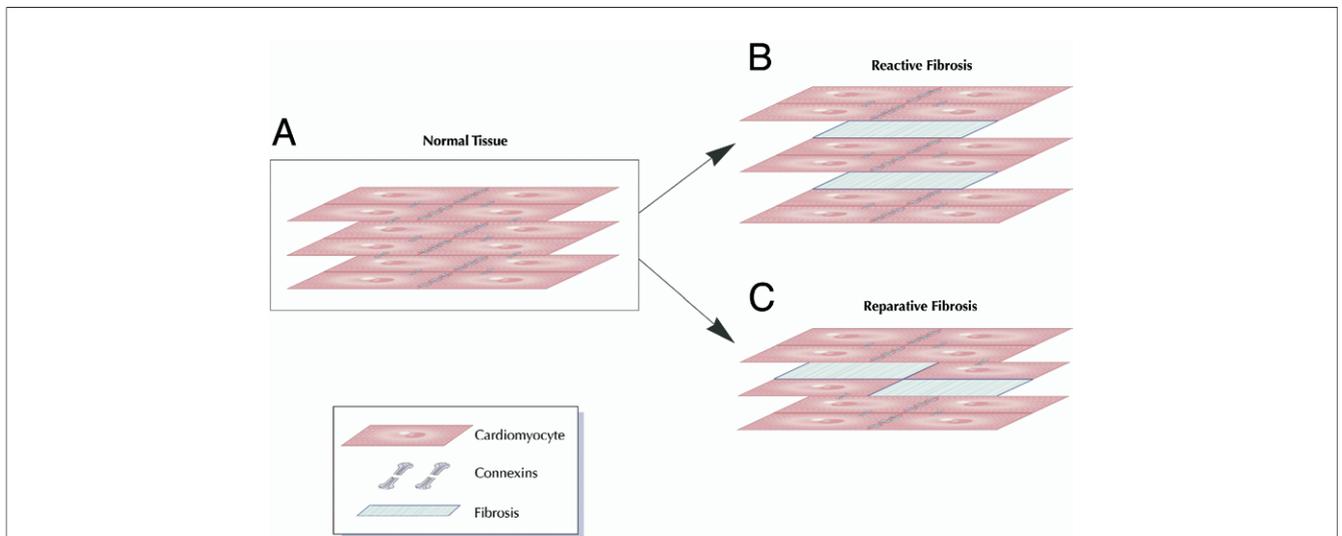


Figure 2 Schematic Illustrating How Fibrosis Disrupts Myocyte Coupling

Cardiomyocytes in normal myocardial tissue (A) are electrically coupled primarily in an end-to-end fashion by intercellular gap-junctional complexes. Reactive fibrosis results in extracellular matrix expansion between bundles of myocytes (B), while reparative fibrosis replaces degenerating myocytes (C). Both patterns of collagen distribution become exaggerated during structural remodeling. Figure illustration by Rob Flewell.

the predominant atrial versus ventricular fibrosis observed in experimental CHF (9).

Platelet-derived growth factor, a member of the PDGF/vascular endothelial growth factor family, is highly expressed in the myocardium throughout development and adulthood. It stimulates proliferation, migration, differentiation, and physiological function of mesenchymal cells (65); however, its role in cardiac fibrosis has only recently been investigated. Transgenic mice with cardiac-specific PDGF overexpression show cardiac fibrosis followed by dilated cardiomyopathy and cardiac failure (66,67). Atrial fibrillation susceptibility has not been evaluated in these animals but would be interesting to address, given the existence of a fibrotic and potentially arrhythmogenic substrate. Connective tissue growth factor has emerged from pathway analysis in a genomic study of the CHF-related AF substrate (26).

Cellular mediators. Fibrosis results when circulating and locally synthesized profibrotic factors act on resident cardiac cells to increase collagen production without offsetting increases in collagen degradation. Cardiomyocytes account for approximately 45% of the atrial myocardium by volume, compared with approximately 76% in the ventricles (68,69). Nonmyocytes are thought to compose approximately 70% of cardiac cells by number (70): atrial-ventricular differences in the composition of this heterogeneous population of cells may contribute to the greater atrial ECM volume compared with ventricles in normal hearts (68,69), which becomes

exaggerated with remodeling (9). There is a complex interplay among these cell types, the most numerous of which is the cardiac fibroblast. The fibroblast was traditionally thought to be a passive bystander in the myocardium, but is now recognized to participate actively in shaping and responding to the cardiac milieu (71). Figure 3 is a schematic representation of cardiomyocyte-fibroblast crosstalk in the promotion of atrial fibrosis.

Exposure to AngII (72) or TGF- β_1 (73) dramatically influences cardiac fibroblast function, upregulating ECM protein synthesis and secretion. Both AngII production and AT1 receptor expression are increased during remodeling in fibroblasts *in vivo* (74). Increases in AngII and activated TGF- β_1 concentrations reciprocally enhance each other's production (56,75), and induce expression of additional profibrotic molecules in fibroblasts (76,77), creating positive feedback cycles for fibrosis. Mechanical stretch induces collagen synthesis (78), along with increased AngII and TGF- β_1 expression in cardiac fibroblasts (79), and thus chronic atrial dilation may contribute to structural remodeling and the domestication of AF (80). Fibroblast stretch-sensing mechanisms show exquisite sensitivity, with different types of deformation causing differential ECM expression profiles (81). In addition to profibrotic actions, mechanical stretch of fibroblasts can directly modulate myocyte electrical activity, a potentially proarrhythmic mechanism called mechanoelectric feedback (82).

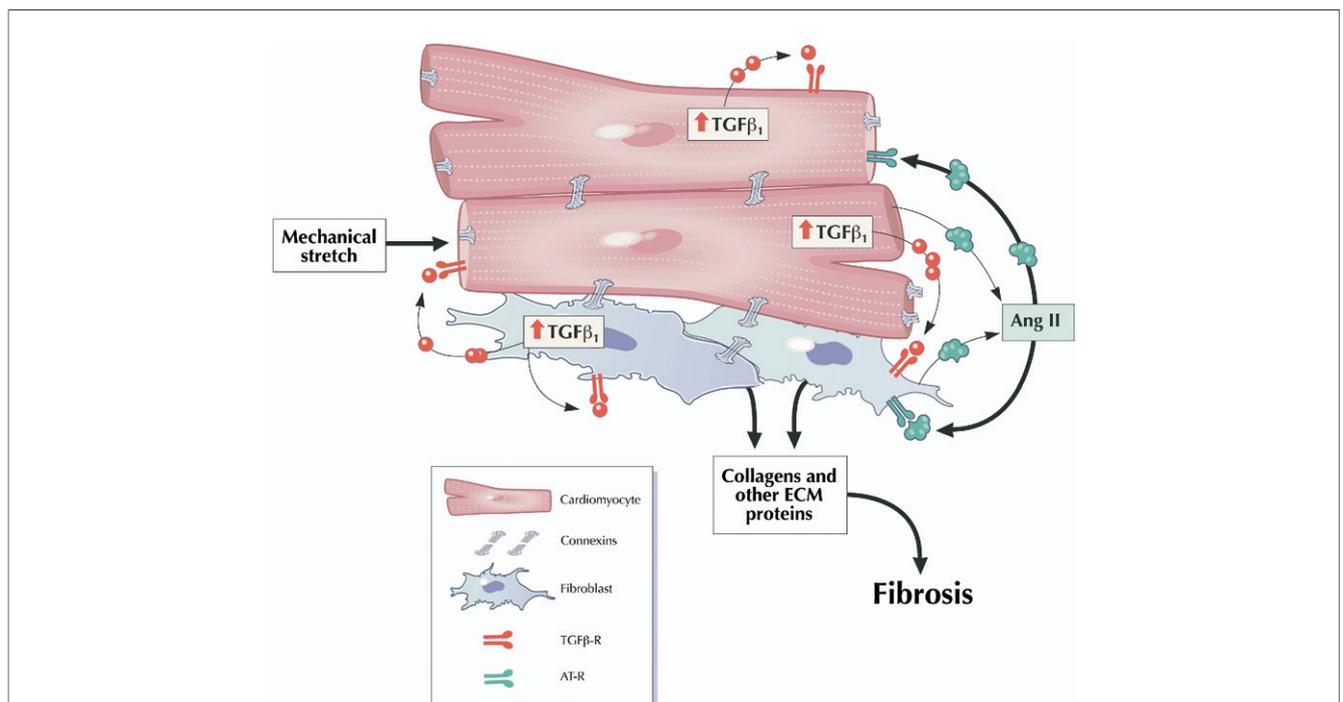


Figure 3 Cardiomyocyte-Fibroblast Crosstalk

Autocrine and paracrine mechanisms act to amplify humoral and mechanical stimuli resulting in tissue fibrosis. Figure illustration by Rob Flewell. Ang II = angiotensin II; AT-R = angiotensin receptor; ECM = extracellular matrix; TGF = transforming growth factor; TGF β -R = transforming growth factor beta receptor.

Although cardiomyocytes probably do not directly synthesize collagen (83), they can importantly influence structural remodeling through interactions with neighboring fibroblasts. Mechanical stretch induces cardiomyocyte mitogen-activated protein kinase signaling through direct activation of AT1 receptors (84). Angiotensin II is produced by stretched cardiomyocytes (85), with direct fibroblast-activating consequences. Furthermore, AngII acts as a paracrine/autocrine hypertrophic signal, and eventual myocyte failure and death further promotes fibroblast chemotaxis. Rapid cardiomyocyte activation seems to cause AngII upregulation (52,86) and tachypaced atrial cardiomyocytes secrete factors that cause differentiation to a secretory phenotype in cardiac fibroblasts (87). In coculture experiments, cardiomyocytes potentiate AngII-stimulated collagen synthesis in fibroblasts (88,89). The potential importance of cardiomyocyte–fibroblast interactions in fibrillating atria has recently been emphasized based on observations on atrial myocytes from AF patients (90).

Therapeutic Implications

Conventional antiarrhythmic drug approaches have limited effectiveness and are associated with risks of serious complications, particularly proarrhythmia (91). Accordingly, attenuation and reversal of structural remodeling have increasingly become the focus of attempts at therapeutic innovation, and several agents have shown efficacy in animal models (Table 2). Several ACE inhibitors reduce fibrosis, normalize connexin 43 abnormalities, and improve AF indices in experimental models (26,48,92–94). Retrospective analyses point to the value of ACE inhibitors in AF prevention, particularly in patients at the highest risk of structural remodeling (95). Angiotensin II type 1 receptor blockers seem to offer a benefit similar to that of ACE inhibition, with improvement in both AF susceptibility and structural remodeling (96–98). Antialdosterone therapies also seem to reduce atrial fibrosis (99). Pirfenidone, 5-methyl-1-phenyl-2(1H)-pyridone, an antifibrotic agent, reduces TGF-β₁ levels and prevents development of the AF

substrate in VTP-induced CHF (100). Both CHF-induced atrial structural remodeling and AF promotion are also attenuated by the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor simvastatin, which improves hemodynamic function and directly inhibits profibrotic atrial fibroblast responses (101). Recently, omega-3 poly-unsaturated fatty acids have been found similarly to prevent the CHF-associated AF substrate (102).

The potential for reversing fibrosis is of particular clinical interest because it is often not possible to begin treatment in humans before a significant degree of atrial remodeling has already occurred. Cessation of VTP without pharmacological intervention allows the reversal of CHF and normalization of atrial size and function; however, fibrosis and conduction abnormalities persist along with a substrate that can support prolonged AF (103,104). Brilla et al. (105–107) have published several reports showing the regression of established fibrosis in the ventricles with ACE inhibition. Similar investigations of the atria are limited, although one study has shown that rats treated for 1 month with an aldosterone antagonist beginning 3 months after myocardial infarction have less atrial fibrosis than control rats (99), suggesting possible reversal of fibrosis.

Although animal studies on fibrosis suppression as an approach to preventing development of the AF substrate are promising, confirmatory evidence of clinical value is essential. A number of clinical trials support the concept (95,108), but to date all of the results available are from retrospective analyses of databases from ACE inhibitor and AT1-receptor blocker trials with other end points. The results of ongoing prospective trials in this area are anticipated with interest. In addition, there are theoretical reasons why there may be differences in efficacy among compounds with closely related mechanisms of action, such as ACE inhibitors and AT1-receptor antagonists (109). If AF-preventing efficacy of antifibrotic therapies is confirmed by prospective trials, it will be important to perform comparative studies between candidate compounds/targets to determine relative effectiveness.

Table 2 **Fibrosis-Targeted Therapies With Antiarrhythmic Efficacy in Animal Models of AF**

Drug Class	Mechanism	Notes	Ref. #
ACE inhibitors	Inhibitors of ACE, reduce AngII production	Clinically approved for heart failure; beneficial effects on atrial fibrosis, reversal of ventricular fibrosis in animal models	26,48,92–94, 105–107
ARBs	AT1 receptor antagonist	Clinically approved for heart failure; beneficial effects on atrial fibrosis in animal models	96–98
Spironolactone	Aldosterone antagonist	Clinically approved for heart failure; reversal of atrial fibrosis in animal models	99
Pirfenidone	Unknown, antifibrotic, anti-inflammatory	Investigational	100
Statins	HMG-CoA reductase inhibitors	Clinically approved lipid lowering agents; Investigational for CHF, beneficial effects on atrial fibrosis in animal models	101
Omega-3 poly-unsaturated fatty acids	Attenuate CHF-induced atrial fibrosis and hemodynamic deterioration	Investigational, atrial fibrosis prevention, and antiarrhythmic efficacy in animal models	102

AngII = angiotensin II; ARB = angiotensin II type 1 receptor blocker; AT1 = angiotensin II type 1; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; other abbreviations as in Table 1.

Important Unanswered Questions

Atrial fibrosis plays an important role in the pathophysiology of AF. Many aspects of the fundamental factors controlling atrial tissue fibrosis remain to be established, as do the precise ways in which fibrosis alters atrial function and interacts with other pathophysiological components to promote AF occurrence and maintenance. Several key issues remain to be resolved to better understand the role of atrial fibrosis in the development of the AF substrate. It is unknown whether structural remodeling caused by other etiologies, such as amyloidosis (110,111), fatty infiltration (112), or hemochromatosis (113), predispose to AF by the same mechanisms as fibrosis. Postmortem studies show that severe atrial pathology does not always result in AF. The quantitative relationship between fibrosis and AF needs to be understood, including issues such as the possibility that there is a threshold for AF promotion and that the fibrosis-AF relationship may be highly nonlinear, even to the extent that very severe fibrosis may make AF less likely. More information is needed about the effect of the spatial distribution and the pattern of fibrosis on atrial conduction and AF susceptibility. The precise mechanisms by which fibrosis alters conduction need to be understood, as does the spatial scale over which conduction changes with different types of fibrosis. The directionality of fibrosis-related conduction changes needs to be appreciated; for example, if most fibrosis runs parallel to muscle bundles, fibrosis-related conduction impairment should be much greater in the transverse than longitudinal direction. The potential interactions between fibrosis and other mechanistic determinants of AF occurrence, such as repolarization properties and distribution, source current (sodium current) availability and density, the occurrence and frequency of atrial ectopic activity, and connexin expression, localization, and function, need to be appreciated. Finally, it will be crucial to resolve definitively the specific causative role of fibrosis in AF promotion. Although susceptibility to prolonged AF tracks the extent of fibrosis in a variety of experimental paradigms, it remains to be proven that fibrosis per se, and not some other associated abnormality, is the critical mechanistic contributor. A better understanding of the roles and mechanisms of fibrosis are likely to help in the development of newer and more effective treatment approaches for AF.

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