

STATE-OF-THE-ART PAPER

Structural and Functional Remodeling of the Left Atrium

Clinical and Therapeutic Implications for Atrial Fibrillation

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Left atrial (LA) structural and functional remodeling reflects a spectrum of pathophysiological changes that have occurred in response to specific stressors. These changes include alterations at the levels of ionic channels, cellular energy balance, neurohormonal expression, inflammatory response, and physiologic adaptations. There is convincing evidence demonstrating an important pathophysiological association between LA remodeling and atrial fibrillation (AF). Measures that will prevent, attenuate, or halt these processes of LA remodeling may have a major public health impact with respect to the epidemic of AF. In this review, we describe the mechanisms involved in LA remodeling and highlight the existing and potential therapeutic options for its reversal, and implications for AF development. (J Am Coll Cardiol 2008;51:1-11) © 2008 by the American College of Cardiology Foundation

The assessment of left atrial (LA) size and its clinical implications have been comprehensively reviewed (1). In this paper, our aim is to review the recent advances in our understanding of LA remodeling and the potential impact of its reversal on the prevention of atrial fibrillation (AF).

Mechanisms of LA Remodeling

“LA remodeling” refers to a time-dependent adaptive regulation of cardiac myocytes in order to maintain homeostasis against external stressors (2). The type and extent of remodeling depends on the strength and the duration of exposure to the “stressors.” Adaptive responses may occur at the ionic/genomic level over the short term (within 30 min of exposure to stressor) (3), which can be reversible, or at the cellular level (hibernation, usually reversible) in the mid-term (within 1 week) (4), and at the cellular/extracellular matrix level (apoptosis and fibrosis, usually irreversible) over the longer term (5 weeks or more) (5). The most common “stressors” of atrial myocytes include tachycardia with high rates of cell depolarization, and volume/pressure overload such as in heart failure syndromes. Specific stressors, such as diastolic dysfunction, ischemia, and valvular diseases impose excess pressure and/or volume load on the LA, which responds with a range of adaptive as well as maladaptive

processes. These include myocyte growth, hypertrophy, necrosis, and apoptosis; alterations in the composition of extracellular matrix; recalibration of energy production and expenditure; changes in the expression of cellular ionic channels and atrial hormones; and reversal to a fetal gene program (6). These changes promote a cascade of reactions, which lead to LA remodeling with structural, functional, electrical, metabolic, and neurohormonal consequences.

In experimental animal laboratories, heart failure-induced LA remodeling is usually achieved through rapid pacing of the right ventricle or of the right atrium with a 1:1 conduction to the left ventricle (LV). Atrial tachycardia-induced remodeling can be induced by isolated rapid pacing of the right atrium while the LV rate and pressure are kept constant. These mechanistic studies contributed substantially to our understanding of the relationship between LA remodeling and AF development.

Structural changes in LA remodeling. A hallmark of LA structural remodeling is atrial dilatation. This is often accompanied by a change in LA function with progressive increase in interstitial fibrosis. Impaired atrial booster pump and reservoir function is compensated by increased conduit function (7,8). In normal persons, the LA is a highly expandable chamber with relatively low pressures. In the presence of acute or chronic stress or injury, the LA stretches and stiffens (8,9). Ultrastructural changes in heart-failure-induced remodeling are marked by extensive interstitial fibrosis and myocyte hypertrophy (5,9,10). Degenerative changes, including cellular edema, nuclear pyknosis, and contraction band necrosis leading to cell loss are

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Abbreviations and Acronyms

- ACE** = angiotensin-converting enzyme
- AF** = atrial fibrillation
- ALT-711** = alagebrium chloride
- Ang-II** = angiotensin II
- ANP** = atrial natriuretic peptide
- BNP** = brain natriuretic peptide
- CRP** = C-reactive protein
- LA** = left atrium/atrial
- LV** = left ventricle/ventricular
- MMP** = matrix metalloproteinase
- TIMP** = tissue inhibitor of metalloproteinase

observed (5). Impairment of LA function from heart failure results from changes in structural proteins and a shift from fast alpha-myocyte heavy chain to slow beta-myocyte heavy chain isomer (7). The shift is an adaptation to chronic overload that maximizes atrial work at the expense of contraction velocity (7). Such changes are described to be adaptive response of dedifferentiation indicative of fetal-like phenotype (4,11,12). In contrast, myolysis and glycogen deposition are prominent findings in tachycardia-induced LA remodeling (4,11). Early changes in cellular ultrastructure begin to appear within 1 week of atrial-tachycardia-induced remodeling (4). The mitochondria increase

in length and in number. The number of myocytes and connective tissue content do not change significantly (4,11). Signs of cellular degeneration, apoptosis, and fibrosis are generally not observed (4,11). The intra- and extracellular changes contribute to modification in electrical make-up rendering the LA more vulnerable to AF development.

Electrical disturbances in LA remodeling. Whereas atrial dilatation is the hallmark of structural remodeling, atrial arrhythmias, especially AF, are the most common manifestations of LA electrical remodeling. Electrophysiological studies comparing heart failure-induced LA remodeling with atrial tachycardia-induced LA remodeling have shown significant differences in electrophysiological properties (13) (Table 1). Effective refractory period is shortened in atrial

tachycardia. The action potential duration is also reduced. Atrial fibrillation is promoted through formation of multiple wavelets, which favor re-entry (14,15). However, heart failure does not shorten effective refractory period (16), or action potential duration (17). The proposed mechanisms by which AF is sustained in this situation include triggered activity and delayed afterdepolarization (16). The differences in electrophysiological properties between atrial tachycardia and heart failure LA remodeling lie within the changes in the ionic channels during the remodeling process (Table 1). Cytosolic calcium overload with inefficient calcium handling is the main mechanism for the shortened effective refractory period (increased refractoriness) in atrial-tachycardia-induced remodeling (3). This has been attributed to a marked reduction of L-type calcium channels (17). In contrast, L-type calcium channels are only mildly reduced in heart failure-induced LA remodeling (17), and the reduction is offset by decrease in potassium currents and increase in sodium-calcium exchange currents, with no net change in action potential duration.

Aside from ionic channel alterations, electrophysiological changes are also contributed by cellular and extracellular modifications during the remodeling process. Some investigators have shown that LA dilatation increases electrical instability with shortening of effective refractory period and atrial conduction (18,19). Left atrial dilation reflects increased fibrosis, which provides circuits for re-entry (20). Patients with markedly dilated atria have reduced maximum diastolic potential (21). Increase in LA pressure, which typically accompanies heart failure, may also contribute to AF promotion and perpetuation (17,20). With increase in atrial pressure and volume, the myocytes are more readily depolarized with greater vulnerability for the development of atrial arrhythmia (21). Left atrial ischemia slows down impulse conduction favoring re-entry (22). In atrial tachycardia models, LA pressure is generally not elevated (3,17),

Table 1. Ionic Changes in Atrial Tachycardia- and Heart Failure-Induced Electrical Remodeling

	Atrial Tachycardia	Heart Failure
Ionic changes (13,17)		
I_{to}	↓	↓
I_{kr}	→	↓
I_{ca}	↓↓	↓
NCX	→	↑
Na	↓	?
Electrophysiological changes (16,17,19)		
Wavelength	↓	↑
Absolute or effective refractory period	↓	→ or ↑
Action potential duration	↓	→ (slow rates); ↑ (fast rates)
Conduction velocity	↑	↓
Membrane diastolic potential (16,21)	?	↓
Mechanism of AF	Multiple wavelets re-entry (15)	Delayed afterdepolarization-dependent triggered activity (16)
Prominent structural change	Myolysis (11)	Fibrosis (9)

AF = atrial fibrillation; I_{ca} = L-type calcium current; I_{kr} = rapid delayed potassium current; I_{to} = transient outward potassium current; Na = sodium channel; NCX = sodium/calcium exchanger; ↑ = increase; ↓ = decrease; → = no change; ? = not known.

but varying degrees of interstitial fibrotic changes have been described, which may play a significant role in perpetuating AF (20,23).

Metabolic changes in LA remodeling. Profound metabolic changes also occur during the remodeling process, which may lead to inefficient bioenergetics (24). The main source of energy is shifted from beta oxidation of fatty acids to fetal glycolysis (25). There is down-regulation of the gene that encodes medium-chain acyl-coenzyme A dehydrogenase, which is important for fatty acid oxidation (25). Even with switching to glycolysis, glucose is not optimally oxidized as a source of energy production in the remodeling myocardium (26). In chronic AF, reduced energy availability is attributed to an increase in energy demand from active myolysis or the remodeling process itself rather than a reduction in energy production (27). Reduced energy availability leads to contractile failure (4,7) and switch in myosin isoform profile (7). Energy depletion also impairs calcium cycling (28,29) and other adenosine triphosphate-dependent ionic channels (2,24,30). In both heart failure- and atrial tachycardia-induced LA remodeling, insufficient energy availability promotes further heart failure and remodeling processes (25-27,31).

Neurohormonal disturbances in LA remodeling. Increases in atrial natriuretic peptide (ANP) (32), brain natriuretic peptide (BNP) (33), angiotensin II (Ang-II), aldosterone, transforming growth factor-beta₁ (34), and sympathetic hyperinnervation (35) have been described in association with the remodeling process. Elevated plasma levels of ANP and the N-terminal fragment of the ANP prohormone are associated with decreased LV function and long-term survival after acute myocardial infarction (36,37). Atrial natriuretic peptide is a direct vasodilator, which lowers systemic blood pressure and inhibits renin and endothelin secretion, myocyte hypertrophy, and fibroblast collagen synthesis (38,39). Mechanical stretching of the LA is the strongest stimulus for ANP secretion, which is augmented by endothelin and inhibited by nitric oxide (32). Some studies suggest that vasoconstrictor hormones such as norepinephrine, epinephrine (32), Ang-II (40), and vasopressin (32) can increase ANP secretion by indirect mechanisms related to vasoconstriction and increased atrial and ventricular stretch. Atrial fibrillation augments ANP levels via the hemodynamic effects of the arrhythmia itself (41,42). However, longstanding AF in severe LV dysfunction and development of LA fibrosis can cause depletion of ANP stores (41,43). Thus, ANP secretion appears to be an adaptive response of the LA to correct the hemodynamic imbalance and prevent further remodeling. However, the compensatory effect is limited by fibrosis (41), a sign of chronic myocardial injury.

Cardiac BNP is another marker for LA and LV remodeling. In the case of LA remodeling, BNP is significantly correlated with indexed LA volume in patients with diastolic heart failure (44), stable chronic heart failure (45), hypertension (33), organic mitral regurgitation (46), idio-

pathic bilateral atrial dilatation (47), and in patients with AF with or without LV systolic dysfunction (48-51). The association between BNP and LA volume in predicting AF was demonstrated in post-thoracotomy patients where patients with larger LA volume and higher BNP levels had higher incidence of post-operative AF (52,53).

Angiotensin II (54,55), aldosterone (54,56), and transforming growth factor-beta₁ (57) contribute to the remodeling process through their proliferative, proinflammatory, fibrotic, and prothrombotic actions. Angiotensin II is both locally and systemically secreted and exerts its actions through angiotensin-I receptors. Renin, produced by the kidneys, converts angiotensinogen from the liver to angiotensin I. Angiotensin I is converted by angiotensin-converting enzyme (ACE) to Ang-II, which is a powerful vasoconstrictor that stimulates aldosterone secretion. Angiotensin II, through its effects on angiotensin I receptors, promotes cellular hypertrophy (40), apoptosis (58), fibrosis (54,55), neutrophil and monocyte infiltration (59,60), endothelial dysregulation with inhibition of nitric oxide formation (60), and increased vasoconstriction and platelet reactivity (61). Angiotensin II additionally mediates thrombus formation through its interaction with thromboxane receptors (61) and nitric oxide/prostacyclin-dependent mechanisms (62,63). Angiotensin II plays a critical role in LA remodeling through its ability to promote interstitial fibrosis. It binds with G protein and activates Erk₁/Erk₂, which are mitogen-activated protein kinases. The activated protein kinases stimulate transcription proteins, which trigger specific genes to encode contractile, structural, and cell-cycle regulatory proteins that promote cellular growth, proliferation, and differentiation (64). Angiotensin II up-regulates transforming-growth factor beta₁, which promotes the expression of collagen type I and type III enhancing fibrosis (65). Aldosterone further promotes fibrosis through its action on cardiac fibroblasts (66) and matrix metalloproteinases (MMPs) (67). Thus, the neurohormonal changes are pivotal in the genesis and the progression of LA remodeling (64,68,69), key to the development and perpetuation of AF (64,70-73).

Systemic inflammation and LA remodeling. The role of systemic inflammation in AF and heart failure development has been more intensely studied in the recent years. Inflammatory cells have been demonstrated to infiltrate atrial tissue of patients with AF (74). Inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor, interleukins, and cytokines have been shown to be elevated in AF (75-77). C-reactive protein predicted the risk of first AF in one study (78) and recurrent AF after initial successful radiofrequency ablation in another (79). C-reactive protein also appeared to correlate well with LA volume in some studies, suggesting a relationship between inflammation and LA remodeling (75,80). However, the precise role of CRP in LA remodeling and in AF remains poorly understood.

Several studies have suggested that inflammation exerts its remodeling effects through reactive oxygen species (81-

83). In a study of patients with coronary artery disease, malonaldehyde, an index of oxidative stress, correlates well with CRP (81). It has been shown that CRP may promote the generation of reactive oxygen species by altering the homeostatic balance of antioxidative enzymes in endothelial progenitor cells (82). Oxygen-free radicals can also activate MMPs resulting in an imbalance between accumulation and breakdown of extracellular matrix enhancing LA fibrosis with consequent dilatation and loss of function (84–86). Down-regulation of tissue inhibitor of metalloproteinases (TIMPs) also promotes LA fibrosis. Deficiency in TIMP-3 has been shown to result in LV dilatation, cardiomyocyte hypertrophy, and contractile dysfunction (87), while down-regulation of TIMP-1 and -2 have been shown to correlate with LA and LV dilatation (88,89). Tissue inhibitor of metalloproteinases and MMPs interact with tissue necrosis factor, angiotensin, and other cytokines in the LA remodeling process.

C-reactive protein also enhances the expression of receptors of advanced glycation end products (90) known to promote arterial (91,92) and ventricular stiffness (93,94). Advanced glycation end products result from the non-enzymatic protein glycation to form irreversible crosslinks between long-lived proteins such as collagen and elastin through a reaction called Maillard reaction (95). Pathophysiological effects of advanced glycation end products lead to decreased compliance in myocardial and vessel walls, endothelial dysfunction, and augmentation of stress signaling and inflammatory response (96,97).

LA Remodeling in Aging and Disease

The endocardium of the LA undergoes physiological cellular transformation with aging. From birth to third decade, there is proliferation of smooth muscle cells, elastic fibers, and collagen in the atrial endocardium (98). By the eighth decade, there is increased infiltration of fatty tissue, as well as increased collagen and atrial amyloid deposition (98). Observational studies have shown conflicting reports regarding the relationship between LA size and aging (98–102). The data support that left atrial size does not change as a function of chronologic aging alone. Rather, LA enlargement and impairment of LA function reflect overt or subclinical cardiovascular conditions that frequently accompany aging (93,98–104). Development of LV diastolic dysfunction with aging is initially accompanied by an increase in LA contractility (104). Early on, this augments LV filling without an increase in LA size (99,100). With progressive abnormality in LV filling, LA size increases and LA function deteriorates (105). Electrophysiological studies have shown that atrial remodeling associated with aging is characterized by anatomical and structural changes, dispersion of atrial repolarization, reduction in atrial voltage with discrete areas of low voltage, widespread conduction slowing, and sinus node dysfunction with an increased propensity to atrial arrhythmias (106,107).

Age-related LA dilatation may also be the consequence, at least in part, of increased arterial stiffness (92). Arterial stiffness exerts its deleterious effects through chronic increase in LV afterload and aortic impedance and filling pressure. When the arteries are compliant and pulse wave velocity is relatively slow, reflected waves return to the central aorta in diastole and, therefore, augment coronary blood flow. When arterial compliance is reduced and pulse wave velocity is elevated, reflected waves arrive earlier and augment systolic blood pressure, rather than diastolic blood pressure, increasing LV workload and compromising coronary blood flow (108). The anatomical and hemodynamic perturbations in the LV are transmitted to the LA, promoting atrial stretch and dilatation. Advancing age has been shown to be associated with increases in vascular and ventricular systolic and diastolic stiffness, even in the absence of cardiovascular disease (93). In the rat model of aging, increased susceptibility to AF is due to heterogeneous atrial interstitial fibrosis and atrial cell hypertrophy contributing to the aging-related atrial conduction slowing, conduction block, and inducible AF (109). In disease processes, such as with hypertension (110), diabetes mellitus (111), hyperlipidemia (110), ischemic heart disease (110), and obesity (112), LA remodeling is accelerated. Mechanisms for accelerated LA remodeling include earlier development and perhaps more severe diastolic dysfunction, deranged plasma volume control, intensified neurohormonal activation, as well as development of an atrial myopathy secondary to oxidative stress and lipooptosis (113).

Reversal of LA Remodeling

Left atrial remodeling is reversible. This is particularly convincing in the earlier stages of LA structural and functional disturbances (16,23,114). Studies have shown, for instance, that LA size and function can improve with certain medications (23,115,116), after restoration of sinus rhythm from AF (117–119), and after repair of the mitral valve in the case of severe mitral regurgitation (120). Table 2 lists the studies that have demonstrated reversal of LA structural, functional, and/or electrical remodeling (23,115,116,121–127). The direct impact of reversing LA remodeling on cardiovascular outcomes remains to be seen, but the evidence, at least indirectly, suggests that the risk of certain outcomes, such as AF, can be significantly reduced. **ACE inhibitors and angiotensin receptor blockers.** In theory, any drug that reduces blood pressure, which can slow the progression of LV diastolic dysfunction or improve diastolic function, can have beneficial effects on LA remodeling (110). However, drugs that modify the renin-angiotensin-aldosterone system appear to have particularly potent effects on LA remodeling, beyond their beneficial effects on blood pressure regulation. In a double blinded placebo-controlled study, we found a significant relative improvement in LA volume of 9.7 ml/m² over 1 year among those actively treated with quinapril (116). Additionally, LA

Table 2 Therapeutic Studies Showing Reversal of LA Remodeling

Author (Ref. #)	Drug/Procedure	Population	Outcomes
Human studies			
Tsang <i>et al.</i> (116)	Quinapril 60 mg/day (n = 9) vs. placebo (n = 12) for 6 months	Diastolic function grade ≥ 1 or LA volume ≥ 32 ml/m ²	Quinapril reduced LA volume by 9.7 ml/m ²
Abhayaratna <i>et al.</i> (115)	Quinapril 60 mg/day (n = 9) vs. placebo (n = 12) for 6 months	Isolated diastolic dysfunction grade ≥ 1 or LA volume ≥ 32 ml/m ²	Quinapril improved LA total emptying fraction (5.4% vs. -2.0%; p = 0.006)
Tops <i>et al.</i> (127)	Catheter ablation (n = 57)	Patients with symptomatic drug-refractory AF	After 3 months, patients who converted to sinus (n = 39) had reduction in LA volume (59 \pm 12 ml vs. 50 \pm 11 ml, p < 0.01)
Hornero <i>et al.</i> (122)	Mitral valve surgery and LA reduction (n = 25) versus mitral valve surgery alone (n = 25)	AF and isolated mitral valve disease	At 3 months, 60% of those who had LA reduction converted to sinus versus 21% in those with mitral valve surgery alone
Animal studies			
Cha <i>et al.</i> (121)	Omapatrilat 10 mg/kg 2 \times /day (n = 8) versus placebo (n = 6)	Heart failure induced by rapid right ventricular pacing for 5 weeks in dogs	Omapatrilat reduced LA area index (0.71 \pm 0.04 mm ² /kg vs. 0.91 \pm 0.06 mm ² /kg, p < 0.05)
Shi <i>et al.</i> (126)	Enalapril 2 mg/kg/day (n = 10) versus placebo	Heart failure induced by rapid right ventricular pacing for 5 weeks in dogs	At the end of the study, 42% of placebo group decreased LA fractional area shortening versus 9% in the enalapril group (p = 0.01); placebo group had longer duration of AF (720 \pm 461 s vs. 138 \pm 83 s, p = 0.001)
Milliez <i>et al.</i> (125)	Spirololactone 10 mg/kg/day (n = 11) versus lisinopril 1 mg/kg/day (n = 11) versus atenolol 1 mg/kg/day (n = 11)	Myocardial infarction induced in Wistar rats	Spirololactone reduced atrial fibrosis more than atenolol and lisinopril (% fibrosis = 5.8 \pm 1.4 in untreated group vs. 4.1 \pm 1.2, 4.3 \pm 0.9, and 4.4 \pm 0.9 in spironolactone, lisinopril, and atenolol groups, respectively; p < 0.05 for all groups)
Lee <i>et al.</i> (123)	Pirfenidone 800 mg 3 \times /day versus placebo versus control group	Heart failure induced by rapid right ventricular pacing for 3 weeks in dogs	Pirfenidone reduced vulnerability to AF; reduced LA fibrosis; reduced expression of TGF- β 1
Li <i>et al.</i> (124)	Sham operated dogs (n = 7) versus control group (n = 6) versus cilazapril 2 mg/kg/day (n = 6)	Sustained AF induced by rapid LA pacing for 6 weeks in dogs	Inducibility and duration of AF were lower in the cilazapril group (AF inducibility, 65.7% vs. 95.7%, p < 0.05; AF duration, 531.5 \pm 301.2 s vs. 1,432.2 \pm 526.5 s, p < 0.01); LA volume was significantly smaller; LA ejection fraction, higher in the cilazapril group
Kumagai <i>et al.</i> (23)	Candesartan 10 mg/kg/day (n = 10) versus placebo (n = 10)	Sustained AF induced by rapid right atrial pacing in dogs for 5 weeks	The mean AF duration in the control group was significantly longer than in the candesartan group (1,333 \pm 725 s vs. 411 \pm 301 s, p < 0.01); candesartan group had a significantly lesser interstitial fibrosis than the control group (7 \pm 2% vs. 16 \pm 1% at the RA appendage, p < 0.001)

AF = atrial fibrillation; LA = left atrium; RA = right atrium; TGF- β 1 = transforming growth factor-beta₁.

function improved in the quinapril group, and deteriorated in the placebo group (115). Angiotensin-converting enzyme inhibition has been shown to have important beneficial effects on atrial stretch (116,128), interstitial fibrosis (54,129,130), inflammation (131–133), bioenergetics (134), and electrical remodeling (23,114). In fact, ACE inhibition has been shown to prevent first and recurrent AF in patients with hypertension (135), and LV dysfunction (135–140). Patients with persistent AF who were treated with angiotensin receptor blockers combined with amiodarone had lower recurrence of AF, when compared with those treated with amiodarone alone (141). The beneficial impact of ACE inhibition on AF has been demonstrated indirectly in a number of large clinical trials, acknowledging that AF was not the primary end point in these studies (Table 3) (135,139,140,142–147). The meta-analysis of 11 randomized controlled trials (n = 56,309) showed that ACE inhibitors and Ang-II blockers were both effective in preventing new or recurrent AF by 28% but the benefit was

greatest in patients with heart failure, LV dysfunction, and prior AF (148).

The effectiveness of angiotensin blocker to reverse LA remodeling and suppress AF lies in its ability to modulate the Ang-II-activated Erk₁/Erk₂ proteins, thereby effectively inhibiting interstitial fibrosis (64). Although Ang-II blockade does not affect atrial myocytic refractoriness (23,114,126), it can reduce interstitial fibrosis that serves as a substrate for the persistence and recurrence of AF. Animal studies have confirmed that the use of angiotensin blockers can mitigate increase in interstitial fibrosis and LA pressure; reduce myolysis, loss of contractile proteins, and LA dysfunction; and shorten the duration of AF (23,114,126).

In the case of lone AF, despite the theoretical absence of cardiac structural abnormalities, atrial fibrosis (149) and even LV diastolic dysfunction (118,150) have been demonstrated. Angiotensin I receptors are up-regulated in these patients as well (73,151). Angiotensin blockers attenuate

Table 3 Clinical Trials Involving ACE Inhibitors or Angiotensin Receptor Blockers and Impact on AF

Clinical Trial, n (Ref #)	Study Design	Mean Follow-Up Time, Unless Otherwise Specified	Risk Ratio (95% CI) for New AF
Hypertension trials			
CAPP, n = 10,985 (143)	RCT (captopril vs. conventional therapy) primary end point—fatal and nonfatal MI, stroke, and other CV deaths; AF was secondary analysis	6.1 yrs	0.87 (0.68–1.11); significant decrease of AF in captopril arm
STOP-2, n = 6,614 (144)	RCT (beta-blockers or hydrochlorothiazide with amiloride vs. enalapril, captopril, or calcium-channel blockers) in older hypertensive patients; primary end points—fatal stroke, fatal MI, and other fatal CV events; AF was a secondary analysis	33,249 patient-yrs	1.12 (0.95–1.32); no difference in AF between 2 arms
LIFE, n = 9,193 (135)	RCT (losartan vs. atenolol) in hypertensive patients with LVH; AF was a secondary end point	4.8 yrs	0.66 (0.54–0.81); significant reduction of new AF in losartan arm
VALUE, n = 15,313 (145)	RCT (valsartan vs. amlodipine) in hypertensive patients at high risk of CV events; primary end points—cardiac mortality and morbidity; AF was a secondary analysis	4.2 yrs	1.20 (0.97–1.48); no difference between 2 arms
Pooled RR			0.94 (0.72–1.23)
Post-MI trials			
GISSI-3, n = 17,748 (146)	RCT (lisinopril vs. placebo); retrospective analysis of AF and atrial flutter incidence in hospital	0.5 yr	0.92 (0.83–1.01)
TRACE, n = 1,749 (147)	RCT (trandolapril vs. placebo) in post-MI CHF; retrospective analysis of AF	2–4 yrs	0.52 (0.31–0.87)
Pooled RR			0.73 (0.43–1.26)
CHF trials			
Val-HeFT, n = 5,000 (140)	RCT (valsartan vs. placebo); retrospective analysis of AF	1.9 yrs	0.67 (0.54–0.83)
SOLVD, n = 374 (142)	Retrospective analysis (enalapril vs. placebo)	2.9 yrs	0.22 (0.12–0.43)
CHARM, n = 6,446 (139)	RCT (candesartan vs. placebo)	3.17 yrs	0.82 (0.68–1.00)
Pooled RR			0.57 (0.37–0.89)

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; CAPP = Captopril Prevention Project; CHARM = Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity trial; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; GISSI-3 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico trial; LIFE = Losartan Intervention for End Point Reduction in Hypertension study; LVH = left ventricular hypertrophy; MI = myocardial infarction; RCT = randomized controlled trial; RR = relative risk; SOLVD = Studies Of Left Ventricular Dysfunction trial; STOP-2 = Swedish Trial in Old Patients with Hypertension-2 study; TRACE = Trandolapril Cardiac Evaluation trial; Val-HeFT = Valsartan Heart Failure Trial; VALUE = Valsartan Antihypertensive Long-Term Use Evaluation trial.

LA remodeling in lone AF and may, therefore, have the potential in reducing AF recurrence after successful conversion to sinus. The impact of angiotensin blockade on AF as a primary outcome in patients without LV systolic dysfunction requires further studies.

Antifibrotic drugs. Pharmacologic therapy targeted at the fibrotic substrate itself may play an important role in the management of AF. Aldosterone receptor antagonists, such as spironolactone and eplerenone, appear to have a beneficial impact in modifying the extracellular matrix, especially in terms of collagen deposition and fibrosis. Spironolactone has been shown to reverse the effects of LA remodeling by reducing atrial hyperexcitability (71), inhibition of vascular Ang-I/Ang-II conversion (152), and attenuation of atrial fibrosis (56,125,153). In animal models, Milliez et al. (125) demonstrated that spironolactone attenuated atrial fibrosis more than did lisinopril and atenolol when given to heart failure rats though all 3 drugs reduced LV filling pressure similarly. Moreover, spironolactone given at 20 mg/kg/day prevented cardiac fibrosis without affecting blood pressure and LV hypertrophy (56). The role of spironolactone and eplerenone on arrhythmia prevention was inferred from the RALES (Randomized ALdactone Evaluation Study) (154) and EPHEsus (Eplerenone Post-AMI Heart Failure Ef-

ficacy and Survival Study) (155) trials where patients treated with these drugs had lower rates of sudden cardiac deaths. No studies have been done to assess the direct effects of aldosterone antagonists on AF prevention and treatment.

Crosslink breakers. Alagebrium chloride (ALT-711), or 4,5-dimethyl-3-(2-oxo-2-phenylethyl)-thiazolium chloride, is the most advanced agent in the new class of compounds that have been shown to chemically “break” advanced glycation end product crosslinks. Conceptually, such effects may restore more normal function to organs and tissues that have lost flexibility as a result of the crosslinks or tissue alterations induced by inflammation and scarring (92). In one study, 16 weeks of treatment with alagebrium resulted in a decrease in LV mass and improvement in LV diastolic filling and quality of life in patients with diastolic heart failure (92). Alagebrium improved total arterial compliance in older humans with vascular stiffening (96,156). Whether ALT-711 has the potential of reversing LA remodeling and reducing vulnerability to AF induced by arterial stiffness requires further investigation.

Other drugs. The effect of beta-blockers on LA remodeling and AF suppression has not been well studied. Metoprolol and carvedilol can attenuate LV remodeling (157–159). Metoprolol, administered 100 to 200 mg daily, was

useful in preventing AF recurrence in patients with persistent AF who were successfully cardioverted to sinus rhythm (either by direct current cardioversion or with antiarrhythmic drugs) (160). Simvastatin has also been shown to reduce the propensity to AF in animal studies (161) and in human studies (162-164), possibly through its antioxidant effects (161,162). Omapatrilat, a vasopeptidase inhibitor, has been shown to protect cellular bioenergetics during stress (121). Omapatrilat prevented derangement of energy-dependent enzymatic and cellular reactions when given to animals before induction of experimental heart failure. The ability of omapatrilat to maintain adenosine triphosphate levels and phosphoryl transfer function of creatine kinase and adenylate kinase in failing atria and ventricle appeared to be related to the reduction of oxidative stress and high energy demand through vasopeptidase inhibition (121).

Electrical cardioversion and radiofrequency ablation. Conversion of AF to sinus rhythm, whether by electrical cardioversion or radiofrequency ablation, has been shown to reduce LA size (117,118,127,165) and improve LA function (166,167). In 57 consecutive patients with symptomatic drug-refractory AF, radiofrequency ablation reverted 39 (68%) to sinus (127). This was accompanied by a significant reduction in LA antero-posterior dimension (4.5 ± 0.3 cm vs. follow-up 4.2 ± 0.2 cm, $p < 0.01$), and LA volume (59 ± 12 ml vs. follow-up 50 ± 11 ml, $p < 0.01$) at 3 months follow-up. In contrast, patients who remained in AF after catheter ablation had increased LA size at 3 months follow-up (4.5 ± 0.3 cm to 4.8 ± 0.3 cm, $p < 0.05$; 63 ± 7 ml to 68 ± 8 ml, $p < 0.05$). Reversal of electrical remodeling can usually be rapidly achieved (168,169), but vulnerability to the recurrence of AF depends on the amount of atrial fibrosis and the size of the LA (117). Normalization of atrial structure and function generally lags behind the reversal of electrical remodeling (169).

Cardiac surgery and surgical ablation. Mitral valve surgery for stenosis or regurgitation can relieve LA pressure and volume overload with reduction of LA size and improved LA function (166). Atrial fibrillation patients who underwent LA reduction together with mitral valve surgery had lower AF recurrence after 3 months when compared to those who did not have LA reduction (122). Further reduction in LA size was seen in those who remained in sinus rhythm when compared to those who had persistent or recurrent AF (122).

Successful surgical ablation of AF (Maze procedure) has been shown to reduce neurohormonal activation as evidenced by a decrease in ANP, BNP, and angiotensin II (77,170). It has been demonstrated to reduce LA size and improve LA transport function and LV diastolic function (171).

Conclusions

There have been considerable advances in our understanding of the mechanisms of LA remodeling. The evidence for

a tight relationship between LA remodeling and AF development is highly compelling. We recognize that an association cannot be regarded as causation, but the evidence to date is supportive of LA remodeling being an integral intermediate in the cascade of events that culminate in AF development. To what extent prevention and reversal of atrial remodeling will translate into a reduction in the burden of AF and other adverse clinical outcomes remains to be seen. We have now reached the stage where we should test the efficacy of various strategies that can identify and reverse LA structural and electrical remodeling in its earlier stages, and determine whether these strategies can effectively lower the risk of first AF. If successful, these primary prevention strategies may exert a major impact on AF as a public health problem.

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