

Ion channel disfunction and fibrosis in Atrial Fibrillation:

two sides of the same coin

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Abstract

45 Atrial fibrillation (AF) is a common heart rhythm disorder that is associated with an increased risk of stroke and heart failure (HF). Initially an association between AF and ion channel dysfunction was identified, classifying the pathology as a predominantly electrical disease. More recently it has been recognized that fibrosis and structural atrial remodeling play a driving role in the development of this arrhythmia also in these cases. Understanding the role of fibrosis in genetic determined AF could be
50 important to better comprise the pathophysiology of this arrhythmia and to refine its management also in non-genetic forms.

In this review we analyze genetic and epigenetic mechanisms responsible for AF and their link with atrial fibrosis, then we will consider analogies with the pathophysiological mechanism in non-genetic AF, and discuss consequent therapeutic options.

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Keywords: Atrial fibrillation, Channel dysfunction, Fibrosis, Genetic, Epigenetic

Abbreviations:

AAD Antiarrhythmic drug

60 ACE Angiotensin-converting enzyme inhibitors

AF Atrial fibrillation

ANP Atrial Natriuretic Peptide

ARB Angiotensin receptor blockers

ARVC Arrhythmogenic right ventricular cardiomyopathy

65 Ca²⁺ Calcium

CAMKII Calcium/Calmodulin-stimulated protein kinase II

COL12A1 Collagen type 12,23 alfa 1 chain

COMP Cartilage oligomeric matrix protein

- 70 DCM Dilated cardiomyopathy
- EACTS European Association for Cardio-Thoracic Surgery
- ECM Extracellular matrix
- 75 ERK Extracellular signal-regulated kinase
- ESC European Society of Cardiology
- FKBP-12.6 FK 506-binding protein
- GATA4,6 GATA binding protein 4,6
- 80 GJA1,5 Gap Junction Protein Alpha 1,5
- GREM2 Gremlin 2 gene
- HF Heart failure
- IK₁ Inwardly rectifying potassium current
- IKACh Acetylcholine activated inwardly rectifying potassium current
- 85 IKATP ATP-sensitive potassium channels
- IK_r Rapid component of the delayed rectifier potassium current
- IK_s Slow component of the delayed rectifier potassium current
- IK_{ur} ultrarapid component of the delayed rectifier potassium current
- ICa,L L-type calcium current
- 90 INa Inwards sodium current
- K⁺ Potassium
- K201 Intraacellular calcium blocker 1,4-benzothiazepine derivative JTV519
- KCNA,E,H,J,N,Q 1-5 Potassium voltage-gated channel subfamily A,E,H,J,N,Q member 1-5
- 95 LQT3 type 3 long T syndrome
- Lcn RNA Long non-coding RNA
- LMNA Lamin A/C

100 LVNC Left ventricular non-compaction
 MIAT Myocardial infarction associated transcript
 miRNA Micro RNA
 105 MMP3 Matrix metalloproteinases
 Na⁺ Sodium
 110 Nav Voltage-gated sodium channel
 NFAT Nuclear Factor of Activated T cells
 NKX2-5,6 NK2 homeobox 5,6 Protein coding gene
 115 NRON Noncoding repressor of nuclear factor of activated T cells
 NUP155 Nucleo-cytoplasmic transport
 120 PCAT1 Prostate cancer-associated transcript 1
 PITX2 Paired like homeodomain 2
 RAAS Renin-Angiotensin-Aldosterone system
 125 RyR2 Ryanodine receptors 2
 SR Sarcoplasmic reticulum
 130 SCN5,10A Sodium channel protein type 5 subunit alpha
 STAT3 Signal transducer and activator of transcription 3
 TGF- β 1 Transforming growth factor beta 1
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Introduction

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Atrial fibrillation (AF) is a common supraventricular arrhythmia associated with increased risk of stroke and heart failure (HF). [1,2] It arises predominantly as a result of structural atrial remodeling linked to volume and pressure overload due to hypertension, ischaemic or structural heart disease. [3] However the presence of family aggregation and genetic susceptibility in this arrhythmia has been recognized for long time. [3] Firstly an association between lone AF and ion channels mutations was identified, and then similar electrical alterations were also reported in non-genetic AF, classifying the pathology as a predominantly electrical disturbance. More recently, however, it has been recognized that atrial fibrosis plays a driving role in the development of this arrhythmia also in these cases (*Figure 1*). Understanding the link between genetic predisposition to AF and atrial fibrosis could be important to refine the management of non-genetic AF patients.

In this review we analyze the genes responsible for AF, in particular ion channel genes, and their possible link to atrial fibrosis, and discuss possible implication in drug treatment.

Genetic of AF and fibrosis

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AF genetic inheritance is most frequently complex and polygenic, with the presence of a large number of common DNA variants that increase AF susceptibility in presence of acquired clinical risk factors – a basis for the “two-hit” genetic model. [4–6] Less frequently, instead, AF is transmitted as a dominant autosomal disease, with substantial risk of family members to develop lone AF early in life. [4,7] Genome-wide association studies have identified more than 160 AF susceptibility loci including genes and regulatory regions of structural and signaling proteins, but also ion channels[4,8]. This functional variability of the AF-related DNA transcripts highlights the wide range of molecular mechanisms involved in the pathophysiology of this arrhythmia, that goes from electrical to structural dysfunction, however, recent studies have argued that ion channel mutations lead directly to structural remodeling, suggesting that fibrosis could be the central mechanism of AF susceptibility in the majority of cases.

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Ion Channels dysfunction and fibrosis in AF

180 Ion channels are membrane proteins responsible for the depolarization and repolarization of the cardiomyocyte. Their mutations are associated with susceptibility to AF with an electrical mechanism that involves abnormally frequent triggered impulses or enhanced electrical re-entry circuits.[9] Recent studies, however, have linked the subsequent increased sodium (Na^+) and calcium (Ca^{2+}) cellular content directly with fibrosis and structural cardiac remodeling. Of note similar ion current alterations can be also produced by mechanical cellular stress, and may be a primary fibrotic-driving
185 mechanism also in non-genetic AF. [10]

Antiarrhythmic drugs (AADs) are associated with a benefit in AF in several studies and on the basis of above mentioned electrical remodeling could have anti-fibrotic proprieties. However historical limitations in non-invasive rhythm monitoring technologies did not allow AF burden to be assessed to measure efficacy of these drugs. Consequently, the presence of a hypotizable antiremodelling effect
190 of AADs that is independent from that of sinus rhythm (SR) maintenance cannot yet be demonstrated. [6]

An improved understanding of the underlying pathophysiology of AF in individual patients could consent to clarify the presence of a per se beneficial effect of these drugs. [6]

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1) Sodium Channels

a) Sodium Channels in cardiomyocytes

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In cardiomyocytes the inwards Na^+ current (I_{Na}) is responsible for the action potential upstroke (phase 0 of action potential - *Figure 2*). At the resting membrane potential, the vast majority of $\text{Nav}1.5$ channels (the type of Na^+ channel that is prevalent in cardiac cells) are in their closed state. Upon depolarization, $\text{Nav}1.5$ channels open up for a short time (1–2 msec) after which they
205 inactivate rapidly. The following “plateau” phase (phase 1 - *Figure 2*) of the cardiac action potential is supported mainly by L-type Ca^{2+} current, but late Na^+ current from slowly inactivating Na^+ channels (such as $\text{Nav}1.4$, $\text{Nav}1.6$, $\text{Nav}1.8$) also contribute to it. [11] Furthermore channels studies have revealed that late I_{Na} could be conducted also by $\text{Nav}1.5$ channels operating in special

gating modes. Although small in magnitude as compared to the peak Na⁺ current (~1–3%), late Na
210 current could alter action potential properties and increases Na⁺ loading in cardiac cells. [12]

b) Sodium Channels disfunction and fibrosis

215 Na⁺ channels mutations are linked to pro-fibrotic effect (*Table 1*). In murine models increased late Na⁺ influx via incomplete inactivation of Nav1.5 due to gain-of-function mutation of SCN5A, is sufficient to cause structural cardiac alterations. [13] Increased cellular Na⁺ causes also Ca²⁺ overload mean action of Na⁺/Ca²⁺ exchanger [14] and L-type Ca²⁺ channels re-opening, leading to activation of calmodulin kinase type II (CaMKII) pathway, hypertrophic cell signaling, [15]
220 interstitial fibrosis pathway. [13,16–19]

Myocardial damage and contractile abnormalities are also present in patients and animal models with type 3 Long QT syndrome (LQT3) caused by gain-of-function mutations of SCN5A, [8,16,17] furthermore LQT3 patients had also an increased risk of AF compared to genotype-negative family members. [17,20] Alteration of channels conducting late Na⁺ currents are also associated to AF in a
225 similar way (es SCN10A). [21] Furthermore non ion-channel mutations could alter Na⁺ current, for example PITX2 loss-of-function. [4,22]

Of note mechanical and oxidative stress of myocytes due to cardiac chamber overload (in disease like AF or HF) could enhances late Na⁺ cellular entry in a similar way, and prolong cellular action potential. [23] In these situations, a change in the expression or function of Na⁺ channels proteins
230 happens, leading to enhanced late Na⁺ inward current. More in detail expression of late Na⁺ channels (for example Nav1.4, Nav 1.6, Nav 1.8) is enhanced [15] and Nav 1.5 channel molecular structure is modified (by phosphorylation or nitrosylation for instance) allowing late reopening of the channel. [10,11,15] Van Wagoner et al. hypotized that atrial mechanical stress could determine cytoskeleton modifications that alters Na⁺ channels function slowing their inactivation. [24]

235 In other cases, AF genetic susceptibility is associated to loss-of-function mutations of SCN5A or other Na⁺ channels, with a mechanism that includes enhanced cellular Ca²⁺ from Na⁺ current reduction, enhanced electrical reentry [21,25] and disruption of cell to cell interactions due to abnormal Na⁺ channel localization. [26,27] A similar Na⁺ current alteration could also be caused by the mutations of microRNA (miRNA) genes (miR-192-5p for example[28]) regulating Na⁺ channel
240 genes (*Table 5*). A similar current alteration leads to myocardial fibrosis, ventricular dilatation, and reduced contractility, [29] in patients and animal models with Brugada syndrome due to mutation of SCN5A or genes of some late Na⁺ current channels, with a considerable overlap with arrhythmogenic

cardiomyopathy (ARVC). [6,17,30,31] Remarkably, in Brugada patients with SCN5A mutations there is also high incidence (20 - 40%) of AF. [17,32]

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c) Implication to treatment

Na⁺ channel blockers reduce I_{Na} current and intracellular Ca²⁺ accumulation from Na⁺/Ca²⁺ exchanger in rat ischemic heart, and the same alteration could also be hypothesized in AF.

250 However AADs targeting Na⁺ channels might have both antiarrhythmic/antifibrotic and proarrhythmic effects if compounds preferentially block late I_{Na} or peak I_{Na} respectively. [15,24,33] Various class I AADs such as Lidocaine, Mexiletine, and Flecainide, and the class III antiarrhythmic drug Amiodarone could inhibit both peak I_{Na} and late I_{Na} and suppress AF effectively only at dosage active on both with a consequent proarrhythmic effect. [10,15]

255 Instead the only drug on the market that selectively inhibits late I_{Na} is Ranolazine. It targets Nav1.5 blocking late I_{Na} with ~40-fold higher potency than peak I_{Na} in a voltage-, and frequency-dependent and atrial-selective fashion. [11,15] Contrary to the results of older studies, in a meta-analysis of 8 randomized clinical trials, Gong et al. found that Ranolazine significantly reduced AF in acute coronary syndromes, after cardiac surgery and after electrical cardioversion of AF. [15,34] Moreover, 260 the combined use of Ranolazine and Amiodarone compared to Amiodarone alone showed a 1.23-times higher conversion rate of AF, probably with also an antifibrotic mechanism. [15,34] Unfortunately, at therapeutical plasma concentrations, Ranolazine is not selective for late I_{Na} current and inhibits also other ionic currents, including early I_{Na}. [15]

Targeting late current Na⁺ channel (for example Nav1.8) with specific inhibitors is also an interesting 265 future AAD therapy but is not possible at now. Some compounds (such as Eleclazine) were synthesized but were discarded during trials due to ineffectiveness or unacceptable side effects. [15]

2) Calcium Channels

270 a) Calcium Channels in cardiomyocytes

During the “plateau” phase (phase 2 of action potential - *Figure 2*), there is a near balance of charge moving into and out of the cell: Na⁺ channels close, delayed rectifier K⁺ channels (IKs) allow K⁺ to leave the cell while L-type Ca²⁺ channels allow the movement of Ca²⁺ ions into the cell. These Ca²⁺ 275 ions bind to and open other Ca²⁺ channels (called Ryanodine receptors 2 (RyR2)) located on the Sarcoplasmic Reticulum (SR), allowing the flow of Ca²⁺ in the cytoplasm. These Ca²⁺ ions are

responsible for the contraction of the heart. [35] However increased Ca^{2+} concentration in the cell also increases activity of the Na^{+} - Ca^{2+} exchangers, and then Na^{+} - K^{+} pumps activity with consequently ions abnormalities. [35] Cellular Ca^{2+} overload that occurs in case of imbalances in this system is the main cause of the structural remodeling of the heart.

b) Calcium Channels disfunction and fibrosis

According to the mechanisms mentioned above, AF-associated mutations causing Ca^{2+} current alterations are linked to pro-fibrotic effect (*Table 2*). They include RyR2 gain-of-function mutations, [36,37] and some mutations in miRNA genes (for example of miRNA-106b-25; *Table 5*) that enhance RyR2 expression. [38] These mutations cause SR Ca^{2+} leak with cellular Ca^{2+} overload, and have a critical role in atrial arrhythmia risk in humans and mice. [39] Moreover mutations in non-ion channel proteins could also contribute to Ca^{2+} overload. For example PITX2 mutations can increased SR Ca^{2+} leak mean abnormal RyR2 phosphorylation. [39] Moreover in mice loss-of-function mutation of the gene encoding for junctophilin (a protein which normally binds and stabilizes RyRs) increase the open probability and leak of RyR, [38,40] and in knock-out mice for FKBP-12.6 (a protein which binds and stabilizes RyRs in their unphosphorylated state) there is an increased leak of RyR. [38,41,42] Notably RyR2 gain-of-function mutations are also linked to structural disfunction in other arrhythmic disease, in particular in catecholaminergic polymorphic ventricular tachycardia (CPVT), [43] and could cause structural cardiac diseases such as ARVC type 2 and left ventricular non-compaction (LVNC) [44] Of note supraventricular dysrhythmias such as AF and sick sinus syndrome (SSS) are frequently present in patients with CPVT with a prevalence of 16–26%. [45]

Another mechanism of Ca^{2+} current alteration that predisposes to AF is linked to shortened action potential due to loss-of-function mutations of L-type Ca^{2+} channels. [25] Furthermore Van den Berg et al report that upregulation of some miRNA genes (for example miR-21, [46] miR-29, [28] miR-328, miR-208a/b [47,48]- *Table 5*) reduces expression of L-type Ca^{2+} channels with the same effect. Short action potential causes prolongation of refractory period and predispose to formation of electrical reentry circuits, with consequent cellular Na^{+} and Ca^{2+} overload. [18]

In non-genetic AF also, atrial diastolic Ca^{2+} leak from SR and the consequent reduction of L-type Ca^{2+} current (ICa,L) density (the last one only in more advanced stages, when AF become chronic) are a hallmark of the electrical remodeling. [46,49] Zhan et al and Guo et al show that isolated mouse atrial myocytes display an immediate elevation of SR Ca^{2+} leak when subjected to acute axial stretch, [49,50] and Heijman et al and Guo et al report the same in sheeps in case of chronic volume overload. [51] Of note in case of chronic overload, various mechanisms of molecular regulation (for example

by phosphorylation or oxidation) cause persistent RyR2 Ca²⁺ leak, [52,53] and downregulation of L-type Ca channels with a reduction of refractory period. Alterations in atrial miRNAs also contribute to these channels altered expression. For example, Barana et al demonstrated high miR-21 levels in isolated myocytes from atrial appendages obtained from patients chronic AF. [46] and Adam et al
315 demonstrated that miR-21 upregulation was correlated positively with atrial Collagen content and increased expression of profibrotic mediators. [54]

c) Implication to treatment

320 Common AADs such as Flecainide and Propafenone have been reported to reduce RyR2 open probability by decreasing their mean open time, even if this is recently be discussed. However the use of these drugs is limited by the fact that they carry substantial risks, particularly proarrhythmia. [39]

Selective RyR2 altering compounds are a promising therapeutic option for the treatment of a variety
325 of cardiac pathology, including AF, but for now they are not used.

The intracellular Ca²⁺ blocker 1,4-benzothiazepine derivative JTV519 (K201), attenuates AF inducibility in dogs, RyR2-induced SR Ca²⁺ leak and arrhythmogenic activity in pulmonary vein cardiomyocytes, probably by increasing the affinity of FKBP12.6 for RyR2. [45,55] Three clinical trials using K201 to treat AF were registered in clinicaltrials.gov between 2009–2011, two of these
330 were prematurely terminated without results available and one completed without reported results. [56,57]

Another interesting compound was ent-veratridine. It prevents the initiation of AF by selectively targeting the RyR2 channels in mouse model, but further research in AF patients is still needed. [39]

335 3) Potassium Channels

a) Potassium Channels in cardiomyocytes

The transient outward current (I_{to}), delayed K⁺ outward-rectifying currents (I_{Ks}, I_{Kr}, and I_{Kur}), and
340 K⁺ inward-rectifying currents (I_{K1}, I_{KACH}, and I_{KATP}) are conducted by cardiac K⁺ channels and are responsible respectively for the phase 1 (the brief period of repolarization before plateau phase - *Figure 2*), the phase 3 of action potential (the repolarization period that restore the rest action potential - *Figure 2*) and the negative cardiomyocyte resting membrane potential. [58]

345 b) Potassium Channels disfunction and fibrosis

The most common AF-promoting genetic paradigm is enhanced reentry caused by action potential duration shortening due to gain-of-function K⁺ channel mutations (*Table 3*). [25,51]. Such as mentioned above, reentry mechanism causes cellular Na⁺ and Ca²⁺ overload, with pro-fibrotic effect.

350 The first gene mutation linked to lone AF caused gain of function in the α -subunit (KCNQ1) of the slow delayed rectifier IKs. Other AF-related gain-of-function mutations of K⁺ channels include KCNE5 (that results in IKs gain-of-function too), KCNH2 and KCNE2 (that result in IKr gain-of-function), and KCNJ2 (that results in IK1 gain-of-function), [25,58] KCNN3 (that encodes for a Ca²⁺ activated K⁺ channel type -the SK3 channel- and is thought to be involved in atrial repolarization),

355 [4] KCNJ3 and KCNJ5 (that result in IK,ACh gain-of -function [59]). Furthermore mutations in genes of some miRNA could regulate the expression of subunits of K⁺ channels (for example loss of function of miR-1, miR-26, and miR-101, that are inhibitory regulators of Kir2.1 subunit of IK1; *Table 5*), and aberrantly methylated genes on genetical basis play significant role in the maintenance of K⁺ ion transport. [25,60,61] Re-entry-promoting shortening of action potential duration is also

360 seen in chronic non-genetic AF due to increased repolarizing currents, particularly IK1 and agonist-independent ‘constitutive’ IK,ACh, all of which are in part Ca²⁺ regulated. Increased inward-rectifier K⁺ currents also produce resting membrane potential hyperpolarization that enhances excitability and stabilizes spiral-wave re-entry. Up-regulation of other K⁺ currents like two-pore K⁺ currents may also contribute to action potential shortening. [51]

365 Another AF-related mechanism involving K⁺ channels is linked to enhanced ectopy due to prolongation of action potential due to loss of function mutations of the above mentioned K⁺ channel genes (for example KCNQ1, KCNH2, KCNA5, KCNE1). [25]

c) Implication to treatment

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The importance of action potential duration as a determinant of reentry led to widespread use of AADs of class III (that prolong action potential) in AF. However, most of these agents target IKr, and their use is limited by potentially life-threatening ventricular arrhythmias. An interesting target of pharmacological therapy could be the IK,ACh, which is prominently expressed in atria [25,62,63]

375 and absent in the ventricles. A highly selective IK,ACh inhibitor has recently been shown effective in several experimental AF models. [25,64,65] Another interesting target could be IKCa, which appears to be important in AF. [25,66–68] A selective small-conductance IKCa channel inhibitor suppresses AF in a range of animal models. However action potential duration shortening is a

mechanism of electrical remodelling in almost advanced in non-genetic AF natural history only and
380 so it is not the ideal target for drug therapy.

Non ion channel mutations and fibrosis in AF

a) Fibrosis pathways in AF

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The reactive fibrosis that is involved in AF pathophysiology is based on an imbalance in myocardial extracellular matrix (ECM) deposition and interstitium degradation. This process creates physical interference in myocardial conduction and favor electrical reentrant circuits. Furthermore fibroblasts differentiate into myofibroblasts and connect themselves with cardiomyocytes through gap junctions,
390 reducing the conduction speed and maximum level of depolarization of action potential. [69]

b) Pro-fibrotic mutations

Multiple mediators are involved in the fibrotic process, for example Renin-Angiotensin-Aldosterone
395 system (RAAS) (*Table 4*). Mutations in non-ion channel genes are responsible for atrial fibrosis through alteration of these pro-fibrotic pathways. The deletion of the gene encoding the Atrial Natriuretic Peptide (ANP) was the first mutation discovered in this group, [5] and results in exaggerated cardiac hypertrophy and fibrosis. [70] Mutations in the genes of matrix metalloproteinases (MMP3), that maintain a balance between connective tissue synthesis and
400 degradation, cartilage oligomeric matrix protein (COMP), that regulate ECM turnover, [71] and Collagen-encoding genes (COL12A1/COL23A1) that regulate fibrosis [72] and gap junction channels GJA5 (encoding Connexin40) [73] and GJA1 (encoding Cx43) also cause heart fibrosis and early AF. [4,74] Genes involved in cardiogenesis are also linked with risk of AF. Mutations in NKX2 DNA tracts, that are homebox-containing transcription factors involved in cardiac
405 development and septation, [4]and GATA4 and GATA6 genes, that work synergistically with them, are associated with AF. [4]In particular, the genes NKX2-5 and NKX2-6 regulates the proliferation of both atrial working and conduction myocardium in coordination with Notch pathway. [4]

A variant of the gene GREM2 that encodes the bone morphogenetic protein and is also linked to atrial differentiation during embryonic development, was found in two probands of a lone AF cohort. [4]
410 Finally mutations in LMNA gene (encoding Lamin A/C) have been linked to AF. [75,76] These proteins play a key role in nuclear architecture maintenance, chromatin organization and gene expression regulation; [77] their alteration causes myocardial fibrosis via aberrant TGF- β 1 signaling

[78,79] and predisposes the patient to development of both electrical instability and mechanical impairment. [80] Of note reported a prevalence of AF is as high as 61% in patients phenotypically affected by dilated cardiomyopathy (DCM) with LMNA gene mutations. [77] Mutation in the gene encoding for a nucleoporin involved in nucleo-cytoplasmic transport (NUP155) is also involved in this pathway, because affecting the formation of the nuclear envelop, delaying or blocks mitosis, and reducing myocyte survival and promoting cardiac fibrosis. [61] Notably NUP155 may also indirectly modulate maturation and trafficking of Ca²⁺ handling proteins and ion channels. [81]

Also epigenetic mutation could be involved in susceptibility to structural derangement and fibrosis in AF. [30,60] For example the connexin expression is regulated by miR-206 and miR-208, [82,83]miR-21 indirectly enhance the extracellular signal-regulated kinase (ERK) pathway and promotes in turn the STAT3 signaling pathway, which endorses cardiac fibroblasts proliferation, favoring heart fibrosis. [84,85] Long non-coding RNAs (lnc RNAs) are also responsible for atrial fibrosis through alteration of fibroblast activity, ion channel function, and cardiomyocytes energy metabolism. [30,86]Some significant examples are PCAT1 (prostate cancer-associated transcript 1) which promotes fibroblast proliferation mean targeting TGF- β 1, MIAT (myocardial infarction associated transcript) that regulates fibrosis, NRON (noncoding repressor of Nuclear Factor of Activated T cells) that inhibits NFAT (Nuclear Factor of Activated T cells, that belongs to the calcineurin pathway) localization to nucleus, [30]

The DNA methylation and histone acetylation in correspondence of the above mentioned genes are another aspects of epigenetic susceptibility to AF, they have a heritable genetic basis too. [61] However, the exact molecular mechanisms remain unknown for many of them.

435 c) Implication to treatment

2020 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) indicate that RAAS is up-regulated in AF, and report that treatment with Angiotensin-converting enzyme (ACE) inhibitors (ACEis) and Angiotensin receptor blockers (ARBs) showed encouraging results in preventing AF in preclinical studies even if recommend their use only in treatment of associated comorbidity. [87] However in basis of above mentioned evidences anti-RAAS therapy may have benefit in all AF forms. A metanalysis of 2005 of 11 trials for a total of 56,308 patients, the use of ACEIs or ARBs reduced the relative risk of developing AF by 28% (95% confidence interval [CI] = 15% to 40%, p <0.0002). [88] Brignole reports that ACEis or ARB could be administered during the peri-

procedural period of an electrical cardioversion of AF to decrease the recurrence rate which is maximal shortly after cardioversion. [89]

However further research is needed in this field.

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Conclusion

As electrical alteration and structural remodelling are intimately linked in AF, a larger use of AADs
455 seems warranted. Classical AADs are associated to Na⁺, K⁺ channels and RyR2 block and so could be associated with antifibrotic effect. However data on their benefit are discordant or incomplete and furthermore they are often associated with significant side effects, including proarrhythmic effect. So there is a need for further research in this field to clarify the direct antifibrotic effects of classical AADs and to synthesize new AADs selective on late INa current or RyR2 compound.

460 In the end a more frequent use of RAAS blockers (as recommended in the European Society of Cardiology Guidelines) could counteract structural atrial remodelling in this arrhythmia without particular side effects, and so a larger use could be advisable.

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