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Authors
Woods, Christopher E
Olgin, Jeffrey

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AF Therapy Now and in the Future: Drugs, Biologicals, and Ablation

Christopher E. Woods, MD PhD and
Division of Cardiology, University of California at San Francisco and Division of Cardiology Research, AUST Development, LLC, Mountain View, CA

Jeffrey Olgin, MD
Division of Cardiology, University of California at San Francisco

Abstract

Rationale—Atrial fibrillation (AF) is a complex disease with multiple interrelating causes culminating in rapid, seemingly disorganized atrial activation. Therapy targeting AF is rapidly changing and improving.

Objective—The purpose of this review is to summarize current state-of-the-art diagnostic and therapeutic modalities for treatment of atrial fibrillation. The review focuses on reviewing treatment as it relates to the pathophysiological basis of disease and reviews pre-clinical and clinical evidence for potential new diagnostic and therapeutic modalities, including imaging, biomarkers, pharmacologic therapy as well as ablative strategies for AF.

Conclusions—Current ablation and drug therapy approaches to treating AF are largely based on treating the arrhythmia once the substrate occurs and is more effective in paroxysmal AF rather than persistent or permanent AF. However, there is much research aimed at prevention strategies, targeting AF substrate—so called upstream therapy. Improved diagnostics, using imaging, genetics and biomarkers are needed to better identify sub-types of AF based on underlying substrate/mechanism to allow more directed therapeutic approaches. In addition, novel anti-arrhythmics with more atrial specific effects may reduce limiting pro-arrhythmic side-effects. Advances in ablation therapy are aimed at improving technology to reduce procedure time and in mechanism targeted approaches.

Keywords

Atrial fibrillation; ablation; arrhythmia

Introduction

Atrial fibrillation (AF) is characterized by rapid, seemingly chaotic atrial activation, characterized by the lack of an organized p wave and irregularly irregular ventricular

Address for correspondence: Dr. Jeffrey Olgin, Gallo-Chatterjee Distinguished Professor of Medicine, Chief, Division of Cardiology, University of California San Francisco, 505 Parnassus Avenue, M-1182A, Box 0124, San Francisco, California 94143-0124.

Disclosures
C.E.W. is a senior scientist at AUST Development, LLC, and inventor of catheter based optical mapping.

activation (QRSs) on surface ECG. AF manifests as a result of multiple heterogeneous groups of disorders. For example, AF can occur idiopathically (so called “lone AF”), be related to familial inheritance with specific genetic mutations, or, most commonly, associated with hypertension or underlying structural heart diseases such as valvular heart disease or cardiomyopathy.

Current therapy for AF is targeted at treating symptoms, and reducing risk of tachycardia-induced cardiomyopathy and stroke. Stroke has been addressed elsewhere recently.[1, 2] In many patients, symptoms of AF can be treated with rate control, typically achieved by AV nodal blocking drugs such as beta blockers or L-type calcium channel blockers. In patients in whom rate control is insufficient, anti-arrhythmic drugs (AADs) and ablation are used to attempt to maintain sinus rhythm (rhythm control). This review will focus on strategies aimed at rhythm control.

Several large randomized trials have shown no mortality benefit of antiarrhythmic derived rhythm control over rate control as a treatment strategy.[3–5, 6] It should be recognized that these studies evaluated current antiarrhythmic drugs, which are imperfect at controlling rhythm and the result of these studies might be different with future approaches of rhythm control that might yield better rates of maintaining sinus rhythm or less off-target effects. Moreover, the benefit from ablation based rhythm control in terms of mortality is unknown and being evaluated in a randomized trial (CABANA trial, see below). Thus, currently the decision on strategy is largely dictated by symptoms, though other factors such as a younger age, absence of structural heart disease, and first presentation may weigh in to favoring rhythm control.

Current anti-arrhythmic drugs (AADs) for atrial fibrillation consist of all class Ic and class III (Singh and Vaughan-Williams classification) drugs. Since no current anti-arrhythmic drug is “atrial specific”, they all have significant risk of side-effects, including pro-arrhythmia (see Table 1).[7–10] Amiodarone is generally considered the most effective drug overall, with a 50-60% efficacy rate (freedom from AF at 1 year).[11 10, 12] The choice of AADs is generally determined by the risk of side-effects and convenience of administration rather than efficacy.[12]

In symptomatic patients and/or when AADs are not tolerated or ineffective, ablation therapy can be performed. Currently, the most widely accepted approaches for ablation involve isolation of the pulmonary veins (PVs), thought to be the origin of the triggers for AF. Current treatment strategies for rhythm control of AF are shown in Figure 1.[12]

With this background, it is clear that better, more targeted approaches are needed to improve therapy of AF. Research and evolving therapy for AF would ideally be aimed at developing approaches to reduce the occurrence of incident AF by preventing the development of the AF substrate; therapies that interrupt or reverse the pathophysiology of AF; AADs that are atrial specific in order to limit side-effects; and ablative approaches that require less ablation of tissue, are easier to perform, and have a higher success rate; and a combination of these all (perhaps by selecting a more “individualized” approach).

Pathophysiology of AF

AF results from the interaction between “triggers” (initiating electrical stimulus) and “substrate” (vulnerable tissue allowing AF to be induced and in some instances sustained).While there has been much progress in the area over the past several decades, a clear understanding of the mechanisms and pathophysiology of AF is still lacking. The most significant clinical advance has been the discovery of the importance of triggers from the pulmonary veins.[13] However, why these triggers form is less clear and our understanding of the various vulnerable substrates is still evolving.

From a clinical standpoint, AF is broken down into one of three clinical entities: 1) paroxysmal AF (PAF), which refers to self-terminating episodes of recurrent AF; 2) persistent, which refers to AF present >7days that requires an intervention with either medical or electrical cardioversion for termination; and 3) permanent AF, where cardioversion is either ineffective or sinus rhythm rapidly reverts back to AF. In some cases a distinction between newly persistent and long-standing persistent AF is made, particularly as it relates to considering effectiveness of ablation, cardioversion or drug therapy. In general, these categorizations are useful in describing the AF patient, but have no direct or clear relationship to the underlying pathophysiology. It is thought that triggers, most commonly arising from the PVs,[13] play a more important role in PAF and as the spectrum moves from PAF to persistent to permanent, the vulnerable substrate becomes more important relative to triggers.[14]

Various forms of mapping, mostly in animal models, have identified 3 electrical mechanisms of atrial fibrillation: Focal AF in which AF results from a rapidly firing stable focus or several foci with fibrillatory conduction; multiple meandering reentrant wavelets; or rotors that are relatively stable and produce other transient rotors and/or fibrillatory conduction. Each of these mechanisms has been identified in humans.[13, 15, 16] However, it is likely that the mechanism is determined by the underlying substrate.[17–20] The current status of genetics and molecular biology of AF, as well the molecular electrophysiology of AF is covered in detail elsewhere in this compendium. In what follows, aspects of the molecular AF remodeling will be addressed only with respect to a discussion of potential therapeutic targets.

Electrical Remodeling in AF

Several electrophysiologic substrates (in isolation or in combination) have been observed *in silico* and in animal models of AF as well as humans with AF. These include shortening of atrial ERP, loss of rate adaptation of ERP (and APD), slowed atrial conduction, and heterogeneous conduction. These electrophysiologic substrates can occur via a variety of changes or remodeling.[21] It has been demonstrated that AF itself results in changes in electrophysiology that promote further AF—so called AF begets AF.[22, 23]

Electrical remodeling plays a role in trigger initiation.[24] It has been demonstrated that decreased ICaL Ito, and Ikur, as well as increased Ik1, and IkACh, and Iks occur.[25,26 27] In addition, downstream second messenger regulation may play a role through phosphorylation of target channels such as ICaL.[28] In addition, calcium overload is important for substrate

remodeling as the cell is exposed to increased cellular calcium concentrations in microdomains of the heart at the higher rates of AF.[29] This elevated calcium concentration is believed to activate calcium dependent calcineurin, calcium/calmodulin kinase II (CAMKII) system involved both in electrical remodeling and in initiating cell death pathways.[29–32] Heat shock protein (HSP) induction has also been reported to protect the heart from the deleterious consequences of AF related calcium remodeling.[33] Along with changes within cells, alterations in how cells are connected likely contribute to AF maintenance. For example, hypophosphorylation of connexin 43 contributes to disrupted passive AP propagation.[34]

Substrate Remodeling and Fibrosis in AF

Some forms of atrial fibrillation in both humans and in animal models demonstrate increased interstitial atrial fibrosis. Biopsy specimens from the left atrium of patients with AF show interstitial fibrosis.[18, 35- 37] The more longstanding the AF, the more pronounced the fibrosis.[38] Studies in humans, using electroanatomic mapping have demonstrated atrial fibrosis in the setting of heart failure [39] and in lone AF.[40] In animals with heart failure induced AF from ventricular tachypacing, marked atrial fibrosis occurs and has been demonstrated to provide the substrate for AF.[41, 42] While there has been debate about whether the fibrosis is causative or merely a result of the AF, several pieces of data suggest that fibrosis is causative and that AF-induced fibrosis may be part of the vicious cycle. Firstly, in animal models reversal or prevention of fibrosis prevents atrial fibrillation[42, 43]; secondly, AF substrate in the absence of any cellular electrophysiologic abnormalities has been demonstrated in a transgenic mouse model of isolated atrial fibrosis; [44, 45] finally, it is been demonstrated that rapid atrial pacing of cariomyocytes itself may stimulate fibroblast function.[38]

The angiotensin system and transforming growth factor-beta1 (TGF-b1) appear to play an important role in atrial fibrosis associated with heart failure models of AF, [12, 42, 45] a mouse model of AF[44,45] and in human AF associated with heart failure.[44] Both angiotensin II and TGF-b1 are upregulated in response to stretch and in response to heart failure (independent of stretch).[43, 46] Inhibition of TGF-b1 signaling prevents atrial fibrosis in animal models and in vitro.[42] In addition, isolated atrial fibrosis and atrial fibrillation have been demonstrated in a mouse model of TGF-b1 over-expression. Moreover, it appears that TGF-b1 induced atrial fibrosis is restricted to the atrium (in the absence of ischemia or infarction) within the heart in heart failure models.[47, 48] Consistent with this, our group has recently demonstrated that in failing human hearts, elevated atrial, but not ventricular, TGF-b1 expression is present and precedes the development of AF.[44] Unlocking the signals that make the atria uniquely susceptible to TGF-b1 induced fibrosis may lead to specific AF prevention therapies.

Oxidative Stress and Inflammation in AF

Oxidative stress has been associated with AF as well. Oxidative stress is involved in fibrosis,[38] and also in electrical remodeling.[31, 49, 50] More generally, inflammatory markers have been demonstrated to be elevated in patients with AF.[51–53] In the cardiovascular

system, reactive oxygen species (ROS) have been shown to be derived primarily from NADPH oxidase (NOX), mitochondrial xanthine oxidase (mictochondrial), and uncoupled endothelial Nitric Oxide Synthase (eNOS).[54, 55] In patients with AF, both increased NOX and eNOS activity have been demonstrated.[56, 57] Animal models have recapitulated these findings with production of superoxide and peroxide from activated NOX,[41, 56, 58] which consequently led to apoptosis, atrial inflammation, and fibrosis.[50, 59–61] The mechanism of downstream ROS is still being elucidated. NF-kB signaling pathways, involving TNF-alpha, iNOS, IL-1β, and MMPs,[62] have been suggested to be regulated by ROS. The Rennin-Angiotensin-Aldosterone System (RAAS) has been linked to ROS in various disease states.[46, 63, 64] In vitro assays have demonstrated that AgII can stimulate NOX activity through TGF-b1, and that inhibition of TGF-b1 blunted ROS formation as well.[65] Ang II increases peroxide production and NOX4 expression in human atrial tissue.[66] Thus, RAAS induced TGF-b1-SMAD pathway and TGF-b1 induced ROS, may act in concert to cause fibrotic remodeling. ROS signaling in general has been shown to modulate both ion channel function and calcium-induced-calcium-release (CICR) directly (eg oxidized CAMKII,[67]) and indirectly through second messenger systems. Oxidized CAMKII is increased in the atria of AF patients, and Ag II increases oxidized-CAMKII in a mouse model.[68] Figure 2 provides an overview of pathophysiologic mechanisms of AF and a more detailed discussion can be found elsewhere in this compendium.

NOVEL THERAPEUTIC STRATEGIES FOR AF

Novel Diagnostic Testing

A combination of new diagnostic modalities focused on genetics, biomarkers, and imaging modalities may help to better define subtypes of AF in the future to guide specific therapeutic targets or ablation approaches. The genetics of AF are discussed in detail elsewhere in this issue. Currently, the genetic studies have not identified particular polymorphisms that can be used for subtyping or to point to specific pathophysiologic targets for therapy. Biomarkers hold the potential to identify underlying substrates of AF, and predict AF progression. Unfortunately, there are no sets of biomarkers that either predict AF occurrence or guide treatment currently. Instead, several association studies present some hope for the future development of biomarker assays as reviewed recently.[69]

Novel imaging approaches may prove useful in identifying subtypes of AF and appropriately targeting therapies. Echocardiography to determine atrial size is generally used to determine the likelihood of success of AF ablation. However, aside from valvular heart disease, there are no other specific criteria used currently to tailor therapy for AF. Late gadolinium enhancement (LGE) in cardiac MRI has been shown to correlate with areas of low voltage by electroanatomical mapping[70] and fibrosis in the atrium.[71,12] Patients with significant fibrosis have lower success rates of ablation.[72] Recently, a potentially simpler approach involving cardiac magnetic resonance T1 mapping has also been introduced as a way to quantify atrial fibrosis .[73] However, more data is needed in larger populations to determine the clinical utility of such imaging in the management of patients with AF.

Noninvasive body surface mapping of AF using 252 body surface electrodes has recently been demonstrated in patients with atrial tachycardia and AF.[74–78] The technique uses the

inverse solution to construct local unipolar epicardial electrograms from body surface EKG potentials in a single beat.[79] With respect to AF, the data has suggested that electrical features of rotors, focal impulses, and multiple wavelets could be defined in the same patients at different times. This study saw no stable rotors, but rather meandering rotors as would be predicted by optical mapping data.[75]

Given the high spatiotemporal resolution afforded by optical mapping, applying this technology to AF clinically may be valuable. Live animal optical mapping has been done epicardially by us[80] and others.[81] We have demonstrated the feasibility of a percutaneous catheter based approach to optical mapping endocardially (Woods CE, unpublished data, 2013). In Figure 3, examples of emerging imaging modalities are presented.

POTENTIAL THERAPIES

Future Antiarrhythmic Therapy in AF

Ion Channel Blockers—Targeting selectively atrial myocytes to reduce "off-target" side effects is a major goal in AF therapeutics.[82] The I_{Kur} and I_{KAch} are predominantly in atrial myocytes; therefore, inhibition of these channels may selectively prolong APD in the atria.[77, 82] AVE0118 targets IKur, and has shown efficacy against AF.[83] However, other studies have shown that IKur blockade may paradoxically shorten APD by a complex interaction with increased I_{CaL} and IKr/s. Tertiapin-Q is a non-selective inhibitor of IKach derived from the honeybee (*Aps mellifera*), and in a rapid atrial pacing model it reduced AF inducibility.[82] In addition, Tertiapin-Q terminated AF in a vagally induced AF model.[84] NTC-801 is the only available specific inhibitor of IKAch.[85] Despite the potential benefit of atrial specific potassium channel modulation, limited data in humans for the above drugs are available. Somewhat discouragingly, recently the selective IKur blocker MK-0448 failed to increase atrial ERP in healthy patients, though it is important to note that the pacing frequencies were well below those of AF.[86]

Vernakalant is a more complex electrophysiologic agent which shows broad potassium channel inhibition, and rate dependent sodium inhibition.[87 88] Based on animal studies, however, these combined effects seem not to be proarrhythmic.[89] Phase I-III data has been promising for Vernakalant both in terms of converting to sinus rhythm and also for maintenance of sinus rhyhtm, and a phase IV trial is underway (for details of this human data, see Cardiome and Astellas, http://www.cardiome.com).

Mitigating calcium overload seems an attractive target for AF therapy. While L-Type Ca channel blockers reduce the likelihood of early recurrence of AF after cardioversion by attenuating changes in atrial ERP,[90] they have no affect on AF in other settings (aside from their role as a rate control agent).[91] Stabilizing the SR RyR-2 has also been proposed as an attractive alternative. Carvedilol decreases RyR-2 open probability,[92] and drugs based on its structure are in development. Another strategy for reducing the open probability of RyR is to mimic FKBP12.6, so called calstabin. The synthetic agent JTV-519 (K201) acts to promote FKBP12.6-RYR-2 interaction, and has been shown to reduce AF in dogs and mice.[93] Clinical trials with this drug have been completed, but the data is not available. (ClinicalTrials.gov Identifier: NCT00626652) HSP induction with orally administrered

geranylgeranylacetone (GGA) has been shown to reduce calcium transient remodeling in a tachypacing model.[33]

Little research has been done to develop compounds that target gap junctions. ZP123 is a synthetic agent that has been demonstrated to increase gap junction conductance. In a mitral regurgitation model of AF, ZP123 was found to improve conduction and reduce AF susceptibility; however, in a canine model of CHF in which there is profound interstitial fibrosis, the compound had no effect.[94, 95] It has also been reported that gene transfer of connexin 43 suppressed AF in a rapid atrial pacing porcine model.[96] Phase II data in humans is completed (ClinicalTrials.gov). A second agent targeting gap junction function, GAP-134, has completed Phase I safety data (ClinicalTrials.gov).

Atrial remodeling also affects contractile function. The role of histone-deacetylase proteins is unknown, but HDAC-6 levels are increased in human AF and inhibition of HDAC-6 by tubastatin-A protected against tachypaced electrical remodeling.[97]

Other non-classical ion channel targets which all possess some component of mechano-electric feedback have recently been implicated in AF.[82] However, the relevance of these targets is unclear. Table 2 summarizes novel atrial specific targets and the status of them with regard to clinical development.

Upstream Therapies

Upstream therapy is a broad term that is used to collectively refer to agents that prevent or reverse the AF substrate. While in theory these could involve AAD, in general they refer to agents that prevent structural remodeling. ACEI decrease fibrosis and AF in animal studies[43, 98,99, 100] Aldosterone inhibitors also reduce atrial fibrosis in rats.[101] Translating these findings to humans has had mixed results. Several retrospective analyses of ACEI/ARB studies demonstrate a trend of benefit in terms of reducing incident AF patients with hypertension and heart failure[102–105] In addition, specifically in patients with left ventricular hypertrophy, the prospective Losartan Intervention For Endpoint Reduction in hypertension (LIFE) demonstrated reduced new onset AF, cardiovascular morbidity and mortality, and stroke.[106] ACEI has also been associated with reduced AF after myocardial infarction in patients with low ejection fraction,[107] and fewer relapses of AF in patients with CHF.[105] A meta-analysis of ACEI/ARB studies in AF has shown that inhibition of the RAAS may be effective at preventing AF in heart failure and those with hypertension and left ventricular hypertrophy, though these were retrospective studies not designed with a primary outcome of AF.[108] Aldosterone inhibition as compared to ACEI has been compared in a randomized fashion, and it was found that both conferred the same AF recurrence rate in patients with PAF.[109] However, the recently published ANTIPAF trial, a prospective randomized trial of the ARB olmesartin aimed at AF specifically did not show any decrease in AF burden or time to recurrence or progression to chronic AF.[110] As mentioned above, TGF-b1 seems to play a central role in atrial fibrosis in conjunction with RAAS, at least in animal models and patients with heart failure induced AF. A novel agent, pirfenidone, has been shown to reduce significantly expression of TGF-b1expression directly, and also reduce tissue fibrosis in experimental animal models in multiple tissue types.[42] However, there are no clinical studies using this agent to treat AF in humans.

Statins may exert a beneficial effect on AF by reducing inflammation independent of their HGM-CoA reductase inhibition.[111] Simvastatin has been shown to reduce electrical remodeling, AF duration, and fibrosis, as well as decreasing atrial fibroblast proliferation in animal models.[112, 113] CRP has also been demonstrated to be reduced in patients with AF treated with statins.[114] However, the data is less clear in regard to the effect of statins on clinical outcomes in AF. Retrospective data has established a trend in patients treated with statin therapy for reduced AF recurrences in patients with LV systolic dysfunction.[115, 116] When examined prospectively, however, the role that statins play in AF prevention seems to be strongest in the post-operative cohort of patients studied.[117] The Paroxysmal Atrial Fibrillation: Role of Inflammation, Oxidative Stress Injury and Effect of Statins (PAFRIOSIES) trial is a prospective randomized trial currently recruiting to better test the hypothesis that statins prevent AF recurrences (ClinicalTrials.gov Identifier: NCT00321802).

Blunting pathologic oxidative stress offers another promising strategy for AF therapy. In a calcium dependent step, oxidation of Met281/282 leads to constitutive activation of CAMKII similarly, but distinctly from, autophosphorylation, and this pathway is downstream of Ang II. In an infarct mouse model, inhibition of oxidized CAMKII overexpression reduced aldosterone dependent deleterious outcomes,[118] and further studies into AF seems warranted. Alda-1, a small molecule activator of aldehyde-dehydrogenase II, has been shown to reduce oxidative stress in myocardial infarction [119] and cardiac arrest in a CAMKII dependent fashion (unpublished results, Woods CE, 2013). PKCε inhibitors are attractive not only because they have been shown to reduce oxidative stress,[120] but they also may reduce Ikach.[121, 122]

Traditional activation of CAMKII via autophosphorylation lies at the intersection of calcium overload and oxidative stress. It has been shown in animal models that inhibition of CAMKII is beneficial in a wide range of cardiovascular diseases including ischemia-reperfusion injury,[123] cardiomyopathic remodeling,[124] arrhythmia remodeling, [125] genetic models of CPVT,[126] as well as AF.[127] However, there have been no studies utilizing such agents in the published literature. Table 3 summarizes upstream therapies.

Future of Ablation for Rhythm Control

Current guidelines recommend ablation for patients with symptomatic PAF who have failed an AAD based on evidence (class I), but acknowledge that based on expert opinion, ablation may be used in some patients prior to a trial of AAD (class IIa). Established percutaneous ablation strategies focus on isolating PV triggers based on the observation that these focal sources can initiate AF.[13] AF ablation approaches have evolved over the past two decades to a consensus that PV antral isolation (or wide-area circumferential isolation, WACA) is the most efficacious approach.[128] The major key to optimizing success appears to be the presence of robust and persistent electrical isolation of the PVs with lesions that not only isolate the PV, but also the antrum (confluence of the PV-atrial junction). Based on consensus statement, success of AF ablation has been codified as freedom from symptomatic or asymptomatic AF, atrial tachycardia, > 30 s of atrial flutter 12 months after AF ablation (excluding a standard 3 month blanking period).[128] Using these definitions,

single procedure success is estimated at 60-80% when sampling multiple trials, with success rate off AAD of ~71%.[129–134] In longer term follow up, the recent MANTRA-PAF study validated this benefit of ablation, but found it similar in comparison to that of AAD therapy.[135] Yet, while the cumulative burden of AF was similar between AAD and ablation at two years, both the burden of AF, and the percentage of patients free from AF was better in the ablation group at the two year mark (85% vs. 71%, P=0.004). It is currently not known whether ablation of AF reduces mortality, but this is being investigated by a large randomized trial (Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA), ClinicalTrials.gov identifier NCT00911508). Cumulative complication rates historically have been reported as high as ~5-6% of patients. However, it is believed that with experienced operators using newer and improved equipment (circular mapping catheters, electroanatomic mapping (EAM) with computed tomography (CT) guidance, esophageal monitoring, and intracardiac echo), major complication rates are ~<2%, with cardiac tamponade occurring <2% of the time, while TIA/stroke, PV stenosis and esophageal fistula, and vascular injury all occurring in <1.5% of patients. Death is a highly infrequent occurrence, occurring <0.1% of the time.[136] Figure 4 provides a summary of current approaches to AF ablation

Novel Catheters for AF Ablation

Novel balloon based and multielectrode based ablation technologies have been or are being developed to circumvent the standard point-by-point ablation RF ablation. The Cryoballoon (Medtronic) uses cryoablation rather than RF, and is the most widely available alternative. The current iteration, with the newer second generation 28 mm balloon, offers improved cooling with front facing freezing, allowing isolation of the PVs with fewer applications.[137] No randomized studies comparing efficacy of RF to cryoballoon have been completed. However, two trials asking this question are in planning stages (Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation: Double Short vs. Standard Exposure Duration (CIRCA-DOSE) (ClinicalTrials.gov Identifier:NCT01913522) and Study Comparing Pulmonary Vein Isolation With the Cryoballoon, Radiofrequency Energy, or Both in the Treatment of Atrial Fibrillation (AF) (CryoVs RFA) (ClinicalTrials.gov Identifier:NCT01038115). While no comparison of complications between Cryoballoon and RF has been completed in a randomized fashion, rates appear to be largely similar, though phrenic nerve palsy is more frequent with the Cryoballoon.[137, 138]

A recent study demonstrated that esophageal injury as visualized by post-procedural gastroesophagoscopy can be minimized by targeting esophageal temperatures above 12 degrees Celsius with 100% sensitivity.[139] A number of other technologies to overcome point by point ablation are on the horizon, including the Cardiofocus balloon, (HeartLight, Cardiofocus),which uses a 980 nm diode laser based endoscopic technology to ablate left atrial tissue in an arc fashion during cardioscopic visualization. Safety and efficacy data demonstrate ~95% acute isolation in patients with PAF, and a comparable freedom from AF to RFCA strategies of ~70%.[140, 141] An ongoing trial comparing the HeartLight to traditional ablation using an older generation Thermocool (Biosense Webster) catheter is underway. The Tailored Treatment of Permanent Atrial Fibrillation (TTOP-AF) multicenter trial compared ablation with the Ablation Frontiers' multi-electrode phased RF system to

medical therapy. The efficacy reported for this device is similar to that reported for conventional RFCA.[142] However, there is evidence of more PV stenosis and subclinical thrombosis with these catheters compared against standard irrigated ablation and Cryoballoon.[143] Irrigated versions of these multielectrode ablation catheters are in development which are hoped to obviate the problems associated with thrombosis. Table 4 summarizes developments in novel AF ablation catheters currently available or in clinical trials.

Targeting Substrate

PVAI is less beneficial for persistent AF where efficacy is 50% or lower.[144, 145] To improve on outcomes in this population, WACA has been extended by targeting non-PV triggers, with empiric linear ablation of the roof or mitral isthmus, as well as by targeting complex fractionated atrial electrogram (CFAE), and rotors.[146] In particular, the role of CFAE is controversial. There is some evidence that CFAE's may represent areas of wavebreak and functional block,[147, 148] and it has been speculated that these regions represent the wavetips around stable rotors. Interestingly, standard WACA may target most CFAE's as well.[144, 145] However, the electrophysiologic basis of CFAE is unknown, and can be varied and due to other phenomenon such as heterogenous conduction or confluent activation wavefronts.[140, 149] Whether to target CFAE's and linear ablation has been addressed. For example, two recent randomized trials have compared broader ablation strategies, versus PVAI aloe. The Randomized Ablation Strategies for the Treatment of Persistent Atrial fibrillation (RASTA) study[150] compared PVAI (WACA) with ablation of induced non-PV triggers, with PVAI plus CFAE ablation, or PVAI plus empirical ablation of common trigger sites, and found PVAI alone to be superior. In contrast, the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF),[151] a randomized comparison of ablation targeting utilizing CFAE alone, PVAI alone, or PVAI + CFAE ablation in patients with either paroxysmal or persistent AF, found that the PVAI + CFAE arm had the fewest recurrences. However, the data is inconsistent between each study. For example, in comparing similar arms from STAR AF and RASTA, patients allocated to PVAI+CFAE arm showed strikingly dissimilar results with 29% vs 74% for RASTA and STAR-AF, respectively, having freedom from AF at one year. Factors that may have influenced these disparate results include the small nature of the studies and different patient populations. To overcome these limitations, several ongoing randomized trials, such as CABANA, EAST, AATAC-HF, CASTLE-AF, and SARA are designed to address the question of hard endpoints for AF ablation such as mortality and cardiovascular death in a variety of patients with and without structural heart disease with large enough numbers to provide more conclusive results.

In the CONFIRM trial,[16] the hypothesis that targeting rotors would improve success after AF ablation was tested, particularly in patients with persistent AF where WACA was less likely to succeed. Using a proprietary software algorithm for "focal impulse and rotor modulation mapping" (FIRM), areas identified as stable rotors were targeted for ablation. In combination with basket catheter (St Jude) contact mapping, FIRM based ablation + PVAI was compared against standard PVAI alone in a non-blinded fashion. In the computational mapping arm, targeting focal sources (eg. rotors) improved freedom from AF to 84%

compared with 44% in the conventional arm at 2 years, with the majority of patients in this study having persistent AF.[16] A randomized prospective multicenter trial is needed.

Targeting the Cardiac Nervous System

It has been shown that atrial neural networks in the heart of both animals and humans are important for AF induction[21, 152]. This autonomic nervous system may be involved in triggering AF, particularly from non-PV sites.[153] Traditionally, ganglionic plexi (GP) have been the focus, and it has been demonstrated that focal ablation of GP can terminate AF.[154] In animal models, GP ablation also decreased acute AF vulnerability.[155] Anatomically guided ablation of GP, rather than WACA, has been reported to have similar efficacy to PVAI alone, [156] and in addition to PVAI has been reported to improve freedom from AF at two years by ~20%.[157, 158] However, GP ablation is also common during WACA because of the anatomic proximity of them to the PVs (see Figure 4).[159–163] WACA, along with electrically isolating the PV from the atria, disrupts the distant cardiac neural network from the PVs.[21] Rather than a purely anatomic approach, high-frequency-electrical-stimulation (HFS) to identify and ablate specific GP capable of triggering AF has been shown to reduce AF inducibility in animal models.[152] In small studies, reports conflict with regard to the success of this approach.[164, 165] Surgical approaches to GP ablation have also been reported successful.[166–168] Transcutaeneous electrical stimulation of the autonomic neurvous system as a way to modulate AF has been studied in animals, and was shown to reverse the acute electrical remodeling of rapid atrial pacing[169] and acetylcholine-induced AF.[170]

Surgical and Hybrid Ablation Approaches to Rhythm control

Based on consensus statement, surgical approaches to AF ablation can be considered for symptomatic and selected asymptomatic AF patients undergoing other cardiac surgery, symptomatic AF patients who prefer or have failed one or more attempts at catheter ablation, or cannot undergo catheter ablation, or those with a low chance of success with traditional ablation.[128] The Cox-Maze III procedure, or so called cut and sew Maze, was introduced in 1987. Isolated, non-randomized and non-controlled studies have reported freedom from AF after this procedure higher than 90%.[171, 172] The Cox-Maze IV procedure improved upon this by using custom devices that ablates tissue using RF (cryoablation), rather than the incisions of the original Maze.[173] This technique has been shown to be equally efficacious in single center reports.[174, 175] A recent systematic review examining both Cox-MAZE III and IV techniques reports that freedom from AF in patients with persistent AF was lower, though still excellent, at ~78 and 84%, respectively.

To reduce the surgical morbidity to the procedure, and eliminate the need for cardiopulmonary bypass, a minimally invasive thoracoscopic approach has been developed. Stand-alone minimally invasive ablation in patients with PAF has a freedom from AF at one year of 91%.[176] However, in patients with persistent AF, the stand-alone epicardial surgical ablation has a similar rate of success as percutaneous ablation approaches, with a freedom from AF at 6 months of ~53%.[177] Challenges for epicardial approach alone include inability to confirm entry/exit block, inadequacy of PV isolation particularly in the posterior left atrium, as well as mitral and cavotricuspid isthmus which are not fully reachable from an epicardial approach. The hybrid approach has been developed, which involves a combined

epicardial approach by a surgeon, and a percutaneous endocardial approach by an electrophysiologist.[166] Using this approach, freedom from AF at one year approaches 90% as reported from a recent meta-analysis.[176] In this analysis, approximately 80% of patients had persistent or long-standing persistent AF with mean LA diameters of 50 mm.[178] Two recent series of patients treated with hybrid ablation have reported lower, albeit similarly good success in patients with long-standing persistent AF and mean atrial size >50mm of around 70% where typical endocardial ablation performs poorly.[179, 180] Prospective trials are emerging. Two recent small randomized trials have been reported comparing PVAI alone to hybrid ablation in patients with persistent[181] and long-standing persistent AF[182] who had a mean left atrial diameter>50 mm. These both found dramatic improvements in efficacy with hybrid ablation over conventional ablation, with 81% and 54% freedom from AF at one and two years. More definitive trials are needed.

Whether endocardial, surgical, or hybrid, ablation emerges as thecommonplace therapy for AF,the major challenges moving forward are to shorten and simplify the procedure, improve safety, and at the same time improve long-term efficacy overall. However, as ablation currently stands, advances in ablation are largely incremental, and this likely reflects a poor understanding of the underlying mechanisms. Better ablative technology and approaches are also fundamentally rooted in understanding and better targeting the mechanism of disease. This was the case for typical atrial flutter ablation where initial success rates were in the 50-60% range until the arrhythmia mechanism and circuit became well defined, leading to current success rates of >95%. Whether it is substantiated or not, FIRM based ablation for AF is an example of this mechanistic approach to persistent AF. At the same time, avoiding wholesale ablation of the entire atrium is necessary as well.

Summary and Conclusion

AF is a complex, heterogeneous disease. Current therapy is aimed at palliating the disease. Research to better understand, sub-classify and identify new therapeutic targets holds the promise that specific therapies aimed at preventing or reversing AF will be developed. Better strategies to predict AF risk, and to diagnose and characterize the underlying etiology and pathophysiology of AF in a patient-specific manner are needed. Better therapeutic strategies for AF should be focused on disease-specific targets that aim to control pathophysiologic remodeling. The hope in the end will be a “cure” for AF or a prevention strategy that will prevent triggers, substrate or both from occurring. For those who have AF, the success of ablative strategies will continue to improve not only in the realm of paroxysmal AF, but this will hopefully extend to persistent AF.

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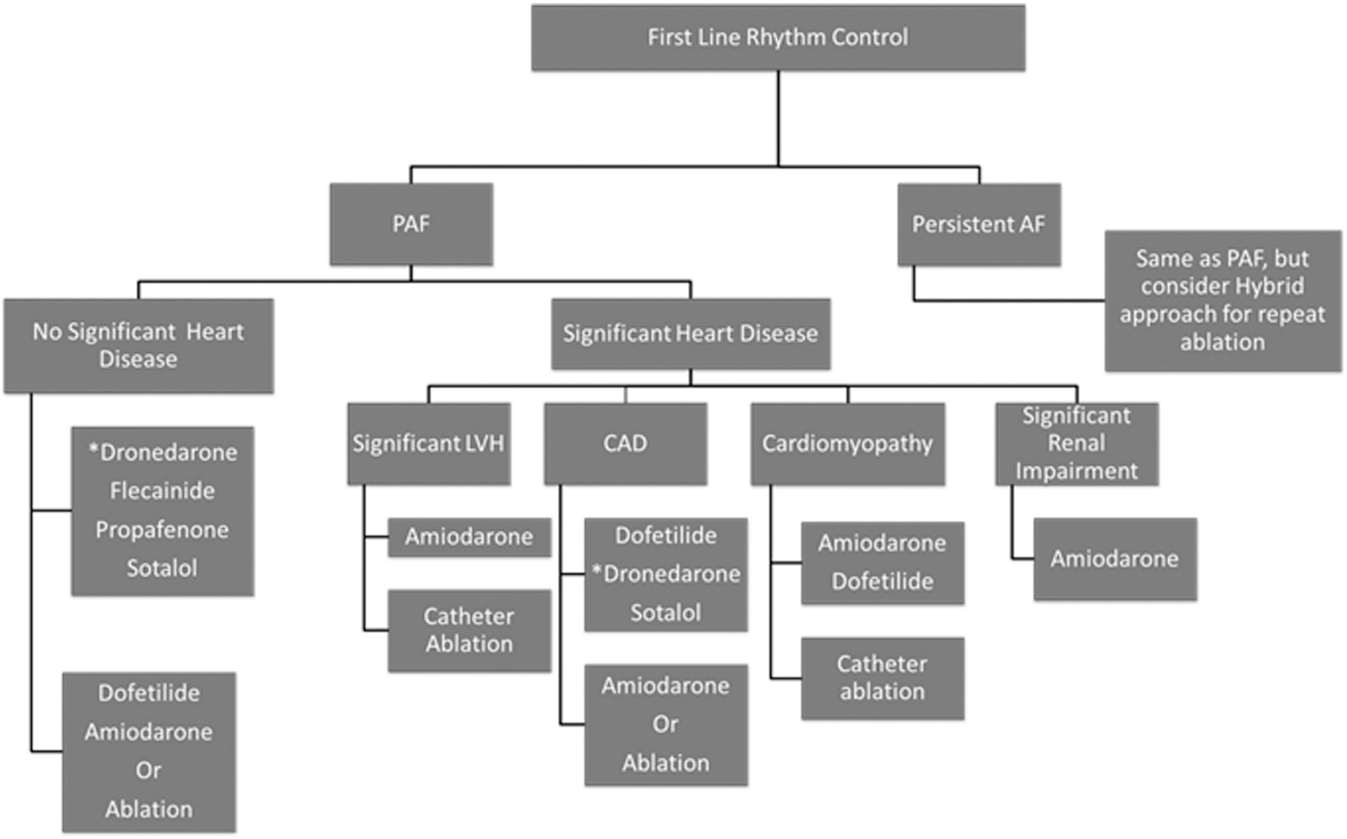

Figure 1.

Rhythm control strategies. Algorithm for treatment decision for antiarrhythmic and ablation to maintain sinus rhythm in patients with paroxysmal or persistent atrial fibrillation. Drugs are listed alphabetically within boxes. *Dronedarone should not be used in patients with long-standing persistent or permanent AF (see text for details). CAD=coronary artery disease. LVH=left ventricular hypertrophy. Ablation can also be considered upfront prior to failed antiarrhythmic medications (class IIa indication) (Modified from Wan et al. Circulation 2011)[183].

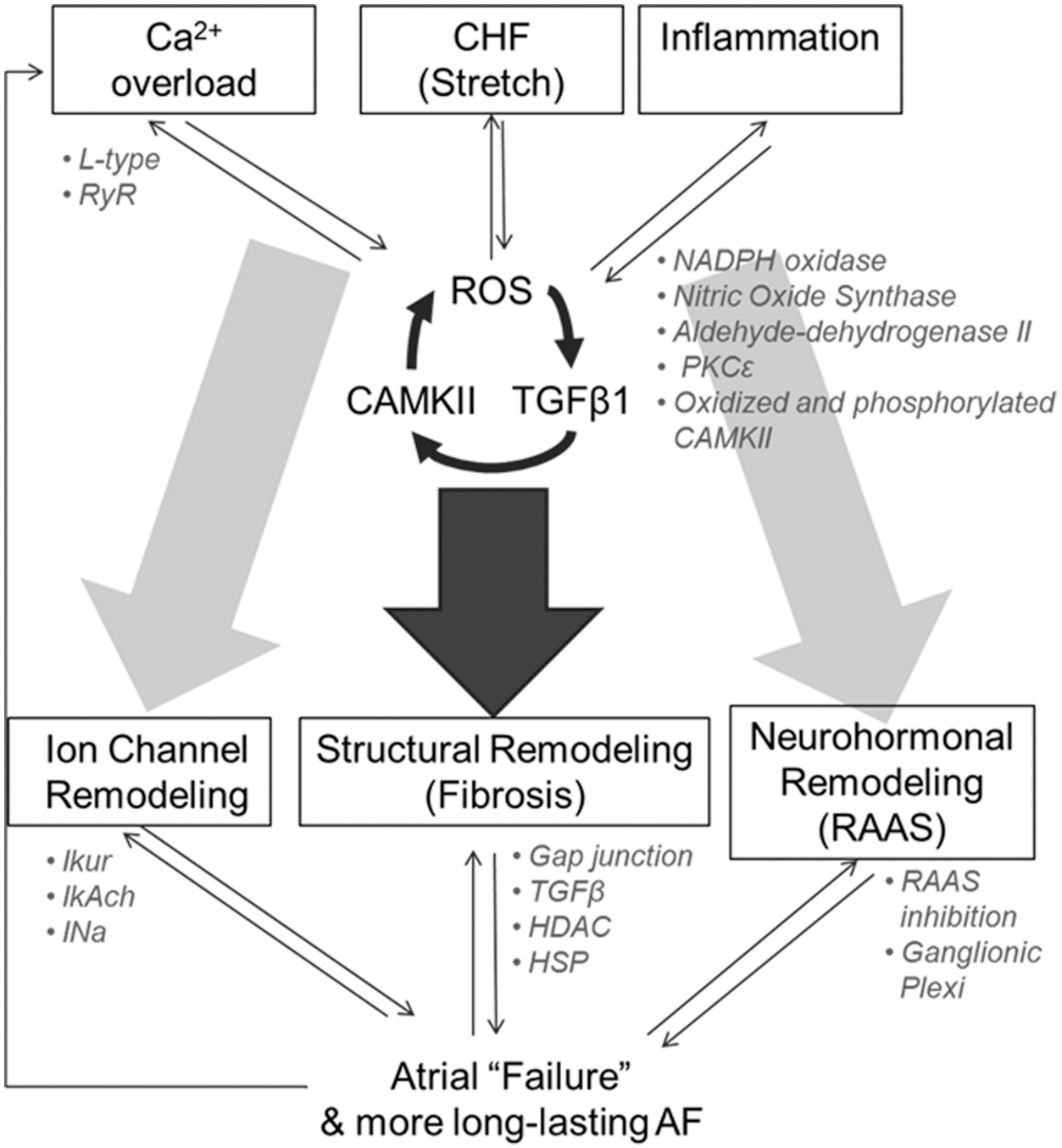

Figure 2.

Remodeling mechanisms in AF. In red are listed potential drug targets. Further details can be found in Tables 2 and 3, and in the text. TGF (transforming growth factor)- β, HSP (heat shock protein), HDAC (Histone deacetylase-6), RAAS (renin-angiotensin-aldosterone system), CAMK (calcium-calmodulin-kinase)-II, L-type (dihyropyridine receptor), RyR (ryanodine recptor-2), PKC (protein kinase C)- ε.

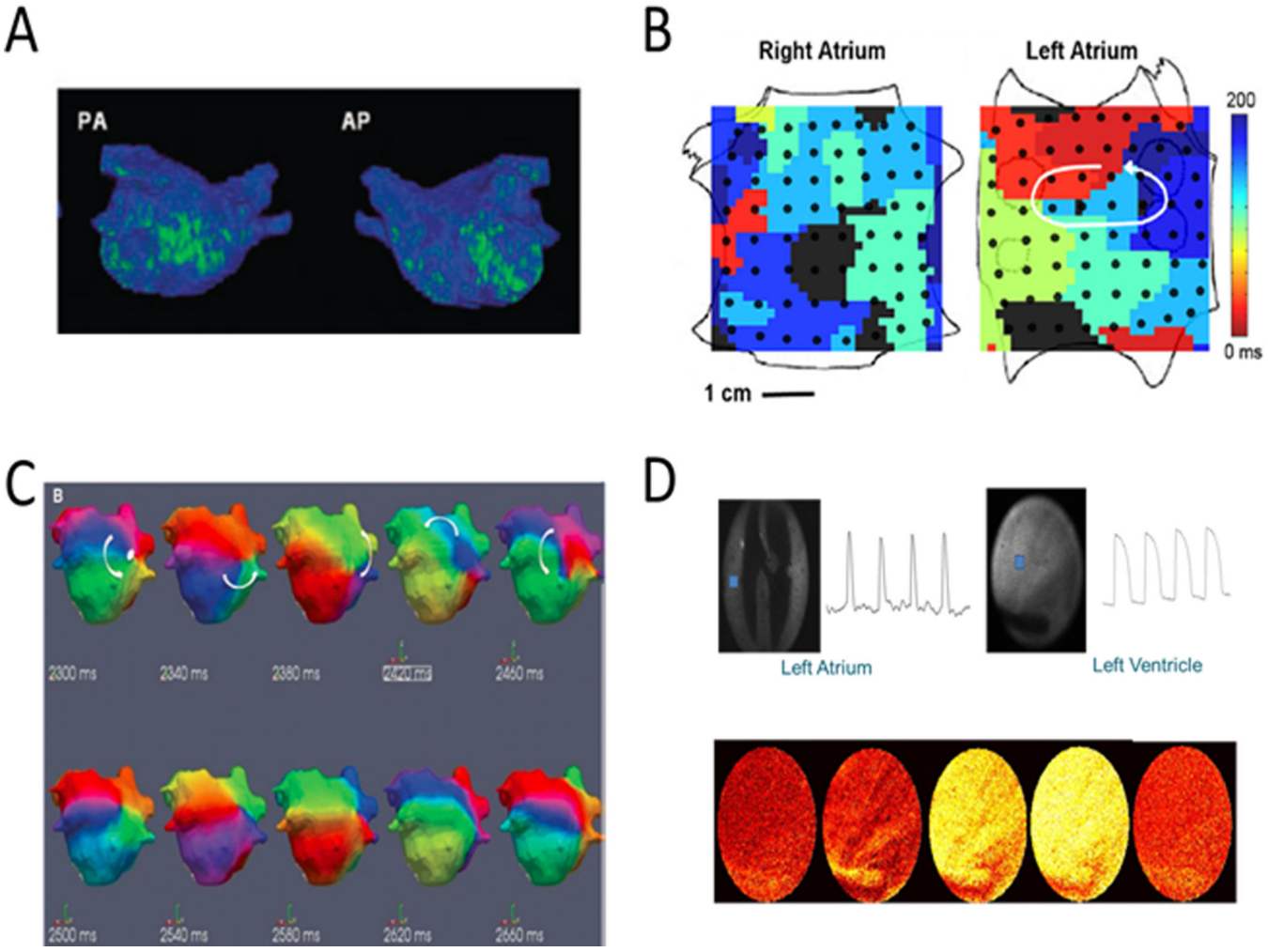

Figure 3.

Emerging imaging modalities for AF. A. MRI based fibrosis imaging of the atria showing the University of Utah Atrial Fibrillation LGE-MRI-based staging system in human. Green areas indicate areas of fibrosis. (adapted from Vergara et al, J Cardiovasc Electrophysiol, Vol. pp. 1-7 2010). B. Left atrial rotor with counterclockwise activation in human mapped computationally using the proprietary FIRM system (RhythmView, Topera Medical, Lexington, Massachusetts).(adapted J Am Coll Cardiol 2012;60: 628–36 2012). C. Phase mapping of posterior human left atrium during paroxysmal AF showing two successive rotations of a rotor near the right PV ostia using 252-electrode vest was applied to the patient's torso for body-surface mapping. The core of the rotor is depicted with a white star. The phases of the voltage propagation period are color-coded with blue representing the depolarizing period, and green representing the end of the repolarization (adapted from Haissaguerre et al. J Cardiovasc Electrophysiol, Vol. 24, pp. 711-717, June 2013). D. Endoscopic optical mapping of pulmonay vein (top left) and left ventricle (top right) in swine-isolated heart with a balloon tipped catheter via transeptal approach. Propagation map at successive time points from ventricular image for one beat shown below (unpublished data, Woods CE, 2013, courtesy of AUST Development, LLC).

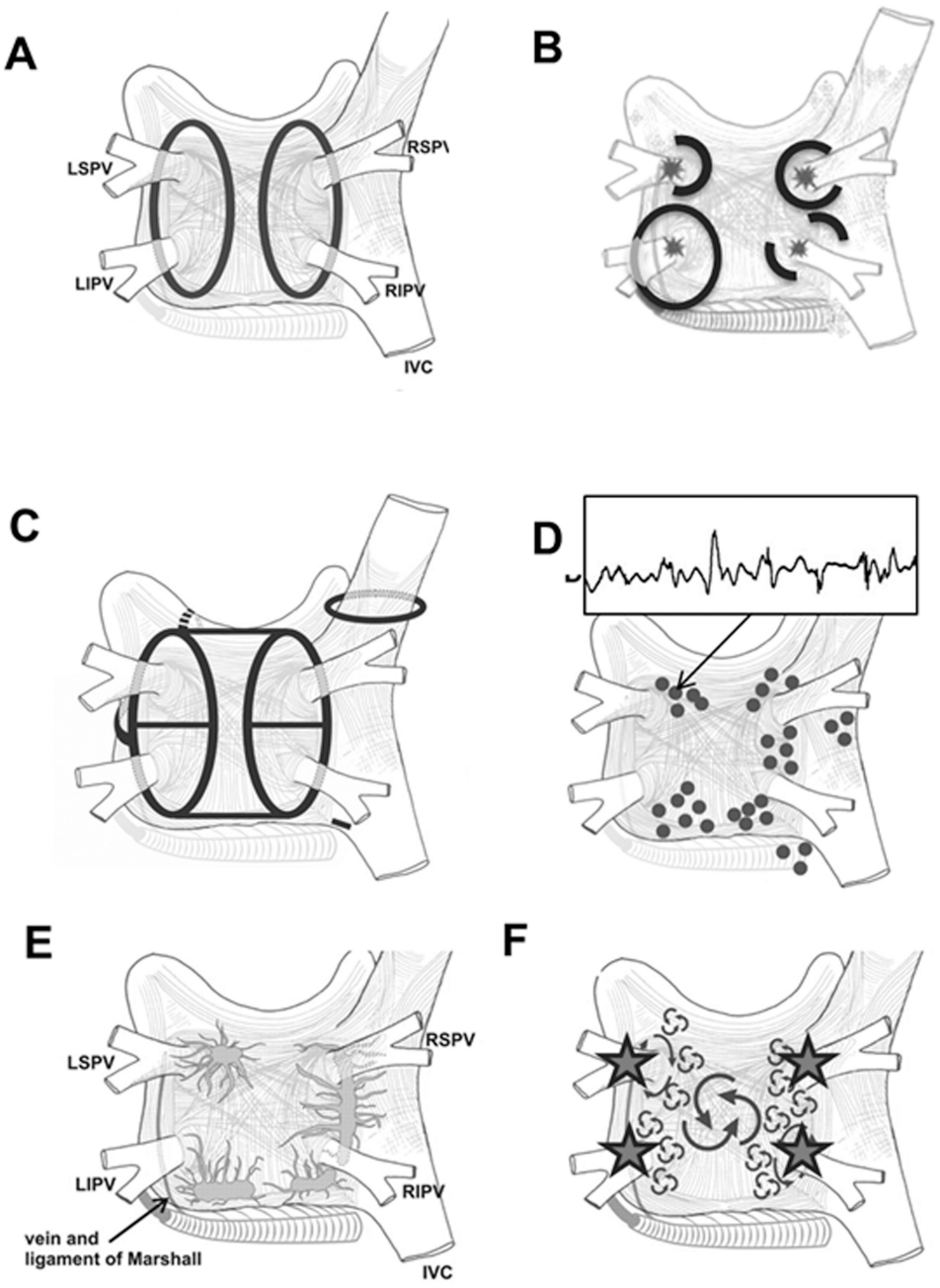

Figure 4.

Current Approaches to AF ablation. A-D Schematic drawing of the left and right atria as viewed from the posterior showing common approaches to AF ablation. In some cases, more than one approach (or combination of approaches in a stepwise fashion) are performed. **A. Wide Area Circumferential Ablation—Antral Pulmonary Vein Isolation.** Ablation of the pulmonary vein antra to electrically isolate pulmonary veins. Wide area ablation also isolates a large portion of the posterior left atria within the circumferential ablation. Variations on this ablation include isolation of each PV antrum separately as opposed to

combination isolation of ipsilateral veins. Endpoints for ablation are bi-directional conduction block into and out of pulmonary veins and intact circumferential lesions. **B. Pulmonary Vein Segmental Ostial Ablation.** Ablation of each PV ostium is done to achieve the same endpoints as in **A.** but without complete empirical ablation around the vein and includes less of the antrum. **C. Linear Ablation.** In some instances (typically in persistent AF or as part of a step-wise approach in subsequent ablations following recurrence), linear lesions are added to pulmonary vein isolation. These are typically roof-lines and mitral annular ablation. Addition of these ablation lines significantly increases the risk of post-procedure atrial flutter. Confirmation of integrity and completeness of the line is important to minimize atrial flutter occurrence. Additional variations are also depicted showing a “roof line” connection the left and right PVs, “mitral isthmus” line connecting the mitral valve to the lesion set around the left PV, anterior line connecting the roof lesion set to the mitral annulus, cavotricuspid isthmus line, figure of 8 lesion set including carinal lesions, and ablation to isolate the SVC. **D: Complex Fractionated Electrogram (CFE) Ablation.** Common sites of complex fractionated electrograms are shown in the figure and an example of a CFE. **E. Ganglionic Plexi Ablation**. The left atrial autonomic ganglionic plexi (GP) and axons (superior left GP,inferior left GP, anterior right GP, inferior right GP, and ligament of Marshall) are shown in gray. The coronary sinus and ligament of Marshall are shown in hatched gray. Ablation of GP’s is performed either by empiric ablation over these areas or by mapping using high-frequency stimulation to identify areas that result in a vagal effect. **F: Rotor Ablation.** Rotors are depicted by large and small gray rotating lines. Stable, “driving” rotors are targeted by novel mapping approaches for ablation. (adapted from 2012 HRS/EHRA/ECAS Expert Consensus[128])

Table 1

Current Anti-arrhythmic drug therapy for atrial fibrillation.

CLASS	EXAMPLES	PRO-ARRHYTHMIA	OTHER SIGNIFICANT SIDE-EFFECTS	CONTRA-INDICATIONS
IC	Flecainide, Propafenone	VT/VF; rapid atrial flutter	Rapidly conducting AF	CAD, Hypertrophy
III	Sotalol, Dofetilide	Torsade des pointes		Prolonged QT (at baseline or QTc>500 on treatment); heart failure (sotalol)
III	Dronederone	Torsade des pointes (rare), VT/VF	Heart failure exacerbation and death (in those with CHF); hepatic injury (rare)	NYHA class IV CHF or class II/III with recent exacerbation; prolonged QT (QTc>500); Permanent AF
III	Amiodarone	Torsade des pointes (rare)	Lung toxicity, hepatic toxicity, thyroid toxicity, optic neuritis (rare)	Liver failure; existing lung disease

Table 2

Potential Novel Antiarrhythmic Agents for the treatment of AF

AGENT	MECHANISM	STATUS
Vernakalant	Non-selective	Phase IV trial
S107	RyR Stabilization	No human data
JTV-519 (K201)	RyR Stabilization	RCTs terminated, data not available
NTC-801	IKAch Inhibition	Phase II, data not available
MK-0448	Ikur Inhibition	Failed to alter ARP in humans
ZP-123	Gap Junction Stabilization	Phase II terminated
GAP-134	Gap Junction Stabilization	Phase I completed

Table 3

Available and potential upstream treatment of AF

Mechanism	Possible clinical Agents	Affect on AF
RAAS inhibition	ACEI/ARB[98–106]	• Limits fibrosis and AF in animal models • Retrospective data promising, mostly in patients with HF or HTN • ANTIPAF trial negative
	Aldosterone[97–106]	• Prevention of fibrosis in animal models • Same recurrence as ACEI in head to head trial
HMG-Co reductase	Statins[107–113]	• Prevents AF in animal models • Association data humans mostly • Prospective data supports use in perioperative AF • PAFRIOSIES trial enrolling for PAF
TGFβ Inhibition	Pirfenidone[40–44]	• Prevents fibrosis and AF in animal model • No human data
	TGFβ Receptor Antibody	• No data
Ca/CAMKII inhibition	No current agents	
ROS inhibition	Alda-1	• No animal or human data
PKCε inhibitors[121–123]	No current agent	• Constitutive IkAch modulated by PKCε in human AF • No agent
Heat Shock proteins inducers	Geranylgeranylacetone (GGA)[34]	• Prevents fibrosis and AF in animal models • No human data
Histone deacetylase-6 (HDAC-6) inhibitors	Tubastatin-A[98]	• Prevents fibrosis and AF in animal models • No human data