Atrial fibrillation (AF) is a complex disease with multiple inter-relating causes culminating in rapid, seemingly disorganized atrial activation. Therapy targeting AF is rapidly changing and improving. The purpose of this review is to summarize current state-of-the-art diagnostic and therapeutic modalities for treatment of AF. The review focuses on reviewing treatment as it relates to the pathophysiological basis of disease and reviews preclinical and clinical evidence for potential new diagnostic and therapeutic modalities, including imaging, biomarkers, pharmacological therapy, and ablative strategies for AF. 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 subtypes of AF based on underlying substrate/mechanism to allow more directed therapeutic approaches. In addition, novel antiarrhythmics with more atrial specific effects may reduce limiting proarrhythmic side effects. Advances in ablation therapy are aimed at improving technology to reduce procedure time and in mechanism-targeted approaches. (Circ Res. 2014;114:1532-1546.)

Key Words: arrhythmias, cardiac & atrial fibrillation & catheter ablation
Several large randomized trials have shown no mortality benefit of antiarrhythmic-derived rhythm control over rate control as a treatment strategy. It should be recognized that these studies evaluated current AADs, 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 (Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial [CABANA], see below). Thus, currently the decision on strategy is largely dictated by symptoms, although other factors such as a younger age, presence of structural heart disease, and first presentation may weigh in favoring rhythm control.

Current AADs for AF consist of all class Ic and class III (Singh and Vaughan-Williams classification) drugs. Because no current AAD is atrial specific, they all have significant risk of side effects, including proarrhythmia (Table 1). Amiodarone is generally considered the most effective drug overall, with a 50% to 60% efficacy rate (freedom from AF at 1 year). The choice of AADs is generally determined by the risk of side effects and convenience of administration rather than efficacy.

In symptomatic patients and 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.

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 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 electric stimulus) and substrate (vulnerable tissue allowing AF to be induced and in some instances sustained). Although there has been much progress in the area during 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. 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 1 of 3 clinical entities: (1) paroxysmal AF (PAF), which refers to self-terminating episodes of recurrent AF; (2) persistent, which refers to AF present >7 days that requires an intervention with either medical or electric 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 patient with AF, but have no direct or clear relationship to the underlying pathophysiology. It is thought that triggers, most commonly arising from the PVs, 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.

Various forms of mapping, mostly in animal models, have identified 3 electric mechanisms of AF: focal AF in which AF is made, particularly as it relates to considering effectiveness of ablation, cardioversion, or drug therapy. From a clinical standpoint, AF is broken down into 1 of 3 clinical entities: (1) paroxysmal AF (PAF), which refers to self-terminating episodes of recurrent AF; (2) persistent, which refers to AF present >7 days that requires an intervention with either medical or electric 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 patient with AF, but have no direct or clear relationship to the underlying pathophysiology. It is thought that triggers, most commonly arising from the PVs, 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.

### Table 1. Current Antiarrhythmic Drug Therapy for Atrial Fibrillation

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Proarrhythmia</th>
<th>Other Significant Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC</td>
<td>Flecainide and propafenone</td>
<td>VT/VF; rapid atrial flutter</td>
<td>Rapidly conducting AF</td>
<td>CAD, hypertrophy</td>
</tr>
<tr>
<td>III</td>
<td>Sotalol and dofetilide</td>
<td>Torsade des points</td>
<td>Heart failure exacerbation and death (in those with CHF; hepatic injury (rare)</td>
<td>NYHA class IV CHF or class II/III with recent exacerbation; prolonged QT (Q tc&gt;500); and permanent AF</td>
</tr>
<tr>
<td>III</td>
<td>Dronedone</td>
<td>Torsade des points (rare), VT/VF</td>
<td>Lung toxicity, hepatic toxicity, thyroid toxicity, and optic neuritis (rare)</td>
<td>Liver failure and existing lung disease</td>
</tr>
<tr>
<td>III</td>
<td>Amiodarone</td>
<td>Torsade des points (rare)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; NYHA, New York Heart Association; VT, ventricular fibrillation; and V, ventricular tachycardia.
likely that the mechanism is determined by the underlying sub-
strate. The current status of genetics and molecular biology
of AF, as well the molecular electrophysiology of AF, is cov-
ered in detail elsewhere in this compendium. In what follows,

electric remodeling plays a role in trigger initiation. It has
been demonstrated that decreased I_{Ca,L}, I_{to}, and I_{kur}, as well
as increased I_{K1}, and I_{kACh}, and I_{ks} occur. In addition,
downstream second messenger regulation may play a role
through phosphorylation of target channels such as I_{Ca,L}. In
addition, calcium overload is important for substrate remodel-
ing as the cell is exposed to increased cellular calcium con-
centrations in microdomains of the heart at the higher rates
of AF. This elevated calcium concentration is thought to
activate calcium-dependent calcineurin, calcium/calmodulin
kinase II (CAMKII) system involved both in electric remodel-
ing and in initiating cell death pathways. Heat shock pro-
tein induction has also been reported to protect the heart from
the deleterious consequences of AF-related calcium remodel-
ing. 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.

Electric Remodeling in AF
Several electrophysiological substrates (in isolation or in com-
bination) have been observed in silico and in animal models
of AF, as well as humans with AF. These include shortening
of atrial effective refractory period (ERP), loss of rate adap-
tation of ERP (and action potential duration [APD]), slowed
atrial conduction, and heterogeneous conduction. These elec-

trophysiological substrates can occur via a variety of changes
or remodeling. It has been demonstrated that AF itself results
in changes in electrophysiology that promote further AF—so-
called AF begets AF.

Substrate Remodeling and Fibrosis in AF
Some forms of AF in both humans and animal models dem-
onstrate increased interstitial atrial fibrosis. Biopsy specimens
from the left atrium of patients with AF show interstitial fibro-
sis. The more longstanding the AF, the more pronounced
the fibrosis. Studies in humans, using electroanatomic map-
ping have demonstrated atrial fibrosis in the setting of heart
failure and in lone AF. In animals with heart failure–induced
AF from ventricular tachypacing, marked atrial fibrosis occurs
and has been demonstrated to provide the substrate for AF. Al-
though 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. First, in animal models re-
versal or prevention of fibrosis prevents AF; second, AF
substrate in the absence of any cellular electrophysiological abnormalities has been demonstrated in a transgenic mouse model of isolated atrial fibrosis; finally, it is been demonstrated that rapid atrial pacing of cardiomyocytes itself may stimulate fibroblast function.

The angiotensin system and transforming growth factor-β1 (TGF-β1) seem to play an important role in atrial fibrosis associated with heart failure models of AF, and in human AF associated with heart failure. Both angiotensin II and TGF-β1 are upregulated in response to stretch and to heart failure (independent of stretch). Inhibition of TGF-β1 signaling prevents atrial fibrosis in animal models and in vitro. In addition, isolated atrial fibrosis and AF have been demonstrated in a mouse model of TGF-β1 overexpression. Moreover, it seems that TGF-β1–induced atrial fibrosis is restricted to the atrium (in the absence of ischemia or infarction) within the heart in heart failure models. Consistent with this, our group has demonstrated recently that in failing human hearts, elevated atrial, but not ventricular, TGF-β1 expression is present and precedes the development of AF. Unlocking the signals that make the atria uniquely susceptible to TGF-β1–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 and also in electric remodeling. More generally, inflammatory markers have been demonstrated to be elevated in patients with AF. In the cardiovascular system, reactive oxygen species (ROS) have been shown to be derived primarily from nicotinamide adenine dinucleotide phosphate oxidase (NOX), mitochondrial xanthine oxidase (mito-oxid), and uncoupled endothelial nitric oxide synthase. Animal models have recapitulated these findings with production of superoxide and peroxide from activated NOX, mitochondrial xanthine oxidase (mitochondrial), and uncoupled endothelial nitric oxide synthase. In patients with AF, both increased NOX and endothelial nitric oxide synthase activity have been demonstrated. Animal models have recapitulated these findings with production of superoxide and peroxide from activated NOX, mitochondrial xanthine oxidase (mitochondrial), and uncoupled endothelial nitric oxide synthase. In patients with AF, both increased NOX and endothelial nitric oxide synthase activity have been demonstrated. The mechanism of downstream ROS is still being elucidated. Nuclear factor-kB signaling pathways, involving tumor necrosis factor-α, iNOS (inducible nitric oxide synthase), interleukin-1β, and MMPs (matrix matrix metalloproteinases), have been suggested to be regulated by ROS. The rennin–angiotensin–aldosterone system has been linked to ROS in various disease states. In vitro assays have demonstrated that angiotensin II can stimulate NOX activity through TGF-β1, and that inhibition of TGF-β1 blunted ROS formation as well. Angiotensin II increases peroxide production and NOX4 expression in human atrial tissue. Thus, rennin–angiotensin–aldosterone system–induced TGF-β1-SMAD pathway and TGF-β1–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 directly (eg, oxidized CAMKII) and indirectly through second messenger systems. Oxidized CAMKII is increased in the atria of patients with AF, and angiotensin II increases oxidized CAMKII in a mouse model. Figure 2 provides an overview of pathophysiologic mechanisms of AF and a more detailed discussion can be found elsewhere in this compendium.

Figure 2. Remodeling mechanisms in atrial fibrillation (AF). In red are listed potential drug targets. Additional details can be found in Tables 2 and 3 and in the text. CAMKII indicates calcium/calmodulin kinase II; CHF, congestive heart failure; HDAC, histone deacetylase-6; HSP, heat shock protein; L-type, dihydropyridine receptor; NADPH, nicotinamide adenine dinucleotide phosphate; PKCε, protein kinase C-ε; RAAS, rennin–angiotensin–aldosterone system; ROS, reactive oxygen species; RyR, ryanodine receptor; and TGF-β1, transforming growth factor-β1.

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 pathophysologic 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.

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 in cardiac MRI has been shown to correlate with areas of low voltage by electroanatomical mapping and fibrosis in the atrium. Patients with significant fibrosis have lower success rates of ablation. Recently, a potentially simpler approach involving cardiac magnetic resonance T1 mapping has also been introduced as a way to quantify atrial fibrosis. However, more data are needed in larger populations.
to determine the clinical use of such imaging in the management of patients with AF.

Noninvasive body-surface mapping of AF using 252 body-surface electrodes has been demonstrated recently in patients with atrial tachycardia and AF. The technique uses the inverse solution to construct local unipolar epicardial electrograms from body-surface ECG potentials in a single beat. With respect to AF, the data have suggested that electric 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.

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 and others. We have demonstrated the feasibility of a percutaneous catheter-based approach to optical mapping endocardially (C.E. Woods, MD, PhD, 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. The Ikur and IkACh are predominant in atrial myocytes; therefore, inhibition of these channels may selectively prolong APD in the atria. AVE0118 targets Ikur and has shown efficacy against

![Figure 3. Emerging imaging modalities for atrial fibrillation (AF).](image-url)

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 with permission of the publisher). B, Left atrial rotor with counterclockwise activation in human mapped computationally using the proprietary focal impulse and rotor modulation mapping system (RhythmView, Topera Medical, Lexington, MA; adapted from Narayan et al with permission of the publisher). C, Phase mapping of posterior human left atrium during paroxysmal AF showing 2 successive rotations of a rotor near the right pulmonary vein 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 with permission of the publisher). D, Endoscopic optical mapping of pulmonary 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 1 beat shown below (C.E. Woods, MD, PhD, unpublished data, 2013; courtesy of AUST Development, LLC). Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
AF. However, other studies have shown that Ikur blockade may paradoxically shorten APD by a complex interaction with increased I_{Ca,L} and I_{Ks}. Tertiapin-Q is a nonselective inhibitor of IkACh derived from the honeybee (Apis mellifera), and in a rapid atrial pacing model it reduced AF inducibility. In addition, Tertiapin-Q terminated AF in a vagally induced AF model. NTC-801 is the only available specific inhibitor of IkACh. 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, although it is important to note that the pacing frequencies were well below those of AF.

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

Mitigating calcium overload seems an attractive target for AF therapy. Although L-type Ca channel blockers reduce the likelihood of early recurrence of AF after cardioversion by attenuating changes in atrial ERP, they have no effect on AF in other settings (aside from their role as a rate control agent). Stabilizing the sarcopasmic reticulum ryanodine receptor-2 has also been proposed as an attractive alternative. Cardexolol decreases ryanodine receptor-2 open probability, and drugs based on its structure are in development. Another strategy for reducing the open probability of ryanodine receptor is to mimic FKBP12.6, so-called calstabin. The synthetic agent JTV-519 (K201) acts to promote FKBP12.6–ryanodine receptor-2 interaction and has been shown to reduce AF in dogs and mice. Clinical trials with this drug have been completed, but the data are not available (ClinicalTrials.gov Identifier: NCT00626652). Heat shock protein induction with orally administered geranylgeranylacetone has been shown to reduce calcium transient remodeling in a tachypacing model.

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 mi-tral regurgitation model of AF, ZP123 was found to improve conduction and reduce AF susceptibility; however, in a canine model of congestive heart failure in which there is profound interstitial fibrosis, the compound had no effect. It has also been reported that gene transfer of connexin 43 suppressed AF in a rapid atrial pacing porcine model. Phase II data in humans are 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 histone deacetylase-6 levels are increased in human AF and inhibition of histone deacetylase-6 by tubastatin-A protected against tachypaced electric remodeling.

Other nonclassical ion channel targets, which all possess some component of mechanolectric feedback, have been implicated recently in AF. 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. Although in theory these could involve AAD, in general they refer to agents that prevent structural remodeling. Angiotensin-converting enzyme inhibitor (ACEI) decreases fibrosis and AF in animal studies. Aldosterone inhibitors also reduce atrial fibrosis in rats. Translating these findings to humans has had mixed results. Several retrospective analyses of ACEI/angiotensin receptor blocker (ARB) studies demonstrate a trend of benefit in terms of reducing patients with incident AF with hypertension and heart failure. In addition, specifically in patients with left ventricular hypertrophy, the prospective Losartan Intervention For End point reduction in Hypertension (LIFE) demonstrated reduced new onset AF, cardiovascular morbidity and mortality, and stroke. ACEI has also been associated with reduced AF after myocardial infarction in patients with low ejection fraction, and fewer relapses of AF in patients with congestive heart failure. A meta-analysis of ACEI/ARB studies in AF has shown that inhibition of the rennin–angiotensin–aldosterone system may be effective at preventing AF in heart failure and those with hypertension and left ventricular hypertrophy, although these were retrospective studies not designed with a primary outcome of AF. Aldosterone inhibition as compared with ACEI has been compared in a randomized fashion, and it was found that both conferred the same AF recurrence rate in patients with PAF. However, the recently published Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) trial, a prospective randomized trial of the ARB olmesartan aimed at AF specifically did not show any decrease in AF burden or time to recurrence or progression to chronic AF. As mentioned above, TGF-β1 seems to play a central role in atrial fibrosis in conjunction with rennin–angiotensin–aldosterone system, 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-β1 directly and also reduce tissue fibrosis in experimental animal models in multiple tissue types. However, there are no clinical studies using this agent to treat AF in humans.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vernakalant</td>
<td>Nonelective</td>
<td>Phase IV trial</td>
</tr>
<tr>
<td>S107</td>
<td>RyR stabilization</td>
<td>No human data</td>
</tr>
<tr>
<td>JTV-519 (K201)</td>
<td>RyR stabilization</td>
<td>RCTs terminated, data not available</td>
</tr>
<tr>
<td>NTC-801</td>
<td>IkACh inhibition</td>
<td>Phase II, data not available</td>
</tr>
<tr>
<td>MK-0448</td>
<td>Ikur inhibition</td>
<td>Failed to alter ARP in humans</td>
</tr>
<tr>
<td>ZP123</td>
<td>Gap junction stabilization</td>
<td>Phase II terminated</td>
</tr>
<tr>
<td>GAP-134</td>
<td>Gap junction stabilization</td>
<td>Phase I completed</td>
</tr>
</tbody>
</table>

ARP indicates atrial refractory period; IkACh, acetylcholine-gated potassium current; Ikur, ultrarapid outward potassium current; RCT, randomized controlled trial; and RyR, ryanodine receptor.
Statins may exert a beneficial effect on AF by reducing inflammation independent of their HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibition. Simvastatin has been shown to reduce electric remodeling, AF duration, and fibrosis, as well as decreasing atrial fibroblast proliferation in animal models. C-reactive peptide has also been demonstrated to be reduced in patients with AF treated with statins. However, the data are less clear with regard to the effect of statins on clinical outcomes in AF. Retrospective data have established a trend in patients treated with statin therapy for reduced AF recurrences in patients with left ventricular systolic dysfunction. When examined prospectively, however, the role that statins play in AF prevention seems to be strongest in the postoperative cohort of patients studied. The Paroxysmal Atrial Fibrillation: Role of Inflammation, Oxidative Stress Injury and Effect of Statins (PAFRIOSEIS) trial is a prospective randomized trial currently recruiting to better test the hypothesis that statins prevent AF recurrences (ClinicalTrials.gov Identifier: NCT00321802).

Blunting pathological 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 angiotensin II. In an infarct mouse model, inhibition of oxidized CAMKII overexpression reduced aldosterone-dependent deleterious outcomes, and additional studies into AF seem warranted. Alda-1, a small molecule activator of aldehyde dehydrogenase II, has been shown to reduce oxidative stress in myocardial infarction and cardiac arrest in a CAMKII-dependent fashion (C.E. Woods, MD, PhD, unpublished results, 2013). Protein kinase C-ε inhibitors are attractive because not only have they been shown to reduce oxidative stress but they also may reduce IkACh.

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, cardiomyopathic remodeling, arrhythmia remodeling, genetic models of catecholamine-induced polymorphic ventricular tachycardia, and AF. However, there have been no studies using 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 before 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. AF ablation approaches have evolved during the past 2 decades to a consensus that PV antral isolation (or wide-area circumferential isolation [WACA]) is the most efficacious approach. The major key to optimizing success seems to be the presence of robust and persistent electric isolation of the PVs with lesions that isolate not only 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). Using these definitions, single procedure success is estimated at 60% to 80% when sampling multiple trials, with success rate off AAD of ≈71%. In longer term follow up, the recent MANTRA-PAF (Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation) study validated this benefit of ablation but found it similar in comparison with that of AAD therapy. Yet, although the cumulative burden of AF was similar between AAD and ablation at 2 years, both the burden of AF and the percentage of patients free from AF were better in the ablation group at

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Possible Clinical Agents</th>
<th>Affect on AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAAS inhibition</td>
<td>ACEI/ARB</td>
<td>Limits fibrosis and AF in animal models</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retrospective data promising, mostly in patients with HF or HTN</td>
</tr>
<tr>
<td></td>
<td>Aldosterone</td>
<td>Prevention of fibrosis in animal models</td>
</tr>
<tr>
<td></td>
<td>Statin</td>
<td>Same recurrence as ACEI in head-to-head trial</td>
</tr>
<tr>
<td></td>
<td>HMG-CoA reductase</td>
<td>Prevents AF in animal models</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Association data humans mostly</td>
</tr>
<tr>
<td></td>
<td>Ca/CAMKII inhibition</td>
<td>No current agents</td>
</tr>
<tr>
<td></td>
<td>ROS inhibition</td>
<td>No current agent</td>
</tr>
<tr>
<td></td>
<td>PKCe inhibitors</td>
<td>Constitutive IkACh by PKCe in human AF</td>
</tr>
<tr>
<td></td>
<td>Heat shock proteins inducers</td>
<td>Prevents fibrosis and AF in animal models</td>
</tr>
<tr>
<td></td>
<td>Histone deacetylase-6 inhibitors</td>
<td>Prevents fibrosis and AF in animal models</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ANTIPAF, Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation; ARB, angiotensin receptor blocker; CAMKII, calcium/calmodulin kinase II; HF, heart failure; HTN, hypertension; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; IkACh, acetylcholine-gated potassium current; PAF, paroxysmal atrial fibrillation; PAFRIOSIES, Paroxysmal Atrial Fibrillation: Role of Inflammation, Oxidative Stress Injury and Effect of Statins; PKC, protein kinase C; RAAS, rennin–angiotensin–aldosterone system; ROS, reactive oxygen species; and TGF-β, transforming growth factor-β.
the 2-year mark (85% versus 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 (CABANA; Clinical Trial.gov identifier NCT00911508). Cumulative complication rates historically have been reported as high as $\approx 5\%$ to 6% of patients. However, it is thought that with experienced operators using newer and improved equipment (circular mapping catheters, electroanatomic mapping with computed tomographic guidance, esophageal monitoring, and intracardiac echo), major complication rates are approximately $<2\%$.

Figure 4. Current approaches to atrial fibrillation (AF) ablation. A to D, Schematic drawing of the left and right atria as viewed from the posterior showing common approaches to AF ablation. In some cases, >1 approaches (or combination of approaches in a step-wise fashion) are performed. A, Wide-area circumferential ablation—antral pulmonary vein (PV) isolation. Ablation of the PV antra to electrically isolate PVs. 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. End points for ablation are bidirectional conduction block into and out of PVs and intact circumferential lesions. B, PV segmental ostial ablation. Ablation of each PV ostium is done to achieve the same end points 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 after recurrence), linear lesions are added to PV isolation. These are typically roof lines and mitral annular ablation. Addition of these ablation lines significantly increases the risk of postprocedure atrial flutter. Confirmation of integrity and completeness of the line are important to minimize atrial flutter occurrence. Additional variations are also depicted showing a roof line connecting 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 superior vena cava. D, Complex fractionated electrogram (CFE) ablation. Common sites of CFEs are shown in the figure and an example of a CFE. E, Ganglionic plexi (GP) ablation. The left atrial autonomic GP and axons (superior left GP, inferior left GP, anterior right GP, inferior right GP, and ligament of Marshall) are shown in gray. Ablation of GPs is performed either by empirical 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 Calkins et al$^{129}$ with permission of the publisher). Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
with cardiac tamponade occurring <2% of the time, whereas transient ischemic attack/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. 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 radiofrequency (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. No randomized studies comparing efficacy of RF with cryoballoon have been completed. However, 2 trials asking this question are in planning stages (Cryoballoon versus Irrigated Radiofrequency Catheter Ablation: Double Short versus 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 [CryoVs RFA]; ClinicalTrials.gov Identifier: NCT01038115). Although no comparison of complications between cryoballoon and RF has been completed in a randomized fashion, rates seem to be largely similar, although phrenic nerve palsy is more frequent with the cryoballoon. A recent study demonstrated that esophageal injury as visualized by postprocedural gastroesophagoscopy can be minimized by targeting esophageal temperatures >12°C with 100% sensitivity. No randomized studies comparing efficacy of RF with cryoballoon have been completed. However, 2 trials asking this question are in planning stages (Cryoballoon versus Irrigated Radiofrequency Catheter Ablation: Double Short versus 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 [CryoVs RFA]; ClinicalTrials.gov Identifier: NCT01038115). Although no comparison of complications between cryoballoon and RF has been completed in a randomized fashion, rates seem to be largely similar, although phrenic nerve palsy is more frequent with the cryoballoon. A recent study demonstrated that esophageal injury as visualized by postprocedural gastroesophagoscopy can be minimized by targeting esophageal temperatures >12°C with 100% sensitivity.

Several 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 cardioselective visualization. Safety and efficacy data demonstrate ≥95% acute isolation in patients with PAF and a comparable freedom from AF to radiofrequency catheter ablation strategies of ≥70%. 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’ multielectrode-phased RF system to medical therapy. The efficacy reported for this device is similar to that reported for conventional radiofrequency catheter ablation. However, there is evidence of more PV stenosis and subclinical thrombosis with these catheters compared against standard irrigated ablation and cryoballoon. Irrigated versions of these multielectrode ablation catheters are in development, which are thought to obviate the problems associated with thrombosis.

**Targeting Substrate**

Pulmonary vein antral isolation (PVAI) is less beneficial for persistent AF where efficacy is ≤50%. To improve on outcomes in this population, WACA has been extended by targeting non-PV triggers, with empirical linear ablation of the roof or mitral isthmus, as well as by targeting complex fractionated atrial electrogram (CFAE), and rotors. In particular, the role of CFAE is controversial. There is some evidence that CFAEs may represent areas of wavebreak and functional block, and it has been speculated that these regions represent the wavefronts around stable rotors. Interestingly, standard WACA may target most CFAEs as well. However, the electrophysiological basis of CFAE is unknown and can be varied because of other phenomenon such as heterogeneous conduction or confluent activation wavefronts. Whether to target CFAEs and linear ablation has been addressed. For example, 2 recent randomized trials have compared broader ablation strategies versus PVAI alone. The Randomized Ablation Strategies for the Treatment of Persistent Atrial fibrillation (RASTA) study 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), a randomized comparison of ablation targeting using 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 are 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% versus 74% for RASTA and STAR-AF, respectively, having freedom from AF at 1 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 (Early treatment of atrial fibrillation for stroke prevention trial), AATAC-HF (Ablation versus Amiodarone for Treatment of Atrial Fibrillation in patients with Heart Failure), CASTLE-AF (Catheter Ablation versus Standard conventional treatment in heart failure patients with Left ventricular dysfunction and Atrial fibrillation), and SARA (Study of Ablation vs Antiarrhythmic Drugs in Persistent Atrial Fibrillation), are designed to address the question of hard end points 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 Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation (CONFIRM) trial, 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, areas identified as stable rotors were targeted for ablation. In combination with basket catheter (St Jude) contact mapping, focal impulse and rotor modulation mapping—based ablation+PVAI was compared against standard PVAI alone in a nonblinded fashion. In the computational mapping arm, targeting focal sources (e.g., 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. 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. This autonomic nervous system may be involved in triggering AF, particularly from non-PV sites.Traditionally, ganglionic plexi (GP) have been the focus, and it has been demonstrated that focal ablation of GP can terminate AF. In animal models, GP ablation also decreased acute AF vulnerability. Anatomically guided ablation of GP, rather than WACA, has been reported to have similar efficacy to PVAI alone, and in addition to PVAI has been reported to improve freedom from AF at 2 years by 20%. However, GP ablation is also common during WACA because of the anatomic proximity of them to the PVs. Electric stimulation of the autonomic nervous system as a way to modulate AF has been studied in animals and was shown to improve freedom from AF at 2 years by 78% and 84%, respectively. Whether endocardial, surgical, or hybrid ablation emerges as the commonplace 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% to 60% range until the arrhythmia mechanism and circuit became well defined, leading to current success rates of >95%. Whether it is substantiated or not, focal impulse and rotor modulation mapping–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.

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 ≥1 attempts at catheter ablation, or cannot undergo catheter ablation, or those with a low chance of success with traditional ablation. The Cox-Maze III procedure, or so-called cut and sew Maze, was introduced in 1987. Isolated, nonrandomized, and noncontrolled studies have reported freedom from AF after this procedure >90%. The Cox-Maze IV procedure improved on this using custom devices that ablate tissue using RF (cryoablation), rather than the incisions of the original Maze. This technique has been shown to be equally efficacious in single center reports. A recent systematic review examining both Cox-Maze III and IV techniques reports that freedom from AF in patients with persistent AF was lower, although 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 1 year of 91%. 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%. Challenges for epicardial approach alone include inability to confirm entry or exit block, inadequacy of PV isolation particularly in the posterior left atrium, as well as mitral and cavitricuspid 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. Using this approach, freedom from AF at 1 year approaches 90% as reported from a recent meta-analysis. In this analysis, ≈80% of patients had persistent or long-standing persistent AF with mean left atrial diameters of 50 mm. 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 >50 mm of ≈70% where typical endocardial ablation performs poorly. Prospective trials are emerging. Two recent small randomized trials have been reported comparing PVAI alone to hybrid ablation in patients with persistent AF and long-standing persistent AF 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 1 and 2 years. More definitive trials are needed.

Whether endocardial, surgical, or hybrid ablation emerges as the commonplace 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.

Conclusions

AF is a complex, heterogeneous disease. Current therapy is aimed at palliating the disease. Research to better understand, subclassify, 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 pathogenesis 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 pathophysiological 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 also hopefully extend to persistent AF.

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