

## Contemporary Review

## Atrial fibrillation nomenclature, definitions, and mechanisms: Position paper from the international Working Group of the Signal Summit

Natasja M.S. de Groot, MD, PhD,<sup>1</sup> Andre Kleber, MD, PhD,<sup>2</sup> Sanjiv M. Narayan, MD, PhD,<sup>3</sup> Edward J. Ciaccio, PhD,<sup>4</sup> Olaf Doessel, PhD,<sup>5</sup> Olivier Bernus, MD, PhD,<sup>6</sup> Omer Berenfeld, PhD,<sup>7</sup> David Callans, MD, PhD,<sup>8</sup> Vadim Fedorov, PhD,<sup>9</sup> John Hummel, MD, PhD,<sup>10</sup> Michel Haissaguerre, MD, PhD,<sup>11</sup> Andrea Natale, MD, PhD,<sup>12</sup> Natalia Trayanova, PhD,<sup>13</sup> Peter Spector, PhD,<sup>14</sup> Edward Vigmond, PhD,<sup>15</sup> Elad Anter, MD<sup>16</sup>

## ABSTRACT

The international Working Group of the Signal Summit is a consortium of experts in the field of cardiac electrophysiology dedicated to advancing knowledge on understanding and clinical application of signal recording and processing techniques. In 2023, the working group met in Reykjavik, Iceland, and laid the foundation for this manuscript.

Atrial fibrillation (AF) is the most common arrhythmia in adults, with a rapidly increasing prevalence worldwide. Despite substantial research efforts, advancements in elucidating the underlying mechanisms of AF have been relatively modest. Since the discovery of pulmonary veins as a frequent trigger region for AF initiation more than 2½ decades ago, advancements in patient care have primarily focused on technologic innovations to improve the safety and efficacy of pulmonary vein isolation (PVI). Several factors may explain the limited scientific progress made. First, whereas AF initiation usually begins with an ectopic beat, the mechanisms of initiation, maintenance, and electrical propagation have not been fully elucidated in humans, largely owing to suboptimal spatiotemporal mapping. Second, underlying structural changes have not been clarified and may involve different types of reentry. Third, inconsistent definitions and terminology regarding fibrillatory characteristics contribute to the challenges of comparing results between studies. Fourth, a growing appreciation for phenotypical differences probably explains the wide range of clinical outcomes to catheter ablation in patients with seemingly similar AF types. Last, restoring sinus rhythm in advanced phenotypic forms of AF is often not feasible or may require extensive ablation with minimal or no positive impact on quality of life. The aims of this international position paper are to provide practical definitions as a foundation for discussing potential mechanisms and mapping results and to propose pathways toward meaningful advancements in AF research, ultimately leading to improved therapies for AF.

**KEYWORDS** Atrial fibrillation; Definitions; Mechanisms; Mapping; Treatment; Ablation

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From the <sup>1</sup>Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands, <sup>2</sup>John A. Paulson School of Engineering and Applied Sciences, Harvard University, Boston, Massachusetts, Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, <sup>3</sup>Cardiovascular Division, Cardiovascular Institute, Institute of Computational and Mathematical Engineering, Stanford University, Stanford, California, <sup>4</sup>Division of Cardiology, Department of Medicine, Columbia University, New York, New York, <sup>5</sup>Institute of Biomedical Engineering, Karlsruhe Institute of Technology, Karlsruhe, Germany, <sup>6</sup>University of Bordeaux, INSERM, CRCTB, U1045, IHU Liryc, Bordeaux, France, Cardiac Arrhythmia Department, Bordeaux University Hospital, INSERM, Bordeaux, France, <sup>7</sup>Center for Arrhythmia Research, University of Michigan, Ann Arbor, Michigan, <sup>8</sup>Cardiac Electrophysiology Section, Division of Cardiovascular Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, <sup>9</sup>Department of Physiology & Cell Biology, Bob and Corrine Frick Center for Heart Failure and Arrhythmia, The Ohio State University Wexner Medical Center, Columbus, Ohio, <sup>10</sup>Section of Electrophysiology, Division of Cardiovascular Medicine, Ross Heart Hospital, The Ohio State University Wexner Medical Center, Columbus, Ohio, <sup>11</sup>Department of Cardiac Electrophysiology and Stimulation, CHU Bordeaux, Pessac, France, <sup>12</sup>Texas Cardiac Arrhythmia Institute, St David's Medical Center, Austin, Texas, Metro Health Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio, Department of Biomedicine and Prevention, Division of Cardiology, University of Tor Vergata, Rome, Italy, <sup>13</sup>Department of Biomedical Engineering, Johns Hopkins University, Baltimore, Maryland, <sup>14</sup>University of Vermont College of Medicine, Burlington, Vermont, <sup>15</sup>University of Bordeaux, CNRS, Bordeaux INP, IMB, UMR 5251, IHU Liryc, Talence, France, and <sup>16</sup>Cardiovascular Division, Shamir Medical Center, Be'er Yaakov, Israel.

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## Introduction

The international Working Group of the Signal Summit is a consortium of experts in the field of cardiac electrophysiology dedicated to advancing knowledge on understanding and clinical application of signal recording and processing techniques. In 2023, the working group met in Reykjavik, Iceland, and laid the foundation for this manuscript.

Atrial fibrillation (AF) is the most common age-related arrhythmia, with a rapidly increasing prevalence worldwide, leading to higher morbidity, mortality, and health care cost.<sup>1</sup> Despite extensive research, progress in understanding the mechanisms of AF has been limited, and current treatments remain only moderately effective. Efforts have primarily focused on technologic advancements to increase safety and efficiency, with limited impact on efficacy.

Since Haïssaguerre and colleagues discovered triggering of AF by foci within the pulmonary veins nearly 3 decades ago, pulmonary vein isolation (PVI) has become the cornerstone of AF therapy.<sup>2–4</sup> The success rate of PVI ranges between 40% and 75% at 1-year follow-up and is largely dependent on patient characteristics (phenotype), the intensity of rhythm monitoring, and the definition of success.<sup>5</sup> Apart from PVI, no additional ablation strategies have shown a reproducible incremental benefit to clinical outcomes.

Progress in AF outcomes has been hampered by a stagnation in understanding the mechanisms of human AF. In addition, comparisons between results have been difficult because of inconsistent definitions and terminology regarding fibrillatory characteristics and mechanisms. The goal of this document is to provide a clear framework for AF-related nomenclature, definitions, and potential mechanisms to accelerate progress in AF treatment.

## Part I. Practical definitions

This section aims to provide definitions as a foundation for discussing potential mechanisms and mapping results. These definitions are designed as an impartial summary of various hypotheses proposed for AF initiation and perpetuation as well as substrate features (Figure 1). Detailed discussions on mechanisms are presented in Part II.

### List of definitions

**Atrium:** refers to the morphologic atrial structure, which includes both muscular and sinus venosus-derived structures (the pulmonary veins, superior caval vein, coronary sinus, and vein of Marshall).<sup>6,7</sup>

**Atrial fibrillation (AF):** a rhythm in which at least 1 portion of the atria is activated by non-sinus waves, which themselves vary in space over time (spatially and temporally unstable).<sup>8</sup> Atrial rates are rapid and variable but are typically higher than 300 waves per minute (>5 waves per second).

**Source:** an atrial location from which an activation wave or waves emerge during AF and spread into the neighboring myocardium.<sup>8,9</sup>

### Abbreviations

AF: atrial fibrillation

PVI: pulmonary vein isolation

**Trigger:** electrical impulses leading to the onset of AF from a nonfibrillatory rhythm.<sup>2</sup>

**Driver:** electrical phenomenon critical to AF perpetuation.<sup>10,11</sup> Driver wavefronts expand into the surrounding tissue and can be spatially and temporally stable or unstable; their elimination should reduce the ability to sustain AF.

**Reentry:** a depolarization pattern whereby the trajectory of at least 1 proportion of the depolarization wave forms a closed path. This closed path is a looped pathway, protecting the reentrant wavelet from external wavefronts. The head of a circulating excitation wave reactivates an area following its own tail when recovered from refractoriness.<sup>10,12</sup> The length of the closed path ranges between millimeters (microreentry) and centimeters (macroreentry).<sup>13</sup> Reentry around a nonexcitable tissue is termed an anatomic reentry, and reentry around an excitable tissue is termed a functional reentry. Atrial tissue is expected to present mixed forms of reentries where the well-established forms of functional and anatomic reentries represent the opposite extremes of excitability in the central area of the rotation. Importantly, tissue structure has a major impact on reentry circuits. For example, the anisotropic structure of the myocardium will introduce elliptic shapes of functional circles, and contiguous connective tissue sheets or scars will lead to so-called excitable gaps, separating the tail of the preceding wavefronts and the head of the next reentrant wave.<sup>14,15</sup>

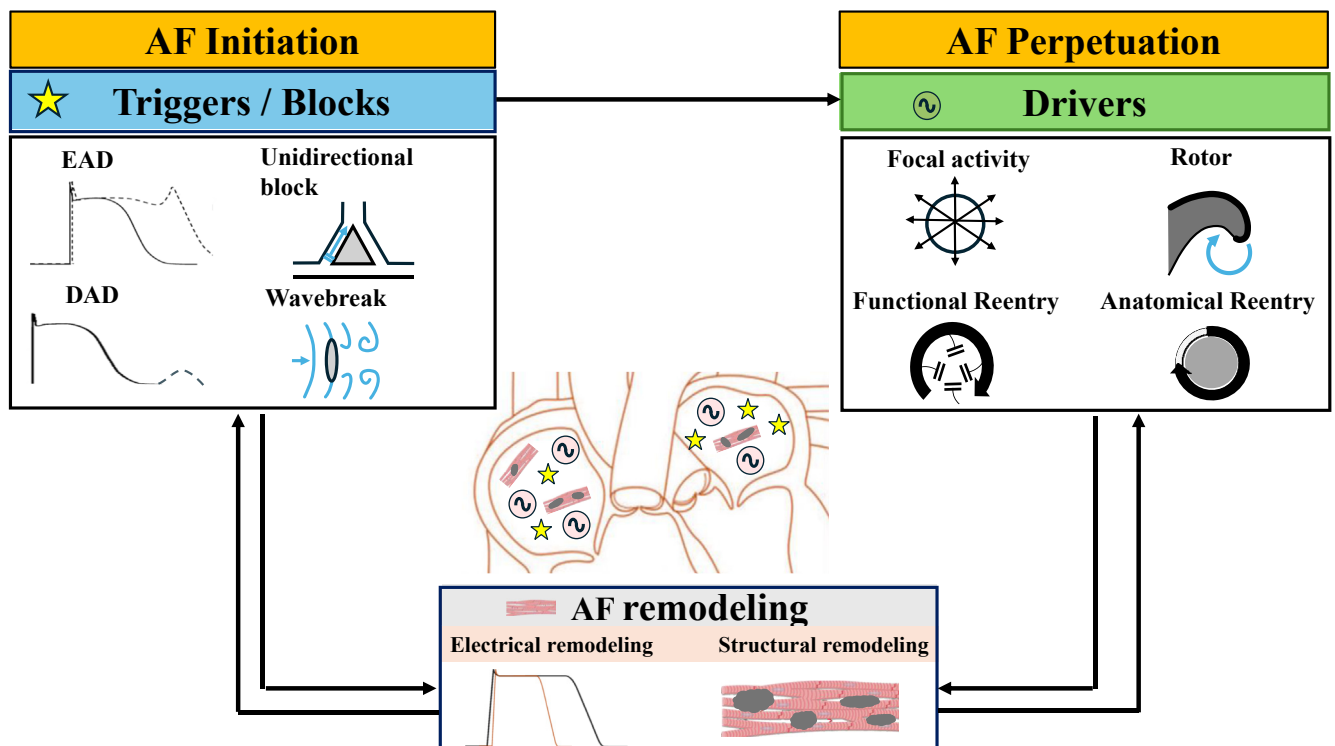
**Rotor:** a 2-dimensional functional reentry circuit consisting of spiral wavefronts that emanate from a core area surrounding the pivoting center of the wave. This central core area is excitable but is not excited during the rotation.<sup>10,12</sup> Wavefronts of rotors self-organize as spirals with reduced curvature and increased velocity toward the periphery of the rotor, where they assume a maximal velocity of a planar wavefront.<sup>16</sup> A rotor can be recognized by the convergence of iso-transmembrane potential or isophase lines toward its pivoting center point.<sup>17,18</sup> Rotors can be meandering or stationary, anchored at regions of slow conduction or gradients of refractoriness or at structural discontinuities.<sup>16,18,19</sup> Rotors and spiral waves are often used as synonyms.

**Resolution:** the smallest change that can be detected in the temporal, spatial, frequency, and voltage domains of signals. In atrial signals, the temporal and voltage resolutions are determined by the recording system properties of sampling rate, gain, and filtering.<sup>20</sup> Current electrophysiology mapping systems have a temporal sampling rate between 1 and 4 kHz and various gain and filtering options. The frequency resolution is determined by the inverse of the recording duration. The spatial resolution is determined by the catheter's electrode size, interelectrode spacing, and accuracy of assigning electrograms on a reconstructed anatomy.

**Substrate for AF:** atrial tissue with structural and/or functional properties that promote initiation and maintenance of AF.<sup>21,22</sup>

## Part II. Basic mechanisms of AF

Mechanisms of AF can be discussed at various functional scales from molecular to tissue, whole heart, individual, and

**Figure 1**

Schema demonstrating the complex interrelationship between triggers, propagation patterns, drivers, and substrate remodeling that contribute to initiation and perpetuation of atrial fibrillation (AF). DAD = delayed afterdepolarization; EAD = early afterdepolarization.

population levels. This section focuses on the level of human atria, referencing relevant experimental works.

Several mechanisms for human AF have been proposed (Figure 1), but none have been definitively established.<sup>2,10,12,18,19,23-30</sup> Multiple mechanisms probably exist and coexist in human AF, and several may coexist in the same patient, depending on the specific substrate. Defining these mechanistic groupings in individual patients could form the basis for "AF mechanistic phenotypes" having unique clinical characteristics and different clinical outcomes.<sup>31</sup>

### Triggers of AF and mechanisms of initiation

Atrial premature complexes (APCs), frequently emerging from the pulmonary vein orifices, are recognized to initiate AF in humans.<sup>2</sup> APCs from other locations have also been shown to initiate AF in humans.<sup>32</sup> The mechanistic hypothesis of APCs relates to cellular  $\text{Ca}^{2+}$  overload and disturbances in  $\text{Ca}^{2+}$  cycling, leading to delayed afterdepolarizations.<sup>33,34</sup> However, because of limitations in mapping intracellular and extracellular potentials and spatial activation patterns, this hypothesis is used primarily for conceptual understanding.<sup>33,34</sup> The APC could then lead to the initiation of reentry.<sup>32</sup>

Short-duration, often self-terminating episodes of AF in normal atria can result from a high atrial rate, which shortens refractory periods, elevates intracellular  $\text{Ca}^{2+}$ , and allows a rapid sequence of electrical excitations.<sup>35</sup> Sustained episodes of AF often involve changes in the electrical cellular phenotype (through ion channel remodeling), cell-cell connectivity, and extracellular connective tissue.<sup>21,22</sup> These changes,

collectively termed atrial remodeling, increase electrical heterogeneity and propagation complexity, promoting the maintenance of atrial reentries.

The autonomic nervous system, through interactions between the sympathetic and parasympathetic systems, also plays a role in AF initiation.<sup>36-39</sup> Experimental data in animals show that paroxysms of AF can occur after an increase in sympathetic tone or a decrease in parasympathetic tone.<sup>37,38</sup> In humans, vagal stimulation is well established to promote AF, although transcutaneous low-level vagal nerve stimulation may reduce the AF burden.<sup>40-42</sup> The mechanisms by which the autonomic nervous system promotes AF are not fully elucidated and appear to be multifactorial, promoting triggered activity due to delayed afterdepolarizations and atrial remodeling.<sup>35,37-39</sup>

### Atrial remodeling

Atrial remodeling promotes AF by acting on fundamental arrhythmia mechanisms, including both ectopic activity and reentry.<sup>9,22</sup> Sustained rapid atrial activation during AF reduces action potential duration by diminishing the inward L-type  $\text{Ca}^{2+}$  current and enhancing the outward  $\text{K}^{+}$  current, thereby shortening the path length needed to sustain a reentrant circuit.<sup>35,43,44</sup> Reentry is also promoted by conduction slowing due to alterations in sarcolemmal  $\text{Na}^{+}$  channels, cell-to-cell coupling, and tissue structure.<sup>9,43,44</sup> Structural changes, which include fibrosis and atrial dilation, cause discontinuous conduction and increase the surface area to host complete reentrant circuits.<sup>22</sup> Importantly, all these elements work in concert

to decrease the tissue wavelength, increasing the likelihood of maintaining reentry.

### Reentrant mechanisms in AF

Macroreentry was first described by Mines<sup>45</sup> at the beginning of the 20th century. The principle was based on electrical excitation circulating around an anatomic obstacle.<sup>46,47</sup> Later, it became evident that the center of circulating excitation could also consist of an excitable but transiently refractory tissue.<sup>10,12</sup> This led to the concept of the "leading circle," describing the smallest circumference on which excitation could circle around a transiently refractory center.<sup>12</sup> A further advancement in understanding reentry and its relationship to fibrillation was the realization that a rotating excitatory wave can be initiated in homogeneously excitable tissue without obstacles.<sup>10-12</sup>

Functional reentry in such scenarios self-organizes following a wavebreak due to refractory substrate in the wake of another wave. Propagation velocity of the circulating wavefront is in general terms affected by the excitability of the downstream unexcited region at each moment and the curvature of the excited upstream region. Rotating excitatory waves assume a spiral shape, with the velocity at the depolarizing front decreasing as curvature increases toward the center of rotation until a propagation block may occur and the repolarization of the wave is initiated. Analogous to phenomena in physics, the functional center of such rotation has been termed a phase singularity point because all the phases of the excitatory cycle (resting, depolarization, plateau, and repolarization) converge toward a virtual single point. Within the area of a rotor, the cycle length is approximately constant, except during initiation, termination, and drifting.<sup>30,48,49</sup>

Shorter reentrant circuits act as the highest dominant frequency sources that can maintain overall activity. Rapidly succeeding wavefronts from these sources propagate through both atria, interacting with anatomic or functional obstacles, potentially leading to "vortex shedding" and new wavebreaks and wavelet formation.<sup>18,23,50-52</sup> However, whereas rotating waves have been observed in human AF,<sup>19</sup> there is limited evidence supporting vortex shedding as a mechanism for AF maintenance. Of note, the number of electrodes used during rotor mapping is critical as use of a low number of electrodes may be associated with a high probability of false detection of the phase singularity.

Experimental studies have shown an average of 3–4 waves simultaneously existing that become fully closed and reenter the original site.<sup>53</sup> A similar number of waves has also been observed in humans by Haïssaguerre and coworkers.<sup>54</sup> Experiments using panoramic biatrial optical mapping of vagally mediated AF found that an average of 2 rotors during each second contributed to vagally mediated AF sustenance.<sup>30</sup> Results in humans with use of nonoptical mapping tools have not unequivocally demonstrated the presence of multiple, fully closed reentrant circuits. Instead, multiple partial and not fully reentrant circuits have been observed, potentially emerging from mother waves and highlighting the phenomenon known

as fibrillatory conduction.<sup>53</sup> As mentioned in Part I, circulating waves interact with structural inhomogeneities, suggesting that they can be a mixed form of functional rotors and anatomic reentries, with possible transformation between these 2 reentry patterns types.

### Maintenance of AF by reentrant mechanisms

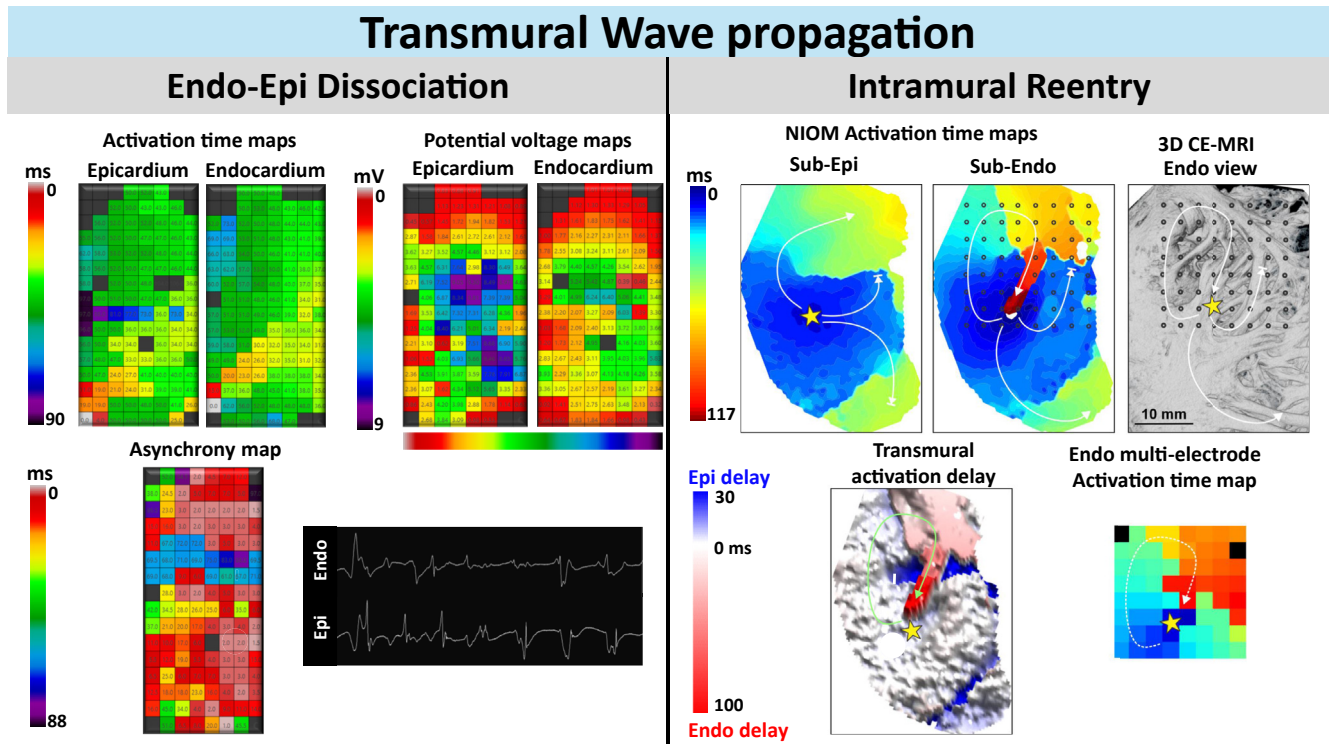
#### Transmural wave propagation

Mapping studies during AF in humans have demonstrated the presence of focal waves, defined as "new" fibrillatory waves that emerge in the middle of the mapping area and cannot be explained by propagation of the fibrillatory wave in the 2-dimensional mapped plane.<sup>55</sup> These were characterized by wide distribution, nonrepetitiveness, and waveforms starting with an R wave. Whereas these features may suggest a focal origin, they can also be explained by transmural conduction with endocardial and epicardial breakthroughs and endocardial-epicardial asynchrony (Figure 2, left panel). Simultaneous endocardial-epicardial mapping studies revealed that asynchronous transmural wavefront propagation underlies the mechanism of most focal waves (65%).<sup>25</sup> Simultaneous endocardial-epicardial mapping of isolated canine atria during atrial tachyarrhythmias found focal activation patterns simultaneously present on the endocardium and epicardium, separated by 1.5 cm.<sup>56</sup> These focal activation patterns could be attributed to small transmural circuits using free-running bundles connecting the endocardium and epicardium. Further evidence supporting reentry has been obtained with near-infrared simultaneous subendocardial and subepicardial optical mapping studies during induced AF in explanted human right atria and during persistent AF in both atria (Figure 2, right panel).<sup>26-29,57</sup> These studies have demonstrated the presence of intramural reentrant circuits within 3-dimensional (3D) fibrotic insulated myocardial bundles, causing transmural activation delays up to 105 ms.

Histologically validated 3D contrast-enhanced magnetic resonance imaging (MRI) of optically mapped AF driver regions suggests the 3D driver substrate or arrhythmogenic fibrotic hubs with anisotropic reentry pathways formed by the combination of intramural fibrotic strands, misaligned epicardial-endocardial myofibers (myofiber discontinuity), and varying atrial wall thickness.<sup>57</sup> The microanatomic intramural reentrant circuits within fibrotic hubs are composed of not 1 but several distinct reentrant paths. These circuits include the common track for preferential conduction in addition to several possible return paths to complete the reentry (Figure 2, right panel).

Ablation targeting these microanatomic reentrant tracks resulted in termination of AF, continuation of AF by another intramural driver, or conversion of AF into macroreentrant tachycardia. Additional studies have shown that the shape of rotating waves is strongly affected by the anisotropy of the cellular network, with connective tissue acting as boundaries and anchors for rotors.<sup>52,58</sup> These findings suggest that intramural reentry circuits may drive the fibrillatory process.<sup>27,28</sup>



**Figure 2**

Left: Simultaneously obtained opposite endocardial-epicardial local activation maps and potential voltage maps constructed during atrial fibrillation (AF); corresponding electrical asynchrony map shows asynchrony up to 88 ms. Examples of opposite endocardial-epicardial electrograms are demonstrated outside the map and clearly show the asynchronous activation. Right: Simultaneously obtained opposite subendocardial and subepicardial activation maps obtained by near-infrared optical mapping (NIOM;  $350 \times 350 \mu\text{m}$  resolution) during AF show focal breakthrough activation with star on subepicardial map and complete reentry common path of microanatomic reentry with solid green arrow on subendocardial map. Corresponding transmural activation delay map shows up to 100-ms subendocardial delayed activation along the common path of the reentry; 3-dimensional high-resolution contrast-enhanced magnetic resonance imaging (3D CE-MRI;  $95 \mu\text{m}^3$  voxel size) defines intramural common reentrant track formed by several fibrotically insulated subendocardial-intramural myocardial bundles. Targeted ablation of the common path of microanatomic reentry terminated persistent AF, confirming driver mechanism.

### Maintenance of AF by focal mechanisms

Whereas there is mounting evidence for reentrant excitation waves as drivers for AF, the role of focal excitation is less certain. This uncertainty may be partially due to the mapping resolution's being too low to resolve excitation patterns at the millimeter level. In a seminal experiment by Spach and colleagues,<sup>59</sup> microreentry was demonstrated in explanted fibrotic human atrial trabeculae. Premature stimulation induced a small excitation wave along the transverse axis of the anisotropic cellular network, which reentered the tissue along its longitudinal axis within a scale of 2–3 mm.

Focal ectopic electrical excitation may originate from abnormal cellular automaticity. It is generally assumed that alterations of cellular  $\text{Ca}^{2+}$  cycling can produce afterdepolarizations.<sup>36</sup> However, whether action potentials emerging from afterpotentials, often recorded from single cells, can excite a wider cardiac tissue has not been resolved. In multicellular tissue, triggering of action potentials by early or delayed afterdepolarizations requires synchronization of changes in the membrane potential between multiple cells. Importantly, the strength of the depolarizing current of the source has to overcome the electrotonic (repolarizing) effect of the surrounding nonexcited tissue (current to load mismatch).<sup>60,61</sup> This may explain why triggered activity observed in single

cells or cell clusters is not regularly observed in whole contiguous cellular networks.<sup>33</sup> Tissue decoupling, as caused by fibrosis, reduces the surrounding sink and may make triggered activity easier to be manifested.

## Part III. Electrical mapping of AF

### Methodologic aspects

Cardiac mapping aims to characterize spatiotemporal patterns of cellular electrical excitation but is not measured directly. Instead, it is deduced from extracellular potentials. Potentials recorded from a single electrode (vs an indifferent reference electrode) represent a summation of complex electrical activity from the underlying excited tissue ("local" intrinsic activity) and electrically active in remote tissue ("extrinsic" component). For a critical appraisal of the impact of signal recording and processing technologies on potential morphology, we refer to a recent position paper.<sup>20</sup>

AF mapping is challenging because of spatiotemporal instability and associated changes in multiple excitation waves and signal morphology (Table 1). In addition, during AF, varying excitation delays between cells and cell groups beneath the recording electrode result in fractionated potentials,<sup>62</sup> hampering accurate determination of local activation

**Table 1** Considerations in mapping of AF

| Arrhythmia-related considerations                                                                                                                          | Mapping/technology-related considerations                                                                                                                                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Spatiotemporal instability<br>Endocardial-epicardial dissociation<br>Anatomic and functional reentries<br>Focal mechanisms participating in AF maintenance | Lack of propagation reference<br>Choice between temporal and spatial resolution<br>Inadequate catheter designs, electrode size, and distribution<br>2-dimensional (surface) mapping of a 3-dimensional arrhythmia<br>Limited spatial resolution<br>Lack of definitions with respect to electrogram morphology |

AF = atrial fibrillation.

times.<sup>63</sup> Current mapping approaches are limited to surface recordings on either the endocardium or epicardium, restricting understanding of transmural activation. This limitation is particularly relevant to remodeled atria with complex 3D activation of atrial myofibers, separated by fibrosis, where transmural activation delays and complex activation pathways are increasingly important.<sup>21,43,44</sup> The activation complexities in AF render mapping tools used for organized tachycardias unsuitable and necessitate mapping techniques with high spatial and temporal resolution to define AF mechanisms and drivers better.

### Technologic considerations

#### Spatial and temporal mapping resolution

Cardiac mapping is a sampling methodology to obtain objective information about the propagation of electrical activation using a limited set of recordings. Optimization of spatial and temporal resolution depends on the complexity of the activation pattern. For continuous propagation, interpolation between sparsely distributed data points can be accurate. However, the more complex and discontinuous the activation pattern, the more closely spaced the recording points must be. In addition, most mapping approaches rely on sequential data acquisition, which is suboptimal for AF, in which activation patterns are continuously altered in time and space. Therefore, simultaneous acquisition across all sites is ideal for mapping AF. Temporal duration of data acquisition at 1 position of 2.5 seconds may not be sufficient, and acquisition during periods up to 10 seconds may help establish the temporal stability of extracted features.

Experimental and modeling studies have provided important information on spatiotemporal features of AF drivers, especially the periodic and meandering nature of reentries and the asynchronous endocardial-epicardial activation.<sup>19,25,27,28,64,65</sup> Near-infrared optical mapping (plane resolution of 0.3 mm) of AF in explanted human atria has indicated that the minimum spatial resolution to detect a reentry circuit is about 3 mm, although its impact on surrounding tissue (rotational activity) may be identified at lower resolution.<sup>66,67</sup>

In optical mapping studies, the adenosine triphosphate-regulated potassium channel opener pinacidil was used to obtain sustained AF by shortening of action potential duration. The temporal stability of an AF driver can be affected by dynamic interaction with other competing drivers.

Whereas several drivers may be active simultaneously, 1 reentrant driver may induce another and then be subsequently terminated by it.<sup>26</sup> Furthermore, beat-to-beat variability of the reentry path activation, due to a dynamic relationship between local conduction, refractoriness, and the structural substrate, may decrease or increase the perceived AF driver stability, spontaneously or during autonomic or pharmacologic modulation. AF drivers identified by 64-electrode basket catheters in clinical human cases and ex vivo human hearts showed wide temporal stability.<sup>68–70</sup> This stability is partially influenced by the AF type, with persistent AF having more drivers and more sustained reentrant and focal activities.

#### Global vs local mapping

In addition to achieving adequate mapping resolution to reconstruct activation patterns during AF accurately, the challenge remains in obtaining sufficient sampling density during beat-to-beat changes of activation patterns. Dense spatial resolution competes with the need for a global analysis of temporal stability. Two main approaches partially address this issue. The first approach combines global or whole atrial chamber mapping with higher resolution mapping of localized regions. The second approach involves local mapping at high spatial and temporal resolution, piecing together sequential maps to identify AF drivers. We recently reviewed the pros and cons of global and local mapping in detail and refer the reader to that document.<sup>20</sup>

### Part IV. Atrial imaging

#### Late gadolinium-enhanced MRI

Cardiac MRI of the atria for AF patients typically involves 3 techniques: magnetic resonance angiography to assess morphologic data, such as shape and volume; cine-MRI to obtain functional data, including strain and ejection fractions; and late gadolinium enhancement (LGE) to visualize structural remodeling, such as fibrosis and scar tissue.<sup>71</sup> However, imaging of the atria poses significant challenges, and there is currently no standardized approach for defining scar tissue.

Research using LGE has demonstrated that even AF patients with minimal comorbidities can exhibit some degree of fibrotic remodeling, including those with lone AF.<sup>72</sup> There is a correlation between fibrosis and AF severity, and patients with long-standing persistent AF exhibit more fibrosis than

those with paroxysmal AF.<sup>73</sup> Nonetheless, the cause-and-effect relationship between fibrosis and AF remains unclear, and only limited data support the notion that ablation of fibrotic tissue has a significant impact on long-term AF outcomes.<sup>74</sup> It is important to note the challenges in accurately quantifying fibrosis by LGE-MRI, particularly owing to its spatial resolution, as a single voxel may average healthy tissue, fibrotic tissue, and blood. Recent trials, such as the DECAF trial, have indicated that targeting atrial scar may not yield beneficial outcomes and could even pose risks to patients.<sup>74</sup> These factors underscore the need for continued research to establish clear definitions and standards in cardiac MRI of AF patients.

### Cardiac computed tomography

Computed tomography can identify atrial dilation, wall thickness alterations, and epicardial adipose tissue—all markers of structural remodeling.<sup>75</sup> Thin-walled areas are more susceptible to fibrosis,<sup>76</sup> disrupting normal conduction and promoting rotational activity.<sup>77</sup> In paroxysmal AF patients, thin-walled areas are independent predictors of low-voltage areas.<sup>78</sup> Thickened pulmonary vein–left atrial junction walls predict transition from paroxysmal to persistent AF and have been linked to complex fractionated electrograms and localized rotational activity, indicating a correlation between structural changes and the AF-related arrhythmogenic substrate.<sup>75,77</sup>

Epicardial fat is a distinct adipose tissue depot that can readily be assessed by computed tomography.<sup>79</sup> Adipocyte infiltration is associated with the presence, severity, and recurrence of AF.<sup>79,80</sup> Fat contributes to AF through multiple mechanisms, including promoting a proinflammatory state through the production of bioactive molecules like adipokines and cytokines, leading to structural and electrical atrial remodeling.<sup>81</sup> In addition, fat has been shown to cause an imbalance in the autonomic nervous system, contributing to AF development (see Part II).

### Modeling of the virtual atria and AF

Atrial geometry and fibrosis patterns imaged in a patient can be incorporated into a virtual model of the individualized atria.<sup>82</sup> This personalized model (digital twin) can then be used to induce AF through rapid stimulation and identify locations of rotors in the virtual model to understand the personal arrhythmia mechanisms better and to design a possible targeted ablation therapy. Atrial modeling studies suggest that the extent and distribution of atrial fibrosis may be determinants of AF initiation and maintenance.<sup>82–84</sup> In studies using patient-specific atrial geometry and fibrosis distribution derived from LGE-MRI, reentrant drivers during AF were localized in boundary zones between fibrotic and nonfibrotic atrial myocardium.<sup>85</sup> These zones exhibited a specific spatial fibrosis pattern characterized by high fibrosis density and entropy, corresponding to atrial areas with a high degree of intermingling between fibrotic and nonfibrotic myocardium. A 3D atrial computational model, based on ex vivo MRI and panoramic optical mapping at submillimeter resolution (0.18

mm<sup>3</sup> and 0.33 mm<sup>2</sup>, respectively), demonstrated that atrial structural fingerprints—consisting of a specific combination of intermediate wall thickness, transmural fibrosis, and twisted myofiber orientation—can identify locations of ex vivo AF drivers in humans (Figure 3).<sup>86</sup> Importantly, this simulation and preclinical data still require validation in randomized clinical trials, particularly to evaluate whether this approach can have an impact on outcomes.

### Part V. Impact on intervention: Ablation therapy

PVI has evolved to become an effective strategy in patients with paroxysmal AF, especially early in the course of the disease process.<sup>87,88</sup> PVI for the treatment of nonparoxysmal AF has not been as successful; recent analyses estimate the single-procedure success rate (12-month freedom from recurrent atrial arrhythmias) at 50%–60%, with modest improvements with new technologies.<sup>3,89</sup> This has led to interest in adjunctive ablation strategies (so-called PVI+) that include ablation of areas of complex fractionated electrograms, areas of low voltages, areas with low LGE-MRI signals, AF drivers identified by various mapping technologies, and empirical lesion sets. Whereas initial observational studies often suggested benefits, these strategies have largely not proved effective in randomized controlled trials.

The recent introduction of pulsed field ablation (PFA), developed largely to mitigate safety concerns with thermal energy delivery, has sprouted hopes that this energy delivery approach would be more efficacious.<sup>90</sup> However, current data suggest that although PFA may indeed reduce the risk of esophageal injury, it has not yet been associated with improved effectiveness in restoring and maintaining sinus rhythm. Furthermore, the ease and speed with which PFA destroys tissue could lead to increased tissue destruction and functional impairment. This underscores the need to further our understanding of AF mechanisms and to refine targeted interventions.

### Remaining issues

#### Clinical mapping

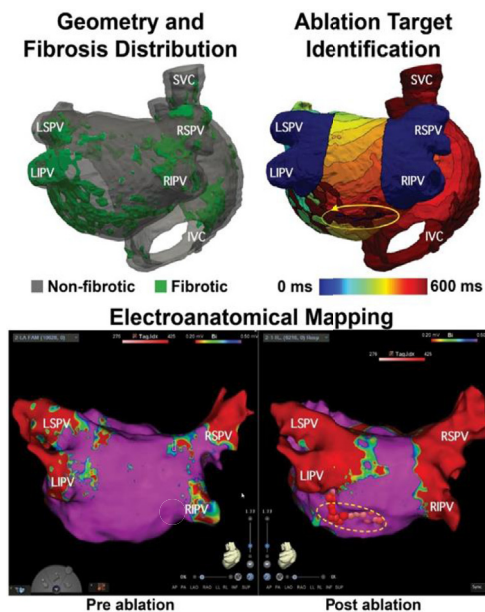
A major challenge in AF mapping is the continuously changing atrial activation patterns during AF. Most novel AF mapping systems aim to provide a high temporal resolution or high spatial resolution. The only proven methods to acquire maps with simultaneous high temporal and high spatial resolution are those that employ high-density recording electrodes over most surfaces of the atrium.<sup>55,91,92</sup> These methodologies usually require open surgical access and therefore have limited utility for clinical AF ablation. However, these data gathered in vivo in patients undergoing cardiac surgery or recorded from Langendorff-perfused explanted hearts from patients undergoing orthotopic cardiac transplantation have served as the cornerstone of our understanding of AF mechanisms.<sup>27</sup>

#### Ablation strategy

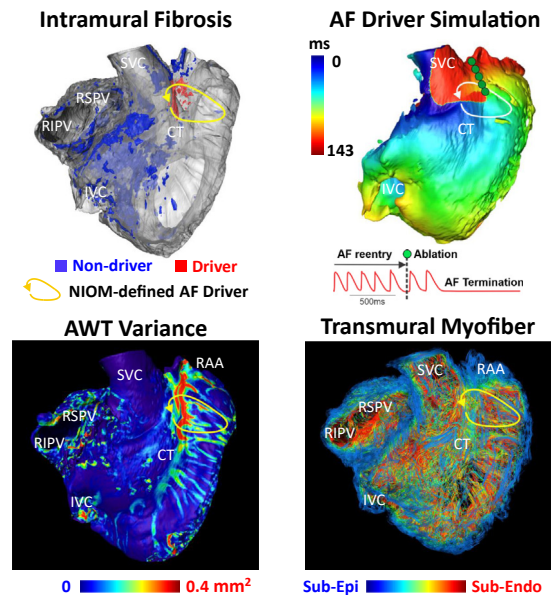
Even if AF drivers can be accurately identified by clinical mapping, the optimal strategy for ablation is still undetermined.

# MRI-based computational identification of AF driver substrate

## In-vivo



## Ex-vivo: 3D fingerprints of AF driver



**Figure 3**

In vivo: Computational guidance of atrial fibrillation (AF) ablation (OPTIMA approach).<sup>97</sup> Top: Patient-derived atrial geometry and fibrosis distribution (left). Activation map after rapid pacing and virtual pulmonary vein isolation ablation, with yellow arrow identifying reentry. Bottom: Sites of ablation delivery (with catheter tip locations marked by red dots) in the left atrium, as rendered by the CARTO intracardiac mapping system at the end of the clinical ablation procedure. The dashed ellipse indicates the locations ablated on the basis of the locations of persistent reentrant drivers, as identified by OPTIMA.

Ex vivo: Ex vivo human donor heart with persistent AF was mapped by panoramic near-infrared optical mapping (NIOM) with 4 CMOS cameras ( $100 \times 100$  pixels,  $0.3\text{--}1 \text{ mm}^2/\text{pixel}$  resolution) and contrast-enhanced magnetic resonance imaging (MRI; 9.2T with  $100 \mu\text{m}^3$  isotropic resolution). Top, left: The 3-dimensional (3D) distribution of intramural fibrosis in the NIOM-defined driver region (red) and the whole atria (blue). Bottom, left: The 3D atrial wall thickness variations. Bottom, right: The 3D transmural myofiber orientation from epicardium (Sub-Epi, blue) to endocardium (Sub-Endo, red). Top, right: The heart-specific 3D human atrial computer model reproduces reentrant AF driver (white arrow) defined by ex vivo NIOM in right atria (yellow arrow). The ablation strategy that created a linear transmural ablation lesion (green dots) through the driver reentrant track to the nearby physical border terminated AF, as seen in the atrial action potential recoding below.<sup>57,86</sup> AWT = atrial wall thickness; CT = crista terminalis; IVC = inferior vena cava; SVC = superior vena cava; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; RAA, right atrial appendage.

Different systems use various criteria to assign a level of importance to individual driver sites. Should solely drivers be the targets for ablation or additional lesions between nonconduction boundaries be created? If there is a common pathway of beat-to-beat variable reentrant circuits, would eliminating this common pathway terminate AF? What is the best method for determining the adequacy of ablation? For example, is it the inability to initiate AF, or is it the absence of AF drivers with repeated mapping? Addressing those variables may contribute to the difficulty of designing future clinical trials.

## Part VI. The future of AF therapy

This section addresses the primary unmet needs in AF mapping and explores potential future therapies. Despite significant efforts during the past several decades to enhance our understanding of the mechanisms underlying AF initiation and propagation, the quest for a cure is ongoing and necessitates reconsidering our current strategies.

We must acknowledge the progress that has been made. The increased availability of safe, effective, and efficient PVI

procedures has enabled treatment of a growing population at earlier stages of AF, likely having a positive global impact. However, significant challenges remain. First, for patients with paroxysmal AF, whereas PVI is effective for most, a substantial minority continues to suffer from AF. Second, in persistent AF, PVI alone results in suboptimal clinical outcomes, and additional ablation strategies have not consistently demonstrated efficacy.

Several factors may explain this lack of advancement. First, we have not yet identified the features that would accurately lead to 1 or several arrhythmogenic substrates or “core” whose elimination would prevent AF. Second, the presumed arrhythmogenic substrate is sometimes diffusely scattered across the atria, especially in phenotypes with advanced disease. Mapping studies have demonstrated the complex nature of the fibrillatory process: a high number of simultaneously present fibrillatory waves in small areas of atrial tissue (eg, 16 waves in  $4 \times 4\text{-cm}^2$  area), asynchronous endocardial-epicardial electrical activation (activation time differences of up to 50 ms) with opposite wavefronts propagating in different directions, and transmurally propagating



**Table 2** Essential features for AF mapping

| Feature                                                                                             | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| High resolution and density panoramic view                                                          | Electrical activity should be recorded from a large area, preferably both atria, to accurately determine AF sources or substrates. Currently, panoramic imaging and high spatial resolution cannot be obtained simultaneously. The precision of wavefront localization diminishes with increasing distance from the electrode. Whereas electrode arrays placed in the center of the atria or electrocardiographic imaging can provide a full panoramic view, this comes at the expense of high spatial resolution. |
| Simultaneous endocardial-epicardial or transmural mapping                                           | Even in the thin-walled atrial tissue, asynchronous electrical activation can occur, leading to transmural activation or intramural reentrant circuits. Therefore, simultaneous endocardial and epicardial or even transmural mapping provides the most accurate data on atrial excitation.                                                                                                                                                                                                                        |
| Extracellular unipolar potentials as a guide to localize dipole densities or transmembrane voltages | Theoretically, unipolar electrograms could be used as input for an inverse solver to determine the true location of current dipoles in the depolarization front or the distribution of transmembrane voltages. In addition, the degree of fractionation caused by the underlying substrate could be unambiguously determined, providing a better characterization of the AF-related substrate.                                                                                                                     |
| Differentiation of local from far-field signals                                                     | Unipolar electrograms, in principle, enable the exact determination of activation times (zero crossing), but they are often distorted by far-field signals. Transmembrane voltages can be used to unambiguously determine the timing of both depolarization and repolarization. Accurate recording of the local component of the extracellular potentials allows the determination of activation times with much greater certainty.                                                                                |
| Noninvasive mapping of atrial excitation                                                            | A noninvasive mapping technique with a high spatial resolution over both atria, capable of identifying AF mechanism, sources, and substrates.                                                                                                                                                                                                                                                                                                                                                                      |
| Automatic identification of AF mechanism and substrates                                             | The mapping system can automatically recognize underlying AF mechanisms, sources, and substrates, providing explanations for the analyzed mapping data. Such a system may require the use of cardiac digital twins and the application of AI to analyze activation patterns and to deduce sources and substrates.                                                                                                                                                                                                  |
| Patient-tailored therapy and in silico testing of proposed treatment                                | The mapping system can suggest the most appropriate therapy for the individual patient, whether it be an ablation strategy or a drug regimen, and can implement the selected treatment in silico to test its effectiveness.                                                                                                                                                                                                                                                                                        |

AF = atrial fibrillation; AI = artificial intelligence.

fibrillation waves acting as sources of new waves.<sup>93</sup> Third, our ablation tools are suboptimal, often resulting in linear and intramural conduction gaps.

In this regard, the Cox-maze procedure, which segments the right and left atria into multiple sections smaller than the fibrillatory wavelength, has been relatively effective in eliminating AF. However, this comes at the expense of surgical intervention with disruption of normal atrial excitation patterns. Ideally, one could identify limited critical zones for any individual patient, but if that is not possible, a catheter-based Cox-maze procedure might ultimately be the answer. We must maintain a broad perspective and remain open minded and unbiased toward any particular approach as we objectively test each hypothesis in large, randomized trials to determine its impact on clinical outcomes related to persistent AF.

With respect to mapping tools, whereas near-infrared optical mapping using nontoxic dyes may provide the desired spatial and temporal resolution in vivo, it is unlikely to be a feasible clinical methodology but may help us understand the propagation of fibrillatory waves in humans. Furthermore, combining optical mapping data with structural imaging may help to enhance modeling using digital twins. Current mapping tools, including catheters and mapping systems, have been optimized for stable rhythms. Table 2 summarizes the ideal features required for mapping AF. This may include

simultaneous mapping of both atria at high spatial resolution. Although electrocardiographic imaging can provide a full bia-atrial panoramic view, this comes at the expense of low spatial resolution. In addition, asynchronous endocardial-epicardial electrical activation requires a solution that enables understanding 3D electrical propagation to determine mechanisms and sources.

With respect to ablation therapies, it is our conclusion that a technology enabling the safe, effective, and efficient execution of a catheter-based Cox-maze procedure is required. It should result in the highest effect on AF with the smallest volume of ablated tissue. Whereas advancements in mapping may allow a patient-tailored approach with limited ablation, a broader strategy creating large-footprint ablation scar must also be considered.

Pharmacologic therapies for AF have long lagged behind ablation technologic developments, and their comparative impact is lower than that of ablation. However, new drugs, such as rapidly acting inhaled class Ic agents, may be of interest for the rapid cardioversion of AF in early disease states.<sup>94</sup> These agents have the potential to delay the progression to persistent AF, in line with the "AF begets AF" model. Other pharmacologic interventions not directly aimed at cardiac ion channels, such as glucagon-like peptide 1 receptor agonists<sup>95</sup> that are used in the treatment of type 2 diabetes, have been shown to protect against AF by preventing

impairments in atrial conduction, atrial electrical remodeling, and atrial fibrosis in mice with diabetes. However, a recent study examining the utility of glucagon-like peptide 1 receptor agonists on AF recurrence after ablation, in propensity score-matched groups of 1625 patients using medication 1 year before and after the ablation procedure, found no difference in clinical outcomes including AF recurrence rates.<sup>96</sup> This underscores the need for future research to determine whether these agents can improve outcomes in AF patients.

Last, we must consider that restoring sinus rhythm in advanced phenotypic forms of AF is often not feasible or may require extensive ablation with minimal or no positive impact on quality of life. This should encourage strategies for early detection and intervention as well as lifestyle modifications to halt or to reverse the AF-related arrhythmogenic substrate. Regardless of which AF therapies are introduced in the near future, a critical appraisal of novel treatments should begin with reporting data using an existing framework for AF-related nomenclature, definitions, and potential mechanisms, as proposed in this paper.

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**Address reprint requests and correspondence:** Prof Dr N.M.S. de Groot, Department of Cardiology, Erasmus Medical Center, Dr Molewaterplein 40, 3015GD Rotterdam, The Netherlands. E-mail address: [n.m.s.degroot@erasmusmc.nl](mailto:n.m.s.degroot@erasmusmc.nl)

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