

Novel approaches to mechanism-based atrial fibrillation ablation

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Abstract

Modern cardiac electrophysiology has reported significant advances in the understanding of mechanisms underlying complex wave propagation patterns during atrial fibrillation (AF), although disagreements remain. One school of thought adheres to the long-held postulate that AF is the result of randomly propagating wavelets that wander throughout the atria. Another school supports the notion that AF is deterministic in that it depends on a small number of high-frequency rotors generating three-dimensional scroll waves that propagate throughout the atria. The spiralling waves are thought to interact with anatomic and functional obstacles, leading to fragmentation and new wavelet formation associated with the irregular activation patterns documented on AF tracings. The deterministic hypothesis is consistent with demonstrable hierarchical gradients of activation frequency and AF termination on ablation at specific (non-random) atrial regions. During the last decade, data from realistic animal models and pilot clinical series have triggered a new era of novel methodologies to identify and ablate AF drivers outside the pulmonary veins. New generation electroanatomical mapping systems and multielectrode mapping catheters, complemented by powerful mathematical analyses, have generated the necessary platforms and tools for moving these approaches into clinical procedures. Recent clinical data using such platforms have provided encouraging evidence supporting the feasibility of targeting and effectively ablating driver regions in addition to pulmonary vein isolation in persistent AF. Here, we review state-of-the-art technologies and provide a comprehensive historical perspective, characterization, classification, and expected outcomes of current mechanism-based methods for AF ablation. We discuss also the challenges and expected future directions that scientists and clinicians will face in their efforts to understand AF dynamics and successfully implement any novel method into regular clinical practice.

Keywords

Atrial fibrillation • Cardiac mapping • Rotors • Arrhythmia mechanisms

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1. Introduction

Interventional procedures for catheter-based ablation of atrial fibrillation (AF) have become the first-line therapeutic option in cases of symptomatic episodes despite the use of antiarrhythmic drugs (AADs).¹ Catheter ablation of AF relies on pulmonary vein isolation (PVI) as the cornerstone of any ablation procedure aiming to prevent subsequent episodes.¹ In fact, AF recurrences often correlate with pulmonary vein (PV)

reconnection.² However, extra-PV regions become more relevant in AF initiation and maintenance as atrial remodelling evolves and the underlying substrate gains complexity.^{3,4}

A common strategy to treat symptomatic AF episodes after permanent PVI is to ablate other atrial anatomical targets, potentially associated with AF initiation and maintenance.⁵ Among other regions, the posterior left atrial wall, the vein of Marshall, and the left atrial appendage (LAA) have been reported to be locations for AF triggers outside de PVs in

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some series.^{5–7} Moreover, extra-PV trigger locations may also participate in AF maintenance as areas for driver sources sustaining the overall arrhythmia.^{8,9} However, many of these atrial regions are empirically targeted for ablation without robust underlying supportive mechanistic insights.¹⁰ Some regions may require ablating extensive areas because of lack of target specificity.⁵ This is highly relevant since the larger the ablated area outside the PVs the higher the risk of severe complications.¹¹

During the last decade, other strategies aiming to localize and target specific AF sources that are thought to maintain fibrillation dynamics have emerged increasingly in research series of complex cases undergoing AF ablation.¹² Such mechanistic strategies are commonly based on complex mathematical analyses, which vary among approaches.¹² Moreover, many of these methods and mapping tools are not commercially available, and conventional laboratories may have problems selecting or even understanding their intrinsic algorithms. Here, we aim to review state-of-the-art technologies and provide a comprehensive characterization, classification, and expected outcomes of current mechanistically based methods for AF ablation. We start by briefly describing experimentally based AF mechanisms and implemented clinical strategies that have been reported throughout the history of modern cardiac electrophysiology. Then, we review the specific approaches aimed at defining and identifying AF drivers and later compare the main clinical outcomes, as well as pros and cons of the different methods. Lastly, we describe from a multidisciplinary perspective the challenges we face implementing such novel methods into regular clinical practice and the expected future directions for the field in the relatively short term.

2. Historical perspective: experimental bases for current mechanistic approaches in the clinic

Irregular pulse and palpitations suggesting underlying irregular atrial and ventricular activity associated with AF were reported long before Einthoven's invention of the string galvanometer could confirm the diagnosis on the electrocardiogram.^{13–16} That technological breakthrough triggered a whole new perspective in the understanding of cardiac rhythm disorders, without which physicians could only infer from physical examination.^{17,18} As an example, during the first quarter of the twentieth century, following the leads of George Mines¹⁹ and Walter Garrey,²⁰ Sir Thomas Lewis used electrocardiographic evidence to postulate that circus movement re-entry around an anatomical obstacle could explain either flutter or AF depending on the size of the circuit and the refractory period of the tissues involved.²¹ By the middle of the last century, Prinzmetal *et al.*²² used surface electrocardiographic together with coloured high-speed cinematographic recordings of the intact heart in dogs to provide support to Scherf's postulate that AF could be sustained by a single ectopic focus.²³ These theories revealed the early scientific interest in understanding the underlying patterns of wave propagation dynamics associated with AF tracings. However, such experimental and theoretical hypotheses did not significantly change AF management, which at the time was associated primarily with the use of digitalis and quinidine.²⁴ A decade later, computational modelling emerged as a relatively powerful tool (at that time) to provide mechanistic insights into complex propagation dynamics during AF. Moe *et al.* developed a new theory based on the idea that fibrillation could exist as a stable, self-sustaining state independent of its initiating agency.²⁵ The experimental and computational data supported re-entry as the most likely

mechanism for atrial fibrillatory activity, although the perpetuation of the arrhythmia would require the coexistence of multiple independent randomly propagating wavelets initiated when an irregular wavefront fractionated at heterogeneously distributed partially refractory tissue islets.²⁶ This theory and its underlying re-entrant nature was consistent with contemporaneous reports of effective restoration of sinus rhythm after synchronized cardiac shocks in patients with AF.²⁷ Support for Moe's modelling predictions came from experimental mapping studies by Allesie *et al.* in the canine heart demonstrating multiple propagating wavelets giving rise to turbulent atrial activity.²⁸ Moe's multiple-wavelet hypothesis became well-accepted amongst clinicians after its ostensible clinical support from the MAZE procedure reported by Cox and colleagues in 1991.²⁹ This procedure achieves high success rates in preventing AF by compartmentalizing the atria to create independent regions unable to sustain the multiple re-entrant circuits potentially associated with AF.²⁹ Recently, the multiple-wavelet hypothesis was reassessed and challenged by Lee *et al.*,³⁰ who repeated the original canine studies but using simultaneous biatrial mapping with higher-resolution multielectrode epicardial plaques. These authors reported AF episodes driven by localized independent repetitive focal sources rather than multiple-wavelet re-entry. Interestingly, the so-called 'double-layer hypothesis' based on high-density human atrial maps might reconcile both Moe's and Lee's observations (Figure 1A). This hypothesis suggests that AF is maintained by endo-epicardial breakthroughs that continuously generate new breakthroughs emerging at the contralateral layer due to endo-epicardial dissociation.³¹ Therefore, Lee *et al.* cannot exclude that their alleged focal sources were actually breakthroughs from wavelets meandering from endocardium to epicardium (and vice versa). Both the multiple-wavelet and double-layer hypotheses go against the existence of localized drivers (Figure 1B).

The understanding about AF drivers moved significantly forward with the advent of cardiac optical mapping using voltage-sensitive probes in whole heart preparations during the last decade of the twentieth century.³² The high spatiotemporal resolution of optical mapping enabled basic scientists to demonstrate that cardiac fibrillation may be sustained by a single, or a small number of high-frequency rotors generating spiral (in 2D) or scroll (in 3D) waves that propagate through the cardiac muscle and interact with anatomic and functional obstacles, leading to fragmentation and new wavelet formation.^{33,34} Thus the idea was put forth that AF maintenance was the result of sustained, functional re-entrant activity generating highly dynamic but complex wave propagation patterns (Figure 1B). This theory also explained the occurrence of hierarchical gradients of activation frequencies at different atrial regions, observed in both experimental animal models and human studies.^{3,35} The latter is incompatible with the multiple wavelet hypothesis, which by definition implies that activation frequency should be the same everywhere in the atria.²⁶ In addition, it is not clear that random disorganized patterns can be self-sustaining rather than an epiphenomenon from other potential underlying, more localized, driving mechanisms (Figure 1B). Either way, the surgical MAZE procedure might effectively control AF either by generating atrial compartments small enough not to be able to fit the minimum number of random wavelets required to sustain AF, or by creating anatomical barriers that terminate rotors by reducing their 'elbow room', or even by isolating atrial regions hosting focal sources (Figure 1C). Moreover, AF termination with ablation at specific target sites in some experimental models and many AF patients supports the idea of driving sources underlying AF (Figure 1D).

Still, some authors deny the existence of rotors arguing that they can only see incomplete re-entries.^{30,31,36} However, these and other authors

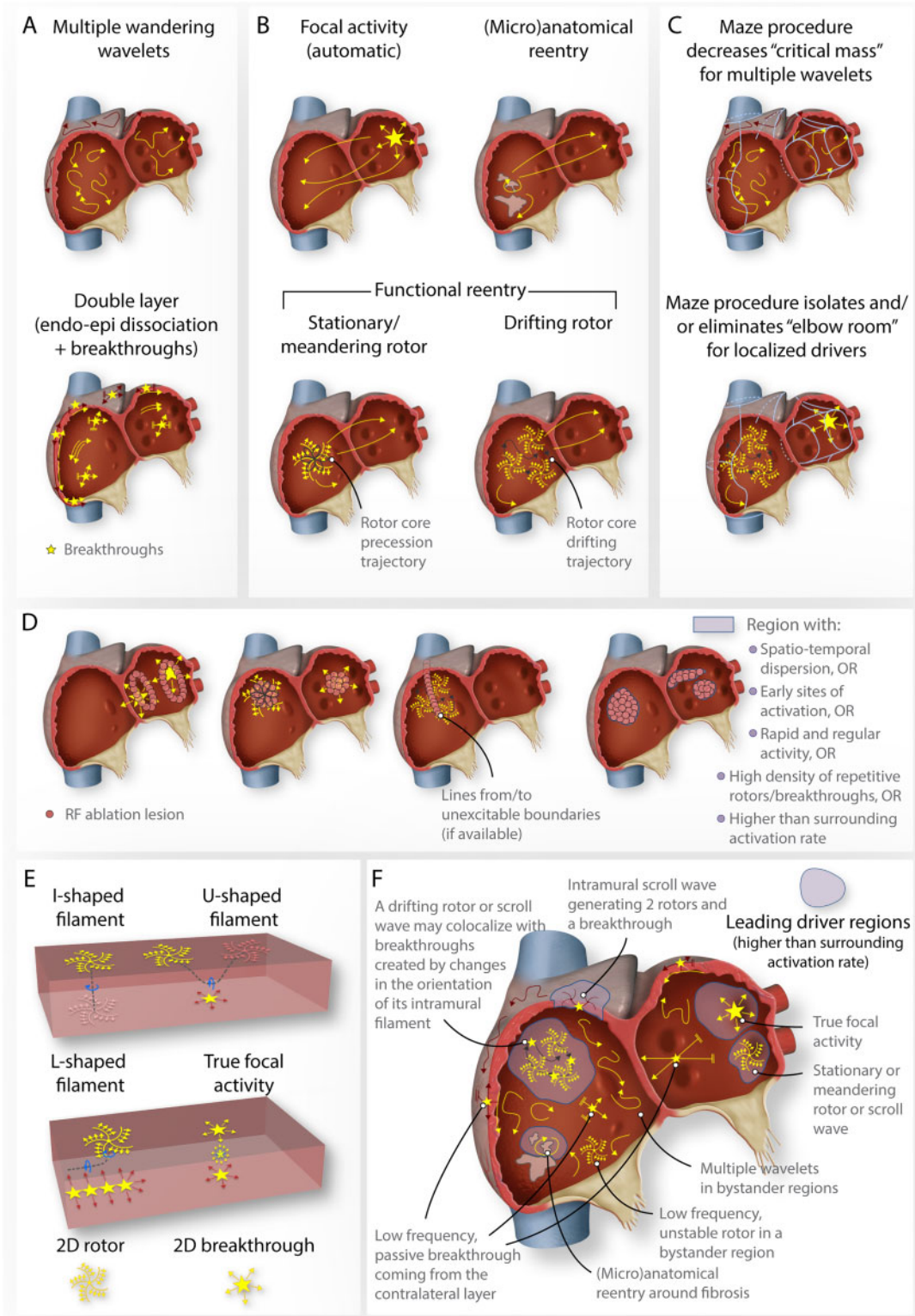


Figure 1 (A) Schematics of postulated mechanisms for atrial fibrillation (AF) maintenance that do not involve localized drivers. (B) Schematics of postulated AF maintenance mechanisms that involve localized drivers. (C) The Maze-Cox procedure may be effective for treating AF allegedly maintained either by non-localized or localized mechanisms. (D) Successful treatment for AF by ablation at specific target sites supports the idea of relatively localized drivers maintaining AF. (E) Schematic of some potential 3D patterns giving rise to 2D rotors and/or breakthroughs as observed by current 2D mapping methodologies. (F) Schematic of structurally and electrically remodelled atria, where several reported patterns might coexist. However, AF may still be driven in a hierarchical fashion by specific regions with higher than surrounding activation rate (leading drivers). Such regions would host re-entrant drivers in many cases, albeit not all re-entrant activity would act as a driver, since rotors are also commonly found in passive bystander regions.

might have missed the true nature of the patterns by their use of multi-electrode plaques that fail to offer the spatial resolution needed to discern the underlying mechanisms.³⁷ Moreover, the electrical signals are usually associated with a methodology (activation sequence analysis) that has been designed for spatially coherent arrhythmias and may not be the most appropriate strategy for AF.

Overall, multiple aspects about AF mechanisms still require further investigation to interpret mapping data. A few considerations might help to reconcile reported observations from different groups. Notably, despite the thin atrial wall, activation patterns are three-dimensional and 2D observations might confound the true nature of the underlying mechanisms sustaining AF. Thus, some observed foci or breakthroughs might be generated by transmural scroll-waves with nonlinear filament shapes (U-shape, L-shape, *Figure 1E*), or by micro-anatomic intramural re-entries.^{38,39} Regardless of the nature of AF drivers and the several active or passive patterns that might be simultaneously present in electrically and structurally remodelled atria, the most widely accepted theory is that AF is maintained by leading high-frequency drivers establishing a spatially distributed hierarchy of progressively slowing activation rates as the wave fronts propagate centrifugally from their source (*Figure 1F*).⁸

In parallel with experimental studies demonstrating rotors as AF sources, in 1998, Haissaguerre and colleagues demonstrated a high prevalence of PV foci initiating AF in patients undergoing catheter ablation.⁴⁰ Local elimination of PV triggers using radiofrequency energy was highly effective in preventing AF in that population subset.⁴⁰ Since then, the role of PVs on AF initiation has mobilized a tremendous amount of predominantly private funding to achieve rapid, effective, and safe PVI using different technologies like single-shot devices,⁴¹ contact force monitoring, or high-resolution electroanatomical mapping,^{42,43} among others.⁵ Conversely, experimental data for the necessary understanding of the mechanisms underlying AF maintenance beyond the PVs have been much more limited and mainly associated with public funding agencies.^{44,45}

During the first decade of the twenty-first century, the hierarchical organization of rotor dynamics and atrial activation frequencies were translated from experimental studies in isolated heart preparations to pilot clinical studies aiming to identify and ablate the fastest activating areas to terminate AF.^{46,47} Using dominant frequency (DF) analysis of endocardial bipolar electrograms, an activation rate hierarchy was particularly evident in paroxysmal AF (PxAF).^{46,47} However, in more complex scenarios like persistent AF (PsAF), atrial frequency domains were less hierarchical and more difficult to distinguish.^{3,47} Later in 2014, DF-guided ablation did not show any incremental benefit on freedom from AF at 6 months of follow-up after PVI plus DF-guided high-frequency sources ablation compared with PVI alone.⁴⁸ This validation failure of DF analysis in the clinic may have been related, among other technical reasons,^{8,12} to the fact that morphology changes and amplitude/frequency modulations in electrograms during AF often result in multiple spectral peaks with similar heights which makes DF analysis challenging (*Figure 2A and B*). Moreover, the approach used bipolar signals acquired with relatively large electrodes, which are prone to fractionation,⁴⁹ making automatic DF analysis even more challenging. More recent approaches using unipolar signals from multipolar catheters, in combination with robust algorithms for QRST subtraction and time domain analysis have helped to overcome many of the limitations of DF analysis (*Figure 2C*).⁸

While technological developments for PVI were undergoing, the slowly but steady increase in experimental data from clinically relevant animal (e.g. sheep)^{45,50–52} models provided enough evidence to trigger the interest on finding new approaches for complex AF cases in the

clinic. Investigators began to search for AF drivers and spatiotemporal organization rather than exclusively relying on electrical isolation of atrial regions without knowing their specific role in AF maintenance.⁵ Narayan and colleagues started this new era of mechanism-based procedures using basket catheters for simultaneous multi-electrode recordings in both atria to identify repetitive rotational and focal activity, which allowed AF termination in a high proportion of patients undergoing ablation.⁵³ Although these initial outcomes were promising, subsequent studies have shown more controversial results.⁵⁴ Since then, an important number of non-invasive and invasive tools have been proposed to guide driver detection and ablation during AF.^{8,55–59} More accurate driver detection among relevant activation patterns like re-entrant activity is increasing with new and robust mathematical methods.^{8,60} However, driver detection during AF is still under development,^{8,59,61,62} and its impact in clinical outcomes compared to other anatomically-based approaches warrants further investigation.

3. Description and classification of mechanism-based approaches for AF mapping and ablation

The vast amount of data coming from novel mechanism-based approaches for AF mapping need an urgent effort to classify the various methodologies from a theoretical and practical perspective. In this section, we briefly outline the main approaches currently reported in the literature and then classify them using a systematic approach.

It can be said that the first attempt to guide AF ablation of extra-PV regions using a somewhat mechanistic approach was reported in 2004 by Nademanee *et al.*⁶³ These authors proposed that areas with complex fractionated atrial electrograms (CFAEs) may be critical for maintaining AF and their ablation might result in better clinical outcomes. CFAEs were described as fractionated or continuous electrical activity at short cycle lengths.⁶³ Indeed, the idea of short cycle lengths as markers of driver activity was not new and had been used for several years in experimental studies that performed spectral analysis of fibrillatory signals.⁶⁴ The frequency of the highest peak in the spectrum at one location (i.e. DF) was often used as a surrogate for the average activation rate (i.e. 1/cycle length) at that location.¹² Since atrial regions with the highest DF (HDF, shortest cycle lengths) could reveal the fastest drivers that maintain AF, targeting HDF areas has been proposed as potentially effective to terminate AF and prevent its recurrence.^{46,47}

Phase mapping has also been a common element in several mechanistic approaches for AF mapping. It was originally designed for high-resolution optical mapping studies to visualize the propagation patterns during cardiac fibrillation by determining the local phase of the activation/recovery cycle at each time point. This approach enables automatic detection of phase singularities (i.e. rotor pivoting points).⁶⁵ A relevant milestone using this signal processing approach in the clinic was the work of Narayan and colleagues in 2012 (FIRMa data in *Figures 3 and 4*),⁵³ who reported the clinical outcomes of the Focal Impulse and Rotor Modulation (FIRM) methodology. They developed a computational mapping system that recorded 128 simultaneous endocardial unipolar electrograms from two basket catheters, one in each atrium, in patients undergoing AF ablation. The system enabled electrophysiologists to visualize interpolated phase movies of the atrial activation patterns and isochronal maps from individual cycles, which were obtained after bi-linear interpolation of the phase state between each electrode and its nearest

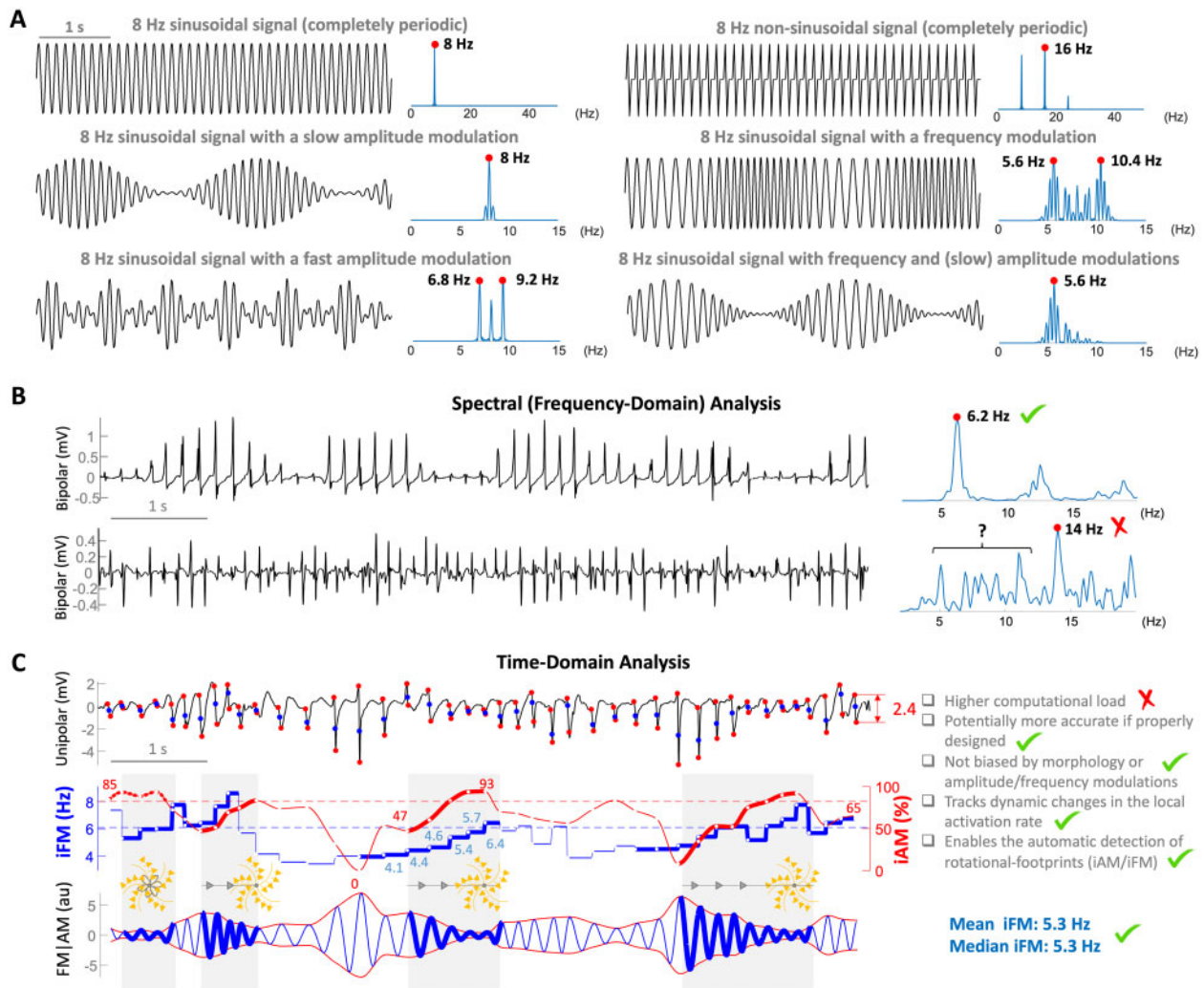


Figure 2 (A). During AF, the morphology, amplitude and frequency modulations often displayed by electrical signals considerably affects the shape of their corresponding spectra. Therefore, the frequency of the highest peak in a given spectrum (dominant frequency, DF) need not be the best estimator of the underlying average activation rate (8 Hz for all signals shown in (A)). (B). Spectral analyses of 2 actual atrial electrograms during persistent AF. (C). Time domain analysis of signals during AF may offer many advantages, although this requires reliable and robust algorithms. iAM, instantaneous amplitude modulation; iFM, instantaneous frequency modulation.

neighbours. Rotational activities around a centre of rotation were identified as rotors. Foci were also identified in regions with centrifugal propagation. In 2014, the same group reported the long-term outcomes of this multi-centre, prospective, 2-arm, non-randomized trial (FIRMb data in Figures 3 and 4).⁹ Later, Miller *et al.* reported additional clinical outcomes using this methodology in a large cohort of patients from a single centre registry (FIRMc data in Figures 3 and 4).⁶⁶ More recently, Brachmann *et al.* reported in abstract form the results of a randomized, multi-centre comparison between this approach and PVI (FIRMd data in Figures 3 and 4).⁶⁷ The study seemingly failed to provide evidence for superiority of FIRM+PVI vs. PVI alone in PsAF patients. On-treatment analysis, FIRM+PVI provided 77.8% single procedure success compared to 65.5% for PVI alone. However, the addition of non-protocol groups with additional ablation at the physician's discretion and not controlled for (PVI plus and PVI+FIRM plus) diluted the power to show any statistically significant difference (overall $p = 0.09$).

Electrocardiographic imaging (ECGi) also enables identification of rotational and centrifugal activation non-invasively. It uses body surface potentials from multiple electrodes positioned on the torso, complemented with the geometric information provided by an imaging technique. Complex algorithms combine imaging and electrical data to solve the electrocardiographic inverse problem in order to obtain estimated cardiac electrograms⁶⁸ that can be displayed over the epicardial^{69–71} or endo-epicardial^{72,73} cardiac anatomy. In 2014, Haïssaguerre and colleagues initially reported the outcomes of a large single-centre series using an ECGi system to guide ablation of AF drivers.⁶⁹ This system added phase mapping capabilities to detect and target rotational and focal drivers in patients with PsAF. Data from ECGi-guided procedures were compared with a retrospective cohort undergoing a step-wise ablation procedure (ECGi data in Figures 3 and 4).¹⁰ In 2017 the same group of investigators reported a comprehensive analysis of alleged driver features detected with this system in relation with AF duration (ECGi data

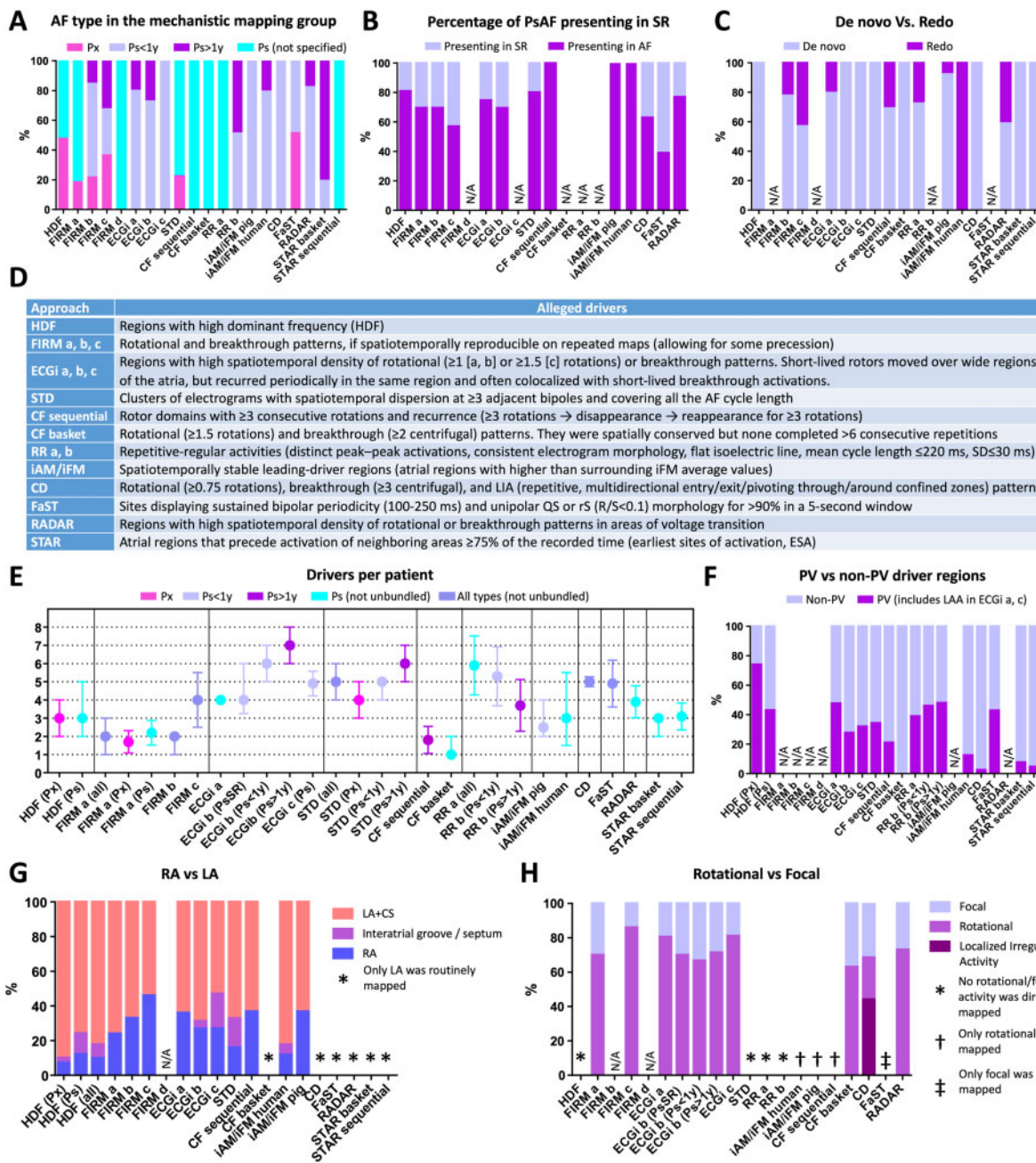


Figure 3 Study population and AF alleged drivers in mechanistic approaches for AF mapping. (A) AF type distribution in the mechanistic mapping groups of the selected studies. (B) Proportion of patients with persistent AF presenting in sinus rhythm. (C) Proportion of first AF ablations (de novo) and repeated procedures (redo) in the mechanistic mapping groups. (D) Description of the alleged AF drivers as defined by each approach. (E) Number of alleged drivers per patient displayed as median and interquartile range (percentile 25th, percentile 75th). In the studies where these data were not reported, they were estimated from means and standard deviations assuming normal distributions. (F) Proportion of alleged drivers in the pulmonary vein region Vs. extra-pulmonary drivers. (G) Proportion of alleged drivers in the right and left atria. (H) Classification of AF alleged drivers according to their activation patterns. CS, coronary sinus; LA, left atrium; LAA, left atrial appendage; m, month; N/A, not available; Ps, persistent; PsSR, persistent presenting in sinus rhythm; Px, paroxysmal; RA, right atrium; SR, sinus rhythm; y, year. Rest of abbreviations as in Table 4.

in Figures 3 and 4).⁷⁰ The same year, a prospective, multicentre, single-arm study reported favourable AF-free survival at 1 year (77%) using the ECGi system in patients with PsAF undergoing catheter ablation (ECGiC data in Figures 3 and 4).⁷¹

In 2017, Seitz and colleagues evaluated the hypothesis that fractionation occurring in a non-simultaneous fashion at neighbouring electrode

locations (time dispersion) and organized in well-defined clusters (spatial dispersion) may indicate the presence of an AF driver. The investigators mapped AF sequentially in each atrium with a multipolar catheter and tagged the locations displaying spatiotemporal dispersion (STD) in the bipolar electrograms. The tagged regions were ablated after completion of atrial mapping. The clinical outcomes of this approach were obtained

A

Approach	Ablation procedure in the mechanistic mapping groups
HDF	1 Alleged drivers: regions with high DF. No empirical PVI was performed → 2 PVI (PsAF only) + additional lines at the operator's discretion (PsAF only)
FIRM a, b, c	1 Alleged drivers: rotational and focal, if spatiotemporally reproducible (allowing for some precession) → 2 PVI + LA roof line (the latter, only in PsAF)
ECGI a, b, c	1 Alleged drivers: rotational (≥ 1 [a, b] or ≥ 1.5 [c] rotations)/focal in decreasing order of density → 2 PVI (only in c). If AF persisted, LA roof/mitral lines
STD	1 Alleged drivers: clusters of electrograms with spatiotemporal dispersion at ≥ 3 adjacent bipoles and covering all the AFCL. No empirical PVI was performed
CF sequential	1 PVI → 2 Alleged drivers: domains with ≥ 3 consecutive rotations and recurrence (≥ 3 rotations → disappearance → reappearance ≥ 3 rotations)
CF basket	1 PVI → 2 Alleged drivers: rotational (≥ 1.5 rotations) and focal (≥ 2 centrifugal activations)
RR a, b	1 Alleged drivers: repetitive-regular activities, targeting the fastest sources first → 2 PVI + mitral isthmus + roof + posterior lines
iAM/iFM	1 Alleged drivers: leading-driver regions (atrial regions with higher than surrounding iFM average values)
CD	1 PVI → 2 Alleged drivers: rotational (≥ 0.75 rotations) + focal (≥ 3 centrifugal activations) + LIA. All identified targets were ablated
FaST	1 PVI → 2 Alleged drivers: focal source and trigger (FaST) sites, displaying sustained bipolar periodicity and unipolar QS/rS morphology
RADAR	1 PVI → 2 Alleged drivers: rotational + focal guided by density maps incorporating spatiotemporal repetition and areas of voltage transition
STAR	1 PVI → 2 Alleged drivers: Early Sites of Activation (ESA, $\geq 75\%$ of the recorded time) targeted in order of percentage of time with early activation

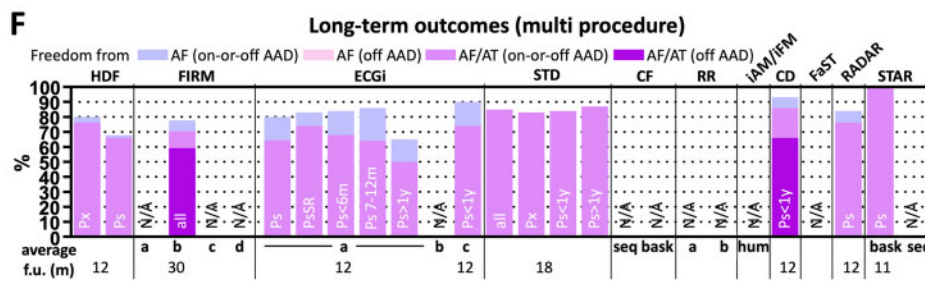
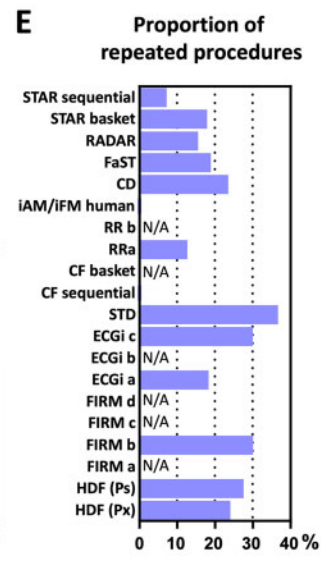
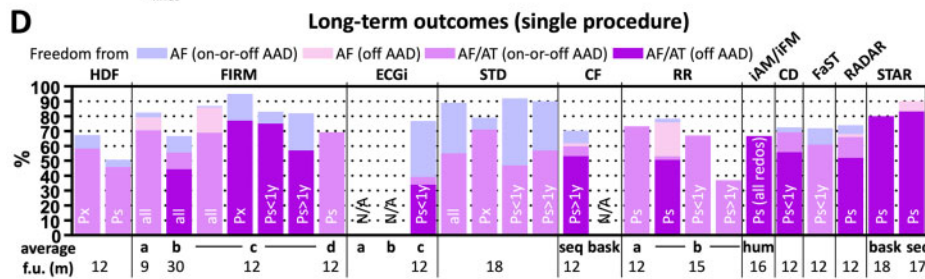
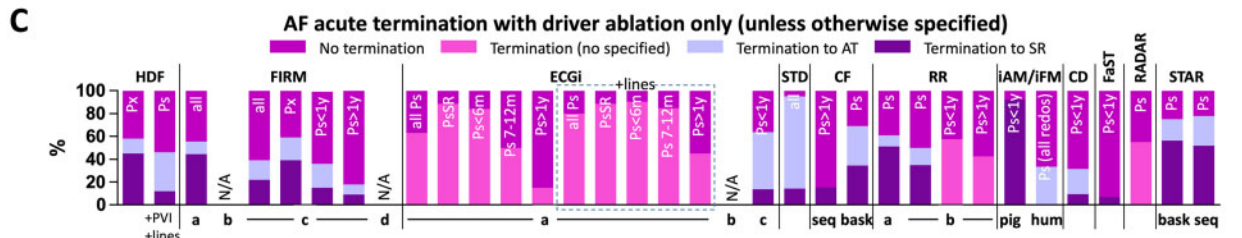
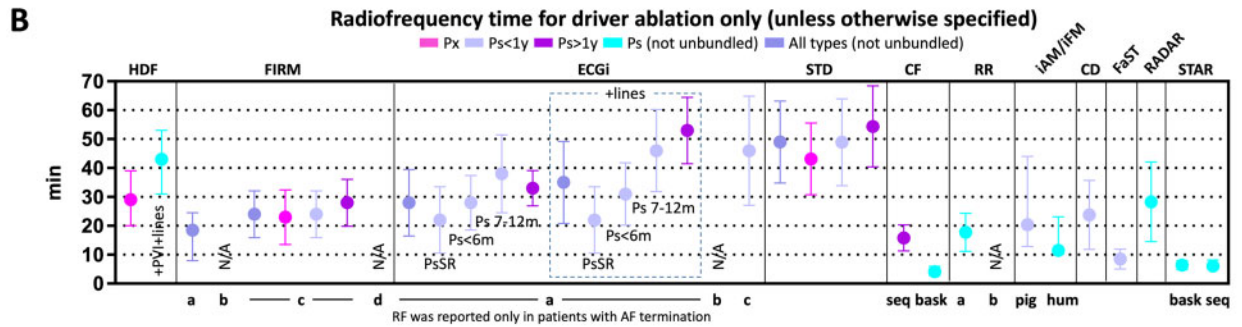


Figure 4 Acute and long-term outcomes of mechanistic approaches for AF mapping and ablation. (A) Ablation procedures in the mechanistic mapping groups from the selected studies. (B) Radiofrequency time for driver ablation only, unless otherwise specified. Data are displayed as median and interquartile range (percentile 25th, percentile 75th). In the studies where these data were not reported, they were estimated from means and standard deviations assuming normal distributions. (C) AF acute termination rates with driver ablation only, unless otherwise specified. (D) Long-term outcomes after a single procedure. (E) Proportion of patients who were submitted to an additional ablation procedure for AF or AT recurrence after the index procedure. (F) Long-term outcomes after multiple procedures. f.u., follow-up. Rest of abbreviations as in Figure 3.

from a prospective, multicentre, single-arm study.⁵⁷ The data were compared with a retrospective validation cohort undergoing conventional AF ablation.

Recently, the CARTO-Finder (CF) extension was incorporated into the CARTO electroanatomical mapping system (Biosense Webster). The new software module enables visual detection of rotational and

focal patterns during AF (by either activation sequence analysis or phase mapping), using either sequential mapping with multipolar catheters (CF sequential)⁵⁵ or simultaneous panoramic mapping with basket catheters (CF basket).⁷⁴ The main clinical outcomes of AF ablation procedures guided with this system were reported in 2017 and 2018.^{55,74}

A novel mechanistic approach by Pappone et al. has also been integrated into another conventional electroanatomical mapping system (Ensite NavX, Abbott), but only for research purposes. This approach was further tested in a prospective, single-centre, randomized trial in 2018.⁵⁸ Bipolar endocardial electrograms were acquired with a multipolar catheter at sequential locations in the left atrium. The regions showing repetitive-regular activities (RR, distinct peak–peak activations, consistent electrogram morphology, flat isoelectric line) with a mean cycle length ≤ 220 ms and a standard deviation ≤ 30 ms were considered ablation targets (RRa data in *Figures 3 and 4*).⁵⁸ Later in 2019, the same group reported a detailed characterization of the atrial substrate using this approach in PsAF patients. The authors combined the analyses with wavefront propagation direction and velocity vector maps, fragmentation maps and peak-to-peak bipolar voltage maps (RRb data in *Figures 3 and 4*).⁶¹

In 2019, Quintanilla et al. reported a completely translational study, including computer simulations, optical mapping of isolated Langendorff-perfused sheep hearts with PsAF, *in vivo* electroanatomical mapping of a clinically relevant porcine model of long-term self-sustained PsAF, and complementary studies in patients with symptomatic PsAF despite ≥ 1 AF ablation procedures.⁸ They worked on the assumption that the amplitude and frequency modulations (AM/FM) used for radio broadcasting are naturally present in signals during cardiac fibrillation, although in a completely different frequency range. Interestingly, they found that the combined analysis of the instantaneous amplitude modulation and instantaneous frequency modulation (iAM/iFM) of single signals during PsAF can detect the footprint of rotational activity in sequentially acquired signals. The approach enabled detection of rotors with high sensitivity and specificity, obviating the need for more expensive panoramic multielectrode acquisition systems. Moreover, spatiotemporally stable regions with higher average iFM than their surroundings often drove PsAF and their ablation terminated AF. Importantly, the study showed that rotational activations were sensitive but not specific to driver regions.⁸

Also, in 2019, charge density (CD) mapping emerged as a novel methodology derived from the principles of electrostatic field theory that derives CD as a spatial representation of the sources of the cardiac field.⁷⁵ This approach uses 48 ultrasound transducers distributed across a propriety catheter to obtain the endocardial end-diastolic surface.⁶⁰ In addition, the system samples the intracavitary voltage field using 48 non-contact electrodes distributed across the splines of the same catheter, and estimates the distribution of positive and negative ionic charges located across the chamber surface (i.e. CD) using an inverse algorithm. In addition to focal and rotational activity, this system enables detection of an additional pattern called ‘localized irregular activity’ (LIA) that the authors consider to be an AF driver as well. That same year, Willems and collaborators reported the first clinical results using this approach in a prospective, nonrandomized, multi-centre, single-arm trial.⁶⁰

More recently in 2020, Chauchan and colleagues reported the results of a single-centre, randomized, and controlled pilot trial based on another method called Focal Source and Trigger (FaST) mapping to guide AF ablation.⁶² The FaST algorithm automatically evaluated the presence of sustained bipolar periodicity and unipolar QS/rS morphology in periodic activations using sequential acquisition with multipolar catheters.

The authors aimed at reducing AF recurrence by decreasing the number of focal sources and triggers potentially initiating and sustaining AF with catheter ablation of FaST sites, which was performed as an adjunctive therapy to PVI.

The RADAR system (different from the RADAR-AF trial using HDF by Atenza et al.⁴⁸) uses sequentially acquired data with a standard electroanatomical mapping system and unipolar signal processing methods to identify AF driver domains.⁵⁹ This methodology identifies distinct repetitive morphological patterns of activation in the coronary sinus. Then, the system stitches all multipolar data from different times and locations but with the same coronary sinus pattern together, in order to generate as many coherent panoramic AF maps as different coronary sinus patterns are identified. The system calculates conduction vectors for each map using distances between electrodes and activation times at each electrode. Focal and rotational patterns can be identified in each individual map and then combined to create a driver density map that is displayed together with areas of voltage transition to highlight potential driver domains.⁵⁹ The initial clinical data of a multicentre, single-arm trial using this approach to guide ablation in PsAF patients were recently reported.⁵⁹

Stochastic trajectory analysis of ranked signals (STAR) mapping is another recently reported approach that uses data on multiple individual wave front trajectories to identify atrial regions that most often precede activation of neighbouring areas with the aim of identifying intermittent potential drivers (earliest sites of activation, ESA). Thus, atrial regions can be ranked according to the amount of time that activations precede those of adjacent regions. The clinical outcomes of an ablation strategy guided by this principle were recently reported either using simultaneous acquisition with basket catheters (STAR basket data in *Figures 3 and 4*)⁷⁶ or sequential acquisition with multipolar catheters (STAR sequential data in *Figures 3 and 4*) in a single-centre, single-arm trial.⁷⁷

In brief, all the aforementioned mechanistic approaches for mapping and ablation of AF may be systematically classified according to five different parameters: (i) Type of acquisition (simultaneous or sequential, contact or non-contact); (ii) Type of signals used for map generation (endocardial extracellular potentials, body surface potentials, tissue charge densities); (iii) Anatomy used for displaying maps (electroanatomical map, computed tomography, magnetic resonance imaging or ultrasound reconstruction); (iv) Mapping strategy: either direct or indirect detection of specific activation patterns (e.g. rotational, focal) or activation rate mapping (either using frequency domain or time domain analysis); and (v) Ablation targets: regions displaying sustained or repetitive patterns regardless of their activation rate hierarchy (focal, rotational, LIA, ESA), high activation rate (HDF, high iFM or short cycle lengths), high regularity, complex fractionation, or spatiotemporal dispersion. *Tables 1–4* present such a classification in detail together with pros, cons, and limitations. *Table 5* classifies all the aforementioned mechanistic approaches according to the above five parameters, in such a way that each approach displays a specific barcode unlike any other.

4. Characterization of alleged AF drivers

AF driver characterization may be affected by the population subset undergoing atrial mapping. *Figure 3A–C* shows a brief description of the different aspects of the baseline population in the mechanism-based mapping group of the aforementioned studies. This issue becomes relevant for data interpretation; thus, in a baseline population with a higher

Table 1 Classification of mechanistic approaches for mapping and ablation of AF according to their acquisition techniques

Type of acquisition	Pros	Cons & limitations
Simultaneous Endocardial basket ^{9,53,66,67,74}	<ul style="list-style-type: none"> • Simultaneous acquisition of the electrical activity on the whole mapped cavity 	<ul style="list-style-type: none"> • Potential suboptimal contact • Poor inter-spline spatial resolution • Extensive interpolation required • Splines may not be equidistantly separated once deployed, affecting interpolation performance • Mechanical artefacts due to motion or contact pressure
Body surface ^{69,71}	<ul style="list-style-type: none"> • Simultaneous acquisition of the electrical activity on the whole heart • Non-invasive • No surgery or sedation required 	<ul style="list-style-type: none"> • Voltages are often low (smoothed by the torso volume-conductor)^{56,100} • Poor sensitivity for detecting very low voltage signals (e.g. scarred and/or previously ablated areas)^{56,100}
Non-contact multipolar catheters to derive charge density ^{60,75,101}	<ul style="list-style-type: none"> • Simultaneous acquisition of the electrical activity on the whole mapped cavity • It allegedly minimizes far-field interferences • Signals ≥ 4 times sharper/narrower than conventional voltages^{60,75,101} 	<ul style="list-style-type: none"> • Correlation with contact-based electrograms considerably worsens >40 mm away from the non-contact catheter¹⁰¹ • Timing accuracy and signal morphology correlation worsen in regions with complex geometry (appendages, venous antra, etc.)¹⁰¹
Sequential Point-by-point contact acquisition ⁴⁷	<ul style="list-style-type: none"> • Better tissue–electrode contact than baskets 	<ul style="list-style-type: none"> • Unable to determine the direction of irregular activation wavefronts or global patterns during AF • Extremely long mapping times
Contact multipolar catheters for local acquisition ^{8,59,62,77}	<ul style="list-style-type: none"> • Better tissue–electrode contact than baskets • Data can be used to create panoramic high-resolution contact maps^{8,59} • Optimal for high-resolution mapping on account of the recently reported spatial stability of AF leading-driver regions⁸ 	<ul style="list-style-type: none"> • Longer mapping times than global acquisition approaches • Not optimal to determine the direction of irregular activation wavefronts during AF, especially if not deployed properly

proportion of PxAF patients, we can expect a higher proportion of drivers in the PV region.⁶² Also, if a high proportion of PsAF patients presents in sinus rhythm at the time of mapping, it likely implies less remodelled atria with a lower number and/or extension of driving regions.^{62,69} The latter may increase the rates of acute AF termination or freedom from AF in the long term.⁶⁹ Conversely, a higher proportion of long-standing PsAF patients or redo procedures has been generally associated with lower rates of acute AF termination on ablation^{8,55,59} and lower long-term freedom from AF.⁵⁹

Figure 3D shows the features of the alleged AF drivers detected with the main mechanism-based strategies. Although the definition of AF driver is not identical across the different studies (Figure 3D), the number of alleged drivers per patient ranged between 1 and 8 (Figure 3E). Moreover, the studies providing unbundled data report a direct relationship between the number of drivers and previous AF duration (See FIRMc,⁶⁶ ECGib,⁷⁰ STD⁵⁷ in Figure 3E), with some exceptions (See RRB⁶¹ in Figure 3E). Consistent with the role of PVs in AF initiation and maintenance, an important proportion of such drivers have been located in the PVs or their surroundings within the left atrium (Figure 3F). This is even more noticeable in populations with a higher proportion of PxAF patients (See HDF-PxAF,⁴⁸ STD,⁵⁷ FaST⁶²) or PsAF patients at early stages of atrial remodelling, still responding to cardioversion and mostly presenting in sinus rhythm (e.g. See FaST⁶² in Figure 3F). The role of PVs in hosting drivers is not negligible either in studies with exclusively PsAF patients (See ECGia,⁶⁹ ECGic,⁷¹ RRA,⁵⁸ RRB⁶¹ in Figure 3F). However,

this proportion was much lower in a study in which all patients were redos and there were few reconnected PVs (iAM/iFM⁸), in another study using CD,⁶⁰ or in the series reported by Honarbakhsh et al. (CF basket,⁷⁴ STAR basket,⁷⁶ STAR sequential⁷⁷) (Figure 3F). These differences among series might be explained on account of the use of basket catheters^{74,76} or non-contact approaches⁶⁰ that may not be well suited to detect and appropriately characterize drivers in such regions.^{74,76}

Overall, mechanism-based mapping during AF shows that the PVs and surrounding antral tissue are not only sources for AF triggers, but also seem common driver sites contributing to AF perpetuation. As AF duration increases, the relative contribution of the PVs and their surroundings to AF maintenance decreases, and relevant areas for AF maintenance become more heterogeneously located.³ Thus, other areas like the posterior left atrial wall and the right atrium increase their driver prevalence (Figure 3G), together with an overall increasing number, distribution, and complexity of AF drivers. Genetic predisposition and comorbidities may play a role in the relevance of certain cardiac regions to host AF drivers.⁷⁸ The posterior left atrial wall is both embryologically related to the PVs and a common location of fibrotic regions,^{79,80} which may explain its potential role as a source for AF triggers and maintenance. The right atrium may also play a relevant role in maintaining PsAF episodes.⁸¹ However, some mechanism-based mapping approaches did not routinely map the right atrium (CF basket,⁷⁴ CD,⁶⁰ FaST,⁶² RADAR,⁵⁹ STAR^{76,77} in Figure 3G), justified mainly as a way not to increase procedure duration.

Table 2 Classification of mechanistic approaches for mapping and ablation of AF according to the type of signals used for creating maps

Signals used for map generation		Pros	Cons and limitations
Endocardial extracellular potentials	Unipolar	<ul style="list-style-type: none"> • Interpretation of their morphology is usually simple¹⁰² • The intrinsic deflection (downstroke) coincides with the upstroke of the underlying actions potentials¹⁰² • Electrogram morphology of a passing wave front is independent of its direction¹⁰² • Initial negative deflections may help in detecting foci¹⁰² 	<ul style="list-style-type: none"> • Far-field (remote) signals are less attenuated (with the square of distance) than in bipolar recordings (with the third power)¹⁰² • Often contaminated by ventricular activity ⇒ appropriate QRST subtraction is critical
	Bipolar	<ul style="list-style-type: none"> • Far-field (remote) signals are more attenuated than in unipolar recordings¹⁰² • More sensitive to local effects¹⁰² • Often proportional to the first derivative of unipolar electrograms ⇒ usually sharper than unipolar (high-frequency components are enhanced by differentiation)¹⁰² 	<ul style="list-style-type: none"> • Amplitudes depend on wavefront orientation and are not directly proportional to those in the underlying action potentials¹⁰² • Exact activation times are more difficult to determine than in unipolar signals • More prone to fractionation (function of the interelectrode distance)⁴⁹
Estimated from body surface potentials by solving the inverse problem (ECGi)	Aggregated	<ul style="list-style-type: none"> • Time-efficient map generation enabling iterative mapping to assess changes following ablation • It can provide non-invasive data on follow-ups and AF recurrences 	<ul style="list-style-type: none"> • CT imaging required ⇒ additional radiation • Activation patterns are displayed on the epicardial surface, but are a composite of endocardial, epicardial, and intramural patterns and interactions • Signals from interatrial septum, PV-LAA ridge, or CS cannot be estimated • Regularization methods are needed to minimize the effects of small errors in data collection (geometrical, inaccurate conductivities, noise. . .)⁷⁵ • Poor sensitivity for highly localized sources or rotors with opposing chirality • Breakthroughs, spontaneous depolarizations, and microreentry are all seen as focal activity⁵⁶
	Endo/Epi/Septal separately	<ul style="list-style-type: none"> • Same as above • Provide endocardial and epicardial activation patterns separately⁷² 	<ul style="list-style-type: none"> • Same as above, except for the three first points
Tissue charge densities estimated from intrachamber electrical fields	Aggregated	<ul style="list-style-type: none"> • Time-efficient map generation enabling iterative mapping to assess changes following ablation⁶⁰ 	<ul style="list-style-type: none"> • Physiological constraints and regularization methods are required for the inverse approach⁷⁵ • Activation patterns are displayed on the endocardial surface mesh, but are a composite of endocardial, epicardial and intramural patterns and interactions • Median timing difference with contact-based electrograms was ~12 ms,¹⁰¹ magnitude which might confound whole rotations with partial rotations, focal activations, or disorganized patterns. • Special caution when interpreting data from regions >40 mm away from the centre of the noncontact catheter (e.g. LAA)¹⁰¹

Table 3 Classification of mechanistic approaches for mapping and ablation of AF according to their mapping strategy

Mapping strategy	Pros	Cons & limitations
Detection of specific activation patterns (e.g. rotational, focal)	<ul style="list-style-type: none"> It enables to automatically detect phase singularities (rotor pivoting points) Intuitive way of displaying activation patterns during fibrillation Marking activations is not usually required 	<ul style="list-style-type: none"> Multiple electrodes/signals are required and depend on their location, contact, separation, and filtering⁸⁷⁻⁸⁹ Low specificity for rotor detection when used with low spatial resolution data (focal activations or unrelated wavefronts might be displayed as rotational activity if reach the surrounding electrodes sequentially)⁸⁷⁻⁸⁹
Activation sequence and/or conduction vector mapping	<ul style="list-style-type: none"> It may be more specific than phase mapping for rotational activity^{31,36,59} 	<ul style="list-style-type: none"> The first limitation above also applies here Low sensitivity for rotational activity when used with low spatial resolution data (re-entry may be detected as centrifugal activations)^{37,88} Not very intuitive for displaying activation patterns during fibrillation (requires to analyse and display maps from multiple sequential very short time windows)³⁶ Marking activations is required (difficult in complex or fractionated signals)
Indirect detection of activation patterns using signal features	<ul style="list-style-type: none"> Unipolar QS/rS patterns with sustained periodicity (focal)⁶² 	<ul style="list-style-type: none"> Intuitive way to detect the potential origin of focal activations Unipolar QS/rS morphology may arise from mechanisms other than truly focal sources (breakthroughs from intramural re-entry or endo-epicardial dissociation, stationary rotors, microreentry, or tissue discontinuities)³⁷ Centrifugal propagation is not assessed⁶² The last limitation above also applies here
CFAEs (rotational?)	<ul style="list-style-type: none"> Visual detection without a proprietary system is possible 	<ul style="list-style-type: none"> Parameters of difficult physiological interpretation have to be set for automatic detection CFAEs are not specific as a footprint of AF drivers.^{93,105,106} Indeed, most CFAE sites lay remote from rotors and foci detected by phase mapping of electrograms acquired with basket catheters.¹⁰³

Continued

Table 3 Continued

Mapping strategy

Cons & limitations

Pros

	Cons & limitations	Pros
Spatiotemporal dispersion (rotational)	<ul style="list-style-type: none"> A clearer, unambiguous, objective, and quantifiable definition of spatiotemporal dispersion would be desirable It may be a footprint of (rotational) drivers,⁵⁷ but its specificity is not demonstrated 	<ul style="list-style-type: none"> Same as above
1iAM/1iFM (rotational)	<ul style="list-style-type: none"> Marking activations is required (may be difficult in complex or fractionated signals) 	<ul style="list-style-type: none"> It detects the footprint of rotational activity using sequentially acquired single signals with very high sensitivity and specificity⁸
Activation rate mapping (hierarchical)	<ul style="list-style-type: none"> Challenging interpretation with multiple spectral peaks of similar height (Figure 2A and B) Time intervals with the highest instantaneous frequencies usually show the lowest amplitudes and vice versa, which bias DF values⁸ Not very sensitive to dynamic variations of the activation rate during selected time windows 	<ul style="list-style-type: none"> Easy to determine and computationally efficient Good surrogate for activation rate when signals are good quality and quite regular in amplitude and frequency
Dominant frequency (DF)		
Frequency domain (spectral) analysis	<ul style="list-style-type: none"> Accurate determination is challenging with complex signals and requires properly designed and robust algorithms that are less computationally efficient than those for determining DF 	<ul style="list-style-type: none"> It enables to automatically detect regions with high regularity/periodicity (low standard deviation of cycle lengths) which is used in some approaches^{58,61}
Time domain analysis		
Cycle length		
Instantaneous frequency modulation (iFM) ⁸	<ul style="list-style-type: none"> Same as above 	<ul style="list-style-type: none"> It tracks dynamic changes in the local activation rate during acquisition (Figure 2C) Automatic detection of transient bursts of focal/breakthrough activity potentially contributing to (re)initiate or maintain AF Automatic detection of rotational footprints using single signals (in combination with iAM)

Table 4 Classification of mechanistic approaches for mapping and ablation of AF according to their ablation targets

Ablation targets	Pros	Cons & limitations
Sustained or repetitive patterns regardless of their activation rates	<ul style="list-style-type: none"> Its role as AF driver is supported by studies using multielectrode plaques and activation sequence mapping³⁶ Several clinical studies reported AF slowing/termination when targeted^{53,59,60,62,69,74} 	<ul style="list-style-type: none"> It does not consider the activation rate hierarchy demonstrated in high-resolution mapping studies during cardiac fibrillation^{8,50,85} ⇒ potentially unspecific (see text) Criteria for 'sustained' or 'repetitive' is not homogeneous among approaches It may be artifactually created by low spatial resolution + activation sequence mapping^{88,89} If created by breakthroughs in one layer produced by waves propagating on the contralateral layer,³¹ ablation would make no sense
Rotational	<ul style="list-style-type: none"> Its role is supported by computational and experimental models of AF mapped with high resolution (optical mapping)^{8,50,104} Several clinical studies reported AF slowing/termination when targeted^{53,59,60,69} 	<ul style="list-style-type: none"> The first two limitations above also apply here It may be artifactually created by low spatial resolution + phase mapping + interpolation⁸⁷⁻⁸⁹
Localized Irregular Activation	<ul style="list-style-type: none"> One clinical study reported AF slowing/termination when targeted⁶⁰ 	<ul style="list-style-type: none"> The first two limitations for centrifugal patterns also apply here Experimental evidence of its role as AF driver is lacking, although it might be consistent with some mechanisms^{8,39} (see text)
Earliest sites of activation (ESA)	<ul style="list-style-type: none"> It might be congruent with sustained focal, breakthrough or even stationary rotational mechanisms 	<ul style="list-style-type: none"> It does not consider activation rate hierarchy^{8,50} It does not seem well suited to identify drifting or meandering rotational activity as ESAs It does not allow to discern the underlying mechanism It is unclear how many electrodes over that area are required to apply this technique successfully⁷⁷
High activation rate (high DF, high iFM or short cycle lengths)	<ul style="list-style-type: none"> It does consider activation rate hierarchy^{8,50} ⇒ potentially more specific Achieved AF acute termination and non-sustainability in 92% of pigs with self-sustained PsAF for several months⁸ 	<ul style="list-style-type: none"> Some claim that regions with lower activation rates may drive if display specific activation patterns (focal, rotational) DF-guided ablation offered suboptimal outcomes using point-by-point bipolar mapping with an ablation catheter⁴⁸ iAM/iFM methodology⁸ needs further validation in larger sets of patients
High regularity	<ul style="list-style-type: none"> Convenient for detecting regions with 1:1 conduction from periodic focal activity/stationary rotors Some approaches consider activation rate hierarchy^{58,61} 	<ul style="list-style-type: none"> Locations potentially hosting drifting rotors (high variability in cycle length) that may act as AF drivers are ignored Some approaches do not consider activation rate hierarchy⁶²
Complex fractionation	<ul style="list-style-type: none"> CFAEs may colocalize with potential drivers of AF (rotor cores)³³ 	<ul style="list-style-type: none"> It does not consider activation rate hierarchy^{8,50} Most CFAEs are passive, consequence of fibrillatory conduction, wavefront collision, drifting/acceleration of rotors, fibrosis, or an artefact of the bipolar recording methodology^{49,105,106} ⇒ unspecific
Spatiotemporal dispersion (STD)	<ul style="list-style-type: none"> It may colocalize with potential (rotational) AF drivers⁵⁷ When targeted, AF termination in 95% of patients was reported⁵⁷ It may explain both successful outcomes after ablating CFAEs and their lack of specificity (CFAEs covered 70% of the STD regions yet 77% of CFAEs were found in regions without STD)⁵⁷ 	<ul style="list-style-type: none"> It does not consider activation rate hierarchy^{8,50,85} Criticized by some as a 'déjà vu' of CFAEs and a 'vague' ablation target,¹⁰⁷ since based on visual identification A software with automatic identification according to objective criteria would be preferable

Table 5 Features of the most representative mechanistic approaches for mapping and ablation of AF according to a classification based on five criteria

Approach/methodology/system	ECGi	CFAE	HDF	FIRM	CINS	NEEES	STD	CF	RR	iAM/iFM	CD	FaST	RADAR	STAR
Companies involved through experimental versions	BW	BW SJM*							ABT					
Companies involved through commercial versions	SJM										ACM	AFTx	RAI	
Representative references	63,92,108	47,48	9,33,66,67	ABT	MDT	EPS	VM	BW	58,61	8	60/51,101	62	59	76,77
1. Type of acquisition	Simultaneous/global													
	Endocardial basket													
	Body surface													
	Non-contact multipolar catheters													
	Point-by-point													
	Contact multipolar catheters													
2. Signals used for creating maps	Unipolar													
	Endocardial extracellular potentials													
	Bipolar													
	Aggregated													
	Estimated from body surface potentials by solving the inverse problem (ECGi)													
	Tissue CD estimated from intrachamber electrical fields													
3. Anatomy used for displaying maps	Electroanatomical map													
	Computed tomography													
	Magnetic resonance imaging													
	Ultrasound reconstruction													
4. Type of mapping	Detection of specific activation patterns (e.g. rotational, focal)													
	Direct													
	Phase mapping													
	AS and/or CV mapping													
	Unipolar QRS and periodicity (focal)													
	CFAEs (rotational?)													
	STD (rotational?)													
	iAM/iFM (rotational)													
	DF													
	Activation rate mapping (hierarchical)													
	Frequency domain (spectral) analysis													
	Time domain analysis													
5. Ablation targets	Centrifugal/focal													
	Sustained or repetitive patterns regardless of their activation rates													
	Rotational													
	Localized irregular activation													
	Earliest sites of activation													
	High activation rate													
	High regularity													
	Complex fractionated atrial electrograms (CFAEs)													
	Spatiotemporal dispersion (STD)													

ABT: Abbott; ACM: Acutus Medical; AS: Activation sequence; BW: Biosense Webster; CD: Charge Density; CF: CartoFinder; CFAE: Complex Fractionated Atrial Electrogram; CINS: CardiInsight; CL: Cycle Length; CV: conduction vector; DF: high dominant frequency; ECGi: electrocardiographic imaging; EPS: EP Solutions; FaST: focal impulse and rotor modulation; iAM: instantaneous Amplitude Modulation; iFM: instantaneous Frequency Modulation; MDT: Medtronic; NEEES: non-invasive endocardial and epicardial mapping system; RADAR: real-time electrogram analysis for drivers of atrial fibrillation; RAI: Rhythm AI, Ltd; RR: repetitive-regular; SJM: St Jude's Medical (currently Abbott); STAR: stochastic trajectory analysis of ranked signals; STD: Spatio-temporal dispersion; VM: Volta Medical.

The insights provided by these mechanism-based approaches using widely different technologies have created a growing body of evidence in favour of organized drivers underlying human AF maintenance. However, the ultimate underlying mechanism in each patient remains unresolved. Thus, different approaches provide different descriptions of the AF drivers and their spatiotemporal stability (e.g. long-standing drivers vs. short-lived but iteratively appearing drivers in restricted regions). In general, most methodologies coincide in that there is a predominant re-entrant nature of AF drivers (Figure 3H). Interestingly, some of these seemingly different underlying mechanisms might converge if one considers the 3D nature of the atrial tissue and the different mapping types (e.g. activation sequence vs. phase mapping), spatial resolution, filtering and interpolation methods used to display the atrial electrical data.¹² For example, excessive interpolation/filtering or lack thereof may lead to differing conclusions about the actual stability of AF drivers.¹² In addition, rotors/intramural re-entry and foci may be dynamic manifestations of the same mechanism within the 3D structure of the atria (Figure 1E).

A good example of how the methodology might affect driver description is represented by the data reported using CD mapping. This strategy found the lowest proportion of re-entrant drivers (See CD⁶⁰ in Figure 3H), although the authors proposed an alternative type of alleged driver called localized irregular activation (LIA: repetitive, multidirectional entry, exit, and pivoting conduction through and around a confined -isthmus like- zone) that accounted for 44% of the patterns targeted for ablation in that study.⁶⁰ Interestingly, from a wider perspective, when LIA patterns are added to the proportion of rotational drivers they converge with the values of the remaining approaches for re-entrant drivers alone (around 70-80%. Figure 3H). Indeed, the authors have also reported that some LIA patterns occasionally alternated with breakthroughs and/or rotational conduction patterns on the same site.⁷⁵ The latter may be consistent with drifting or meandering intramural scroll waves whose filaments are only occasionally perpendicular to the mapped surface,^{51,82} or arrhythmogenic hubs of intermittent re-entry around fibrotic substrates.³⁹

5. Acute and long-term clinical outcomes of mechanism-based approaches for AF ablation

Most mechanism-based ablation strategies reported to date include PVI in addition to targeting any alleged AF driver. Figure 4A summarizes the ablation strategy in the mechanism-based mapping group for each of the methodologies described above. PVI was performed before targeting any extra-PV target in some approaches (CF,^{55,74} CD,⁶⁰ FaST,⁶² RADAR,⁵⁹ STAR^{76,77}), although subsequently in others (HDF for PsAF,⁴⁸ FIRM,^{9,53,66} ECGi,⁷¹ RR^{58,61}). In some series, PVI was not even performed unless drivers were found in the PV region (HDF for PxAF,⁴⁸ STD⁵⁷) or PVs were electrically reconnected in redo procedures (iAM/iFM⁸). Most protocols encouraged the incorporation of any identified targets near the PVs into a wide antral lesion set performed for PVI. For extra-PV sites, some approaches included closely spaced radiofrequency applications to achieve a significant electrogram amplitude decrease or even abatement through the creation of coin-like sets of lesions (HDF,⁴⁸ FIRM,^{9,53,66} ECGi,^{69,71} STD,⁵⁷ iAM/iFM,⁸ CD,⁶⁰ STAR^{76,77}). Others aimed at delivering a pre-specified amount of radiofrequency energy at each site (FaST⁶²). Some ablation strategies aimed at intentionally creating lines by crossing the distribution of singularity points of rotational drivers

up to unexcitable boundaries when available (CF sequential,⁵⁵ CD⁶⁰), or at joining ablated areas when they were closely located (STD⁵⁷). Other strategies intentionally avoided line formation (CF basket,⁷⁴ STAR^{76,77}). In some series, the ablation approach depended on the location and shape of the alleged driver region: encircling of the identified region, point-by-point ablation covering the entire region or linear lesions (RR^{58,61}). In others, the ablation approach was not standardized and left to the operator's discretion (RADAR⁵⁹). In essence, the optimal way of targeting an alleged AF driver is still unresolved. Some approaches even included additional empirical lines on the left atrium after driver ablation (HDF for PsAF,⁴⁸ FIRM,^{9,53,66} ECGi,^{69,71} RR^{58,61}).

Radiofrequency delivery times for ablation of alleged drivers show progressively longer times as AF complexity increases (Figure 4B). In the studies in which data for different AF types were unbundled (FIRMc,⁶⁶ ECGia,⁶⁹ STD⁵⁷), there was a direct relationship between radiofrequency delivery times and previous AF duration. Radiofrequency times for driver ablation in patients with long-standing PsAF (>1 year) were usually the longest, which is consistent with a higher number, extension and complexity of AF drivers (Figure 3E). The longest ablation times have been reported in the approaches in which acute AF termination was a primary endpoint of the procedure (ECGiac,^{69,71} STD⁵⁷), and these times were even longer when considering the additional lines performed in some strategies (ECGiac^{69,71}).

AF termination during the procedure is also affected by the underlying complexity of the atrial substrate based on AF duration. Data from the series that reported unbundled rates (FIRMc,⁶⁶ ECGia,⁶⁹ RRb⁶¹) confirmed that acute termination rates on ablation were lower when AF duration increased (Figure 4C). Acute termination rates (either conversion to atrial tachycardia—AT—or sinus rhythm) were also higher in the approaches that included AF termination as a primary endpoint (ECGiac,⁶⁹ STD⁵⁷), although such an endpoint was associated with longer radiofrequency delivery times. These studies also achieved high rates of freedom from AF after a single procedure at 12 (ECGic⁷¹) or 18 months (STD⁵⁷) (Figure 4D), although with frequent recurrent AT/flutter that required additional procedures (Figure 4E). In this regard, recurrence in the form of AT/flutter before 12 months was not uncommon in patients from the study of Miller et al. (FIRMc) either.⁶⁶ These data indicate that extra-PV lesions may generate additional substrate for macroreentry. Freedom from AF and AF/AT after multiple procedures were considerably better (Figure 4F), although the proportion of patients with recurrent AT after multiple procedures was not negligible in some studies in which single-procedure outcomes were not reported (ECGiac,⁶⁹).

Interestingly, among all the approaches, the outcomes of STAR^{76,77} catch the attention. The authors report substantially better long-term outcomes after multiple procedures (100% free from AF/AT) or even after a single procedure at 17–18 months of follow-up (>80% free from AF/AT off AAD) than the rest of mechanism-based strategies (Figure 4D and F). Surprisingly, these results were obtained with the shortest radiofrequency delivery times for driver ablation (~6 min Figure 4B) in a population that included almost 70% of patients with long-standing PsAF.⁷⁶ The authors also reported acute AF termination on driver ablation in ≥75% of these patients. Conversely, other series have reported only 15% of acute AF terminations in patients with long-standing PsAF after an average of 33 min of radiofrequency delivery for driver only ablation (see ECGiac,⁶⁹ in Figure 4B), or up 45% of acute AF terminations after a median of 53 min when including left atrial lines. Calvo et al. (CF sequential) also achieved remarkable good 12-month outcomes in a series of 13 selected patients with long-standing PsAF (70% in sinus rhythm) after targeting all rotor domains with an average of ~18 minutes of

radiofrequency delivery.⁵⁵ However, the acute termination rate reported by Calvo and colleagues was 15%, which still is far below the $\geq 75\%$ reported for the STAR approach.^{76,77} These results from the STAR series, although striking, might be explained by a different population subset with lower levels of atrial remodelling.⁸³ This may be related to the criteria used for calculating AF duration among series, which could be the time from the first AF episode, the time from the first persistent AF episode (lasting >1 week), or the continuous time from the onset of the latest AF episode. To avoid misinterpretations, it would be desirable to have unified criteria for reporting AF duration and ablation outcomes in future studies.

Nowadays, any evidence against the effectiveness of specific driver-guided AF ablation strategies need not undermine its validity but may instead reflect some shortcomings of the technology (Table 1). Overall, current data from meta-analyses provide some support to target and ablate driver regions in addition to PVI in PsAF patients.⁸⁴ However, the evidence mainly comes from uncontrolled and non-randomized studies, with substantial heterogeneity in reported outcomes.

6. Specificity of mechanism-based approaches for ablation of AF drivers

Most of mechanism-based approaches target and ablate the alleged drivers regardless of their activation frequency dynamics. However, multiple *in vivo* and *ex vivo* experimental studies and several human series support the presence of a spatial activation rate hierarchy during cardiac fibrillation,^{3,8,38,45–47,50,85} with the fastest region domains hosting AF drivers associated with AF termination.^{3,8,38,47,86} The latter notwithstanding, fast dominant regions may be difficult to identify as the AF substrate evolves and atrial signals become fractionated.⁸³ Fully automatic algorithms may fail to detect the fastest domains on complex fractionated signals (Figure 2A and B).⁸ Further details about potential limitations of DF analysis have been discussed elsewhere.^{8,12}

This issue of hierarchical organization on AF dynamics may substantially affect the specificity of detected drivers on several mechanism-based approaches including those relying on a spatiotemporal probabilistic density criterion. Therefore, many mechanism-based ablation approaches may be potentially unspecific and detect other secondary patterns of activation as drivers. In other approaches, the methodology completely ignores regions hosting signals that are not almost completely periodic (e.g. RR, FaST),^{58,62} so they may completely miss potential driver regions hosting drifting rotors that give rise to decreased periodicity by producing modulations in the instantaneous frequency of the signals due to a Doppler effect (Figure 2C).⁸

It is worth mentioning that in a recent comprehensive translational study,⁸ half of leading-driver locations were found in the coronary sinus/left atrial floor or left atrial appendage/free wall. However, such driver locations may be difficult to map with some proprietary systems, especially those using basket catheters,^{53,67,74,76} or surface (epicardial or endocardial) potentials from the ECGi^{69–71} and CD⁶⁰ technologies. Although the latter systems certainly offer advantages for rapid and efficient map creation, they also may not be optimally suited to map certain atrial regions. For these reasons, and in order to overcome the spatial resolution limitations of some panoramic and simultaneous acquisition systems,^{87–89} we submit that single-signal algorithms (e.g. iFM/iAM or FaST mapping),^{8,62} or others using high-density sequential local

acquisition with multipolar catheters (e.g. STD,⁵⁷ RR,⁵⁸ CF sequential,⁵⁵ STAR sequential⁷⁷ or RADAR mapping⁵⁹) could be integrated into standard electroanatomical mapping systems to improve driver detection accuracy and reduce the cost of mechanism-based approaches for PsAF ablation. Recent data also support short and mid-term stability of AF driver maps,⁸ which potentially overcomes any alleged problem of sequential mapping in a highly dynamic arrhythmia like AF.

7. Scientific and clinical challenges of implementing preclinical work and novel mapping methods into clinical practice

Most of novel mapping methods described in this article will never make it into everyday clinical practice. This section discusses some of the reasons and obstacles in such an implementation, using several examples from the past.

Most importantly is to understand the key stakeholders who are involved in such an endeavour. First, the basic scientists; that is basic electrophysiologists. For the majority of them this is not just an intellectual challenge, they strive to investigate fundamental mechanisms and bring new theories and concepts to be implemented in the clinical setting. Those who select the field of AF rely on their previous education or develop their experience along their career, thus increasing knowledge of mechanisms, but often such knowledge reaches clinical practice only indirectly, or not at all. Second, translational electrophysiologists, combine their basic research with their own clinical practice, implementing their clinical understanding in order to turn those fundamental ideas into practicality. This comes from being exposed to various technologies that may be similar, matching or even opposite to their methods. A third group is the clinical electrophysiologists who perform clinical cases. Many of the clinical electrophysiologists prefer a method or technology that will allow them to conduct a case safely with a reasonable outcome in the shortest possible time. All the above-mentioned groups contribute to the mission of AF treatment; however, most likely, only through collaboration with industry will their methods/concepts be implemented into the clinic.

The other half of this partnership is the medical device companies and their engineers. Industry, in general, is challenged by supporting all the abovementioned electrophysiologist groups in solving the mystery of AF, while maintaining a profitable income. This partnership may not be so easy to explain since either side hangs on to the other. This means that an invention or new idea will make it to realism if it can be turned into a unique software module or device that will create a market advantage to an individual company. A couple of major obstacles in this partnership are apparent: (i) it is extremely challenging to obtain a consensus regarding clinical need among the above various groups. While some highlight the need for advanced mapping techniques,⁹⁰ others demand integrating imaging modalities,⁹¹ while still others mandate advanced ablation technologies;⁵ and (ii) Companies are constantly striving to identify new technologies and be the first to introduce them to the market, even if they do not satisfy all electrophysiologists' requests.

A key consideration by the clinical electrophysiologists and industry for implementing a new technique is the degree of interface with their current workflow. This deserves some more explanation: assume that the current treatment consensus is PVI,¹ and that the majority of the clinicians will choose the technology because it will allow them to reach

that first line of treatment safely and in the shortest possible time. Companies will accept this direction only if a new device is associated with that consensus. The best example so far is the adoption of the cryoballoon ablation technology.⁵ It complements perfectly the aspiring thinking of clinicians: simple to apply, shorter procedure, effective workflow, and equal clinical outcome as a more difficult ablation procedure based on point-by-point radiofrequency delivery.⁴¹ Moreover, it is a device that creates the perfect competitive advantage for a medical device company in the AF ablation market. Such a rare consensus between the clinician and a medical device company creates its large implementation.

However, not every new technology turns into an equivalent success. For instance, in 2004, Nademanee et al. established the concept of CFAEs.⁶³ While the mapping method came from Nademanee, collaboration with mapping companies yielded special dedicated software produced and embedded in the system. At the time, this appeared like a breakthrough technique, which helped in its adoption. Later, the results from the STAR-AF 2 trial showed that the addition of further ablation (lines or CFAEs) to PVI increased ablation time but did not reduce the recurrence of AF in patients with PsAF.⁹² Moreover, novel approaches as the strategy reported by Seitz et al.⁵⁷ have provided a more advanced interpretation of high-density maps with CFAEs and their potential correlation with underlying AF drivers.⁹³ Therefore, further technical development, improved substrate characterization, and the potential to increase previous clinical outcomes have made conventional CFAE ablation no longer attractive to device companies. The clear message is that once the scientific track has surfaced, many others will focus on improving and implementing new techniques.

One of the most challenging theories in mapping AF, spiral waves (rotors), was introduced in the early 1980s. While the physical phenomenon was known for many years, the biophysical evidence was not. Jalife et al. validated, for the first time, the biophysical concept by visualizing spiral waves in isolated beating hearts.³² The spiral wave/rotor theory was confirmed later on by many additional basic, translational, and clinical electrophysiologists.^{38,46,50,51,53} Yet, the technology was not implemented extensively in clinical labs for treating patients, which reflects the difficult step of moving knowledge from basic and preclinical science to the clinic. Although there is no straightforward answer to explain why such robust experimental data did not move directly into the clinic, some historical events may contribute to the understanding: In 2006, Haïssaguerre et al. following PVI were able to demonstrate localized sources during mapping of PsAF using a multipolar catheter.⁹⁴ Yet, the company producing this catheter did not adopt the localized sources as a therapeutic strategy, and did not market the catheter as a tool for treating AF. At that time, electroanatomical mapping systems and computational algorithms were still not ready to process thousands of complex signals and identify highly dynamic rotational patterns as those observed with optical mapping.^{50,51} Moreover, during the first decade of the twenty-first century, many questions were still open to understand the role of PVI in different AF settings. It took several more years of additional preclinical work until Narayan et al. pioneered a new perspective of clinical mapping with the FIRM concept.⁵³ Their mapping technique seemed to be the best formula to be adopted not only by the clinical electrophysiologists, but also by industry, given that the basket was a 'single use' strategy, had a high price tag, and provided a potential link to pre-clinical studies in animal models. Yet, while industry build-up grew high, several groups of electrophysiologists remained sceptical. The combination of a non-disclosed formula with the inability to duplicate similar successful outcomes in general practice contributed to the low rate of adoption of the technique. Clinicians, who were early adopters, reported

longer procedure time (by more than 45 minutes), complained about the mismatch between basket catheter size and heart anatomy (non-contact), and were frustrated by inability to interpret the acquired maps. All those reasons contributed to disbelief and lack of new reports for additional development by the company.

Non-invasive strategies as the ECGi also face problems for clinical implementation and further technological development may be at risk. Part of the reasons associated with low clinical implementation of novel mechanism-based technologies have already been described above; however, further understanding of AF mechanisms is still mandatory. Broad implementation of mechanism-based strategies for AF mapping in the clinic will require to fulfil: 1) most important of all, increased cooperation between basic electrophysiologists and industry; 2) ease of use, regardless of whether it is new software or a device; 3) minimal interference with the lab workflow (minimal prolongation, or better yet, shorten the procedure time—the mapping step should not exceed 20 minutes); 4) provide a clear and better acute clinical result (ablating the mapped sources should end all atrial arrhythmias in >75% of cases); and 5) deliver a better long-term clinical outcome. Ultimately, commercial considerations, which are not always exposed by the companies, may cause good technologies to vanish.

8. Looking into the future of mechanistic human AF mapping technologies

The perfect AF mapping technology is still on the fence at both experimental and clinical levels. In fact, three-dimensional mapping of complex activation patterns during AF is still not possible with current optical mapping technology.⁹⁵ However, this scientific breakthrough may be closer with the advent of photoacoustic voltage-sensitive dyes that might allow (with the proper technology)⁹⁶ obtaining 3D information of wave propagation dynamics within the myocardial wall during fibrillation. On the other hand, the recent demonstration of co-existing electrical and mechanical rotors in the heart has opened a new horizon in the characterization of the spatiotemporal organization of cardiac fibrillation.⁹⁷ Christoph et al. demonstrated that optical mapping in combination with ultrasound imaging can provide simultaneous measurements of membrane potential, intracellular calcium, and mechanical contraction at the organ level. This technology has shown co-existing electrical and mechanical rotors in the ventricles of pigs.⁹⁸ While not quite there yet, further technological advances in high-resolution ultrasound and optical mapping may provide insights into the dynamics of atrial fibrillation as well, and form the basis for translation of electromechanical imaging into clinical application. Until then, current data support AF dynamics as a deterministic phenomenon rather than random. Therefore, we consider that, whichever the mechanism-based strategy, it is important to establish a hierarchical criterion based on activation frequency to be able to discern which alleged drivers are truly relevant for AF maintenance. This should require novel and advanced signal processing algorithms that may accurately measure atrial activation rates for complex or low-voltage signals. Perhaps, in the mid-term, further development of novel *in vivo* optical mapping approaches would facilitate this task.⁹⁹ Optical action potentials would eliminate far-field problems associated with current bipolar and unipolar signals. The latter may be critical for accurate mapping in complex substrates with highly fractionated signals. Microfibre technology incorporated into catheters with several mapping splines or wide

illumination through balloon-type catheters, in combination with percutaneous intracoronary injection of novel voltage sensitive and near-infrared dyes may represent a significant step forward in cardiac mapping of complex arrhythmias.⁹⁹ In our opinion, current mechanism-based procedures for AF mapping can already increase their specificity. A sequential strategy based on delivering energy first on stable driver locations following an order established by their frequency hierarchy through accurate measurements of their dynamically changing activation rate may do the job.⁸ This would prevent unnecessary scar formation, potentially reducing the likelihood of iatrogenic atrial tachyarrhythmias,^{57,66,71} and other potential sequelae associated with extensive atrial ablation.¹¹

Conflict of interest: D.F.-R. and J.G.Q. are inventors of the patent #EP3636147A1 related to a method for the identification of cardiac fibrillation drivers.

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