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Medical Devices & Supplies

Next Big Things: Why Pulsed Field Ablation Will Revolutionize the Treatment of AF

Catheter ablation of cardiac arrhythmias represents one of the best end markets in MedTech, with worldwide sales growing at an 11% CAGR over the past decade to top $7.2B in 2022. This remarkable growth has been fueled primarily by improvements in catheter-based treatment options for atrial fibrillation, a condition which results in a fivefold increase in stroke risk and that the CDC estimates will affect >12M Americans by 2030. While our clinical understanding of AF and the tools available to electrophysiologists to address it have both improved markedly over the past two decades, catheter ablation remains an imperfect procedure today, associated with mediocre long-term efficacy and rare but potentially serious complications. Many of these drawbacks are related to the energy used to ablate the myocardium, either RF or cryo. Pulsed field ablation (PFA) has the potential to revolutionize the treatment of AF by eliminating many of these shortcomings.

Safer, faster, more effective. PFA uses an electric field to create nanoscale pores in the cell membrane, a process known as irreversible electroporation (IRE) which leads to cell death but leaves the extracellular matrix intact, facilitating fibrous scar formation. Cardiomyocytes have a lower threshold to electric field strengths, which enables their selective targeting while sparing adjacent structures such as nerves and blood vessels. And unlike radiofrequency or cryoablation, PFA waveforms deliver energy below the thermal threshold. This avoids the conductive heating/cooling which leads to many of the complications associated with thermal energy sources. Early clinical data suggest that this unique mechanism of action enables PFA systems to rapidly create transmural lesions, resulting in greater first treatment efficacy with fewer adverse events than traditional ablation techniques.

While we're bullish on PFA as a technology, we don't believe all PFA systems are created equal. The pulsed field waveform is significantly more complex than the energy modalities that preceded it, with numerous variables determining the "dose" being delivered to the myocardium and the quality of the resulting lesion. And while a wide variety of PFA systems have demonstrated the ability to achieve acute electrical isolation, sub-threshold dosing or gaps in the lesion set can result in eroding durability over time. Certain catheter designs may also be more prone to complications, something we expect both clinicians and patients to have a low tolerance for. Finally, we see ease of use as a key consideration, with PFA offering the potential to democratize AF ablation by enabling lower volume centers and less skilled operators to achieve high-quality results. Taking all these criteria into account, while we believe MDT's PulseSelect and JNJ's Varipulse have the potential to be competitive as the PFA market develops, we currently view BSX's Farapulse as the best positioned technology.

Stock implications. We estimate that ablation catheters represent ~40% of the $7.2B WW EP ablation market, of which we think BSX has just a low double-digit share today. Raising that share to 25% by 2026 could add nearly $800M in revenue over the next four years. At the other end of the spectrum, ABT is several years behind its competitors in the race to develop a PFA system, putting its own $2B EP business at risk. Meanwhile, we see mixed implications for MDT, with success in PFA likely necessary to offset potential losses in its Arctic Front cryo franchise, which we believe could be meaningfully cannibalized as PFA adoption ramps.

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Medical Devices & Supplies

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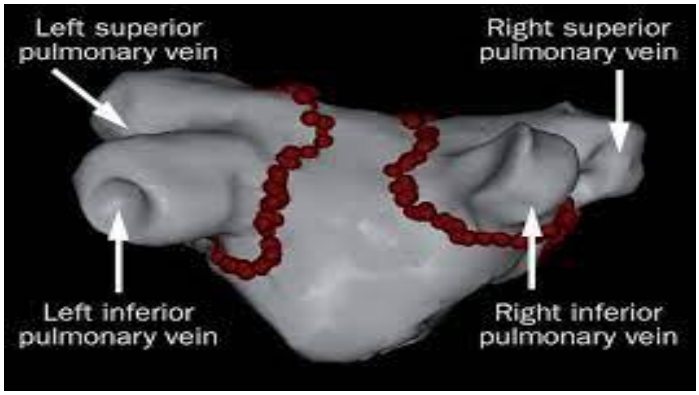
Pulsed Field Ablation: The Science Behind the Technology

Atrial fibrillation (AF) is a type of cardiac arrhythmia characterized by rapid and irregular beating of the left atrium. While its full pathoetiology is unknown, in many cases these aberrant heart rhythms are driven by ectopic signals originating from the pulmonary veins. Atrial fibrillation is typically classified as either paroxysmal or persistent. Paroxysmal atrial fibrillation (PAF) is defined as AF that terminates spontaneously or with intervention within seven days of onset while persistent episodes have durations lasting longer than one week. If left untreated, AF can lead to blood clots, stroke, heart failure, and other heart-related complications.

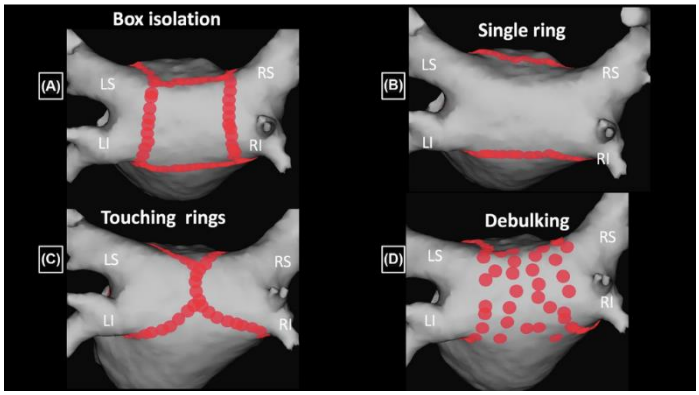
Dr. James Cox developed the first open surgical approach to the treatment of AF in 1987 with the introduction of the Cox maze procedure, in which a maze-like pattern of incisional scars is made in the atria to block abnormal electrical currents. While this procedure proved highly effective, its invasiveness led to limited use outside of situations when it could be performed concomitantly to CABG or surgical valve repair/replacement. In 1998, Dr. Michelle Haissaguerre described the first use of catheter ablation for the treatment of AF, kicking off a revolution that resulted in the >$7B global market we see today. Dr. Haissaguerre found that ~95% of AF triggers originated in the pulmonary veins. This established pulmonary vein isolation (PVI), in which the ostia and/or antra of the pulmonary veins are ablated, as the foundational element of AF procedures. Physicians may supplement PVI with additional lesions to electrically isolate other regions of the heart, such as the posterior wall of the left atrium, or focally ablate other trigger areas.

Fig. 1: Pulmonary Vein Isolation



Source: *Nature Reviews Cardiology* – Latchamsetty & Oral 2014

Fig. 2: Posterior Wall Ablation

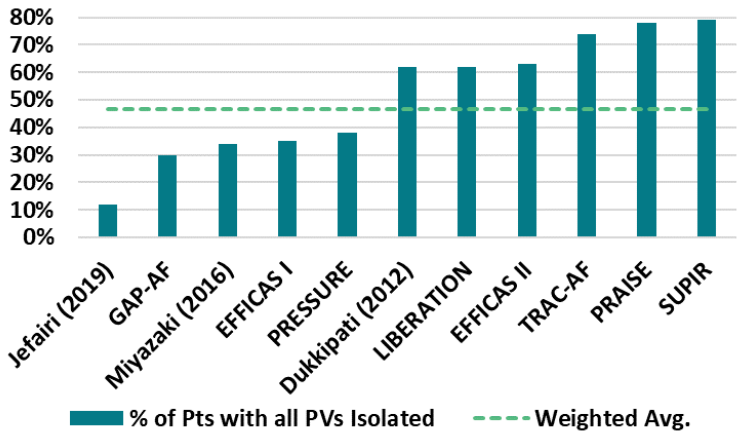


Source: *Journal of Cardiovascular Electrophysiology* –Sugumar et al 2017

While catheter ablation for AF is now widely accepted as an alternative to drug therapy, it remains an imperfect procedure. In 2019, the >2,200-patient CABANA trial demonstrated that catheter ablation significantly improves quality of life in AF patients compared to medical management. Meanwhile, the recently published EARLY-AF study found that patients with paroxysmal AF who underwent cryoablation as first-line therapy were less likely to progress to persistent AF (1.9% vs. 7.4%) or be hospitalized (5.2% vs. 16.8%) than those who were given antiarrhythmic drugs. While we believe EARLY-AF has the potential to drive further adoption of catheter ablation as a treatment option, it also demonstrated some of the shortcomings of current ablation technologies. In particular, 57% of patients in the treatment arm experienced recurrent atrial tachycardias, suggesting that the PVI procedure was either incomplete or insufficient to resolve their arrhythmia. This is consistent with a recent literature review by Reddy et al. of 11 PVI studies using a variety of ablation catheters (RF, cryo, and laser), which found that just 74% of treated pulmonary veins were still electrically isolated when they were remapped on follow-up, while only 47% of patients had a durable PVI.

Besides mediocre efficacy, current ablation technologies are also prone to rare but potentially serious complications. In many cases this is due to thermal damage to structures such as the esophagus and phrenic nerve which lie in close proximity to the pulmonary veins. Several large real-world studies of catheter ablation in the U.S. and Japan have found in-hospital complication rates of 2-7%. Some of these events, such as atrio-esophageal fistula and stroke, can be deadly, while others like phrenic nerve palsy can materially impact patient quality of life. While this pales in comparison to the risks associated with leaving atrial fibrillation untreated, patients and physicians have an understandably low tolerance for poor outcomes from what is still, at its core, an elective procedure.

Fig. 3: PVI Success with Traditional Ablation Modalities

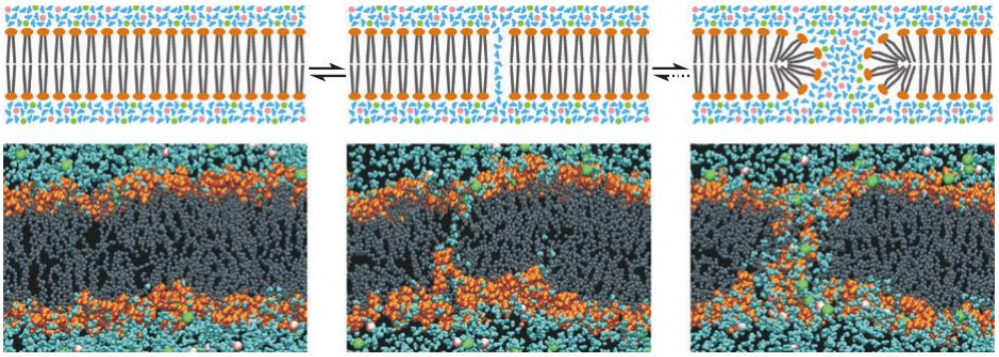


Source: Reddy et al 2019

We believe the complexity of AF ablation with current tools has also held back adoption of the procedure. Creating lesion sets with focal point-to-point ablation catheters requires significant operator skill, with procedures routinely lasting 3-4 hours. To aid physicians in this endeavor, a host of advanced electroanatomical mapping and navigation systems have been developed over the years. While this has added complexity to the procedure, its impact on outcomes has been less clear. Meanwhile, even procedures using "single-shot" PVI systems can take an hour or more and may require additional tools, such as an esophageal temperature probe, to guard against adverse events. As a result, we believe there is a clear need for a technology that simplifies the ablation procedure while delivering better efficacy and fewer complications than currently available options.

Pulsed field ablation (PFA) has the potential to satisfy this unmet need. This new modality uses an electric field to create nanoscale pores in the cell membrane, a destabilizing process known as irreversible electroporation (IRE). Once formed, these pores enable the passage of cellular contents out of the cell and ultimately lead to cell death. This is done while leaving the extracellular matrix intact, preserving the tissue's structural integrity. Experiments with IRE as a method of ablating cancerous tumors began in the early 2000s, with the first animal work evaluating its potential for the treatment of atrial fibrillation published in 2007. Researchers discovered that cardiomyocytes have a lower threshold to electric field strengths than other types of cells, such as nerve cells and smooth muscle, which enables their selective targeting while sparing adjacent tissues. And unlike thermal ablation techniques such as radiofrequency or cryoablation, PFA relies on energy inputs below the thermal threshold. This unique mechanism of action avoids the conductive heating/cooling used by thermal energy sources and allows for discriminate ablation of the myocardium while minimizing the thermal complications associated with RF and cryoablation.

Fig. 4: Electroporation of the Cell Membrane

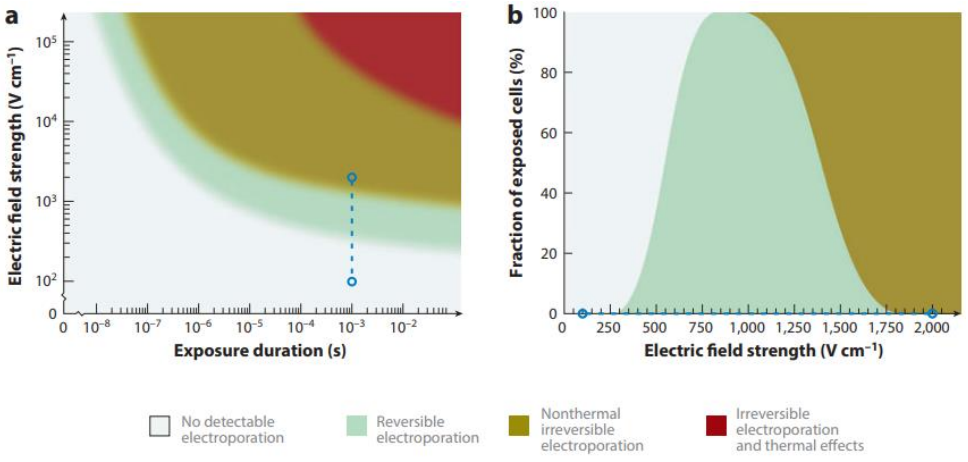


From left to right: (A) normal cell membrane, (B) reversible electroporation, (C) irreversible electroporation
Source: *Annual Review of Biomedical Engineering* – Martin Yarmush et al 2014

PFA may also be more forgiving than RF in terms of tissue contact. One of the biggest challenges with RF catheters historically has been ensuring good contact with the tissue being ablated, which is directly correlated with the quality of the lesion. This led to the introduction of force-sensing catheters, which our analysis of hospital purchasing data indicates are now used in the majority of U.S. EP ablation procedures. While tissue proximity still plays an important role with PFA catheters, as the electrical field only extends a few millimeters from the electrodes, the impact of that field on the myocardium is not contingent on physical contact with the tissue. This should make the procedure less cumbersome and easier to perform, especially for less experienced operators.

While all PFA systems have the same mechanism of action, a wide variety of parameters can impact their safety and efficacy. As shown in Figure 5, successful IRE can be achieved through many different combinations of electrical field strength and duration of exposure. This requires a delicate balance, however, as delivering too little charge can result in reversible electroporation, while too much induces a thermal effect. With reversible electroporation, the membrane pores are not large enough to cause permanent cell death. This can still result in cardiac stunning and loss of ECG signal, which could be falsely interpreted as electrical isolation but will not lead to a durable lesion. On the opposite end of the spectrum, PFA can result in thermal effects if improper parameters are selected (high voltage, increased pulsed width, etc.) or too many applications are delivered to a particular location.

Fig. 5: Electroporation and Thermal Effects Caused by Exposure to PFA

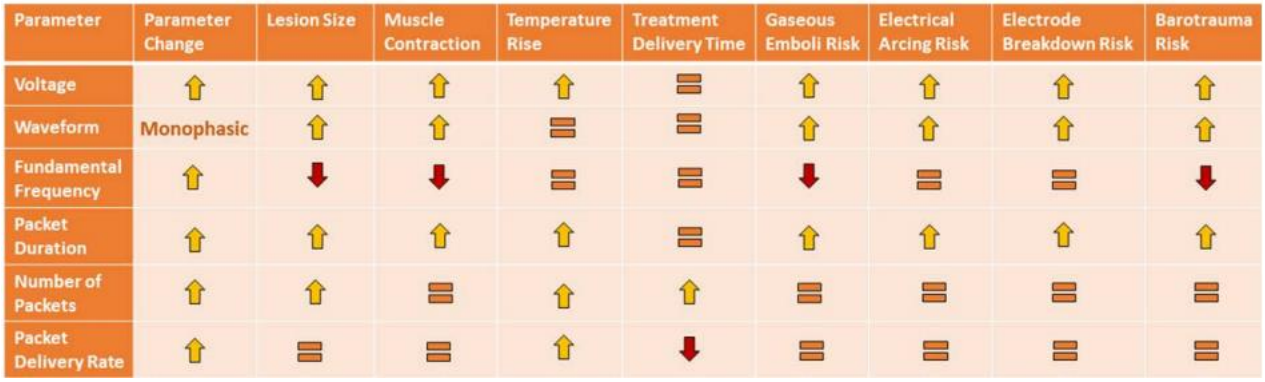


Source: *Annual Review of Biomedical Engineering* – Martin Yarmush et al 2014

PFA Parameters

Not all PFA technologies are created equal. As one speaker at the 2022 AF Symposium stated, "Once you've tried one PFA system, you've tried one PFA system." Unlike RF catheters that all share similar architecture, PFA design involves an extensive list of parameters that can alter the therapeutic effect of the device with even small modifications. These variables include voltage, polarity, waveform, pulse duration, and the number and configuration of electrodes. Each of the companies currently developing a PFA system has come up with a unique combination of these parameters in an effort to optimize the electrical field for ablation while minimizing deleterious effects such as heat generation, microbubble formation, and musculoskeletal stimulation. Figure 6 illustrates the potential effect of changing various PFA parameters on therapy delivery. We walk through the implications of parameter selection in more detail below.

Fig. 6: Effects of Variable Titration on PFA Treatment Delivery



Parameter	Parameter Change	Lesion Size	Muscle Contraction	Temperature Rise	Treatment Delivery Time	Gaseous Emboli Risk	Electrical Arcing Risk	Electrode Breakdown Risk	Barotrauma Risk
Voltage	↑	↑	↑	↑	=	↑	↑	↑	↑
Waveform	Monophasic	↑	↑	=	=	↑	↑	↑	↑
Fundamental Frequency	↑	↓	↓	=	=	↓	=	=	↓
Packet Duration	↑	↑	↑	↑	=	↑	↑	↑	↑
Number of Packets	↑	↑	=	↑	↑	=	=	=	=
Packet Delivery Rate	↑	=	=	↑	↓	=	=	=	=

Source: *Circulation: Arrhythmia and Electrophysiology* – Verma et al 2021

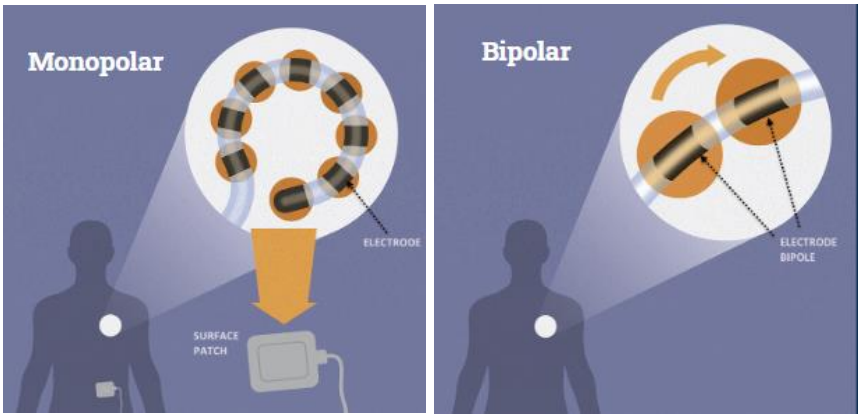
Voltage

Voltage directly affects PFA field density and treatment magnitude. However, higher voltages can be associated with thermal effects, increased muscle contraction, microbubble formation, and damage to other nerves and smooth muscle cells. To avoid complications, we expect most companies developing PFA catheters to restrict physicians to either one predefined voltage or low, medium, and high settings that cap voltage delivery at or around 2kV.

Polarity

Monopolar devices use electrodes with a single polarity. In this type of device, the electrical current flows between the electrode and a return patch placed externally on the body (usually the lower back for cardiac procedures). While this allows for greater field penetration and a deeper lesion, it also results in increased musculoskeletal recruitment and nerve stimulation (i.e. pain). Although we believe monopolar designs could have an advantage in patients with hypertrophic (thick) atria or ventricular tachycardia where deeper lesions are required, they may also result in more collateral damage to nearby structures, increased risk of coronary spasm, and a higher incidence of conduction disturbances as the electrical current travels through the heart on its way to the return patch. Meanwhile, bipolar devices feature sets of electrodes with alternating polarities, with the electrical current traveling from one electrode to the next. This yields an electric field that is more predictable, shallower, and localized, while reducing musculoskeletal activation and microbubble formation. While both monopolar and bipolar PFA devices are being developed today, we see bipolar as the superior parameter choice for most atrial fibrillation applications.

Fig. 7: Monopolar vs. Bipolar

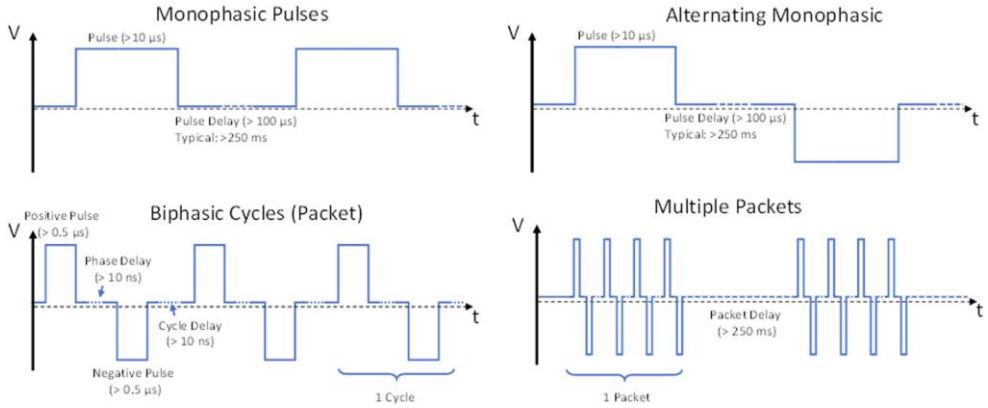


Source: www.bostonscientific.com

Waveform

PFA can be delivered via monophasic or biphasic waveforms. Monophasic waveforms are known to cause significant muscle activation, which may require the use of general anesthesia or neuromuscular paralysis agents. These waveforms can also be arrhythmogenic and cause microbubble formation. In contrast, biphasic waveforms are considerably less arrhythmogenic, lead to fewer microbubbles, and have limited skeletomuscular engagement, which allows for delivery under conscious sedation. They are also more efficient at lower energies given the reversal of current flow.

Fig. 8: Waveform and Pulse Parameters



Source: *Circulation: Arrhythmia and Electrophysiology* – Verma et al 2021

Pulse

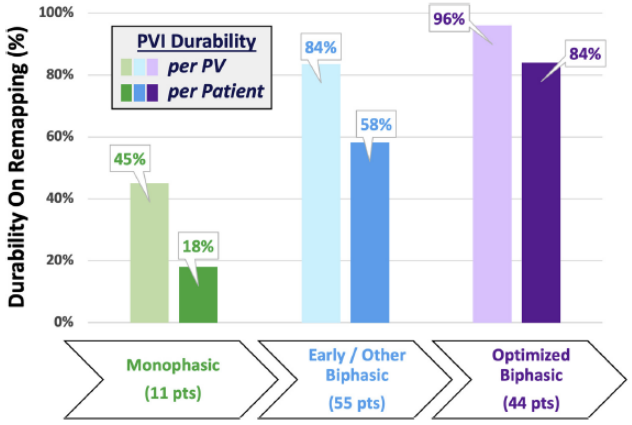
Pulse and interpulse duration can also be modulated, with longer pulse durations associated with higher permeability of cells to the electric field. Meanwhile, amplitude, frequency, and the asymmetry of the pulse can also impact the treatment effect. Repetition can have an impact on cell permeability as well, as impedance drops with each successive application, allowing more energy to enter the tissue. To take advantage of this, many devices use what are known as packets, or multiple pulses delivered in rapid succession (over nanoseconds to milliseconds). While this may increase the treatment effect, it has safety tradeoffs, the most important being cumulative temperature rise if there is insufficient time for heat to dissipate between applications.

Electrode Configuration

Electrode spacing, count, and geometry can all impact performance. Closer electrode spacing leads to smaller lesions. However, spreading the electrodes too far apart can cause gaps in the middle where the field strength falls below the therapeutic threshold. Overlapping electrodes can interfere with one another, forcing them to be deactivated in order to deliver an energy application. This could also result in lesion gaps. Meanwhile, we view catheter designs that require the physician to achieve a specific orientation to produce a circumferential lesion (e.g. deliver energy, rotate 180 degrees, and deliver energy again) as potentially problematic, as they increase the odds of operator error resulting in lesion gaps and expose different tissue segments to different doses.

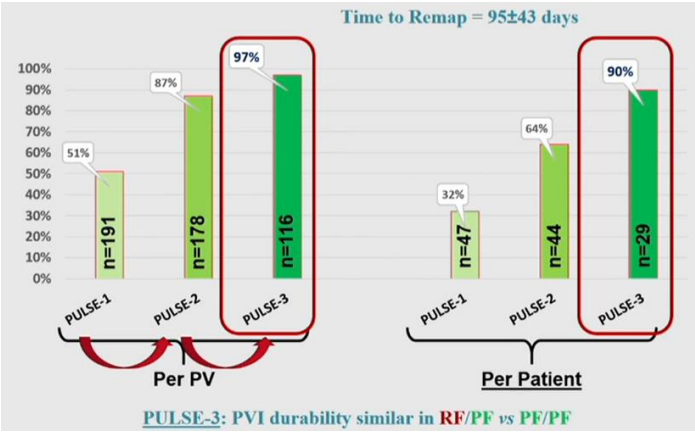
We've already seen how parameter selection can have a dramatic impact on therapeutic effect. In Farapulse's Impulse, PEFCAT, and PEFCAT II studies, patients were treated with either a monophasic, non-optimized biphasic, or optimized biphasic waveform. As Figure 9 shows, there was a stark difference in the percentage of patients with durable PVI on remapping depending on whether they were treated with the monophasic waveform (18%) or the final optimized biphasic waveform (84%). Affera's early work demonstrated similar sensitivity to parameter settings, with PVI durability improving from 32% to 90% as that waveform was titrated.

Fig. 9: Impact of Parameter Selection – BSX Farapulse



Source: *JACC: Clinical Electrophysiology* – Reddy et al 2021

Fig. 10: Impact of Parameter Selection – MDT Sphere-9

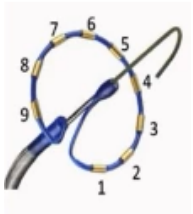
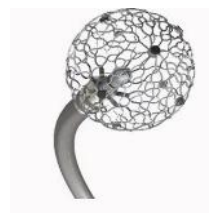


Source: 2022 AF Symposium

PFA Competitive Landscape

There are at least ten PFA programs in commercial development today. For the purposes of this discussion, we'll spend most of our time discussing the six being pursued by the four major incumbents in the EP market: J&J, Abbott, Medtronic, and Boston Scientific. As Figure 11 shows, these companies have taken a variety of approaches in catheter design. There are some similarities, however, with most choosing bipolar, biphasic energy delivery in the 1-2kV range, which we view as the optimal parameter selections for most AF cases. Below we discuss the device-specific attributes of each of these programs, as well as our view on the advantages and/or disadvantages of each approach.

Fig. 11: PFA Competitive Landscape

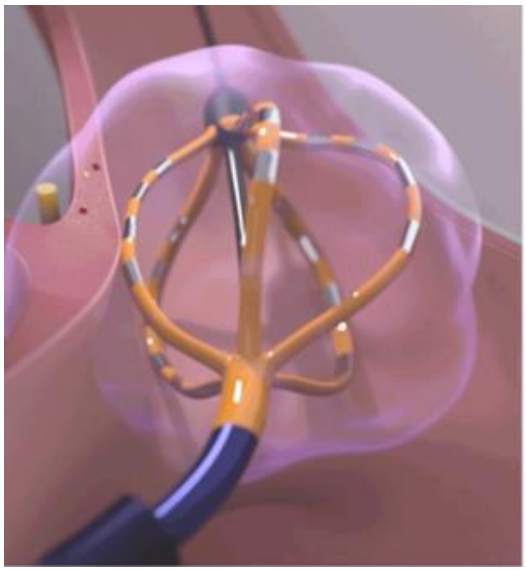
	PulseSelect MDT	Farapulse BSX	Varipulse JNJ	Sphere-9 MDT	Sphere PVI MDT	Circular IRE Catheter ABT
						
Description	*Over-the-wire circular multielectrode array with 9 electrodes*	*Over-the-wire catheter with variable pentispline distal morphology (basket and flower) consisting of 20 electrodes*	*Circular lasso-shaped catheter with adjustable diameter featuring 10 electrodes and individual irrigation pores*	*Lattice-tip catheter with an expandable 9mm diameter nitinol lattice containing nine mini-electrodes*	*Over-the-wire multi-segment lattice-tip catheter with variable distal morphology and a maximum diameter of 34mm*	*Circular lasso-shaped catheter with a variable hoop diameter featuring 14 electrodes*
EU Status	Investigational	CE Mark Approved	Investigational	Investigational	Investigational	Program Terminated
U.S. Status						
Trial Enrollment	Complete (Dec. '21)	Complete (Jun. '22)	Complete (Nov. '22)	Complete (Dec. '22)	Feasibility Ongoing	Program Terminated
Data Presentation	March 6, 2023 (ACC)	2H23	1H24	1H24	N/A	N/A
Estimated Approval	2H23	1H24	2H24	2H24	N/A	N/A
Energy Modality	PFA	PFA	PFA	PFA or RF	PFA	PFA
Catheter size	9F	13F	7.5F	7.5F	8F	8F
Voltage	0.5-1.5 kV	1.8 - 2.0 kV	1.8 kV	2.0 kV	1.3-2.0 kV	2.1 kV
Polarity	Bipolar	Bipolar	Bipolar	Monopolar	Monopolar	Monopolar
Waveform	Biphasic	Biphasic	Biphasic	Biphasic	Biphasic	Monophasic
Electrodes	9	20	10	9	6	14
Diameter	25mm	31-35mm	25-35mm	9mm	34mm	16-27mm
Integrated Mapping	No	No	Yes (Carto 3)	Yes (Affera Prism-1)	Yes (Affera Prism-1)	Yes (EnSite Precision)

Source: www.bostonscientific.com, AF Symposium 2022, www.medtronic.com, www.affera.com

Farapulse (BSX)

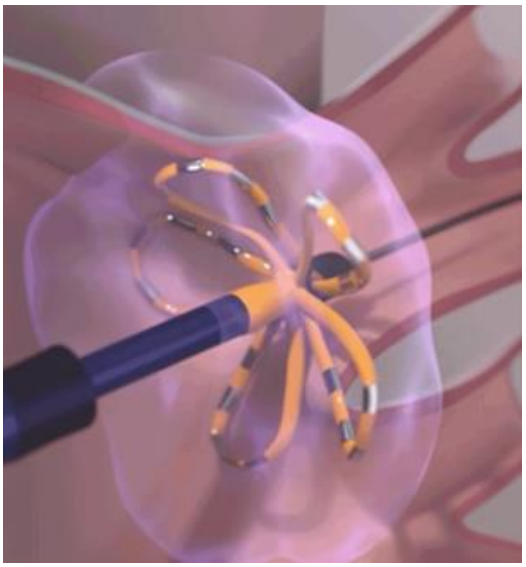
Design: Boston's Farapulse is one of only two PFA systems commercially available in Europe today (the other being Galaxy Medical's Centauri) and the one with by far the most real-world experience to date. The system uses an over-the-wire pentispline catheter with 20 electrodes (4 per spline). Each electrode emits 1.8-2.0 kV bipolar, biphasic energy while the third electrode on each spline can pace and record electrograms. The Farawave catheter features variable distal end morphology, allowing the operator to transition from its baseline linear form for sheath introduction to a basket and petal configuration (Figure 12 & 13). These configurations were purpose-built for ablating different areas of the heart. The basket pose allows for self-centering at the ostium of the pulmonary veins, while the flower pose maximizes lesion area at the antrum and posterior wall. The device comes in two sizes: 31mm and 35mm diameter as measured in flower configuration. Farawave has radiopaque markers at the distal tip and proximal to the splines for easy tracking. It uses a 14F steerable sheath that has unidirectional deflection from 0-180°. Given the device's size, access to the right pulmonary veins can sometimes be challenging. However, feedback from physicians who are actively using the system in Europe indicates that this can be easily overcome by making the transeptal puncture more anteriorly.

Fig. 12: Farapulse Basket Configuration in Ostium



Source: www.farapulse.com

Fig. 13: Farapulse Petal Configuration at Antrum



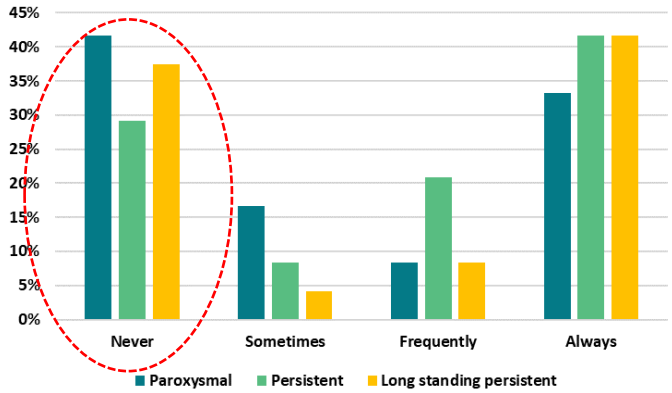
Source: www.farapulse.com

Access, Guidance, & Mapping: The Farapulse procedure uses a single transseptal puncture for entry of the catheter into the left atrium. This puncture must be performed more anteriorly to allow enough space for the catheter to maneuver to the right pulmonary veins. The procedure is usually performed via fluoroscopic guidance. Some electrophysiologists are also making use of intracardiac echo (ICE) for better visualization of endocardial structures and catheter positioning, which may require an extra groin puncture. Use of a mapping system requires catheter exchanges, which we see as a drawback of the current design as it increases the risk of introducing air embolisms. Boston is working on integrating Farapulse with its Rhythmia EAM system, although it remains to be seen whether the limited number of electrodes and large inter-electrode distances on the Farawave catheter will be able to create sufficiently detailed maps. Based on our recent conversations with clinicians, our sense is that fluoroscopy and ICE are likely to be sufficient for paroxysmal patients requiring PVI, while more complex procedures may require high-resolution mapping.

How big of an issue is Farapulse's lack of EAM integration? As part of the MANIFEST-PF retrospective real-world registry, Farapulse users were asked a variety of questions about how they performed the procedure. The vast majority (91%) said that they relied on fluoroscopy for intra-procedural imaging, with smaller subsets making use of ICE (22%) and TEE (8%). Meanwhile, EAM utilization was relatively low, with 59% of respondents saying they either never or sometimes used it in paroxysmal cases compared to 41% who use it always or frequently. While EAM utilization was somewhat higher for persistent and long-standing persistent patients, a significant percentage of physicians are routinely completing Farapulse cases in those populations without the aid of advanced mapping as well. We believe this provides solid evidence that Farapulse can be successful without EAM integration, making it more of a "nice to have" than a "need to have" feature for Boston.

Other interesting takeaways from MAINFEST-PF include an average procedure time of just 65 minutes, 82% of patients treated under conscious sedation rather than general anesthesia, and 16% discharged the same day they were treated. We believe these stats speak to the ease of use of the Farapulse system and comfort level physicians have been able to quickly build with such a novel technology just two years into its commercial launch.

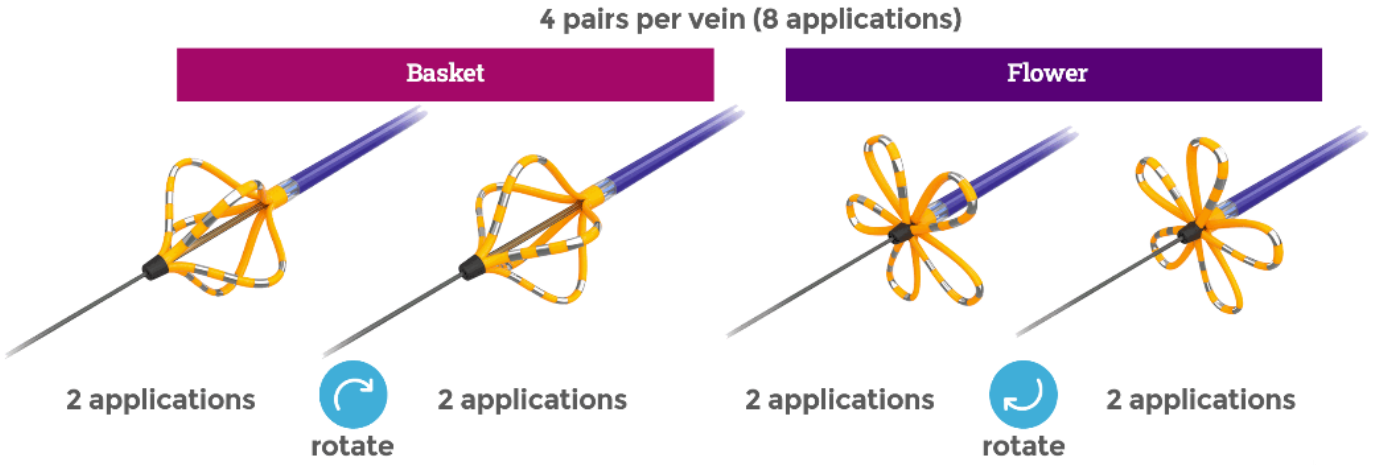
Fig. 14: Real-World EAM Utilization By AF Type



Source: Adapted from *Europace* – Ekanem et al 2022

Dosing: Boston recommends that physicians apply 4 applications to each pulmonary vein: 2 in the ostial (basket) and 2 in the antral (flower) positions. The catheter is rotated in between each application to fill in potential lesion gaps between the splines. The over-the-wire design allows for easy positioning at the ostium of the vein and excellent tissue contact. Meanwhile, the atraumatic nature of the flower shape reduces the risk of cardiac tamponade and perforations, allowing for safe movement within the atrium.

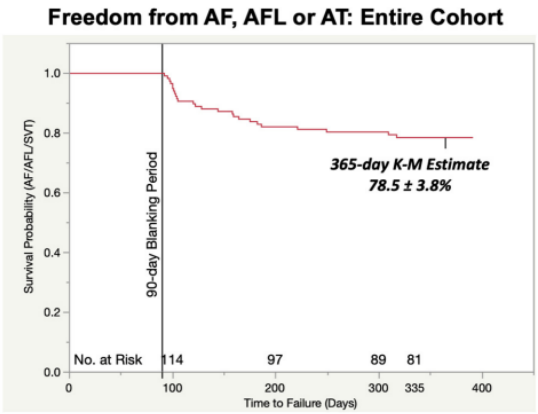
Fig. 15: Farapulse Therapeutic Dosing Strategy



Source: www.farapulse.com

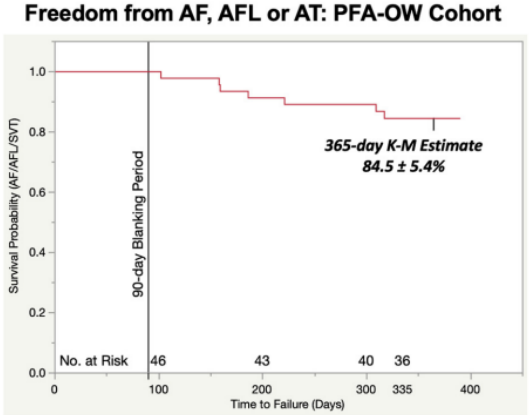
Clinical Results: To support CE Mark approval, the Farapulse system was studied in three multicenter clinical trials (IMPULSE, PEFCAT, and PEFCAT II) which collectively enrolled 121 patients. Invasive remapping was performed at 2-3 months with reconnected PVs reisolated at that time. After a 90-day blanking period, arrhythmia recurrence was assessed at 1-year. For the overall cohort, freedom from all atrial arrythmia was 78.5%. However, this includes patients treated with the original monophasic and subsequent unoptimized biphasic waveform. Of those patients who received the optimized biphasic waveform (N=46), 84.5% were free from atrial arrhythmias one year post procedure.

Fig. 16: Farapulse Efficacy – Full Cohort



Source: *JACC: Clinical Electrophysiology* – Reddy et al 2021

Fig. 17: Farapulse Efficacy – Optimized Waveform



Source: *JACC: Clinical Electrophysiology* – Reddy et al 2021

Meanwhile, the safety of the Farapulse system has been evaluated over a large patient experience, which includes not only the IMPULSE and PEFCAT I/II studies but also the PersAFOne trial in persistent AF (N=25) and MANIFEST-PF retrospective real-world registry (N=1,758). These results were very encouraging overall, with just 2-4% of patients experiencing a safety event. The most commonly reported event was cardiac tamponade (1-4%), while a small number of patients experienced vascular complications. There were no cases of atrioesophageal fistula, PV stenosis, or persistent phrenic nerve injury.

Fig. 18: Farapulse Safety

	IMPULSE + PEFCAT + PEFCAT II	PersAFOne	MANIFEST-PF
Total Primary Safety Events	2.5%	4.0%	1.6%
Death	0.0%	0.0%	0.1%
Myocardial Infarction	0.0%	0.0%	0.0%
Diaphragmatic Paralysis	0.0%	0.0%	0.0%
Stroke or TIA	0.0%	0.0%	0.5%
Cardiac Perforation or Tamponade	1.7%	4.0%	1.0%
Vascular Complications	0.8%	0.0%	3.3%
Prolonged or Repeat Hospitalization	0.0%	0.0%	0.0%
Heart Block	0.0%	0.0%	0.0%
PV Stenosis > 70%	0.0%	0.0%	0.0%
Atrioesophageal Fistula	0.0%	0.0%	0.0%
Pericarditis Requiring Intervention	0.0%	0.0%	0.0%
Pneumothorax	0.0%	-	-
Pulmonary Edema	0.0%	-	-

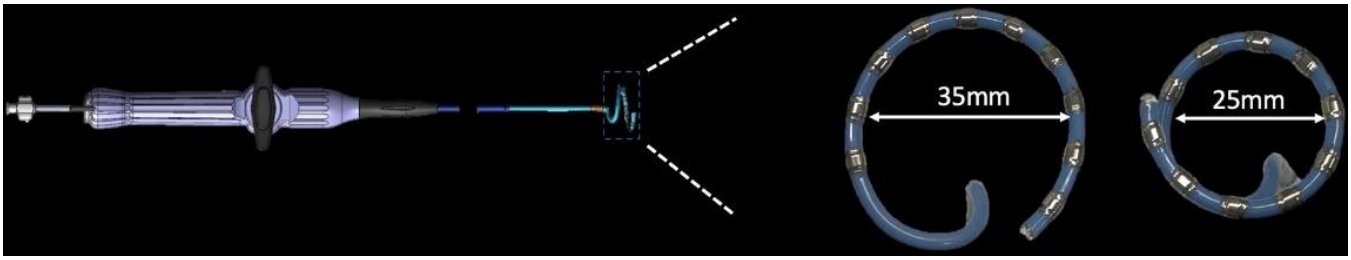
Source: *JACC* (2020), *JACC: Clinical Electrophysiology* (2021), *Europace* (2022)

Nephron View: With strong durability and safety results and the most real-world experience to date, we see Farapulse as the most de-risked of the PFA systems currently in development. We also think it's the most elegantly designed PFA catheter for paroxysmal AF cases primarily requiring PVI. Feedback from clinicians suggests that it is remarkably easy to use, with the potential to democratize AF ablation by enabling lower volume centers and less skilled operators to achieve high-quality results. We do see opportunities for Boston to improve the system, however, starting with Rhythmia integration and iterating the introducer sheath, which has been described to us as somewhat bulky and cumbersome to navigate. Boston is also working on additional catheter configurations that would enable more precise focal ablation with the system. The results of the ADVENT U.S. pivotal trial are on track to be presented in 2H23, likely at the TCT conference in October.

Varipulse (JNJ)

Design: Biosense Webster's Varipulse is a circular lasso-shaped 7.5F catheter with 10 electrodes and individual irrigation pores. The catheter has an adjustable diameter range between 25-35mm, allowing it to conform to a wide range of PV ostia sizes. It features bidirectional flexion (180° deflection to one side and 90° to the other) to facilitate engagement of all pulmonary veins. Energy (1.8kV) is applied in a bipolar configuration between both adjacent (1-2 and 2-3) and skipped electrodes (1 to 3). The system also offers the physician the option to choose which electrodes deliver energy in a particular application and deactivate any overlapping electrodes (often electrodes 1 and 10). Each application includes trains of microsecond long biphasic pulses for a total application duration of 250 milliseconds. Varipulse has a magnetic sensor to facilitate visualization and is fully integrated with J&J's CARTO 3 EAM system. Finally, the catheter features 10 individual irrigation pores to enable a 4mL/min flow rate.

Fig. 19: Varipulse Catheter

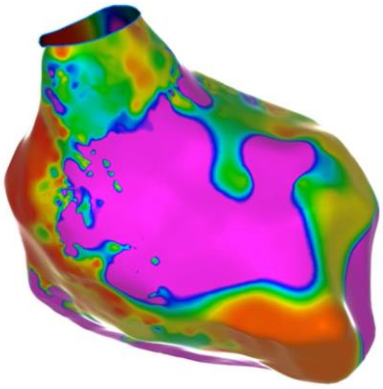


Source: *Circulation: Arrhythmia and Electrophysiology* - Yavin et al 2021

Access, Guidance, & Mapping: Varipulse is fully integrated with J&J's Carto high-density mapping system, which confers several advantages from an access and navigation standpoint. First, it eliminates the need for additional vascular access or transeptal punctures for ICE, as well as catheter exchanges to validate ablation results. Meanwhile, the mapping system can aid in catheter positioning, dosing, and lesion assessment.

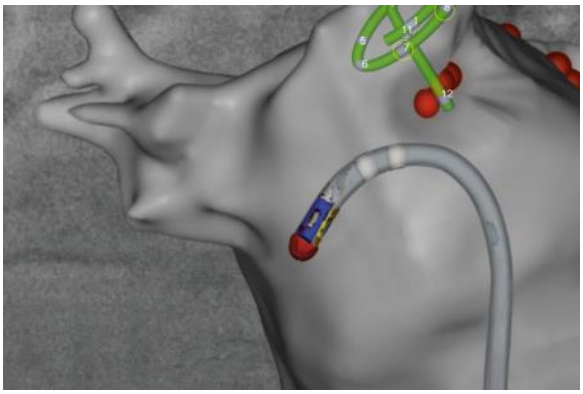
Dosing: The Varipulse procedure requires 12 applications per vein. The catheter is first positioned in the ostium, where 3 ablations are delivered. The catheter is then rotated 180 degrees and 3 more ablations are performed. This process is then repeated at the antrum. Rotation of the catheter is necessary due to the coil shape of the device, which can result in the first and last electrode overlapping in smaller PV ostia. Those electrodes must be manually deactivated prior to delivering energy, leading to a non-circumferential lesion. Meanwhile, full expansion of the catheter to a 35mm diameter in the antrum creates a gap between the first and last electrodes (see Figure 19), necessitating repositioning to complete the lesion set. Varipulse's eccentric shaft also makes positioning in the left atrium more challenging, because the loop must be properly oriented.

Fig. 20: Carto 3 Mapping



Source: www.jnjmedtech.com

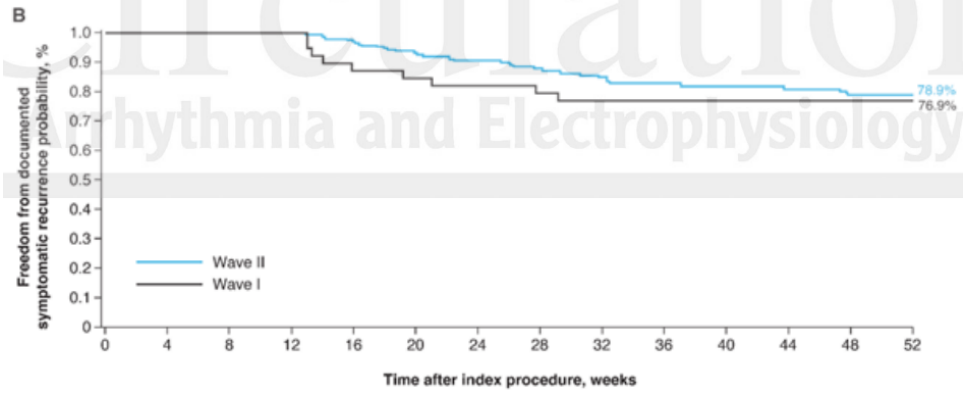
Fig. 21: CARTO 3 Guidance



Source: www.jnjmedtech.com

Clinical Results: The Varipulse system was studied in the inspIRE trial, which enrolled 226 subjects with paroxysmal AF. The study was divided into two cohorts, with Wave 1 (N=40) assessing initial safety prior to moving on to Wave 2 (N=186). The trial was stopped early after an interim analysis indicated it was likely to meet its prespecified performance goals. At 12 months, 70.9% of patients met the primary efficacy endpoint with confirmation of acute electrical block in all PVs and freedom from documented symptomatic or asymptomatic atrial arrythmia. Meanwhile, 78.9% of Wave 2 patients achieved clinical success, defined as 12-month freedom from documented symptomatic atrial arrhythmia.

Fig. 22: Varipulse Efficacy – inspIRE



Source: *Circulation: Arrhythmia and Electrophysiology* – Duytschaever et al (2023)

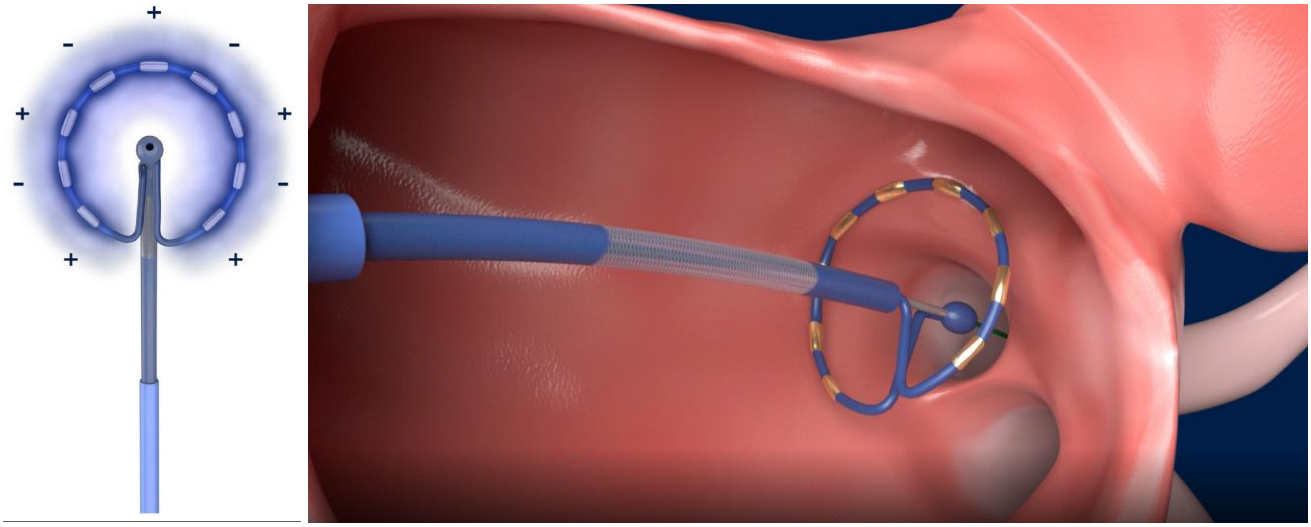
No adverse events were reported across either cohort. However, 39 Wave 1 patients underwent pre and post-procedure cerebral MRIs, with silent cerebral lesions (SLCs) observed in 4 of the first 6 patients treated. A number of workflow changes were implemented after this finding, including a 10-second pause between PFA applications, minimizing catheter exchanges, and strict adherence to anticoagulation protocols. After these changes, only 4 SLCs were observed in the next 33 patients. All lesions were asymptomatic and transient, with no patients reporting worsening neurological function. While the high incidence of SCLs seen in the initial Varipulse experience was somewhat alarming, the reduced incidence after workflow changes and lack of clinical consequences provide some comfort that this is not a serious safety concern. We also don't believe it to be device-specific, with SCLs a known risk when performing EP ablation regardless of energy modality, as well as other procedures requiring access to the left side of the heart (LAA closure, TMVR, etc.).

Nephron View: We see Varipulse as a competitive PFA system that is likely to produce solid results when the admIRE U.S. pivotal trial reads out next year. It may also be the first PFA system with EAM integration to receive FDA approval, as neither BSX's Farapulse nor MDT's PulseSelect offers this feature today. While integration confers some potential advantages, particularly in complex cases, we don't see it as a gamechanger for PVI procedures. Varipulse's irrigation ports are another novel aspect of its design. However, given the limited thermal effect associated with PFA procedures, we don't see a strong clinical rationale for irrigation with this modality. On the other hand, we view the potential for non-circumferential lesion creation as a weakness of the Varipulse design, with the need to orient the catheter loop appropriately and rotate it in between ablations making it a more challenging system to use and raising the chance of operator error leading to incomplete lesion sets.

PulseSelect (MDT)

Design: Medtronic's PulseSelect catheter is an over-the-wire circular array with 9 gold electrodes. The device delivers a controlled biphasic, bipolar electrical field (0.5-1.5 kV) in millisecond trains of pulses that can be optimized by pre-selecting which electrodes the operator would like to deliver the energy. The catheter has a 9F shaft and the diameter of the device when fully deployed is 25mm. It is capable of recording pulmonary vein and atrial potentials and can also perform pacing, while each electrode has thermoreceptors to measure temperature changes from baseline to one second post-delivery.

Fig. 23: PulseSelect Catheter Design



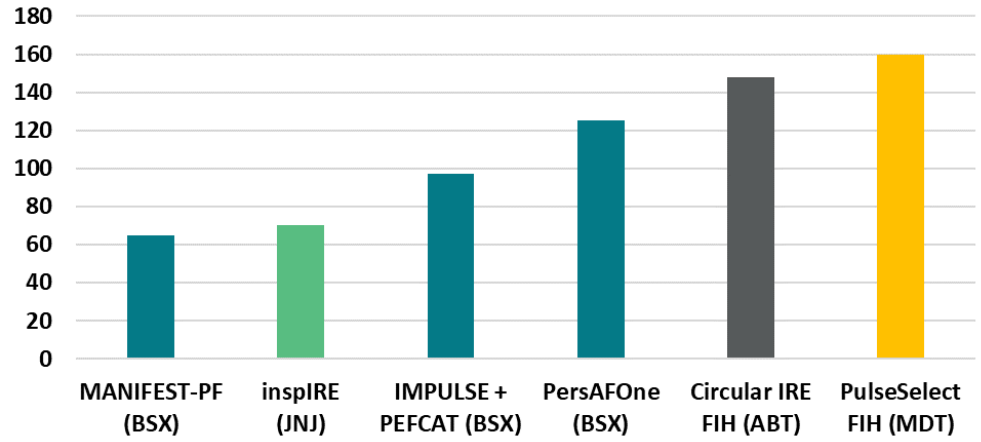
Source: *Circulation: Arrhythmia and Electrophysiology* – Verma et al 2022, www.medtronic.com

Access, Guidance & Mapping: PulseSelect does not offer integrated mapping today. However, Medtronic gained access to the Prism-1 cardiac mapping and navigation platform with its August 2022 acquisition of Affera. Prism-1 is the EAM system used with Affera's Sphere-9 and Sphere PVI PFA catheters and we expect Medtronic to eventually integrate PulseSelect with it as well. The potential timing of an integrated PulseSelect offering is unclear, however, with enrollment in the PULSED AF U.S. pivotal trial already completed prior to the Affera deal.

Dosing: Medtronic recommends that each pulmonary vein receive 8 PFA applications (4 ostial and 4 antral) to optimize results. Similar to what we see with Varipulse, the physician has the option of selecting which PulseSelect electrodes deliver energy with each application. We see some potential advantages to the PulseSelect design which may make it easier to use, including the fact that the catheter shaft is centered within the electrode array (as opposed to eccentrically positioned) and the electrodes cannot overlap with one another. However, no energy is delivered across the bottom portion of the PulseSelect catheter loop, where there is a fairly large gap bordered by two positively charged electrodes. Just as we noted with Varipulse, this creates the potential for non-circumferential lesion creation. And even if the physician adjusts for this by rotating the catheter between applications, the result will be variable doses of energy delivered to different tissue segments.

Clinical Results: The results of the PULSED AF U.S. pivotal trial are scheduled to be presented on Monday, March 6 at the American College of Cardiology scientific sessions in New Orleans. We've seen very little clinical data on the PulseSelect platform to date, with only acute outcomes from a 38-patient FIH study published thus far. While acute isolation was achieved in all those patients, no subsequent remapping was done to gauge durability. As we've seen in other PFA studies, safety was very strong, with no serious adverse events reported related to the ablation catheter itself and only one patient suffering a vascular complication related to access. One aspect of the PulseSelect FIH experience that did stand out to us was the procedure time, which came in at 160 minutes. This is much higher than we've seen in other PFA trials, even ones like PersAFOne which focused on persistent AF patients (92% of subjects in the PulseSelect study were paroxysmal). While the PulseSelect study protocol required a 20-minute wait after the final pulmonary vein was isolated prior to the catheter removal, this still strikes us as a very long procedure time and could indicate some ease of use issues with the catheter. We'll be keeping an eye on this metric when the PULSED AF results read out next month.

Fig. 24: Skin-to-Skin PFA Procedure Times (mins)



Source: Company reports

Nephron View: We see PulseSelect as another high-quality entrant into the PFA field, with several puts and takes in its design relative to Varipulse. This includes features that break in Medtronic's favor, such as the central shaft position and lack of overlapping electrodes, while the absence of integrated imaging with PulseSelect gives J&J its most notable advantage. In both cases, however, we see the lack of circumferential lesion creation as a potential problem from both an efficacy and ease of use perspective, which is one of the main factors behind our preference for Boston's Farapulse.

Affera Sphere-9 / Sphere PVI (MDT)

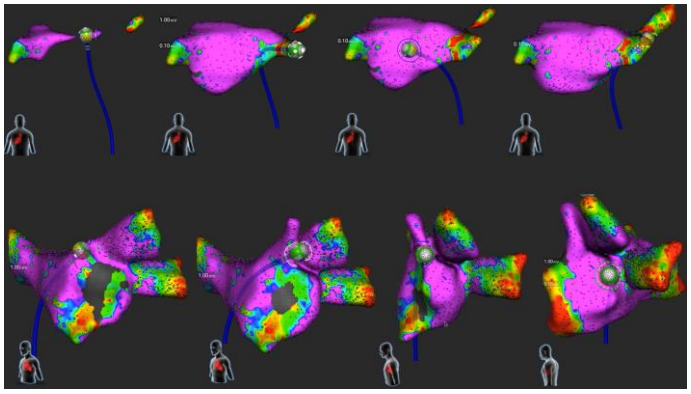
Design: Medtronic's acquisition of Affera gave it access to two more PFA catheters: Sphere-9 and SpherePVI. Sphere-9 is a lattice-tip ablation catheter with nine mini-electrodes on the spherical surface. The system allows for delivery of either radiofrequency or pulsed field ablation by toggling from one mode to the other. In RF mode, each mini-electrode acts as a temperature sensor, with energy output modulated based on the hottest thermocouple. Meanwhile, the PFA mode delivers a proprietary monopolar biphasic waveform in a train of microsecond-scale pulses delivered over a 3-5 second period. The catheter has a 7.5F shaft that is bidirectional while the head of the sphere is 9mm in diameter. This makes it the only one of the PFA programs in late-stage development that could be considered a focal ablation system. How important this niche will be in the PFA era remains to be seen, as we suspect the ease of achieving PVI with "single-shot" systems like Farapulse, Varipulse, and PulseSelect will drive a shift in favor of that approach as first-line therapy for paroxysmal AF patients. For patients with complex disease or those requiring redo ablation, however, a focal ablation catheter is likely to be required.

Fig. 25: Affera Sphere-9 and Sphere PVI

Source: Company reports

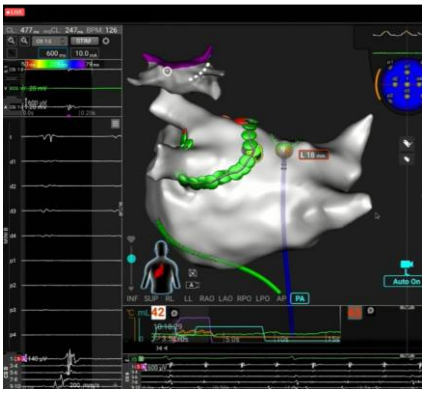
To fill the single-shot gap in its portfolio, Affera developed the Sphere PVI catheter. Sphere PVI employs a similar spherical design as Sphere-9, but is much larger at 34mm. While it only has 6 electrodes, the entire lattice delivers energy during applications. An 8F shaft and over-the-wire delivery system facilitates easy cannulation of the pulmonary veins, where the lattice is expanded to the basket configuration. The lattice can then be compressed to a flatter configuration for antral ablations or mapping.

Fig. 26: Affera Mapping System



Source: www.affera.com

Fig. 27: Affera Guidance



Source: www.affera.com

Access, Guidance, & Mapping: One advantage of the Affera catheters is that they can perform all aspects of the ablation procedure, including pacing and mapping with the fully integrated Prism-1 EAM system. At the start of the procedure, the catheter is maneuvered around the left atrium to construct a digital rendering of the chamber geometry, along with a corresponding voltage map. The ability to toggle between PFA and RF with Sphere-9 can also eliminate the need for catheter exchanges in complex cases requiring both forms of energy delivery. Another nice feature of the system is its ability to measure and show the distance from the catheter tip to the closest lesion. By doing so, it ensures optimal spacing for creating both PF (~4mm) and RF (~6-7mm) lesions.

Dosing: The Sphere PVI dosing protocol calls for 4 lesions per vein, starting distally in the ostium and then pulling back gradually to cover the antral region. Sphere-9 ablation procedures involve the operator creating point-to-point lesion lines to isolate target regions of the atrium. One strategy we've seen employed is to use PFA for posterior lesions where there is concern about RF causing esophageal injury, and then switch to RF for the anterior portion. Given what we know about PFA so far, however, we don't see the clinical value of this approach, as there isn't any reason at this point to think that PFA is less effective than RF for the anterior segment of a PVI. Asking the physician to toggle back and forth between energy sources also introduces the possibility that they could make a mistake and deliver RF in a sensitive area, leading to a complication (see clinical discussion below). This flexibility could be valuable in other lesion sets, however, such as near the AV node (where PFA could cause an AV block) or mitral isthmus (where the risk of coronary spasm is higher).

Clinical Results: Limited data is available on the Sphere PVI catheter, with a 50-patient feasibility study now underway. The SPHERE Per-AF U.S. pivotal study for Sphere-9 completed enrollment in December 2022 after randomizing 477 patients with persistent AF to treatment with either Sphere-9 or J&J's Thermocool SmartTouch SF catheter. The results from a 76-patient FIH experience with Sphere-9 have been published, detailing high acute success rates with the creation of a variety of lesion sets in both PFA and PFA/RF modes. However, no remapping was done to assess durability. From a safety perspective, there were no cases of death, stroke, phrenic nerve paralysis, pericardial tamponade, or atrioesophageal fistula reported, although one patient did suffer a vascular complication requiring surgical repair and four others had minor access site hematomas. Interestingly, however, two patients in the PFA/RF cohort did have esophageal abnormalities following treatment. The authors concluded that this was due to inadvertent posterior delivery of RF energy in cases where the operator thought they were anterior enough to avoid heating the esophagus but the 9mm diameter of the catheter tip resulted in a broader thermal effect than intended. While both injuries were considered minor, this highlights the risks involved with a dual-energy system.

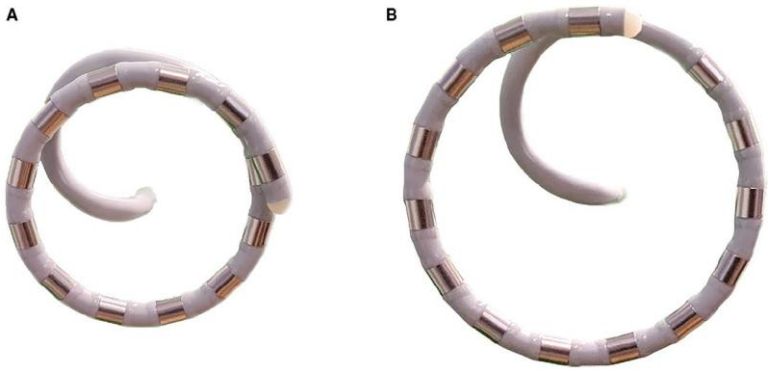
Nephron View: The Affera portfolio is one of the more novel entrants into the PFA field and we view the Prism-1 system as an elegant and intuitive EAM offering. We see the lead product, Sphere-9, as filling an important niche as the only focal PFA catheter in late-stage development. While we wouldn't expect this to be the case for long, with Boston working on a focal version of the Farawave catheter (dubbed Farapoint), Sphere-9 could become the product of choice for ablation procedures requiring complex lesion sets in the interim. Moving beyond that niche role could be challenging, however, as performing simpler PVI ablations with a focal catheter is much more time-consuming and dependent on operator skill than with single-shot devices. The PFA/RF combo approach also necessitates general anesthesia and esophageal temperature monitoring, while the monopolar energy delivery has the potential for increased muscle and nerve stimulation. Sphere PVI profiles much more as a workhorse device for paroxysmal AF cases, in our view. However, it's likely to be the fourth single-shot system to come to the U.S. market and second within Medtronic's own portfolio, raising the bar for how effective it will need to be to garner significant adoption.

Circular IRE Catheter (ABT)

Abbott has fallen behind in the race to develop a PFA system, putting its $2B Electrophysiology franchise at risk. While the results of a successful 10-patient FIH experience with a circular IRE catheter were published in 2020, no further progress with that system has been reported. And CEO Robert Ford disclosed on the company's 4Q22 call that management has elected to move forward with another approach after a bakeoff between its two internal programs. We aren't surprised at this decision based on the design of the circular IRE catheter and our review of the early clinical experience with that product. While Abbott hasn't disclosed any details about this new PFA platform, our own diligence indicates that it features 8 splines and will be integrated with the company's Ensite EAM system. The company is telling physicians it hopes to be in the clinic with the new catheter later this year. In the meantime, below we walk through what we know about Abbott's now terminated circular IRE program.

Design: Abbott's initial foray into the PFA field was a circular, lasso-shaped, non-deflectable 8F catheter with a variable hoop diameter (16-27mm) featuring 14 electrodes spaced about 3.5mm apart. It was delivered via Abbott's deflectable Agilis sheath for maneuverability to the PVs. Similar to Affera, the device was monopolar and delivered energy between the circular catheter and two grounding patches placed on the lower back of the patient. Importantly, however, it was the only device we've reviewed thus far that used monophasic energy, delivering a single capacitive discharge per application.

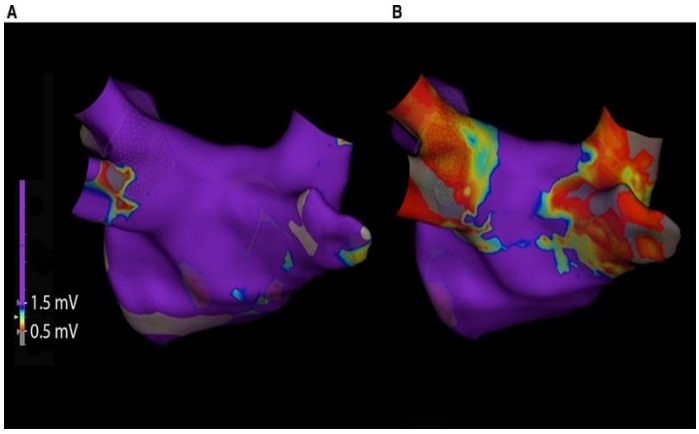
Fig. 28: Abbott's Circular IRE Catheter



A: 16mm; B: 27mm
Source: *Circulation: Arrhythmia and Electrophysiology* –Loh et al 2020

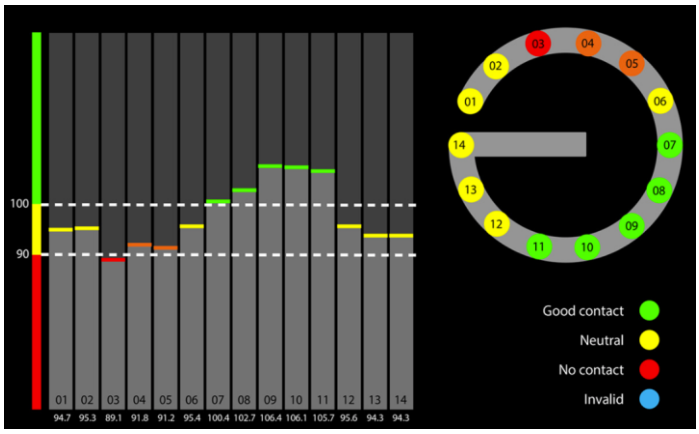
Access, Guidance, & Mapping: In the first-in-human study, the protocol recommended two transseptal punctures to advance both an Agilis steerable sheath and a non-steerable sheath into the LA. In a larger subsequent study, only the Agilis sheath was introduced. Three-dimensional mapping of the LA and PVs were created using Abbott's Ensite cardiac mapping and imaging system, with J&J's Lasso circular mapping catheter used for assessment of PV isolation. One of the unique features of Abbott's design was the incorporation of a multielectrode impedance system (MEIS) to measure tissue contact. This MEIS provided the physician with visual cues about the extent of tissue contact for each electrode, allowing them to reorient the device until circumferential contact was achieved (see Figure 30). While we see this as an interesting feature, its clinical relevance when delivering PFA is unclear, as tissue contact is less important with this modality than when using RF.

Fig. 29: EnSite Precision Voltage Mapping



Source: *Circulation: Arrhythmia and Electrophysiology* –Loh et al 2020

Fig. 30: Multi-Electrode Impedance System



Source: *Circulation: Arrhythmia and Electrophysiology* –Loh et al 2020

Dosing: Abbott recommended at least 2 applications per vein for isolation, with an average of 2.7 used in the early clinical experience. Because of the 3.5mm electrode spacing, the catheter was also rotated slightly before the second application to increase the likelihood of circumferential lesion creation and to decrease the risk of gaps between the electrodes. It isn't clear whether overlapping electrodes could be deactivated, as is the case with Varipulse.

Clinical Results: Of all the PFA programs advanced by the major EP players, we see Abbott's circular IRE catheter design as posing the greatest safety risk due to its use of monopolar and monophasic energy. And while it's difficult to know how much of an issue those parameter choices would have been had the program continued into larger patient cohorts, the early experience does contain some notable red flags. In particular, transient ST elevations were observed immediately after pulse delivery in several patients, suggesting that the monopolar energy delivery may have caused coronary spasm or depolarization of the left ventricle as the current traveled through this chamber on the way to the grounding patches. Meanwhile, one patient suffered a superficial esophageal lesion, something we haven't seen with any of the other PFA programs.

Nephron View: Given the circular IRE catheter's questionable safety profile and lack of differentiation compared to competitive products that were farther along in their development, we think Abbott likely made the right decision to take its PFA program in another direction. The challenge for the company now is that it's likely to be several years behind its peers in bringing a PFA catheter to market, exposing it to potential share losses in an EP business that has already been slowly losing ground over the last several years due to the company's lack of advanced RF and/or cryo offerings. The good news for Abbott is that its direct exposure to the ablation catheter segment of the market is relatively limited, with ablation catheters only making up ~25% of its EP revenue today and the rest split between Ensite (20%) and diagnostic and mapping catheters (55%). However, we still see this as a strategic vulnerability for the company in an important business.

Other PFA Technologies in Development

Four other companies have made significant progress developing PFA systems. And while we don't see any of these companies as significant competitive threats today, we do believe they bear monitoring going forward. Below we provide brief descriptions of these technologies and their progress to date.

Fig. 31: Other PFA Technologies in Development

From left to right: Kardium Globe PF, Galvanize Centauri, Adagio CryoPulse, Acutus AcQBlate Force
Source: www.kardium.com, www.galvanizetx.com, www.adagiomedical.com, www.acutusmedical.com

Globe (Kardium): The Globe PF system is an all-in-one solution featuring a 30mm spherical array of 122 gold electrodes capable of high-definition mapping and PFA delivery. This builds on a previous RF Globe system that received CE Mark in June 2020 following positive results from the GLOBAL-AF study (76% freedom from AF at 12 months). Each electrode has the ability to record electrograms, ablate, pace, and measure tissue contact and temperature. And the operator has individual power control over each electrode, allowing them to create point and linear lesions in addition to single-shot PVI. In terms of mapping, it is the only system we've seen thus far which continually records and displays electrical activity for real-time assessment of isolation. In November 2022, Kardium announced success in its FIH study with 100% acute PVI achieved in 38 patients. Following these results, the company now plans to move forward with the PULSAR global pivotal study (N=435) evaluating the Globe PF system in symptomatic paroxysmal or persistent AF patients, with enrollment expected to begin in 2023.

Centauri (Galvanize Medical): Previously under the umbrella of Galaxy Medical prior to that company merging with Galvanize Therapeutics in September, the Centauri system is a generator that produces pulsed electric field energy and is compatible with any commercially available focal ablation catheter. This open architecture approach allows physicians to deliver PFA through their favorite RF catheter. The custom monopolar waveform was designed to reduce microbubble formation, while the generator allows for modulation of energy and optimizes dosing parameters based on tissue impedance. This approach was found to be safe in the ECLIPSE-AF study (N=50), which also reported 100% acute PVI using a wide variety of catheters. However, just 84% of pulmonary veins were still electrically isolated following a remapping procedure, which compares to 96% in the Farapulse IMPULSE and PEFCAT I/II studies. Centauri received CE Mark in August 2022 and is now available in Europe, with our checks indicating that ~300 commercial cases have been performed to date. While some of the physicians we spoke with about this device like the idea of being able to stick with a catheter they are already very familiar with, others expressed concerns about this approach. In particular, RF catheters are not designed to handle the electrical current used in PFA procedures, which could cause them to short out or malfunction, potentially putting the patient at risk.

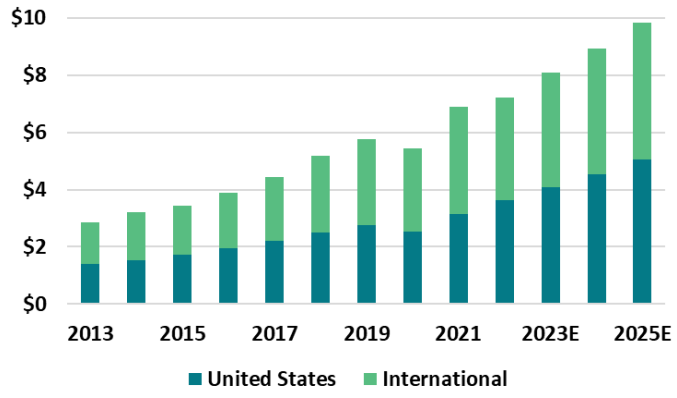
CryoPulse (Adagio Medical): Adagio Medical is taking a multi-modal approach, with a proprietary pulsed field cryoablation catheter that delivers ultra-low temperature cryoablation followed by PFA. This mechanism of action freezes the targeted myocardial tissue and acts to focus the pulsed field on the frozen area. The company believes that this approach will reduce complications such as skeletal muscle contraction, phrenic nerve injury, and microbubble formation. Meanwhile, preclinical work has shown that freezing the tissue first lowers tissue impedance, resulting in deeper lesions once PFA is applied. The cryo treatment also adheres the catheter to the wall of the atrium, ensuring good contact for PFA delivery. Adagio's catheter is lasso-shaped (like J&J's Varipulse) with 16 electrodes and can produce both circular lesions and linear lesions 11cm long. Enrollment in the PARALELL first-in-human study (n=78) began in October 2022, with the company currently targeting completion of that trial in 2024.

AcQBlate Force (Acutus): While Acutus has traditionally focused on its imaging and mapping platforms along with access and diagnostics, the company announced in late 2020 that it would be pursuing development of its own PFA program. Acutus' system is a single point ablation catheter that can deliver either RF or PFA therapy (biphasic, bipolar, 1.75kV) and is compatible with its non-contact AcQMap 3D mapping system. The AcQBlate catheter also takes contact force measurements. The device's European trial (n=65) in paroxysmal and persistent AF completed enrollment in August 2022, which puts it on track for a data readout by the end of 2023 and potential CE Mark clearance in 2024. In November, CEO David Roman noted that Acutus is carefully watching the evolution of PFA and assessing the best path forward for the company, including the potential for partnership.

Market Opportunity

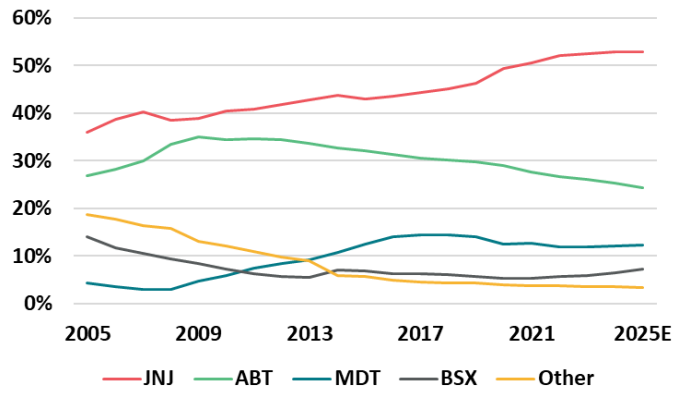
The worldwide EP ablation market topped $7.2B in 2022 and has grown at an 11% CAGR over the past decade, making it one of the more attractive end markets in MedTech. J&J's Biosense Webster franchise has enjoyed a strong #1 position throughout this entire period, driven by its market-leading Carto mapping platform and a strong ablation catheter lineup led by its Thermocool SmartTouch SF system. Meanwhile, Abbott became the #2 EP player following its 2017 acquisition of St. Jude. While Electrophysiology has been a solid business for Abbott ever since, the company hasn't been able to reverse its underperformance vs. the broader market, with 2022 marking ten consecutive years of share losses and its overall market position shrinking from 34% of global EP sales to 27% during that time. Those losses have mostly accrued to J&J, with Medtronic's share only rising slightly (9% to 12%) and Boston Scientific remaining a distant #4 at 6%. Medtronic did gain ~500bps of market share from 2013-2016 on the back of initial adoption of its Arctic Front cryoablation system. However, that momentum had already begun to slow by the time the FIRE and ICE trial was published in 2016 showing that cryo was noninferior to RF for the treatment of paroxysmal AF, with the company backsliding a bit in recent years as competitors introduced more advanced force-sensing RF catheters and Boston entered the European cryo market with its PolarX system.

Fig. 32: WW EP Ablation Market Revenue ($B)



Source: Company reports and Nephron Research

Fig. 33: WW EP Ablation Market Shares



Source: Company reports and Nephron Research

We believe pulsed field ablation has the potential to disrupt the status quo going forward. Our analysis of hospital purchasing data suggests that RF systems account for 85-90% of U.S. ablation catheter volumes today, with cryo making up the other 10-15% (20-25% of sales due to cryo's higher ASP). This favors companies like J&J and Abbott whose portfolios include advanced mapping systems and force-sensing RF catheters. Based on our conversations with European clinicians who are using PFA today, we believe that mix could change substantially over the next few years, with PFA systems used in the majority of cases. We expect particularly high adoption in PVI cases, which Boston estimates make up ~50% of the market. Much of that is likely to come at the expense of cryo, which has gained traction primarily for its ease of use and relative safety compared to RF when ablating near the esophagus, both areas where PFA shines as well. Boston is seeing significant Farapulse adoption among heavy RF users too, however, a dynamic we also found in our own checks. We also think that PFA has the chance to drive an overall acceleration in EP market growth by making catheter ablation of AF safer and easier to perform, although at this point we aren't modeling an inflection in procedure volumes.

We see Boston as the biggest potential beneficiary of this revolution. Overall, we estimate that ~40% of worldwide EP revenue comes from ablation catheters, equating to $3B in annual sales. Our math suggests that Boston likely has just a low double-digit share of that segment today. If the company's share were to double to 25% by 2026, it would translate into nearly $800M in incremental revenue over the next four years. That would add 60bps to Boston's overall 2022-2026 revenue CAGR compared to our current model, which only assumes that Boston's EP franchise (ex-Baylis) grows by about $400M during that period. We see this upside scenario as realistic given Farapulse's initial success and a potential U.S. launch of Boston's PolarX cryoablation catheter later this year.

Meanwhile, we view Abbott as the company with the most downside exposure. While EP sales only accounted for 4% of the company's total revenue in 2022, that franchise makes up a critical part of its Cardio & Neuro segment, where it's been the fastest growth business over the past six years other than Structural Heart. With Abbott now likely to be several years behind its competitors in the race to develop a PFA system, the company's long-running EP share losses could accelerate going forward. The picture is more mixed for Medtronic and J&J. While we think both companies are well-positioned to field competitive PFA platforms, success in this new modality is likely to at least partially cannibalize their strong existing franchises in cryo and RF, respectively.

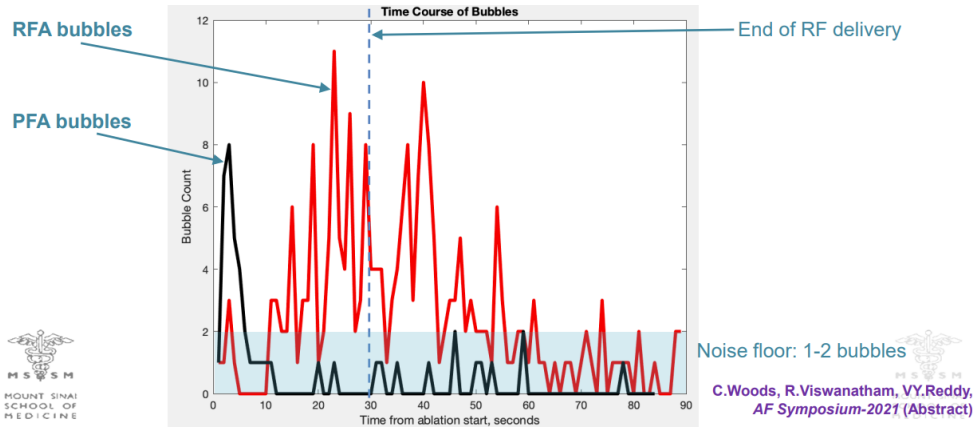
What Could Go Wrong?

MedTech innovation often follows a similar cycle. New technology is first met with skepticism as it challenges long-held medical norms. It's then embraced with exuberance as promising early data teases a great leap forward in quality of care. That's often followed by a moment of panic as outcomes look more pedestrian in larger patient series or more intense clinical scrutiny reveals unforeseen drawbacks. Examples of this include the late stent thrombosis scare, concerns about TAVR durability, or the failed HTN-3 trial for renal denervation. Then finally the pendulum swings back to center as our understanding of the technology matures and it takes its rightful place in the treatment paradigm.

Pulsed field ablation is currently in Phase 2 of this 4-step process today, with physicians at the recent 2023 AF Symposium we attended clearly enthusiastic about the potential for PFA to positively impact their practice. What isn't clear at this point is what, if anything, could temper that enthusiasm (i.e. Phase 3). One early candidate to emerge has been concern about microbubbles, which are formed as a result of electrolysis. These bubbles can travel to the brain and cause cerebral embolic events like strokes and TIAs. And while there have been few reports of symptomatic neurological complications with PFA to date, diffusion weighted MRI imaging of early PFA patients has identified silent cerebral lesions (SCLs), most notably in J&J's inspIRE trial where four of the first six patients treated had abnormal scans. However, it isn't clear whether those emboli were due to microbubbles created during the PFA application itself or due to air that was introduced to the system during routine catheter exchanges. J&J reported a steep drop in the percentage of patients with abnormal scans (just 4 of the next 33) after making protocol adjustments that addressed both of those potential causes.

As for whether treating a patient with PFA puts them at increased risk of microbubble formation compared to other catheter ablation modalities, a 2021 paper from Woods et al suggests otherwise. The authors compared microbubble formation following pulsed field and radiofrequency ablation and found that, while PFA results in more microbubble formation immediately after the ablation is begun, overall bubble counts are actually higher with RF. This study also determined that the vast majority of PFA microbubbles are less than 20 microns in size, while RF delivery was associated with a long tail of bubbles >50 microns in size.

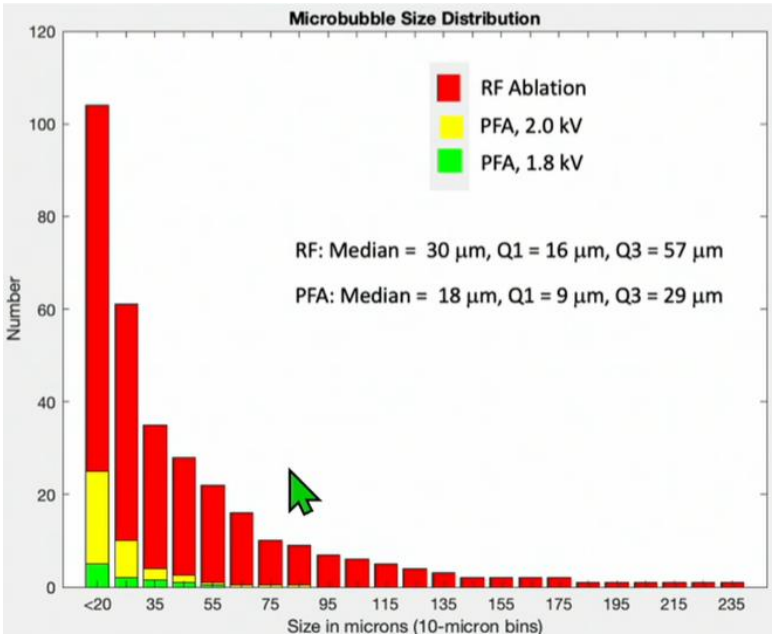
Fig. 34: Microbubble Formation – PFA vs. RF



Source: AF Symposium 2021 – Woods et al

While we don't see microbubbles as a major safety concern for PFA, that doesn't mean manufacturers shouldn't be looking for ways to minimize this risk. That includes protocol-based measures like those J&J employed, as well as parameter choices. For instance, monopolar and monophasic waveforms are both thought to lead to more bubble formation than bipolar and biphasic energy delivery. The Woods paper also reported a significant drop-off in bubble formation with a slight reduction in voltage (from 2.0kV to 1.8kV), which may suggest that less energy delivered over more applications will prove to be a safer approach. How the industry balances these safety considerations with optimizing the efficacy of these systems going forward will be interesting to watch.

Fig. 35: Microbubble Size Distribution – PFA vs. RF



Source: AF Symposium 2021 – Woods et al

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