THE AFIB REPORT

Your Premier Information Resource for Atrial Fibrillation

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Welcome to the belated Oct/Dec 2015 issue of our newsletter. We are making progress with the website overhaul and are now approaching the core of the revamp Along the way, I'm discovering all the many steps and details needed to get to this point with such a large existing website. Soon we'll be turning things over to the coders in the coming weeks after sending out this issue to you all.

By the next issue, our new logo should be ready for the newsletter to give a glimpse of our new look. Thereafter, once the most of the big decisions are in place and rebuild in the next phase, I plan to increase publication frequency again to gradually catch up hopefully by early fall with our normal newsletter schedule. The format is likely to change as well once the new website is up, as we gradually begin to morph some of this content into more frequent, but smaller bites at a time chunks within a new website blog.

*Leading off this issue is a **Short Cuts** brief summary of two recent reports from the world of AFIB news. First off with a look at the reasons behind a surprising lack of compliance noted in many users of the new DOAC drugs (Direct Oral Anti-Coagulants – a new acronym replacing NOAC). The second short cut recent news highlight is on progress with the Watchman Left Atrial Appendage (LAA) roll out and the path laid down by Medicare's CMS to insure reimbursement for the procedure.*

*Next in line, is a review of four timely key topics shared at the recent large **AF Symposium 2016**, held each January in Orlando, and that I had the pleasure to attend this year. We'll start this Symposium overview with a summary of the latest insights on fundamental research into AFIB origins that underscore real progress made each year toward ever deeper understanding of core AFIB mechanisms.*

*We'll then visit the latest directions in genetics, as well as interesting insights on fibrosis, and the role of each in AFIB, an update on additional DOAC issues includes the imminent release of a highly effective reversal agent, **Annexa-R,** for all three Factor Xa inhibitors (Eliquis, Xeralto & Savaysa), to join with the already available antidote for Pradaxa called **Idarucizumab** … a real tongue twister, indeed!*

To wrap up our initial summary of the 2016 AF Symposium, is an overview of current thinking on Non-PV AFIB trigger detection and ablation as clearly one of the key themes of this conference. There has been a literal explosion in recognition of the importance of addressing Non-PV triggers in AFIB ablation by a much wider number or EP's compared to just two years ago, which is a very welcomed advance indeed. We'll look forward as well to reviews of other key topics shared at AF Symposium 2016 in future

This issue ends with an in-depth special report on the status of a patient-specific Non-PV trigger/ substrate ablation via FIRM (Focal Impulse and Rotor Modulation) mapping and targeting strategy as of early 2016, with some surprising findings from the latest four consecutive, truly independent studies investigating FIRM that were published from 2015 to early 2016. FIRM mapping and strategy has been a big topic of interest on our forum and from individual inquiries over the last four years since the new AFIB ablation approach was first announced at AF Symposium 2012. The heart of this focus will be our review of the initial prospective arm of a larger OASIS-randomized controlled trial, that follows 29 non-paroxysmal patients for a mid-term follow up after a FIRM-guided only ablation.

Best wishes and NSR for all!
Shannon

Short Cuts:
Poor DOAC Adherence & Watchman progress

Orlando: Jan 15, 2016 Excerpts from article by: Bruce Jancin. Cardiology News Digital Network.
A surprising retrospective study by Xiaoxi Yao PhD of Mayo Clinic in Rochester, Minn. on nearly 65,000 AFIB patients who started DOAC (Direct Oral Anticoagulation) therapy with apixiban, dabigatran, rivaroxaban or warfarin. The study revealed that during a median 1.1 years of follow-up fewer than half of all patients adhered to treatment consistently!

Adherence rates, while uniformly suboptimal, but nevertheless varied considerably with the lowest 38.5% for dabigatran, 40.2% for warfarin, 50.5% for rivaroxaban and finally 61.9% for the highest apixiban group.

The authors noted that such poor adherence in real-world clinical practice was very much unexpected in light of these DOAC class of drugs increased convenience, fewer drug interactions relative to warfarin and no need for regular monitoring. Ironically, the big expectation for DOACs was increased compliance!

Understandably, adherence rates were better among patients with greater stroke risks as reflected by their CHAD2DS2-VASc scores. At the highest end of the spectrum, the adherence rate for apixiban was 50% in those with CHAD2DS2-VASc scores of 0 to 1, and rising to 62% with scores of 2 to 3 and with a slight further increase to 64% with a risk score of 4 or more. For lower risk cases, the cost of these drugs is clearly a reason for non-adherence, especially in countries with little to no insured drug coverage.

The authors then wanted to see if the actual stroke rate was worse with lower adherence. This proved to be the case for those with a CHA2DS2-VAS score of ≥2, with a clear dose-response connection between event rate and cumulative time off the OAC during follow-up. Those with risk scores between 2 and 3 had stroke rates nearly twice as high among those on OAC for a total of 3-6 months, and three times higher stroke rate if off therapy for more than 6 months.

A surprising finding was among patients with CHA2DS2-VASc scores of 2 or more, there was no significant relationship between cumulative time off OAC and risk of major bleeding, unless they were off therapy for a total of 6 months or more; only then was the major bleeding risk lower in those whose total time off OAC was less than a week. Although one would expect that patients off OAC to have significantly lower risk of intracranial (IC) bleeding than when on OAC, this proved not to be true!

Dr. Yao concluded; “For patients at higher risk for stroke there is little difference in IC hemorrhage risk whether they are on, or off OAC therapy. So higher risk patients should definitely adhere strictly to OAC therapy. Yet, in lower risk patients with risk scores from 0 to 1 the benefits of OAC may well be outweighed by harm from the therapy.”

Progress with Watchman/FDA Guidelines

SNOWMASS, COLO. Once again, we share timely excerpts below from Bruce Jancin of Frontline Medical Communications, published in the 02/11/16 edition of: http://www.anticoagulationhub.com.

Just two weeks ago at the Annual Cardiovascular Conference at Snowmass, maestro interventional cardiologist at Mayo Clinic, Dr. David Holmes, and co-developer of the Watchman device, updated the audience on recent progress in the gradual roll out and inevitable maneuverings required for the Watchman Left Atrial Appendage (LAA) occluder device roll out to become a mainstream reimbursable therapy.

For background, as reported by Mr. Jancin; “*the Watchman device was granted FDA marketing approval as the sole authorized LAA closure device in the US on the backs of two compelling positive randomized controlled trials. A follow-up meta-analysis of those trials showed significantly fewer hemorrhagic strokes, fewer CVD (cardiovascular disease) or unexplained deaths and fewer non-procedural bleeding*

events in Watchman recipients than in patients randomized to warfarin. And a cost effectiveness analysis has concluded that after 8 years, the Watchman becomes "the dominant strategy" – meaning more effective and less costly for stroke prevention in AFIB patients having a contraindication to warfarin – compared with the novel oral anticoagulant apixaban'. (J. Am. Coll Cardiol. 2015 Dec 22:66[24]:2728-39) http://www.ncbi.nlm.nih.gov/pubmed/26616031

(**Editors note:** the study, found at the above reference link, is an important analysis pointing to the long term benefit of Watchman versus DOAC therapy, both in terms of efficacy and cost effectiveness by year 8 where the Watchman becomes the winner overall as 'the dominant strategy' for this class of 70 year old afibbers with moderate stroke risk scores. The metrics might well look even better for younger patients with similar risks yet a longer time horizon).

Of interest*, 'the CMS (Centers for Medicare and Medicaid Services) will cover Watchman implants (for now) only when the catheter-based procedure is performed by an experienced interventional cardiologist or EP in an experienced center as defined by the SCAI/ACC/HRS standards, and only in patients enrolled in the national prospective registry. This registry will monitor operators and device-related complications, stroke and systemic embolism rates, deaths, and major bleeding rates for 5 years post-procedure',* as shared by Mr. Jancin reporting on-hand at the Snowmass conference.

Dr. Holmes emphasized how incredibly important this Watchman registry will be not only for telling how well the operators are doing, but in giving guidance and refinement for the future, as well while insuring reimbursements for the operators and patients benefit alike.

The one hitch reported in this news report is that: *'…* the *preliminary National Coverage Determination states that coverage will be limited to AFIB patients with high stroke-risk and HAS-BLED scores as well as contraindications to warfarin, whereas the FDA-approved indication says patients must be deemed by their physicians to be suitable for warfarin.'*

'According to Dr. Holmes: "In this particular case, CMS was not talking with FDA … But as soon as CMS comes through with their final regulatory coverage determination, I think we will finally be there' (meaning that this hitch will get sorted out). 'We'll then be able to offer this as a strategy for stroke prevention in selected patients with AFIB, realizing that with this device there's a 40% reduction in composite endpoint of cardiovascular or unexplained death, stroke and systemic embolism compared to warfarin.'"

'That figure of a 40% relative risk reduction comes from the 46 mo. follow-up data in the randomized PROTECT-AF trial (JAMA. 2014 Nov 19;312[19]:1988-98)'
http://www.ncbi.nlm.nih.gov/pubmed/25399274

'Dr Holmes concluded noting that worldwide experience to-date has been that roughly 95% of AFIB patients are able to safely go off warfarin or DOACs within a maximum of 12 months after Watchman placement.' (All quotes and excerpts reported by Bruce Jancin)

Highlights of AF Symposium 2016

ORLANDO FL. This past January I had the pleasure of attending the largest annual AFIB-centric meeting in the US, that for the last few years has been held in Orlando for obvious winter weather reasons, after many years in Boston in January.

As usual, this highly organized and expertly put on conference owes major credit due to Dr. Jeremy Ruskin for his tireless efforts to recruit the very best EPs and Cardiologist from around the world each year to come and share their latest discoveries and perceptions from this exploding field of AFIB. In

addition, many thanks to the expert staff at AF Symposium led by Muriel Corcoran that make sure the whole event runs like a well-oiled machine every year.

In this issue, we start with a summary look at a handful of key topics and themes shared at the symposium. Yet, with the understanding that in this one issue, we can only scratch the surface of all the fascinating discussions and debates worthy of being reviewed. As such, we'll touch on additional relevant topics from this symposium in future issues.

Evolution of Core AFIB Driver Understanding

Ionic mechanisms in AFIB

A basic question/request, so often asked on our forum over the years, goes something like: 'when will 'they' start making real progress towards a better fundamental understanding behind core AFIB causes?' Rest assured, major strides are constantly being made by many dedicated and very bright research scientists towards this goal across the world!

Once again, Dr. Stanley Nattel from McGill University in Montreal Canada, led off with a review of progress in understanding ionic mechanisms in arrhythmo-genesis and atrial metabolic dysfunction as both mechanisms for AFIB and as potential therapeutic targets. Dr. Nattel emphasized that: *"ultimately AFIB is an "electrical derangement" and such derangements always cause arrhythmias by effecting the ion channels that control cardiac electrical activity. Dr. Nattel went on to say: "… Alterations in (ion) currents that determine action potential duration (APD) are well known to govern the likelihood of reentry, with either a reduced calcium current or increased potassium current shortening APD and promoting AF-maintaining reentry."*

"Furthermore, the size of the sodium current also determines excitability and sodium channel blockers stop or prevent AFIB by reducing excitability, thus destabilizing AF-maintaining rotor's", said Nattel.

In practical terms, recent work indicates that: *"blockers of plateau potassium currents can enhance AFIB selectivity of optimized sodium channel blockers and lay the groundwork for new 'designer' multiple channel blockers as new classes of more effective AADs (anti-arrhythmia drugs) that in the future could far exceed the performance of current, much less specific, channel blocking AADs*".

One way these more specific multi-channel blocking drugs might help, is not only increasing efficacy in reducing AFIB, but also by combining a potassium blocker with sodium blocker that would have no impact on the ventricles, as do many of todays AADs, and thus eliminate the dreaded pro-arrhythmia potential that now plaques a good many of the better AADs, and making for safer rhythm control drugs.

Genetics, Fibrosis and AFIB

Looking first at genetics was **Patrick Ellinor M.D. PhD**. of *Mass General Hospital* and *Harvard Medical School*. Dr. Ellinor's laboratory use genetics to elucidate the molecular basis of arrhythmias, and AFIB in particular. After noting the heritable nature of a good amount of AFIB, he quantified that number across the board saying that there is a 40% increased risk for familial AFIB with just one sibling having the arrhythmia.

Dr. Ellinor's group is conducting a genome wide association study in 2015 via genetic fingerprinting in an effort to capture 90% of variations between individuals.

And for those of you familiar with genetics, they listed at least 14 AFIB-related Loci from ≈ 6,700 cases. Among these are *transcription factors* such as: PITX2, PRRX1 & ZFH3. *Ion Channel Loci* include KCNN3, HCN4 and CAV1/2. *Unknown category AFIB Loci* are C90RF3, SYNPO2C and SYNE2.

Geneticist are also busy studying the whole genome sequence in early-onset AFIB which is almost always genetic in nature. Genetic-related AFIB typically features ion channel dysfunction. And one of the

goals among AFIB-allied genetic researchers is to build a high-resolution map of all genetic variations. To do so, the following efforts are underway at centers around the world.

- **Broad-Bayer Genetic Collaboration on Cardiovascular Therapeutics**
- **Focus on MI & AFIB Genetic – a 5-year effort underway**
- **Focus on Heritable AFIB**
- **Focus to Identify many new AFIB related Genetic Loci**
- **Focus on the Genetics of AF Risks**

Big strides in our core AFIB understanding, as well as practical therapeutic options, are likely to come from the results of these in-depth genetic efforts in the coming years.

Fibrosis

Without question, the development of cardiac fibrosis has a strong association with AFIB and its progression. Such increases in fibrotic changes are often a reflection of structural remodeling which tends to expand the greater one's cumulative AFIB burden.

However, the idea that fibrosis is *'the'* core cause of AFIB doesn't hold much water now with increased understanding of the disease process. The degree of fibrosis is strongly mediated by genetic predisposition, and not solely by length of time with the disease or overall AFIB burden.

Some long standing persistent AFIB patients who lack the genetic tendency to for laying down fibrotic scarring, may have very little fibrotic burden even after many years of AFIB. While even short timer's in the first year or two of paroxysmal AFIB episodes can demonstrate substantial fibrosis. These are exceptions, not the rule, to be sure, yet indicate a heterogeneous association of fibrosis with AFIB.

Renowned AFIB researcher ***Dr. Jose (Pepe) Jalife*** of *University of Michigan*, and pioneer of the 'rotors as drivers of AFIB' theory, asked the question: ***'Is fibrosis the cause or consequence of AFIB?"***

To study this question, and to investigate a potential upstream therapy to prevent fibrosis, the aldosterone antagonist drug ***Eplerenone*** was compared to a Galectin-(GAL-3) inhibitor. GAL-3 is a protein that regulates inflammation, immunity and cancer as well as fibrosis. Serum levels of GAL-3 increase in persistent AFIB, but interestingly inflammation markers do not rise with increases in GAL-3.

Administering a GAL-3 inhibitor reduces rotor frequency seen during AFIB mapping. Keep in mind that sustained AF tends to increase atrial dilatation, collagen formation and increases fibrosis as a result.

The theory then, was that since the adrenal mineralocorticoid hormone, Aldosterone, in excess levels promotes a fibrotic substrate, then perhaps blocking Aldosterone would mitigate AFIB cellular hypertrophy and dilatation, and also should reduce serum evidence of fibrosis and P3NP. Indeed, Eplerenone did show reduction in fibrosis on direct tissue examination.

However, there was ***zero*** change in AFIB dominant frequency (DF) with Eplerenone! Only the Galectin 3 inhibitor prevented sustained AFIB, not Eplerenone, though both drugs reduced cardiac fibrosis! This is a key finding. It underscores the reality that though fibrosis is an important factor in AFIB, in many cases its only a consequence and not a cause of AFIB triggering or maintenance.

Direct Oral Anticoagulants (DOAC) and Reversal Agent Update

In addition to the surprising anomaly of DOAC drugs having overall less compliance among all but higher CHA2DS2-VASc score patient groups that we looked at earlier in the first *Short Cuts* summary in this issue, several other DOAC related tips and insights shared at AF Symposium are keepers.

While most patients figure warfarin is the only OAC with drug interaction issue, that really isn't true said **Dr. Jeffery Weitz** of *Thrombosis & Atherosclerosis Research Institute* in *Ontario, Canada*. Drug interactions among DOACs can vary because they all depend on P-glycoprotein transporters, but only Xeralto and Eliquis are significantly metabolized by CYP3A4 enzyme.

This factor, Dr. Weitz noted, may make one DOAC favored over another with certain concomitant meds. And yet, warfarin may still be the choice for patients who take multiple drugs that induce or inhibit P-glycoprotein and/or CYP3A4, simply because unlike DOACs warfarin can be monitored.

The next big question remains safety of the new DOACs. DOACs are associated with less intracranial bleeding than warfarin. And even without a specific reversal agent the outcome of patients with intracranial hemorrhage or major extracranial bleeding is no worse, and possibly better, than with warfarin outside of a major trauma scenario.

Reversal Agents begin to arrive

Dabigatran (Pradaxa) the first approved DOAC also is the first to get a fully approved direct reversal agent; Idarucizumab - don't even bother trying! Within the next month or two, most EPs and cardiologists expect FDA approval of Andexanet Alfa (Annexa-R) for rapid direct reversal of all three Factor Xa inhibitor DOACs: Xeralto (Rivaroxaban), Eliquis (Apixaban) and Savaysa (Edoxaban).

A point of concern and relevance is the high cost of these new reversal agents. Although no prices had been released as of this report for the (Annexa-R), speculation is that a typical IV bolus could run from $8,000 to $10,000 a dose! In light of this, another advantage of the shorter half-life of Eliquis is that it requires a good deal lower dose of Annexa-R compared to the longer half life Factor Xa DOAC drugs Xeralto and Savaysa.

There still remain many practical questions that only more time in the field can answer, such as how to identify patients that need reversal and how to monitor the extent of reversal? Will there be overuse of these reversal agents due to medico-legal concerns if they are withheld due to cost in patients with life-threatening bleeding?

Although these and more questions remain to be answered, without question DOACs are rapidly moving to the forefront of OAC therapy world-wide.

Non-PV Trigger Ablation Beyond the PVI Alone

As noted above, the topic of Non-PV (non-Pulmonary Vein) trigger detection and ablation was a major focus of numerous presentations by speakers from many regions of the world at the 2016 symposium. I found this a big change, and a big step in the right direction in my view … even compared to just 2014, the last of these large AF Symposiums I was able to attend.

For many years, those pioneering EP's bold enough to branch out beyond the well-defined conservative vision of anatomical-only pulmonary vein isolation alone in search of better outcomes for a larger array of patients with more advanced AFIB, remained controversial. This view was especially true for many of those wedded to a PVI-alone, not only for standard paroxysmal AFIB but for all forms of AFIB, and thus mostly by those EPs not seeking out large numbers of persistent and LSPAF patients to fill out their own caseload volume to begin with.

This year, lo and behold, it seemed like nearly everyone and their uncles were trumpeting the latest thinking from their centers on Non-PV trigger detection and ablation, and thus, expanding the scope of their patient lists they are now treating successfully. A real advance all around if you ask me!

It must make those early pioneers feel proud and fulfilled that their long efforts at pointing the field forward are now bearing such fruits. Pioneers such as the Bordeaux group and Andrea Natale's group

as well as University of Penn, University of Kansas and a number of others who were beating the drum toward what must have seemed a headwind of resistance years ago in the early days. These innovative EPs deserve credit for blazing the trail and are now rewarded by what seems a majority of centers from all parts of the world that are now including Non-PV triggers as a cornerstone of their advanced ablation protocols.

The question now, is not so much should we look beyond the PVs in challenging cases, but how do we detect consistent Non-PV triggers or substrate areas that are sources of AFIB genesis and/or maintenance, and go about reliably ablating these extra-PV sources for a durable arrhythmia free outcome?

While some Non-PV trigger protocols are focus on areas of fibrosis and scarring, as have some of the pioneers in this field long have done with their own non-PV trigger detection and ablation methods. Legends like Andrea Natale and Michel Haissaguerre each shared further Non-PV nuances and insights in their talks at AF Symposium 2016, born of their many years of investigation and successful careers at ablating well beyond the PVs and LA posterior wall, when so many of their challenging cases demand it.

After acknowledging the key role of fibrosis in AFIB, Dr. Natale noted in his talk that Non-PV trigger sites are not necessarily homogeneous with scar/fibrotic locations. In those with the most severely scarred and fibrotic atria, the Coronary Sinus (CS) and Left Atrial Appendage (LAA) are the most important AFIB sources remaining to isolate to achieve durable NSR. And yet, Dr. Natale noted these two key structures have little to no scar at all … indeed, the LAA, in particular, has almost no fibrotic scarring whatsoever!

Andrea Natale also stressed that though most advanced AFIB cases have extensive fibrosis/scarring, some such tough cases have very minimal fibrosis. This is the exception to be sure, not the rule, but the point being that the degree of fibrosis is largely genetically determined and is not just a function of AFIB duration or total accumulated AFIB burden. In his talk, Dr. Natale also underscored that: *while fibrosis can harbor Non-PV triggers, not all fibrotic regions are equal trigger sources for arrhythmia. In fact, Natale noted that in their unprecedented group experience, trigger sources are less often found within or around scarring or fibrosis.*

Professor Haissaguerre of Bordeaux noted similarly in his 2016 AF Symposium talk that: *"While other strategies target fibrosis, and while fibrosis is an important element, not all fibrosis carries the same arrhythmogenic potential and are not all equal to ablate!" …* Indeed, wise words from the two most experienced ablationist in the world.

We wrap up our initial review of AF Symposium 2016 here, with more to come in future issues, and with a lead in to the following important special report on a controversial patient-specific Non-PV substrate ablation method base on FIRM rotor mapping, and often combined with standard PVAI ablation.

Special Report:
A Review of FIRM - Focal Impulse & Rotor Mapping in 2016

The previous overview on Non-PV trigger ablation dovetails synergistically into the following special report looking at recent results from Topera/Abbott Medical's FIRM (Focal Impulse and Rotor Mapping), a patient specific system of substrate-based Non-PV source detection and ablation examined below. An early handful of studies published on FIRM were universally positive. And yet, debate about FIRM, as a proprietary computational algorithm-based mapping system, was highly charged, controversial and the most polarizing discussion at the recently completed AF Symposium 2016.

In review, non-PV trigger/substrate detection and ablation for AFIB extends beyond targeting the original anatomical-only, 'standard of care' PVI/PVAI (PV Antrum Isolation, shortened to 'PVAI' from

here on). The PVAI has been, and remains, the basic foundation of accepted catheter ablation for AFIB, and is recognized as an effective strategy for successful treatment of typical straight-forward paroxysmal AFIB; with addition of LAPW (left atrial posterior wall) isolation increasingly considered a key element by the majority of experienced operators, even in most paroxysmal cases.

For more advanced paroxysmal (PAF), persistent (PeAF) and long standing persistent (LSPAF) cases, a growing consensus now support the need to address Non-PV triggers in both the LA and RA beyond just the PV antrum/posterior wall area alone … this, in order to achieve maximum success and long-term durability from a more targeted expert ablation process and particularly in more challenging AFIB.

The key question remains; what method of Non-PV trigger detection and strategy for addressing these focal triggers and substrate areas gives the most reliable and consistent added benefit, over and above a well-done standard PVAI ablation alone?

A number of the top volume persistent and LSPAF centers in the world, such as Andrea Natale's multicenter group, the Bordeaux multicenter team, U. Penn, U. Mass, U Kansas and a fair number of other highly-experienced centers, have all developed their own non-proprietary techniques or approach's for Non-PV trigger detection and ablation ... most of which are fairly closely related. Yet, with each center having their own wrinkles in definition, detection and/or process for addressing these added sources of arrhythmia in other parts of the left/right atriums.

Which brings us to the FIRM rotor/focal impulse mapping and ablation system and strategy. Which detects targeted person-specific rotors in the left and right atria that are defined and detected as sustained clockwise or counter-clockwise activation around a center of rotation (think spiral), and are located via FIRM by electrode coordinates. Focal impulses show centrifugal activation from an origin.

First insights from OASIS-RCT - a FIRM-centric Randomized Control Trial

FIRM mapping and ablation has been a real topic of interest on our forum; and with many folks from outside our group who have contacted me over the last 4 years. Thus, the relevance in reviewing this recently published preliminary arm of the first truly independent randomized controlled trial (RCT): OASIS-RCT, looking prospectively at results from a modest FIRM-only ablation cohort consisting of a mix of only persistent and LSPAF cases. All without prior ablation history and no PVAI being performed … just FIRM ablation alone used in virgin hearts with this most challenging type of AFIB.

The complete larger analysis of OASIS-RCT is due for publication later this year and will include, in addition to this initial mid-term arm, a larger group followed up over a longer period of time comprising cases where both FIRM-guided rotor ablation plus PVAI was performed and compared to a control group having a state-of-the-art persistent and LSPAF protocol of extended PVAI + non-PV trigger ablation. The purpose being, to see how FIRM + PVAI stacks up to one of the most robust methods we know of to-date for ablation of these most challenging AFIB cases to treat.

After all, such has been the main premise and appeal from the outset; that the concept of FIRM-mapping and ablation would result in a dramatic reduction in total patient-specific ablation lesion sets required to achieve superior long term outcomes in both paroxysmal as well as non-paroxysmal classes of AFIB. And thus, FIRM technology holds promise to usher in a new paradigm of understanding and improved ablation methodology for the benefit of both EPs and patients alike.

Certainly an appealing premise indeed! So without further adieu, lets dive in to our review of this initial arm of OASIS-RCT from a large multicenter group of highly experienced ablationists in the US and Europe, followed by a brief overview of several other recent independent investigations into FIRM efficacy from experienced ablation centers to see where FIRM stands as of early 2016.

Acute and Mid-term Outcomes of FIRM-Guided-Only Ablation in Non-Paroxysmal AFIB Patients.

Milan & Foggia Italy, Bronx NY, Ankara Turkey, Bad Neustadt & Bochum Germany, Lexington KY, Cleveland OH, San Francisco CA, Stanford & La Jolla CA, Austin TX.

Study Premise

Since FIRM-guided focal and rotor ablation targets are purported to sustain AFIB not only in paroxysmal, but particularly in persistent and LSPAF (Long-standing Persistent AF) cases, this world-class international multi-center group set out to evaluate short to mid-term outcomes of FIRM-guided-only ablation in prior-ablation-naive non-paroxysmal patients for this initial phase of the larger OASIS-RCT.

The complete OASIS-RCT is the first prospective randomized control trial on FIRM. It is underway at 3 major centers (2 in US & 1 in Europe), and all ablations, including the larger arm with FIRM-guided plus PVAI compared to a control arm of extended PVAI + non-PV trigger arms were performed by highly-experienced persistent and LSPAF ablation operators.

A handful of prior studies in the first few years after FIRM-guided ablation was announced in early 2012 showed very favorable, impressive looking results with high degrees of acute AF termination or at least slowing of AFCL (AFIB cycle length) reported during the procedure in mostly mixed groups of patients with both paroxysmal and persistent AFIB. In the bulk of these cases, both FIRM-guided and PVAI ablation were combined. Also, a fair number of these early patients evaluated had undergone a mean of 1.2 prior PVI ablations before the FIRM + PVI follow-up ablation process.

In addition, to my knowledge none of these positive early studies were conducted as fully independent prospective RCTs … the type required to give the most reliable, robust and confidence-inspiring perspective on such an all new approach to AFIB-mapping and ablation. And most of these early reviews of FIRM included variable degrees of guidance from the developers of FIRM technology.

To be sure, such a scenario does not inherently invalidate those early non-randomized results, not by any means. Yet, it does imply the wisdom of at least holding out for fully independent well-designed RCTs conducted by top-volume persistent AFIB ablation centers to confirm those early encouraging results before accepting any such new technology as a carte blanche new ‘gold standard’ treatment paradigm.

Ideally, such reassuring scrutiny would include a prospective multicenter RCT investigating both FIRM-only and FIRM + PVI/PVAI ablation compared directly to existing state-of-the-art mapping and ablation strategies for these most challenging cases of AFIB. And ideally, with readily replicable and well-vetted published results all telling the same general story as the initial positive reports from the originating center(s) of any new technology and process.

This defines precisely the aim and design of the OASIS-RCT. If the results from all arms of the OASIS trial confirm and reinforce the initial positive findings of the early non-randomized studies, that would surely lead to a major boost of confidence in, and acceptance of, the new FIRM concept and technology; especially if after one or more additional RCTs all concur and underscore essentially the same findings.

Methods and Endpoints

Initially, this early to mid-term FIRM-only ablation arm of the OASIS-RCT recruited 30 symptomatic non-paroxysmal patients across the 3 centers. However, one case was excluded due to unfavorable cardiac anatomy, thus leaving 29 (persistent N=20, LSPAF = 9) net cases to follow-up in this first arm of OASIS.

FIRM mapping-identified rotors were found in all 29 persistent and LSPAF patients. A mean of 4 rotors (±1.2) per patient were found in this RCT which was a greater number of rotors compared to most previous FIRM studies (range: 1.9 to 2.8 rotors per patient). This difference may well have been due to the more challenging nature of the AFIB in this overall group.

As a result, with more rotors per patient, RF time required was understandably longer in this cohort than in prior FIRM-only reports (35min vs 14-20min), though with an RF time per rotor comparable to that experienced with the previous studies. Keep in mind, these times reflect doing only FIRM-targeted mapping and ablation with no added time required for a combined FIRM+PVAI ablation.

The primary endpoint sought was single-procedure freedom from any AFIB/AT (all atrial tachy-arrhythmia) and off all AAR drugs, after a minimum mean follow-up time of just 5.7 months, to insure full coverage beyond the blanking period in all patients. This shorter than usual mid-term result was set for this initial FIRM-only ablation cohort of the larger OASIS trial, since the optimal results from AFIB ablations typically decline the further out from the blanking period the patient group is followed.

Thus, such a mid-term post-ablation view would tend to give a more positive outlook for a FIRM-only outcome compared to, say, a more typical 12mo. to 24mo. follow-up. And with this most difficult class of cases, keeping follow-up to just beyond the blanking period would thus not unnecessarily prevent a patient from getting a timely follow-up ablation, if needed, as might a longer fixed-term of follow-up mandated as a set protocol.

Exclusion criteria were: paroxysmal AFIB, prior AFIB ablation, any contraindication for ablation, and inability of unwillingness to sign a consent form.

According to the OASIS study authors: *"a 3D map using conventional EAM (electro-anatomical-mapping) (CARTO-3D) was made, the FIRMap® 64-pole basket catheter was advanced into the right and left atriums with FIRM mapping performed in AFIB. Unipolar electro-grams captured by FIRMap were exported to the dedicated, proprietary mapping system (RhythmView®, Abbott Medical) where processing revealed rotors defined as clockwise and counterclockwise activation around a center of rotation located by electrode coordinates"*.

"RF catheter ablation was repeated for all rotors identified until an acute primary endpoint of AFIB source (rotor or focal impulse) elimination was achieved and confirmed with FIRM re-mapping of each rotor site. If failure to get AFIB termination; then organization of AFIB to AT, or slowing of AFCL ≥ 10% were included as acceptable endpoints. If AFIB persisted despite elimination of all rotors, the patient was cardioverted into NSR to end the procedure. Follow-up was done in an outpatient clinic setting with a full cardiology exam, 12 lead EKG and 7 day Holter monitor every 3 months."

Results

When the concept of FIRM mapping and ablation was first introduced in early 2012, many of us afibbers and EP's alike were initially excited and enthused about the prospect of a much simpler to perform system promising superior and faster results with a minimum of burns required for all forms of AFIB … what's not to like?

For many, the initial zeal took a more 'wait and see', but still hopeful turn after carefully reading through the first few FIRM studies. Studies that, as noted above, were promising in outcomes for the largely FIRM guided plus PVI cohorts, but had not included any full RCTs by fully independent operators. Without any RCT investigations done among the early promising studies, it warranted a more cautious outlook until more rigorous RCTs might confirm those early results for any such all new technology.

In addition to the FIRM + PVAI given to most participants, a fair number among the overall cohorts studied in these early reports had also undergone prior PVI. That is all fine as a demonstration of concept, and yet such a format makes one less confident as to how much of the credit one could then ascribe to the FIRM ablation phase itself, outside of the multiple PVI's in these early studies (≈2.2 mean total PVI ablations inclusive of the FIRM + PVI with a fair number of cases). Nevertheless, I had hoped and expected that the first group of truly independent well done studies and RCTs would show results at least in the same ball park, and thus hopefully would affirm the new technology.

Alas, this has not been the case so far. In this modest size, but strong prospective arm of OASIS-RCT, looking at FIRM-only guided ablation of 29 non-paroxysmal, prior ablation-naive cases, *zero* AFIB terminations occurred with no patients converting directly to NSR during the procedure. AFIB slowing of ≥10% occurred in 2 (7%) cases, and organization of AF to AT happened in 10 (34%). DC cardioversion was required in all (100%) of participants. Mean procedure length was 222min ± 49min.

After 5.7 months of mean follow-up, single procedure freedom from AT/AFIB and off all AAD's (anti-arrhythmic drugs) was just 17% (5/29); and 28% (8/29) when including *'with or without'* AADs. All basic stats for age, LA diameter, number of rotors, or RF time between cases with acute success, and those without, were similar. Also, there was no relationship between acute procedural success and freedom from AFIB/AT at 5.7month follow-up. All 29 patients were free of any procedure-related adverse events as a credit to the highly-skilled operators at the 3 high-volume persistent/LSPAF ablation centers.

This result stands in stark contrast to the outcomes posted by early non-randomized studies of both FIRM-guided + PVI in a mixed group of paroxysmal and persistent AFIB cases where single-procedure freedom from AFIB alone was reported as 86% (CONFIRM N=36 … though freedom from all AFIB/AT was 70.6% in CONFIRM), and 71.4% freedom from all arrhythmia from (Miller et al, N=78 in a mixed group) both of which far exceeded this FIRM-only phase outcome from the larger OASIS-RCT. [1]

The authors of this initial prospective arm of the OASIS-RCT concluded their report with entirely opposite findings relative to the earlier positive studies, by stating:

"given the aforementioned results, the FIRM-guided only ablation arm was deemed futile, resulting in premature trial arm termination: FIRM-identified rotor-only ablation does not appear to be effective in non-paroxysmal AFIB, and should not be employed as a sole ablation strategy in this population.' 'Whether FIRM-guided ablation in addition to PVAI ablation is beneficial or superior to an ablation strategy encompassing both PVAI and non-PV triggers is being assessed in the ongoing OASIS–RCT." (ClinicaLTrials.gov Identifier: NCT02533843)
Gianni C. et al. Acute and Early Outcomes of FIRM-guided rotor-only ablation in patients with non-paroxysmal AFIB, Heart Rhythm, http://dx.doi.org/10.1016/j.hrthm.2015.12.028

Most recent independent studies on FIRM (2015 to early 2016)

1. In addition to this current study on mid-term FIRM-only ablation outcomes in non-paroxysmal cases, the following numbered summaries underscore the consistently similar disappointing findings of these four most recent consecutively published studies investigating FIRM mapping and ablation technology.

2. A recent long term follow-up out of **UCLA, Virginia Commonwealth University** followed 43 mixed class patients after FIRM + PVI and reported 70% of patients had experienced recurrent AFIB/AT at long term follow-up. Only a net 21% were free of all AFIB/AT and off all AAR drugs after 18mo (±7mo.). Of these 43 patients, 67% also had a prior PVI ablation in addition to the current FIRM + PVI ablation.

The authors of this first independent long range study out of **UCLA/VCU** concluded: ***'In a cohort of patients at 2 medical centers treated with FIRM-guided rotor ablation and PVI, we observed a low rate of acute AF termination and a high rate of recurrence during long term follow-up (different from previous studies). Prospective randomized controlled trials with this technology are needed to clarify its role as an ablation strategy.'***
Buch et al. Long-term clinical outcomes of Focal impulse and rotor modulation for treatment of atrial fibrillation: A multicenter experience. http://dx.doi.org/10.1016/j.hrthm.2015.10.031

3. A **Hamburg Germany** study by **Tilz et al**., This top Hamburg group headed by renowned **EP Karl Heinz Kuck** achieved AF termination in 11 of 24 cases (46%) in a FIRM-only ablation protocol, though

[1] *Narayan SM, et al. PRECISE Rotor Elimination without Concomitant pulmonary vein isolation for the Successful Elimination of Paroxysmal Atrial Fibrillation. Heart Rhythm 2013;10:LBCT4. Note: I was unable to locate this PRECISE study of 31 FIRM-only Paroxysmal cases via PubMed or Heart Rhythm Journal search function, either as an abstract or full study under the above reference. Therefore, I do not cite any results, but list the reference here wishing others better luck.*

all but 1 had induced, rather than spontaneous AFIB, and 24% experienced recurrence of arrhythmia over 9 month's follow-up. Dr. Kuck, noted at AF Symposium 2016 that while he remains very interested in investigating rotor mapping, he has stopped doing all rotor-guided ablations using either FIRM or via a novel non-invasive body surface mapping vest technology at his center due to the consistent lack of predicable outcomes and efficacy. Ethically, he thus refuses to continue doing rotor-guided ablations at this time on humans until we have a better understanding about the core issues and connections between rotors and AFIB to guide us.
Tilz RR et al. Nine months outcomes following Focal impulse and rotor modulation for treatment of atrial fibrillation using the novel 64-pole basket catheter: acute and medium term results: Europace 2015;17:iii68.

4. *Schade A, et al,* Following pure FIRM rotor-only ablation in 21 persistent AFIB patients, 67% had early to midterm recurrence of AFIB/AT. ***Schade A, et al. FIRM only ablation in patients with persistent atrial fibrillation: acute and medium term results. Europace 2015;17: iii68.***

Editors comments:

What could explain such a stark contrast in results? Dismissing out of hand the possibility of inadvertent bias or error in the structure, or data analysis, from the earlier non-randomized group of studies, what other explanations might there be for such a huge disconnect between those first four universally positive reports early on, in comparison to this modest size arm of the first independent prospective RCT on FIRM-only mapping and ablation strategy. Noting as well, the similarly disappointing results from these most recent four independent studies on FIRM published in the 2015/early 2016 time frame.

A possible issue could be the acknowledged low signal quality and poor atrial contact coverage of the current 64-pole FIRM basket catheter used (only ≈43% of LA surface contact area with this catheter as noted by Kuklik et al[2]. In addition, the possibility of any proprietary phase interpolation algorithm, as used in FIRM, to be innately biased toward rotor detection could be a factor in these poor outcomes.

Certainly, one real factor could be the difference in populations studied; the OASIS-RCT subset recruited 100% symptomatic non-paroxysmal cases that were generally overweight with a mean BMI (body-mass index) of 31.2 and large LA size (mean of 47mm) and with other co-morbidities etc. … possibly a more challenging overall group of patients than in some of the earlier positive studies.

Another possible explanation is that ablation limited to rotors may not be sufficient to maintain NSR in non-paroxysmal AFIB. Such a premise might also depend on the low-accuracy of FIRM-mapping in identifying rotors. As such, even if this were true with this iteration of FIRM mapping, it may not inherently reflect other rotor-mapping approaches such as non-invasive body surface phase-mapping technology currently under preliminary investigation in Europe. But if it turns out that ablation limited only to rotors is inadequate for most non-paroxysmal patients, then this discrepancy might reflect a limited role for pure substrate modification without including a PVAI in this challenging class of patients.

On the other hand, nothing we have seen so far inherently invalidates the original premise of rotors potential relationship with AFIB. It's entirely possible that further refinements to FIRM mapping catheters or algorithms might yet clarify key insights into this technology. Or perhaps, other approaches to mapping rotors and focal impulses such as non-invasive body surface mapping, as is currently under investigation in Europe by the Bordeaux group might define the value of rotor mapping and the utility of targeting rotors as patient-specific Non-PV drivers for treating this vexing arrhythmia.

And yet, it must be acknowledged that there remain logical arguments by highly respected researchers in this field, such as world-renowned EP scientists Drs. Maurits Allessie, Natasja de Groot and Albert Waldo, as several prominent skeptics, that challenge the premise of algorithmically-defined and detected rotors as directly causing or driving AFIB. On the flip side, the 'rotors as AFIB drivers'

[2] *Kuklik P, et al. Technical challenges of rotor identification during atrial fibrillation using phase singularity detection. Eurospace 2015;17:ii20.*

proponents such as the very bright and renowned 'pioneer of rotors', Dr. Jose Jalife, from *University of Michigan* also makes a passionate and compelling argument for the 'rotors in AFIB ablation' camp.

Science can be messy and takes real time to reveal its secrets. Yet, until we have more confident answers, either way, to this fundamental question on the core role of rotors in the genesis and maintenance of AFIB, it remains a possibility that these recent rather dismal outcomes from at least four consecutive independent reviews, including this arm of the first RCT on FIRM, might yet point to an inherent limitation in targeting rotors for ablation as a consistent, replicable and practical AFIB solution.

Conclusion

In light of this recent new input above, I suspect a lot will ride on the full longer-term results of the complete OASIS-RCT due out sometime this summer. Should this longer term rigorous RCT from one of the leading multi-national ablation research centers in the world, plus any subsequent additional well-structured future RCTs looking at FIRM ablation, fall short of at least a similar ball park replication and validation of the kind of promising views that initially excited a large number of EP's and patients starting in 2012, such a scenario could make it tough for FIRM to gain future traction.

However, it's still far too premature to jump to such conclusions. The FIRM developers must be able to objectively and convincingly explain these discrepancies, and importantly both the completed OASIS-RCT, and other independent RCTs on FIRM, must at least reinforce the general story told by the early promising studies. Otherwise, enthusiasm and confidence in FIRM may well go the way of both CAFÉ-only ablation and renal denervation, as both once promising and exciting new approaches that have largely fallen out of favor due to the inability of other EPs and centers to replicate the early positive results posited by the original developers of these once confident and alluring concepts.

Our best rule of thumb advice for those seeking an ablation for AFIB is to ***never*** choose an ablation based on technology first and foremost. A far wiser path, in our long collective experience, is to carefully vet and select the most experienced and confidence-inspiring expert ablationist one can arrange for oneself, and then fully trust that he or she will be more than capable of selecting the very best technology to help deliver you to long-term freedom from the beast with the least amount of total overall ablation burden required for a case like yours. For a patient to demand, up front, that their EP use a specific technology, whether accepted or (as yet) unproven, is simply putting the cart before the horse.

The truth, both sides acknowledge, is still unproven and thus remains unknown. And Dr. Jalife, while fully convinced in rotor mapping and ablation as the way forward, also acknowledges the limitations of our current understanding and execution while rightly calling for more patience and time to sort out the nuances and reality toward a consistent verdict. This investigation into rotors and drivers of AFIB is vital research, without question, and regardless of the outcome of this important debate we are sure to make great strides in our core knowledge of AFIB and its therapeutic treatment.

We look forward to these developments that may help define the ultimate role, or limitation as the case may be, of rotor-mapping as well as the practical utility of targeting such rotors for ablation. However, the jury will likely remain in doubt until FIRM mapping, in whatever version, and/or alternative methods of body surface mapping-based rotor detection and ablation, are first proven consistently reliable long-term treatments for AFIB by well-designed fully independent randomized control trials.

Best wishes until our next issue of The AFIB Report!
Shannon

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