DOI: 10.19102/icrm.2016.070203

YEAR IN REVIEW EXPERT COMMENTARY

New 2015 Discoveries in Electrophysiology

JOHN D. DAY, MD, FHRS¹

Intermountain Medical Center Heart Institute, Intermountain Medical Center, Salt Lake City, UT

The year 2015 ushered in many new discoveries in the field of electrophysiology (EP). These latest studies will change future guidelines and practice patterns. As in previous years, let me share with you my top 10 EP stories for 2015.

1. Botox may cure atrial fibrillation

Having chaired the late-breaking clinical trials this past year at the HRS Annual Scientific Sessions in Boston, I was most impressed by the small study presented by Jonathan Steinberg and colleagues. This study was later published in the December issue of *Circulation Arrhythmia and Electrophysiology*.¹ I bring this study to the Journal's readers attention first as it challenges everything we thought we knew about how to treat atrial fibrillation (AF).

The design of this study was simple. Sixty AF patients undergoing coronary artery bypass graft (CABG) surgery. Of these 60 patients, 30 were randomized to a Botox fat pad injection and 30 were randomized to a fat pad saline injection during their surgical procedure. To ensure no episodes of AF were missed, all patients underwent implantation of the Medtronic Reveal XT loop recorder.

As the autonomic nervous system plays an important role in the development and maintenance of AF, one would expect that the neurotoxin Botox would just help with postoperative AF. The surprise of this study was that 1 year after CABG, all 30 of the Botox-treated patients were still AF free.

This persistent Botox effect was still in effect long after the effects would have been expected to wear off. Of course, it should be noted that extremely short episodes of AF may have been missed because of how the implantable loop recorder documented AF.

This study raises many important points. First, Botox injections are incredibly cheap at the time of CABG compared with extra hospital days from postoperative

AF. Second, could the real answer to AF treatment be autonomic nervous system modulation rather than antiarrhythmics or pulmonary vein isolation procedures? Lastly, can we expect to soon see catheters that would allow us to inject pericardial fat pads with Botox percutaneously to treat AF?

Stay tuned, as this study could completely change AF ablation procedures as we now know them.

2. Anticoagulating CHA₂DS₂-VASc 1 AF patients unlikely to help

As readers of this Journal are well aware, the 2014 HRS/ACC/AHA AF guidelines were unclear on how to manage AF patients with a CHA₂DS₂-VASc score of 1. Specifically, the guidelines state that anticoagulation, aspirin, or no stroke prevention therapies are all reasonable options.

Since the guidelines were published, there have been many studies evaluating the role of anticoagulation in CHA₂DS₂-VASc 1 patients. Of these studies, Friberg et al.² in the *Journal of the American College of Cardiology* deserves special attention.

In this study, a total of 140,420 CHA₂DS₂-VASc 1 AF patients were retrospectively evaluated for risk of stroke. Depending on which definition of stroke was used, women had an annual stroke risk of 0.1–0.2%. In contrast, men had an annual stroke risk of 0.5–0.7%.

This study was especially important because it challenges the 2014 AF Guidelines in that female gender really did not represent a risk factor for stroke in this large retrospective study. Also, this study helps clarify the risks versus benefits of life-long anticoagulation therapy for our CHA₂DS₂-VASc 1 AF patients.

With an annual stroke risk of less than 1% for CHA₂DS₂-VASc 1 AF patients, it makes the leap toward life-long anticoagulation therapy very unappealing, especially when you consider the bleeding risk.

For example, from the ARISTOTLE Trial,³ the annual risk of a life-threatening bleed (gastrointestinal bleeds were not considered life-threatening in this study), was 2.13% for apixaban and 3.09% for warfarin. When you weigh these life-threatening bleed risks versus the annual stroke risk in this Friberg article, it definitely tips the

The author reports no conflicts of interest for the published content. Manuscript received January 21, 2016, Final version accepted February 4, 2016.

Address correspondence to: John D. Day, MD, Intermountain Heart Rhythm Services, Intermountain Medical Center, 324 10th Avenue, Suite 206, Salt Lake City, UT 84103. E-mail: John@DrJohnDay.com

balance toward no anticoagulation therapy for CHA₂DS₂-VASc 1 AF patients.

3. ICDs remain extremely underutilized for the highest risk patients

In an interesting *JAMA* article,⁴ Dr. Sean D. Pokorney and colleagues showed that even in the highest sudden death risk patients, implantable cardioverter-defibrillators (ICDs) are prescribed less than 10% of the time.

In this study, Pokorney et al.⁴ retrospectively evaluated 10,318 Medicare beneficiary patients with a prior myocardial infarction and an ejection fraction of $\leq 35\%$ from 441 US hospitals. Not surprisingly, the ICD-treated patients fared better, with a 42% improved event-free survival.

In my mind, the bigger issue is why are fewer than 1 in 10 Medicare patients being treated with this potentially life-saving therapy? While many possible explanations exist—everything from lack of education among referring physicians to fear of reprisal from the Department of Justice—the bottom line is that patients are not being adequately treated. This study is a call to action for medical societies and all readers of this Journal to increase education efforts regarding this potentially life-saving therapy.

4. Weight loss puts 46% of AF into remission without drugs or procedures

This study⁵ finally got the cardiology world talking about lifestyle modification to treat AF. In this study, Dr. Prash Sanders and colleagues enrolled 355 overweight AF patients with an average baseline weight of 220 pounds. Of these 355 patients, 38% were successful in losing an average of just 36 pounds. Remarkably, 46% of these successful weight loss patients had their AF go into remission without drugs or procedures.

Not only did their AF go away but many other chronic medical conditions disappeared as well. For example, diabetes was reversed in 88% of these patients. Hypertension, C-reactive protein, hyperlipidemia, and many abnormal echo abnormalities were all reversed as well.

This study is a wake-up call for readers of this Journal. We need to be up front and direct with our patients. We need to tell them that if they really want to beat AF they have to adopt healthier lifestyle patterns.

5. Apixaban safe may be safe for valvular heart disease

As readers know, the ARISTOTLE trial was the large multicenter study that successfully navigated apixaban (Eliquis) to FDA approval. In this study,⁶ approximately one-quarter of the patients had valvular heart disease. While patients with moderate to severe mitral stenosis and mechanical valve patients were excluded, other forms of valvular heart disease, such as mitral valve repairs or bioprosthetic valves, were included.

How did these valvular heart disease patients fare? As you might have suspected, these patients also fared very well on apixaban in this study.

Does this mean we can start using apixaban for AF patients with a history of mitral valve repair or bioprosthetic valves? Not so fast.

While it may be best for the patient, should something bad happen, this off-label use could come back to haunt you. Also, novel oral anticoagulants (NOACs) should never be considered for rheumatic moderate to severe mitral stenosis or mechanical valves. Hopefully, ongoing studies will change FDA NOAC indications for patients with a history of mitral valve repair or those with bioprosthetic valves.

6. Leadless pacemakers are the future

In another *New England Journal of Medicine* article, Vivek Reddy et al.⁷ provided compelling evidence of safety and efficacy for the new Nanostim leadless pacemaker.

As most of the readers of this Journal are aware, the Nanostim pacemaker is an extremely small 1-ml “pellet” that is delivered to the right ventricle through a catheter. There are no leads and no pectoral pocket. Everything is contained within this 1-ml “pellet.”

In a report of 526 patients treated with the Nanostim leadless pacemaker, 96% underwent a successful implantation. Of these patients, the leadless pacemaker performed as expected.

From a safety standpoint, the tamponade rate was 1.3%, “pellet” repositioning was required in 1.3%, and device dislodgement requiring retrieval was seen in 1.7%. While these complication numbers may seem high, remember that this is a first-generation device and all operators were inexperienced. As we have learned from the Watchman experience, these numbers decrease dramatically with experience and ongoing modifications of the technology.

While this pacemaker is just a rudimentary “VVI pacemaker” at this time, it is just a matter of time before a dual-chamber or even a cardiac resynchronization therapy leadless pacemaker will be available. At our center, we participated in this Nanostim study. Our patients also fared well and we were favorably impressed with this new technology.

7. Physical activity may reverse AF

In recent years, we have heard much about extreme levels of exercise causing AF. Unfortunately, many physicians and patients may have interpreted these studies as exercise causes AF.

Fortunately, this past year we saw two large studies, one in *Circulation*⁸ and one in *JACC*,⁹ both confirming that regular physical activity can reverse or suppress episodes of AF. Specifically, the *Circulation* article showed that for every one additional metabolic equivalent patients can do on a treadmill test, their risk of AF was decreased by 7%. Similarly, the *JACC* article showed that for every one MET increase in exercise level, AF could be reduced by 20%.

I should point out that at the time of the writing of this article, yet another major study, this one from 2016, was published in *Circulation*¹⁰ showing that AF could be reduced by 41% with regular short bursts of high-interval training.

What should we make of all these studies? When it comes to exercise and AF there seems to be a U-shaped curve. In other words, both the “couch potato” and extreme endurance athlete are at high risk of developing AF. The sweet spot seems to be moderate levels of daily exercise to prevent and reverse AF.

8. Nothing beats pulmonary vein isolation for treatment of persistent AF

Much has been written in this Journal and elsewhere about how to best treat persistent AF. Unfortunately, nothing seems to better pulmonary vein isolation (PVI). In this *New England Journal of Medicine* article, Dr. Atul Verma et al.¹¹ performed a well-designed multicenter study of 589 patients to evaluate the effects of PVI alone or PVI plus lines (roof and mitral isthmus), or PVI plus complex electrogram ablation for persistent AF in the STAR AF Study.

At the end of 18 months here is what they found. Of the PVI ablation only patients, 59% were AF free. Unfortunately, in the PVI plus lines and PVI plus CFE groups the 18-month AF-free survival rate was only 49% and 46% respectively.

What does this study tell us? While PVI alone fared the best, a 59% success rate at 18 months is very unsatisfactory. Until newer techniques, such as an effective AF driver/rotor mapping system or a means to treat the autonomic nervous system are available, PVI remains the cornerstone of AF ablation—even for persistent AF. In the meantime, it may be best to limit our persistent AF ablations to PVI and any other specific triggers or flutters we identify at the time of ablation.

9. DFT testing should be abandoned

For decades, defibrillation threshold testing (DFT) was performed with ICD implantations. Early on this testing was probably useful, as we really did not know how best to defibrillate the heart at that time.

In recent years, more and more studies have shown that DFT testing at the time of ICD implantation is ineffective and may even increase procedural complication rates. This study in the *European Journal of Cardiology*¹² is one more line of evidence against routine DFT testing.

In this study, 1,077 patients were randomly assigned to DFT testing at the time of ICD implantation or no testing with the first shock programmed at 40 J. Interestingly, with DFT testing, only 5% of the patients had an inadequate defibrillation safety margin requiring revision of the ICD system. Interestingly, while efforts to revise the ICD system in these 5% of patients provided no benefit it did add 30 more minutes to the procedure time, 40% more radiation, and many unnecessary shocks.

I should point out that researchers did not include right-sided implants or patients with hypertrophic cardiomyopathy (HCM) or arrhythmogenic right ventricular dysplasia (ARVD).

What are we to make of this and other recent studies evaluating the efficacy and safety of routine DFT testing at the time of ICD implantation? Basically, except for rare cases, such as right-sided implants or HCM/ARVD patients, DFT testing should probably not be routinely performed.

10. Cryoballoon versus radiofrequency ablation of AF

Which technology is best for the catheter-based treatment of AF, cryoballoon (CB) or radiofrequency (RF) energy? This study, the FreezeAF Study,¹³ adds to the growing body of literature on this subject.

In this study, 315 patients with paroxysmal AF were randomly assigned to CB or RF catheter ablation. At the end of 12 months, the multiple ablation success rate was statistically identical—71% for RF and 74% for CB. Interestingly, the redo ablation rate was identical for both technologies at 20%.

From a safety standpoint, the reported complication rate of CB was more than double that of the RF treated patients. This unacceptably high complication rate was driven primarily by phrenic nerve palsy that occurred in 6% of the CB treated patients versus 0% in the RF-treated patients.

What is the take home message of this study? While the CB performed just as well as RF for efficacy, phrenic nerve palsy remains a significant complication with CB that must be solved. For anyone who has cared for patients who have had their lives debilitated by lifelong oxygen therapy and shortness of breath, this is a real problem.

This study is a call to action for electrophysiologists and companies to come together to find an effective solution that can eliminate this excessive risk for patients.

References

1. Pokushalov E, Kozlov B, Romanov A, et al. Long-term suppression of atrial fibrillation by botulinum toxin injection into epicardial fat pads in patients undergoing cardiac surgery: One-year follow-up of a randomized pilot study. *Circ Arrhythm Electrophysiol*. 2015;8(6):1334–1341.
2. Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA₂DS₂-VASc score of 1. *J Am Coll Cardiol*. 2015; 65(3): 225–232.
3. Hylek EM, Held C, Alexander JH, et al. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, characteristics, and clinical outcomes. *J Am Coll Cardiol*. 2014;63(20):2141–2147.
4. Pokorney SD, Miller AL, Chen AY, et al. Implantable cardioverter-defibrillator use among Medicare patients with low ejection fraction after acute myocardial infarction. *JAMA*. 2015;313(24):2433–2440.

5. Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: A long-term follow-up study (LEGACY). *J Am Coll Cardiol*. 2015;65(20):2159–2169.
6. Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. *Circulation*. 2015;132(8):624–632.
7. Reddy VY, Exner DV, Cantillon DJ, et al. Percutaneous implantation of an entirely intracardiac leadless pacemaker. *N Engl J Med*. 2015;373(12):1125–1135.
8. Qureshi WT, Alirhayim Z, Blaha MJ, et al. Cardiorespiratory fitness and risk of incident atrial fibrillation: Results From the Henry Ford Exercise Testing (FIT) Project. *Circulation*. 2015;131(21):1827–1834.
9. Pathak RK, Elliott A, Middeldorp ME, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. *J Am Coll Cardiol*. 2015;66(9):985–996.
10. Malmo V, Nes BM, Amundsen BH, et al. Aerobic interval training reduces the burden of atrial fibrillation in the short term: A randomized trial. *Circulation*. 2016;133:466–473.
11. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med*. 2015;372(19):1812–1822.
12. Bänsch D, Bonnemeier H, Brandt J, et al. Intra-operative defibrillation testing and clinical shock efficacy in patients with implantable cardioverter-defibrillators: the NORDIC ICD randomized clinical trial. *Eur Heart J*. 2015;36(37):2500–2507.
13. Luik A, Radzewitz A, Kieser M, et al. Cryoballoon versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation: The prospective, randomized, controlled, noninferiority FreezeAF Study. *Circulation*. 2015;132(14):1311–1319.