

On the Beat: Key Articles from June 2017

“Hard Hitting” Article Summaries

Atrial Fibrillation Anticoagulation

DOI	Title
10.1016/j.jacc.2017.03.600	<i>Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction</i>
<p>Summary: Yao, et al demonstrated that dosing of direct oral anticoagulants in patients with pre-existing renal dysfunction is inappropriate (ie, overdosed) in as many as 43% of patients. Moreover, as many as 13% of patients were underdosed. Overdosing led to increased bleeding risk without incremental stroke benefit, and underdosing led to increased stroke risk without incremental reduction in bleeding risk.</p>	
<p>Commentary: These results are provocative in that they indicate, in a real life sample of patients, frequent inappropriate dosing of direct oral anticoagulants in patients. Another article published this month by Yang, et al in Heart indicates that patients with kidney disease also carry a reduced time in therapeutic range when managed with warfarin. These results together indicate the importance of close consideration for anticoagulation management when considering renal dysfunction in atrial fibrillation patients.</p>	
10.1161/STROKEAHA.116.016281	<i>Using Artificial Intelligence to Reduce the Risk of Nonadherence in Patients on Anticoagulation Therapy</i>
<p>Summary: In this small, randomized study by Labovitz, et al, a smartphone-based artificial intelligence program was used to monitor anticoagulation adherence. The program visually identified the patient, the medication, and ingestion of the medication in real-time. Plasma drug concentration levels indicated 100% adherence in the intervention group and 50% in the control group, with an absolute improvement in adherence amongst patients on direct oral anticoagulants of 67%.</p>	
<p>Commentary: Adherence gaps in anticoagulation have been shown by multiple investigators to lead to increased stroke risk in patients with atrial fibrillation. A study published this month by Sorenson, et al in European Heart Journal – Cardiovascular Pharmacotherapy suggested in a real-world sample that adherence to both direct oral anticoagulants and warfarin is not ideal. With improving methods for ambulatory tracking of patients using artificially intelligent programs, it may be possible to improve medication adherence amongst appropriately prescribed patients.</p>	

Cardiac mapping and ablation

DOI	Title
10.1016/j.jacep.2017.01.016	<i>Pulmonary vein re-isolation as a routine strategy regardless of symptoms: The PRESSURE randomized controlled trial</i>
Summary: Das, et al indicate in their randomized controlled trial that aggressive re-evaluation of patients undergoing pulmonary vein isolation after index ablation for pulmonary vein reconnection with intent to re-ablate significantly reduced arrhythmia recurrence (17.5% vs 42.5%) with concomitant improvement in quality of life.	
Commentary: The study by Das, et al clearly points out the potential for pulmonary vein reconnection, which has been noted by prior studies as well even in the absence of apparent clinical recurrences. Despite a > 20 minute waiting time at time of index ablation with repeat evaluation of the veins, there were frequent late reconnections noted as indicated by the need for repeat ablation. Further study is needed regarding the cost-effectiveness and risk/benefit of an invasive approach to re-evaluate pulmonary vein isolation irrespective of evidence of clinical atrial fibrillation recurrence.	

Risk stratification and management

DOI	Title
10.1016/j.jacep.2016.12.015	<i>Cost-effectiveness and clinical effectiveness of the risk factor management clinic in atrial fibrillation: The CENT study</i>
Summary: Pathak, et al complement prior work by evaluating the cost and clinical efficacy related to an aggressive risk factor-targeted clinic for patients with atrial fibrillation. In targeting a well supervised approach to weight loss, improvement in fitness, and reduction in other clinical risk factors such as diabetes, hypertension, etc, they demonstrated that patients undergoing such a risk factor-mediated treatment strategy had less arrhythmia recurrence (79% freedom vs 44%) with a corresponding incremental cost benefit of \$62,653 per quality adjusted life year.	
Commentary: The work by Pathak, et al is complementary to a growing body of evidence of the critical role adiposity plays in atrial fibrillation pathogenesis, and the potential for reversal of these mechanisms by weight loss. Other articles published this month by Fenger-Gron, et al in the Journal of the American College of Cardiology, Winkle et al in Heart Rhythm, Baek et al in the Journal of the American Heart Association, and Yagawa et al in Circulation Journal provide further evidence of the link between obesity and risk associated with atrial fibrillation and associated outcomes.	

10.1093/europace/euw125	<i>Smart detection of atrial fibrillation</i>
<p>Summary: Krivoshei, et al studied algorithms applied to information gathered on pulse wave signals via a smartphone-based LED light / camera lens. They demonstrated that using such a tool on patients, atrial fibrillation could be discriminated from sinus rhythm with a sensitivity and specificity of at least 95%.</p>	
<p>Commentary: The need for early identification of atrial fibrillation, particularly in those with risk factors for stroke, is important to identify patients who should be on anticoagulation. However, cost-effective methods for population-wide identification of patients with atrial fibrillation are currently lacking. Ideal methods would consist of ambulatory technology with integrated sensors that is cheap, “intelligent” (and thus not burden the healthcare system for continuous review of data), continuous, and minimally disruptive into patients’ daily lives (ie, using tools that are already commonly used by patients). Smartwatches and smartphones demonstrate increasing promise in this regard and the work by Krivoshei, et al complements other evolving data in using ambulatory, low cost, patient-owned technologies to detect atrial fibrillation.</p>	
10.1093/europace/euw398	<i>Is epicardial fat depot associated with atrial fibrillation? A systematic review and meta-analysis</i>
<p>Summary: Gaeta et al demonstrated in this meta-analysis of existing studies that there is a significant association between epicardial fat and atrial fibrillation risk. They demonstrated that more epicardial fat was associated with more persistent rather than paroxysmal forms of atrial fibrillation as well as any atrial fibrillation versus none.</p>	
<p>Commentary: The role of epicardial fat in arrhythmogenesis is still unclear, though many studies suggest an association. Gaeta, et al reviewed 7 available studies meeting criteria to evaluate the correlation of epicardial fat depot with atrial fibrillation risk. While these findings may or may not indicate a causative association, they are suggestive of need for further study. Furthermore, there is a growing body of basic physiologic evidence reviewed this month by Antonopoulos, et al in the Journal of Physiology that epicardial fat and the heart communicate via complex bidirectional pathways that can alter both normal myocyte function as well as fat accumulation. However, whether directed targeting of the fat itself or these pathways to alter arrhythmogenic potential is unknown.</p>	

ICDs, pacemakers and CRT

DOI	Title
10.1016/j.jchf.2017.02.018	<i>Impact of current versus previous cardiac resynchronization therapy guidelines on the proportion of patients with heart failure eligible for therapy</i>
<p>Summary: Lyons, et al evaluated the effect of changing guidelines based on increasing bodies of evidence related to indications for cardiac resynchronization therapy on real-world patient samples. They demonstrated that based on recently refined guidelines, resulting from an evolving evidence-base, the proportion of patients eligible for cardiac resynchronization therapy would decrease by as many as 15% based on current as compared with older guidelines.</p>	
<p>Commentary: The real-world impact of changing guidelines is often hard to gauge. Given the evolving data related to the role of cardiac resynchronization in patients with heart failure with reduced ejection fraction, it is possible that qualifications for device therapy may continue to change. Close consideration of evidence and changes in guidelines is critical to inform appropriate decision making in device implantation in these patients. Marzec, et al in JAMA: Cardiology this month noted that, despite these findings of fewer patients potentially meeting indications, that there continue to be gaps in actual referral for cardiac resynchronization therapy amongst those meeting indications. These findings were similarly shown this month by Randolph, et al in the American Heart Journal, in which they demonstrated that there is frequent underutilization of resynchronization therapy, in particular amongst qualifying women and black patients.</p>	
10.1136/heartjnl-2016-310677	<i>Sex-specific outcomes with addition of defibrillation to resynchronisation therapy in patients with heart failure</i>
<p>Summary: Barra, et al studied gender specific survival in patients receiving cardiac resynchronization therapy. They demonstrated in this multicenter observational cohort study that addition of defibrillator to resynchronization therapy in patients meeting primary prevention indications for device implant primarily conferred benefit in men rather than women.</p>	
<p>Commentary: These findings suggest that there are gender specific benefits related to device therapy. Another article published in the Journal of the American Heart Association by Varma, et al this month showed that resynchronization therapy added to pacing or defibrillator therapy tended to offer women a substantial survival benefit when compared with men. This survival benefit was additionally noted by Randolph, et al in the American Heart Journal this month, where they also noted significantly greater underutilization of resynchronization therapy amongst women than men despite the greater conferred benefit. Whether these outcome differences hold with randomized prospective studies remains to be seen.</p>	

[10.1111/jce.13192](https://doi.org/10.1111/jce.13192)

Mortality Effect of ICD in Primary Prevention of Nonischemic Cardiomyopathy: A Meta-Analysis of Randomized Controlled Trials

Summary: Luni, et al performed a meta-analysis on the role of defibrillators in primary prevention of sudden death. They included six studies that met criteria and found that while there was an overall significant survival benefit in patients with nonischemic cardiomyopathy, but once accounting for those who were on adequate beta-blockade and ACE/ARB, there was no statistical difference in outcome with primary prevention ICD use.

Commentary: The study by Luni, et al adds further credence to the findings of the DANISH study that the survival benefit of primary prevention ICDs in nonischemic cardiomyopathy may not be equivalent to that seen in ischemic cardiomyopathy. This month, Al-Khatib, et al also performed their own analysis in JAMA Cardiology, suggesting an overall mortality benefit in nonischemic patients, though they did not get to the granularity of appropriateness of current management at the time of ICD implant. The perceived lower relative mortality benefit of ICDs in nonischemic cardiomyopathy, thus, may be partly due to improvements in the clinical and pharmacologic management of these patients.

[10.1111/jce.13178](https://doi.org/10.1111/jce.13178)

Significant Discrepancy Between Estimated and Actual Longevity in St. Jude Medical Implantable Cardioverter-Defibrillators

Summary: Doppalapudi, et al demonstrated that up to 74% of patients have a significant discrepancy between actual and estimated battery life amongst patients with St. Jude Current/Promote devices. This discrepancy was most significant in the 18 months prior to reaching ERI.

Commentary: These findings suggest a significant discrepancy in estimated and actual battery life. Concerns regarding rapid battery depletion have been raised in recent device advisories. However, these findings, while on a small number of patients (n=40), is provocative in the potential need for more frequent monitoring in patients with these devices for a significant period of time prior to reaching ERI.

Sudden Death / Cardiac Arrest

DOI	Title
10.1161/CIRCULATIONAHA.116.026910	<i>Association between midwall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction</i>
<p>Summary: Halliday, et al demonstrate in patients with dilated cardiomyopathy and mild to moderately reduced left ventricular systolic dysfunction, evidence of mid-wall late gadolinium enhancement on MRI may identify patients at risk of sudden cardiac death, with a hazard ratio of 35.9 for aborted sudden cardiac death.</p>	
<p>Commentary: These results complement findings by Baritussio, et al published in Resuscitation this month that indicate the incremental value of MRI in defining potential arrhythmogenic pathology in out of hospital sudden cardiac arrest survivors. Further study is needed to clarify the role of MRI in risk stratification, and how these results should inform ICD decision making, but the findings are relevant in counseling patients who may not meet classic indications for defibrillator implantation.</p>	
10.1161/CIRCULATIONAHA.116.026318	<i>Optimizing a drone network to deliver automated external defibrillators</i>
<p>Summary: Boutilier, et al demonstrate the potential role of drones in delivering automated external defibrillators to patients suffering out of hospital cardiac arrest. They demonstrate in this study that use of a drone based network for AED delivery can reduce time to AED arrival by as much as 6 minutes and 43 seconds compared to traditional response times in urban areas, or as much as 10 minutes and 34 seconds in rural areas.</p>	
<p>Commentary: The findings by Boutilier, et al, though simulated, are provocative in terms of the potential for using evolving technologies to disrupt traditional care delivery systems, in particular for acute / emergency care situations. Claesson, et al in JAMA this month demonstrated the feasibility and corresponding reductions in response time in a real-world case example, suggesting potential real-life clinical benefit, though further rigorous studies will be required to clarify overall risks and outcomes.</p>	

Cellular Electrophysiology

DOI	Title
10.1016/j.hrthm.2017.01.027	<i>Antiarrhythmic effects of interleukin 1 inhibition after myocardial infarction</i>
<p>Summary: de Jesus, et al investigated the effect of inhibition of interleukin 1 beta, a key regulator of the post-myocardial infarction inflammatory response, on arrhythmic potential. In murine models, they demonstrated that the interleukin 1 beta receptor antagonist, anakinra, improved conduction velocity, improved calcium handling, reduced spontaneous and inducible ventricular arrhythmias, and reduced action potential duration dispersion. These findings were due to increased expression of connexin 43 and sarcoplasmic reticulum Ca²⁺-ATPase.</p>	
<p>Commentary: The finding of a novel target for arrhythmogenesis can be critical to development of future therapies. The findings by de Jesus complement a growing body of evidence of the critical role of inflammation mediated pathways in arrhythmogenesis. This month, Lazzerini, et al published a review summarizing the link between systemic inflammation and arrhythmic risk in European Heart Journal. In addition, Yucel, et al demonstrated in Scientific Reports the relationship between lipopolysaccharides and electrophysiologic dysfunction in stem cell derived cardiomyocytes, which may be partly mediated through interleukin pathways. Interestingly, a currently clinically available interleukin 1 beta inhibitor, canakinumab, has also been shown in preliminary data to reduce major cardiovascular events including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, when added to optimal medical therapy in post-myocardial infarction patients in the randomized, double blind, placebo-controlled CANTOS study, suggesting there may also be clinical benefits beyond the translational work done to date.</p>	
10.1161/CIRCEP.116.004508	<i>Induced Pluripotent Stem Cell–Derived Cardiomyocytes Provide In Vivo Biological Pacemaker Function</i>
<p>Summary: Chauveau, et al demonstrated in canines with atrioventricular block, that injection of induced pluripotent stem cell derived cardiomyocytes into the epicardial surface of the heart develop inherent pacemaker activity that improves over four weeks of maturation and is responsive to epinephrine, though with relatively low intrinsic rates.</p>	
<p>Commentary: The potential to restore pacemaker activity in patients with severe conduction disease holds the potential to dynamically progress the options in care for patients with electrophysiologic disease. While these translational studies are early, they reflect significant progress in the path towards a viable biological pacemaker. Significant remaining questions include ensuring robustness of the heart rate conferred by the biologic pacemaker, durability of pacemaker activity, and arrhythmogenic potential.</p>	

10.1152/ajpheart.00741.2016	<i>Detachable glass microelectrodes for recording action potentials in active moving organs</i>
<p>Summary: Barbic, et al demonstrate a new glass microelectrode that may allow for determination of cellular action potential duration in an actively moving organ. They demonstrate utility of these devices for action potential recordings over both long durations of time and in both the beating heart as well as neural tissue.</p>	
<p>Commentary: Current cellular electrophysiology patch clamping and action potential studies require immobilization of the cells being studied, whether mechanically or pharmacologically. However, such directed efforts to immobilize the cell may alter electrophysiologic parameters of the cell. The ability to record cellular action potentials in actively moving cells may allow for studies on cellular electrophysiology that more closely approximates real-world, beating heart conditions.</p>	

Genetic Channelopathies (LQTS, Brugada, CPVT, etc)

DOI	Title
10.1161/CIRCEP.117.005053	<i>Electrical Substrate Elimination in 135 Consecutive Patients With Brugada Syndrome</i>
<p>Summary: Pappone, et al demonstrated in a large cohort of patients with Brugada syndrome (135), that there is an arrhythmogenic electrical substrate that primarily localizes to the right ventricular epicardium, and that ablation of this region led to normalization of the electrocardiogram and non-inducibility of ventricular arrhythmias both acutely (in all patients) and over long-term follow-up in 133/135 patients.</p>	
<p>Commentary: The findings by Pappone, et al complement prior work by Nademanee and others that support a role for targeting substrate in the region of the right ventricular epicardium in both preventing recurrent ventricular arrhythmias in patients with Brugada syndrome and in normalizing electrocardiographic Brugada pattern. These findings complement evidence at the translational level that suggest mutations in SCN5A lead to accentuated transmural gradients that predilects to the right ventricle with preferential prolongation of action potentials of right ventricular epicardial myocytes. Whether substrate distribution and efficacy of epicardial ablation is dependent on specific genetic cause remains to be determined, in particular given other literature published this month by Makarawate, et al in Journal of the American Heart Association that specific SCN5A genetic polymorphisms may confer greater risk of arrhythmic events than others.</p>	

Ventricular Arrhythmias

DOI	Title
10.1016/j.jacc.2017.04.035	<i>Cardiac sympathetic denervation for refractory ventricular arrhythmias</i>
<p>Summary: Vaseghi, et al demonstrated that cardiac sympathetic denervation may be an effective therapy in many patients with intractable ventricular arrhythmias, with a >50% reduction in sustained VT, ICD shock, transplant or death over one year follow-up and nearly 1/3 of patients no longer requiring antiarrhythmic therapy. However, bilateral sympathectomy was superior over left side only sympathectomy. Advanced heart failure and VT cycle length were also associated with poorer outcomes.</p>	
<p>Commentary: The article by Vaseghi, et al complements an evolving literature suggesting the critical nature of the cardiac nervous system in arrhythmogenesis. However, the complex nature of cardiac innervation likely requires individualized consideration of both patient selection and approach to denervation. Other articles published this month further support potential role of autonomic modulation in ventricular arrhythmias, including those by Yu, et al published in Heart Rhythm regarding a potential anti-arrhythmic effect of renal denervation in specific canine models. A review article by Zaglia, et al in the Journal of Physiology this month summarizes some of the concepts tying the role of the cardiac nervous system to arrhythmogenesis.</p>	
10.1016/j.hrthm.2017.02.033	Initial international multicenter human experience with a novel epicardial access needle embedded with a real-time pressure/frequency monitoring to facilitate epicardial access: Feasibility and safety
<p>Summary: DiBiase, et al demonstrated initial feasibility of an epicardial access system with an integrated pressure monitoring system in achieving epicardial access in patients undergoing electrophysiologic procedures necessitating this approach. In all 25 patients included, epicardial access was successfully, obtained, with one instance of a delayed pericardial effusion.</p>	
<p>Commentary: With increasing indications for epicardial puncture (left atrial appendage occlusion, epicardial ganglia modulation, ventricular arrhythmia mapping and ablation, etc), tools to optimize safety and efficacy of achieving epicardial access are critical. The study by DiBiase, et al indicates the potential initial feasibility of one such tool, though relative safety compared with traditional approaches needs to be evaluated. This month, Silberbauer, et al published an alternative approach in JACC: Clinical Electrophysiology using intentional coronary venous perforation to facilitate traditional subxiphoid access. Consideration of these variable approaches in the context of physician experience will be crucial to optimize wider spread comfort with epicardial access in necessary cases.</p>	

10.1093/europace/euw096	<i>Long-term benefit of first-line peri-implantable cardioverter–defibrillator implant ventricular tachycardia-substrate ablation in secondary prevention patients</i>
<p>Summary: Acosta, et al studied the role of peri-ICD implant targeted substrate based ablation in secondary prevention patients. They demonstrated that early ablation of substrate was associated with decreased recurrence of ventricular arrhythmias and defibrillator shocks over an average follow-up of almost 4 years. However, patients with lower ejection fractions (EF<35%) received less benefit, with a similar frequency of VT recurrence but lower overall burden in those receiving upfront ablation versus those who did not.</p>	
<p>Commentary: These findings complement prior data from the SMASH-VT and VTACH trials supporting a role for early ablation to reduce future arrhythmia events in patients receiving defibrillators. However, practice patterns vary in performing early ablation in patients, and whether a mortality benefit exists remains unclear.</p>	

Other EP Concepts

DOI	Title
10.1016/j.ijcard.2017.01.157	<i>Practice variation in the re-initiation of dofetilide: An observational study</i>
<p>Summary: Turagam, et al report results of a survey of 347 providers in the US and worldwide regarding the degree of practice variability when reinitiating dofetilide. They noted that there was a wide degree of practice variation, with up to 21% of providers always admitting patients to the hospital for reinitiation, and 37% of physicians admitting patients <10% of the time. 4% of physicians reported major adverse events with drug re-initiation in patients who tolerated their de novo start.</p>	
<p>Commentary: Given the proarrhythmic effects of antiarrhythmic drugs, strategies to reduce that risk are important. While most studies suggest the overall risk of major adverse events (eg, torsades de pointes) is rare, the risk is nevertheless present. Due to this, there are strict guidelines for de novo initiation of dofetilide. However, guidelines for reinitiation after any period of cessation are less clear. The 4% major adverse event rate suggests need to better understand how to optimally monitor these patients especially after a period of cessation. This month, Piccini, et al and the Cardiac Safety Research Consortium published recommendations for long-term electrocardiographic monitoring in clinical drug development. Consideration of the impact of antiarrhythmic drug management in situations that are not well outlined by existing protocols (eg, dose reduction and re-escalation as an outpatient, reinitiation as an outpatient, etc) likely require further study to inform current clinical practice.</p>	