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YEAR IN CARDIOLOGY SERIES

The Year in Review of Clinical Cardiac Electrophysiology

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This past year saw multiple important advances in the field clinical cardiac electrophysiology. Seminal articles describing new anticoagulant drugs for stroke prevention in atrial fibrillation were published. New results that raise questions regarding the safety of dronedarone and several new promising techniques in AF ablation were described. Important articles that refine our understanding of the risk of sudden death among Wolff-Parkinson-White patients were published. In the basic and translational sciences, the application of gene therapy to the study and potential treatment of arrhythmias was described, whereas genetic determinants important to the optimal treatment of inherited arrhythmia syndromes were further elucidated. Issues relevant to cardiac rhythm device therapy included investigations into the St. Jude Riata lead, new applications of device monitoring, predicting response to cardiac resynchronization therapy, and the use of pacemakers for vasovagal syncope. (J Am Coll Cardiol 2013;61:772–82) © 2013 by the American College of Cardiology Foundation

This review encompasses articles that were published between April 1, 2011, and June 1, 2012, in the field of cardiac electrophysiology that were felt to be particularly relevant to general cardiologists. The year saw many contributions that are pertinent to both researchers and clinicians. In addition, the year saw exciting new basic research that will fuel future applications, such as the first electrophysiological validation of stretchable and flexible electronics that can match the epidermis (1), but we are not able to cover all such basic work in this review. We apologize for the required omission of many excellent studies.

Atrial Fibrillation

Although warfarin has been established as an effective drug to prevent stroke in atrial fibrillation (AF), the associated inconvenience of frequent monitoring and dose adjustments, dietary restrictions, and the delayed and then prolonged effect are continued challenges that many patients and physicians would prefer to avoid (2–4). Several agents with more predictable pharmacokinetics and pharmacodynamics have been developed and recently studied in large randomized trials. Dabigatran, a direct-thrombin inhibitor, was the first such drug to receive Food and Drug Administration approval for the prevention of stroke and thromboembolism in nonvalvular AF based largely on the phase-3 RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study (5) previously reviewed in 2010 (6). Two important randomized studies comparing factor Xa inhibitors to warfarin in AF patients were published this year.

The ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial was a multicenter, randomized study comparing fixed-dose rivaroxaban (20 mg daily or 15 mg daily in patients with a creatinine clearance of 30 to 49 ml/min) to adjusted-dose warfarin (with a target international normalized ratio [INR] of 2.0 to 3.0) in 14,264 patients (7). Importantly, whereas the RE-LY study was open labeled, the ROCKET AF trial involved a "double-blind, double-dummy" design, meaning that all patients received both active drug and placebo in a blinded fashion. Those who received rivaroxaban underwent point-of-care monitoring that included sham INR values and drug dose adjustments. Inclusion criteria included electrocardiographically (ECG) confirmed AF plus a history of stroke, transient ischemic attack, or systemic embolism or at least 2 of the following: heart failure (HF) or a left ventricular ejection fraction (EF) of 35% or less, hypertension, an age of 75 years or more, or the presence of diabetes mellitus. The mean and median $CHADS_2$ scores were 3.5 and 3.0, respectively. The primary efficacy analysis was performed in the "per protocol" population (meaning including only patients that received at least 1 dose of a study drug, did not have a major protocol violation, and were followed for events while receiving a study drug or within 2 days of discontinuation) rather than by intention to treat and found

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that stroke or systemic embolism occurred in 1.7% per year in the rivaroxaban group compared with 2.2% per year in the warfarin group (for the rivaroxaban group, hazard ratio [HR]: 0.79, 95% confidence interval [CI]: 0.66 to 0.96; $p < 0.001$ for noninferiority). In an intention-to-treat analysis for the same efficacy endpoint, the point estimate again favored rivaroxaban and met the criteria for noninferiority, but did not reach statistical significance for superiority (HR: 0.88, 95% CI: 0.74 to 1.03; $p < 0.001$ for noninferiority, $p = 0.12$ for superiority). Whereas major bleeding and the combination of major bleeding and clinically relevant nonmajor bleeding were similar between groups, rates of intracranial hemorrhage were significantly lower in the rivaroxaban group than in the warfarin group (0.5% vs. 0.7% per year; HR: 0.67, 95% CI: 0.47 to 0.93; $p = 0.02$ for superiority). Rates of major bleeding from a gastrointestinal site were more common in the rivaroxaban group (3.2%) compared with the warfarin group (2.2%, $p < 0.001$). Although not statistically significant in either case, there were less deaths in the rivaroxaban group in both the as-treated safety population (1.9% vs. 2.2% per year in the warfarin group; HR: 0.85, 95% CI: 0.90 to 1.02; $p = 0.07$) and in the intention-to-treat analysis (4.5% vs. 4.9% per year in the warfarin group; HR: 0.92, 95% CI: 0.82 to 1.03; $p = 0.15$). Although INR values in the warfarin group were in the therapeutic range a median of 58% of the time, the effect of rivaroxaban did not differ across quartiles of the duration of time that INR values were therapeutic according to the study center.

The second trial to compare a factor Xa inhibitor to warfarin in AF was the ARISTOTLE (Apixiban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (8). A total of 18,201 AF (or atrial flutter) patients with at least 1 additional stroke risk factor (an age of at least 75 years, previous stroke, transient ischemic attack or systemic embolism, symptomatic HF within the past 3 months or an EF of no more than 40%, hypertension, or diabetes mellitus) were randomized in a double-blind, double-dummy fashion to apixiban 5 mg twice daily (or 2.5 mg twice daily for those more than 80 years old, body weight of no more than 60 kg, or serum creatinine of 1.5 mg/dl or more) versus warfarin titrated to an INR of 2.0 to 3.0. The mean $CHADS_2$ score was 2.1. Patients in the warfarin group had an INR in the therapeutic range a median 66.0% of the time. Using an intention-to-treat analysis, the primary outcome of stroke or systemic embolism occurred significantly less frequently in the apixiban group (1.27% vs. 1.60% per year in the warfarin group; for the apixiban group, HR: 0.79, 95% CI: 0.66 to 0.95; $p < 0.001$ for noninferiority and $p = 0.01$ for superiority). The rate of hemorrhagic stroke was 49% lower and the rate of ischemic or uncertain type of stroke was 8% lower in the apixiban group. Major bleeding was significantly less frequent in the apixiban group (HR: 0.69, 95% CI: 0.60 to 0.80; $p < 0.001$) as was intracranial hemorrhage (HR: 0.42, 95% CI: 0.30 to 0.58; $p < 0.001$). The rate of death from any cause was 3.52% per year in the apixiban group and 3.94% per year in the warfarin group (HR: 0.89, 95% CI: 0.80 to 0.99; $p = 0.047$).

Taken together, these 2 factor Xa inhibitors appear to be promising alternatives to warfarin in preventing thromboembolic complications in at-risk AF patients. Some similarities and differences are worth highlighting. The most important similarities between these 2 drugs are also shared with dabigatran: these drugs can achieve efficacy that is at least as good as warfarin without requiring any monitoring or frequent dose adjustments. Because all of these new drugs directly inhibit clotting factors, rather than inhibit synthesis of factors, there are no known dietary restrictions and the time to peak effect with initiation and loss of effect with discontinuation is relatively rapid. In addition, each of these 3 drugs (dabigatran, rivaroxaban, and apixiban) is associated with a significantly reduced incidence of intracranial hemorrhage—this complication, and in particular the possibility of hemorrhagic stroke, is 1 of the most feared consequences of warfarin therapy. Although not yet proven, some have speculated that a reduction in factor VIIa (an expected effect of warfarin, but not the current agents) may specifically reduce protection against bleeding in the central nervous system (8,9). Both dabigatran and rivaroxaban increased the risk of gastrointestinal bleeding compared with warfarin. Although the increased gastrointestinal bleeding with dabigatran could be in part attributed to the tartaric acid component of the drug that is required for absorption, this would not explain the same observation with rivaroxaban. Finally, although apixiban was the only 1 of the new drugs that exhibited a statistically significant reduction in death compared with warfarin, the point estimate in mortality reduction for each drug versus warfarin was generally similar (HR: 0.88, $p = 0.051$ with dabigatran; HR: 0.85, $p = 0.07$ for the rivaroxaban in the as-treated safety population; HR: 0.89, $p = 0.047$ with apixiban).

One of the major limitations of the new anticoagulants is that methods to reverse the drugs have not been well established. An important study was published this past year to test the effect of prothrombin complex concentrate (PCC), which contains a high concentration of factors II, VII, IX, and X; protein C; protein S; and antithrombin, on coagulation in the presence of dabigatran or rivaroxaban (10). Twelve healthy volunteers receiving either dabigatran or rivaroxaban were given 50 U/kg of PCC in a randomized, double-blind, placebo-controlled, crossover trial. The prothrombin time, known to increase with rivaroxaban in a concentration-dependent manner (11), was significantly prolonged with rivaroxaban and was completely reversed with PCC; a placebo infusion of saline did not reverse the prothrombin time prolongation. Similarly, endogenous thrombin potential, a marker of thrombin generation known to decrease with rivaroxaban (12), significantly decreased as expected with the drug and was normalized with PCC; again, saline infusion had no effect. In contrast, PCC had no effect on the significant prolongation of several

clotting assays with dabigatran: these included activated partial thromboplastin time, endogenous thrombin potential lag time (the parameter of endogenous thrombin potential influenced most by dabigatran [13]), thrombin time, and ecarin clotting time (known to prolong in a linear fashion with dabigatran [14]). In short, the available assays suggested that PCC may reverse rivaroxaban, but not dabigatran. It is important to emphasize, however, that these assays are all surrogates that may not accurately reflect actual responses in bleeding patients, and the investigators appropriately cautioned that the effects of PCC have yet to be confirmed in the clinical setting.

A novel, major trial examining the effects of dronedarone in a population with permanent AF was examined in the PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone Study on Top of Standard Therapy) study. The rationale for the study was based on evidence that dronedarone may have beneficial effects in high-risk AF patients independent of sinus rhythm maintenance, including slowing of the heart rate (15), blood pressure lowering (16), and adrenergic blockade (17,18). In addition, the rate of death from arrhythmia was significantly reduced in the ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Atrial Flutter) trial (16), and a post hoc analysis of ATHENA demonstrated that dronedarone was associated with a reduced risk of stroke (19). The PALLAS study randomized 3,236 patients with permanent AF or permanent atrial flutter (with evidence of a persistent atrial arrhythmia for at least 6 months) to dronedarone 400 mg twice daily or matching placebo in a double-blinded fashion. Patients had to be 65 years of age or older and have at least 1 of the following risk factors: coronary artery disease; previous stroke or transient ischemic attack; symptomatic HF; an EF of 40% or less; peripheral arterial disease; or the combination of an age of 75 years or older, hypertension, and diabetes. The study was terminated for safety reasons after a median of 3.5 months of follow-up. The first coprimary outcome of a composite of stroke, myocardial infarction, systemic embolism, or death from cardiovascular causes occurred in 43 patients receiving dronedarone and 19 patients receiving placebo (HR for the dronedarone group 2.29, 95% CI: 1.34 to 3.94; $p = 0.002$). The second coprimary outcome of unplanned hospitalization for a cardiovascular cause or death occurred in 127 patients receiving dronedarone and 67 patients receiving placebo (for the dronedarone group, HR: 1.95, 95% CI: 1.45 to 2.62; $p < 0.001$). There were 25 deaths in the dronedarone group and 13 in the placebo group (HR: 1.94, 95% CI: 0.99 to 3.79; $p = 0.049$). There was more death from cardiovascular causes (HR: 2.11, 95% CI: 1.00 to 4.49; $p = 0.046$), more strokes (HR: 2.32, 95% CI: 1.11 to 4.88; $p = 0.02$), and more hospitalizations for HF (HR: 1.81, 95% CI: 1.10 to 2.99; $p = 0.02$) in the dronedarone group.

Several reasons for these higher rates of adverse events in the dronedarone group were suggested by the investigators of the PALLAS (20) study. First, they emphasized that the early trial termination markedly reduces the statistical power of the study, increases the uncertainty about the interpretation of the p values, and may bias the HRs away from the null. They also point to the ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease) trial, wherein patients with severe HF randomized to dronedarone exhibited significantly increased mortality (21), a finding that has been attributed to the potential negative inotropic action of the drug. Although the mean time in the therapeutic INR range was significantly lower among the dronedarone group (55.6% vs. 58.6%; $p = 0.02$), the magnitude of this difference did not appear to be sufficient to explain the differential stroke risk. Dronedarone can result in increased digoxin levels, and, of the participants on digoxin (representing approximately one-third of all participants), the digoxin levels drawn on day 7 were 1.2 ± 0.8 ng/ml in the dronedarone group versus 0.9 ± 0.6 ng/ml in the placebo group. Of interest, a post hoc analysis of the DIG (Digitalis Investigation Group) trial found that a digoxin level greater than 1.2 ng/ml was associated with a significantly increased risk of death from cardiovascular causes (22). Regardless of the mechanism, it is clear that dronedarone should be avoided in permanent AF patients with cardiovascular risk factors.

Atrial Fibrillation Ablation

This past year brought an abundance of interesting and important publications in the field of AF ablation. The field continues to evolve, with general trends toward increasing safety and effectiveness matched by greater transparency and rigor in assessing outcomes. Although achieving pulmonary vein isolation remains the mainstay of curative AF ablation procedures (23), several adjunct approaches demonstrated evidence of additional benefit, including targeting areas with high dominant frequencies (defined as the frequency with the maximum power derived from spectral analysis and fast-Fourier transform of sinus rhythm bipolar electrograms) (24), ablating ganglionated plexi in the right atrium of vagal AF patients (25), and a combined endocardial and epicardial approach (26). In addition, although radiofrequency energy using irrigated bipolar catheters remains the mainstay of ablation technologies, continued advances in alternative methods, such as using cryoballoons (27), multipolar ablation catheters (28,29), direct visual guidance (30,31), and laser (30,31) were reported. Concern regarding the safety of the multielectrode radiofrequency ablation catheter was raised regarding both pulmonary vein narrowing (29) and subclinical thromboemboli (28). Perhaps most novel was an approach that leverages electrical signals from a 64-pole basket catheter in the left atrium to perform physiologically guided computational mapping in humans

that frequently revealed sustained electrical rotors and repetitive focal beats that appeared to drive AF activity (32). Identification of these potential drivers of AF may open the way to new ablation targets that may be tailored to individual patients. Although the outcomes of AF ablation have generally focused on symptom improvement, 2 new studies provide early evidence that there may also be more tangible benefits related to "hard" outcomes, including improvements in renal function among those with mild to moderate kidney dysfunction (33), and, compared to historical controls, lower rates of stroke and mortality (34). Finally, because "curative" AF ablation may not be a viable option for all patients, a meta-analysis of studies comparing atrioventricular (AV) nodal ablation and pacemaker placement versus drug therapy demonstrated that AV nodal ablation can significantly improve symptoms and quality of life in appropriately selected patients (35).

Wolff-Parkinson-White Syndrome

Two important papers provided insights into the risk of malignant arrhythmias in Wolff-Parkinson-White (WPW) patients. Although an accessory pathway may be responsible for bothersome episodes of supraventricular tachycardia due to AV reciprocating tachycardia (AVRT), the combination of a propensity to AF and anterograde conduction that can deliver dangerously rapid rates from the atrium to the ventricle makes WPW a potentially life-threatening condition. In general, it is believed that symptomatic patients with WPW should undergo electrophysiology study (EPS) and possible ablation (36). This past year, Pappone et al. described their findings after following 379 Italian WPW patients with inducible AVRT (essentially documenting objective proof of "symptoms") who underwent EPS but not ablation for a mean of 3.6 years (37). Ablation was not performed either because informed consent was obtained only for EPS or because of patient discomfort or anesthesia-or vascular-related complications. The mean age was 23 years. Twenty-nine (8%) patients had a malignant presentation over the follow-up period, defined as syncope/pre-syncope in 25, rapid pre-excited AF causing hemodynamic collapse in 3, and ventricular fibrillation (VF) in 1. Importantly, 10 (3%) were lost to follow-up and were excluded from the analyses—although the reader should consider the "worst-case scenario" in which all 10 died of WPW-related arrhythmias, and no such analyses were provided. Those with a malignant presentation were more often male, had a shorter accessory pathway effective refractory period during EPS, more often had AVRT that triggered AF during EPS, and more often had more than 1 accessory pathway. In multivariate analyses, only a shorter accessory pathway effective refractory period and AVRT triggering AF were independent predictors. Although 8% had such a presentation, including only 4 (1.4%) with cardiac arrest, it is important to emphasize that these events occurred over only a mean follow-up of <4 years and that the lifetime risk may be substantially higher.

In contrast to those with symptoms or documented tachyarrhythmias, the risk of malignant arrhythmia in asymptomatic WPW patients was examined in a meta-analysis of 20 studies involving 1,869 such patients with 11,722 person-years of follow-up (38). All studies reported sudden cardiac death events, and a total of 10 sudden cardiac death episodes were reported from a total of 6 different studies. Five of these 6 studies originated from Italy. In a random effects model that was employed due to heterogeneity across studies, the risk of sudden cardiac death was 1.25 (95% CI: 0.57 to 2.19) per 1,000 person-years. One important limitation is that 6 of the deaths occurred in patients who might have in fact been symptomatic, all from 2 Italian studies. Excluding the Italian studies, the random-effects model yielded an overall sudden cardiac death rate of 0.36 (95% CI: 0.05 to 0.94) per 1,000 person years. The investigators pointed out that this number is not too different from sudden cardiac death rates that have been described in the general population: 0.09 (0 to 35 years of age) (39), 0.028 (1 to 35 years of age) (40), 0.032 (14 to 35 years of age) (41), and 0.13 (35 to 49 years of age) (42) per 1,000 person-years. Although not determined in a traditional multivariable model, risk factors for sudden death in this heterogeneous mixture of reports included male sex, inclusion in a study of children (<18 years of age), and inclusion in an Italian study. No deaths occurred in the 57 asymptomatic WPW patients (from 2 of the studies) who underwent catheter ablation.

Ventricular Arrhythmias

Kim et al. (43) examined cases of cardiac arrest that occurred during the running or at the finish-line recovery area within 1 h after the completion of a marathon or half marathon from a prospectively compiled database of cardiac arrests between the years 2000 and 2010. This report from the RACER (Race Associated Cardiac Arrest Event Registry) study defined cases of cardiac arrest by an unconscious state and an absence of spontaneous respirations and pulse as documented by a medical professional. Survivors were defined as those that were successfully resuscitated and discharged from the hospital. The investigators utilized websites, online databases for the local newspapers for all towns and cities with an identified marathon or half marathon, and direct outreach to race organizers to collect information. This was supplemented by completed questionnaires and medical record review obtained from consenting cardiac arrest survivors and the next of kin of nonsurvivors. Fifty-nine cardiac arrests were identified among 10.9 million registered race participants (from 40 marathons and 19 half marathons), for an overall incidence of 1 per 184,000 participants (or 0.54 per 100,000, 95% CI: 0.41 to 0.70). The mean age of runners with a cardiac arrest was 42 ± 13 years. The majority of cardiac arrest victims

were men (51 of 59, 86%), and cardiac arrest was more common among marathon versus half marathon runners. Forty-two (71%) of the 59 runners with cardiac arrest died. Those who died were younger (39 ± 9 years of age) than those who did not die (49 ± 10 years of age). Again, men and those running a marathon (vs. a half marathon) were at higher risk of death. Sufficient medical information to determine the cause of death was available for 31 of the 59 runners with cardiac arrest. Of these 31, 23 died: hypertrophic cardiomyopathy (8 of 23) and possible hypertrophic cardiomyopathy (7 of 23) were the most common causes of death. Nine of these 15 with cardiac hypertrophy had an additional clinical factor or postmortem finding, including obstructive coronary disease in 3, myocarditis in 2, bicuspid aortic valve or a coronary anomaly in 2, an accessory AV bypass tract in 1, and hyperthermia in 1. Causes of death in those without cardiac hypertrophy included hyponatremia in 1, hyperthermia in 1, arrhythmogenic right ventricular cardiomyopathy in 1, and no evident abnormality on autopsy or presumed primary arrhythmia in 2. Of those who survived, ischemic heart disease was the predominant cause of cardiac arrest (5 of 8). Of note, none of the runners with serious coronary atherosclerosis had angiographic evidence of acute plaque rupture or thrombus, suggesting that demand ischemia may have been important. Of the 31 cardiac arrest cases with complete medical information, the strongest predictor of survival was initiation of bystander-administered cardiopulmonary resuscitation ($p = 0.01$) and an underlying diagnosis of hypertrophic cardiomyopathy ($p = 0.01$). In a multivariate logistic regression model in which those 2 factors had to be excluded because of perfect prediction, factors associated with survival were an initial rhythm of ventricular fibrillation or tachycardia (odds ratio: 0.04, 95% CI: 0.003 to 0.556) and the number of previous long distance races completed (odds ratio: 0.53, 95% CI: 0.29 to 0.98).

Translational Sciences

One of the most exciting areas of translational cardiac electrophysiology relates to use of gene or cell therapy to modify cellular electrophysiological properties to treat cardiac arrhythmias. A very thoughtful overview of the state of the art using regenerative therapies both for treatment of cardiac tachyarrhythmias or AV block is summarized in a recent review by Boink and Rosen (44). Most recent advances have focused on a gene therapy for AF. Initial studies focused on the use of AV nodal gene transfer using adenoviruses with an active gene mutant resulting in the inhibition of G protein overexpression and consequent heart rate control in a porcine AF model (45). More recent studies have focused on gene transfer directed toward prevention of AF (46). For example, Amit et al. produced AF in pigs using atrial burst pacing (46). One group was treated with an adenovirus containing the KCNH2-G628S gene mutant, which has a dominant negative effect on the I_{Kr} potassium channel and thereby prolongs the atrial effective refractory period (a known antiarrhythmic action for reentrant arrhythmias). The preparation was applied in a poloxamer-trypsin solution and painted with a brush over the surface of the atrium. A control group was treated in an identical fashion, but without the mutant gene. By day 10, none of the controls and all of the treated animals were in sinus rhythm. After the tenth day, the numbers of treated animals gradually reverted to AF in a fashion that correlated with the expected duration of transgene expression. The investigators showed that the atrial action potential duration (APD) was prolonged in the treated group (not in the controls), and there was no effect on the contiguous ventricular APD. The latter observation is of great import in that the observed effects were restricted to the atria, obviating possible deleterious effects of ventricular APD prolongation and the consequent risk of torsades de pointes. Soucek et al. used a similar approach to utilize gene transfer via adenoviruses carrying CERG-G627S, a mutant with dominant negative effects on the I_{Kr} channels (47). The investigators applied the mutant gene with direct injections (8 to each atrial site) followed by electroporation (delivery of high-voltage electrical burst applications to enhance gene transfer to atrial tissue). Similar to the previous study, they found that the treated animals remained in sinus rhythm for a longer period compared with control animals. In addition, they found that the antifibrillatory effects coincided with prolongation of the atrial effective refractory period. Of interest, both groups used genetic material known to cause the long-QT syndrome as a therapeutic agent to prevent AF.

Although the previously mentioned studies focused on use of genetic manipulations to increase APD, other techniques have focused on enhancing atrial conduction. Igarashi et al. sought to improve atrial conduction (again a known antiarrhythmic technique for re-entry) by use of genetic transfers that enhanced gap junction protein connexin (Cx) 40 and 43, the predominant atrial gap junction proteins (48). They used a porcine atrial pacing model to produce AF and, using the direct painting approach described previously (46), compared swine treated with either Cx40 or Cx43 to control animals. They found that in controls with AF, there was reduced and lateralized Cx43 expression, which was reversed by gene transfer. In addition, both Cx40 and Cx43 improved conduction and reduced AF compared with controls. Again, these important observations provide proof of concept that impaired atrial cell-to-cell conduction has a beneficial effect on the prevention of AF.

In contrast, Tsai et al. (49) took a different approach by studying the effects of stretch on an atrial cell monolayer and reversal of these effects using gene manipulation that resulted in overexpression of sarcoplasmic endoplasmic reticular calcium ATPase 2 (SERCA2). The rationale behind this study stemmed from the close relationship between atrial stretch (e.g., from valvular heart disease, HF, and

hypertension) and AF, as well as the close relationship between pacing-induced action potential duration repolarization alternans (APD-ALT) and initiation of AF in humans (50). The investigators used an atrial cell monolayer cultured in a silicone membrane subjected to mechanical stretch. They used high-resolution dual calcium and voltage mapping to record action potentials and calcium transients in controls and stretched myocytes at different pacing rates. They found greater susceptibility to APD-ALT as well as calcium transient alternans in stretched preparations. Cells exhibiting the greatest degree of APD-ALT also showed the greatest magnitude of calcium alternans. Stretch magnified the effect of pacing on the induction of APD-ALT. In addition, they found that mechanical stretch was associated with decreases in SERCA2 expression as well as defective calcium cycling, without changes in other proteins involved in calcium metabolism. Moreover, targeted overexpression of SERCA2 resulted in robust improvement in calcium uptake and prevented stretch-induced development of APD-ALT. These important observations serve as a possible explanation for the close association among atrial stretch, atrial pacing, and development of AF and raise the possibility of a therapeutic effect of SERCA2 overexpression in the treatment of AF.

As impressive as these studies are in relationship to proof of concept of gene therapy, nevertheless, as emphasized by Boink and Rosen (44), many hurdles remain. For example, the adenovirus vector used provided only short-lived effects. More suitable vectors giving longer lasting effects include the adeno-associated virus or the lentivirus. However, each has their potential problems, including limitations in size of gene insertion, acquired resistance to the virus, host inflammatory response, potential problems with spread to other organs, and mutagenesis. Further laboratory testing is required before applying these methods to humans.

Genetic Arrhythmia Syndromes

The long QT syndrome (LQTS) is the most common genetic arrhythmic syndrome, and LQT1 mutations (arising from mutations in KCNQ1 gene) account for over 50% of genotyped patients (51). The University of Rochester LQT registry continues to provide important data on the genotype-phenotype interactions for patients with LQTS. In a seminal article, Barsheshet et al. provided a mutation-specific response to beta-blocker therapy for a subtype of LQT1 patients (52).

A schema of the membrane spanning alpha-subunit of the KCNQ1 channel is shown in Figure 1. The C-loops attach the S2-S3 segments and S4-S5 segments. The N and C regions are intracytoplasmic. The KCNQ1 gene encodes I_{Ks}, which is responsive to beta-adrenergic stimulation, and hence shortens the action potential duration during exercise. Decreased I_{Ks} function allows for afterdepolarization-driven ectopy arising from increased L-type Ca^{2+} currents. Prior studies suggested that the C-loops modulate protein kinase A phosphorylation of the channel proteins (53). The investigators sought to determine mutant-specific responses to beta-blocker therapy and described several important clinical observations. First, C-loop mutations were associated with the highest risk of aborted cardiac arrest or sudden death independent of clinical factors. Beta-blocker therapy was associated with a startling risk reduction of life-threatening events (88% risk reduction) for those with C-loop mutations. Finally, expression studies of C-loop mutations showed impaired regulation of beta-adrenergic response, explaining the salutary response to beta-blockers in those with C-loop abnormalities. This important study opens the door to further evaluation of mutation-specific clinical manifestations of genetic disorders.

Another important paper from the LQT registry focused on the risk of life-threatening cardiac events for genotype-positive LQT patients with normal corrected QT (QTc)

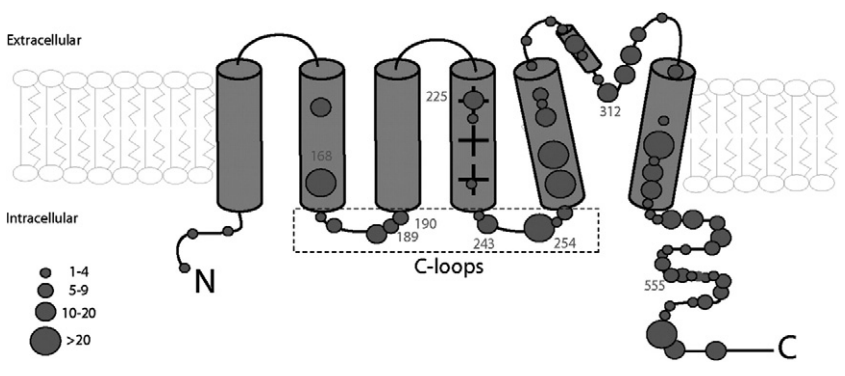

Figure 1 **Frequency and Location of Mutations in the KCNQ1 Potassium Channel**

Diagrammatic location of 99 different mutations in the KCNQ1 potassium channel involving 860 subjects. The alpha-subunit involves the N-terminus (N), 6 membrane-spanning segments, 2 cytoplasmic loops (S2-S3 and S4-S5), and the C-terminus portion (C). The **size of the circles** reflects the number of subjects with mutations at the respective locations. Reprinted from Barsheshet et al. (52), with permission from the American Heart Association.

intervals (54). Mutations affecting the transmembrane-spanning region of the KCNQ1 channel are associated with a higher risk of cardiac events compared with other regions (55). In the study by Goldenberg et al., approximately 25% of patients at risk had a concealed (normal range QTc) pattern (54). The cumulative probability of aborted cardiac arrest or sudden death until age 40 years was 4%, which was significantly higher than that for unaffected family members (0.4%) but lower than that for the group with a prolonged QTC (15%). LQT1 and LQT3 patients with a mutation in the membrane-spanning region had a 6-fold increase in risk for life-threatening events (9% from birth to age 40 years). This paper provides important practical information for patient management of patients with LQTS and a normal QTc. Aggressive management is required for high-risk groups (i.e., transmembrane lesions in LQT1 and LQT3), whereas those at very low risk (concealed LQT2 and nontransmembrane missense mutations in LQT1 and LQT3) require only general health recommendations such as avoidance of QT prolonging drugs and avoidance of electrolyte disorders.

Implantable Cardioverter-Defibrillators

In November 2011, St. Jude Medical issued a medical device advisory to inform physicians of increased failure rates of Riata and Riata ST (Riata/ST, St. Paul, Minnesota), specifically highlighting externalized conductors from silicone insulation abrasion (56). This advisory became a Food and Drug Administration class I recall on December 14, 2011. The failing leads have since attracted intense print and electronic media coverage. The failure mechanism of the affected high voltage defibrillation lead is unique in that the conductor cables erode through the silicone insulation material from inside-out. The conductor cable may externalize, and become physically located outside of the lead body. The externalization produces no electrical malfunction as long as the ethylene tetrafluoroethylene coating the cables remains intact. The Riata/ST failure rates, including leads with externalized cables but no detected electrical malfunction, were reported to be 6% to 15% (57,58). A search for Riata/ST lead failure on the U.S. Food and Drug Administration's Manufacturers and User Defined Experience (MAUDE) medical device database found 721 instances, 105 of which involved reports of inside-out insulation defect (15%) (59). The single-coil leads accounted for 25.7% of the defective leads even though they represented only 10.7% of the Riata/ST leads sold in the United States. The most common location of insulation defects was distal to the proximal coil (108 of 226 defects). Because these affected leads were extracted as a result of events leading to clinical attention, not surprisingly, only 6 were without electrical malfunctions. Among those with electrical defects, noise and other sensing issues were most common (47% of all defects) followed by impedance changes (28%) and pacing (12%). Inappropriate shocks were reported in 31 of 105 patients (30%).

The MAUDE database was subsequently re-queried for patient deaths associated with Riata/ST lead failure (60). Data from Medtronic Quattro Secure model 6947 dual-coil HV lead (Mounds View, Minnesota), a nonrecall lead, were used for comparison. Deaths were categorized into lead-related, indeterminate and lead-unrelated. There were 71 deaths associated with Riata/ST and 62 with Quattro Secure. Twenty-one deaths were judged to be Riata/ST lead-related (1 was a duplication), whereas 5 were judged to be Quattro Secure lead-related. Indeterminate deaths were proportionally higher in Quattro Secure (32 of 62, 52%) than Riata/ST leads (25 of 71, 35%). If both lead-related and indeterminate deaths were included in the comparison, the discrepancy between Riata/ST ($n = 46$) and Quattro Secure ($n = 30$) is not as striking as presented. The study made the very important observation that short-circuiting between HV components as a result of insulation erosion, but not externalized conductor cables, has resulted in death in patients with Riata/ST leads. As pointed out by a follow-up letter to the editor (61), the readers should not regard the data as a true measurement of frequency of adverse events, or as a controlled comparison between the 2 HV leads. The MAUDE database provides no denominator required for accurate determination of event frequency, and clinical details are highly variable among submitted reports.

This unusual form of failure and lack of information on the behavior of externalized but electrically intact cables present a difficult and challenging management problem for clinicians. The exact rate of externalization is not known. According to St. Jude Medical, the incidences of lead insulation abrasion and conductor externalization were very low, at 0.63% and 0.10%, respectively (56). The actually incidence is likely higher because externalized but electrically intact cables are unlikely to be discovered unless fluoroscopy screening is performed on all patients with the affected leads. In a small study in which patients underwent high-resolution, cine-fluoroscopy either "electively" or because of detected electrical abnormalities, abnormal fluoroscopic findings (abnormal cable spacing with or without gross cable extrusion) were present in 43% of 87 patients studied (62). Among 64 patients without any detectable electrical abnormalities, remarkably, 24 patients (38%) had abnormal fluoroscopic findings. In addition, the durability of the ethylene tetrafluoroethylene coating as an insulation barrier, especially when the cables are exposed to the vascular system, is unknown. The extruded cables make lead extraction, an already high-risk procedure under most circumstances, even riskier. Lead abandonment with new replacement is an alternative option, but little is known about complications arising from potential electrical or mechanical interactions between the externalized cables and the new replacement lead.

Promising results on the use of an entirely subcutaneous implantable cardioverter-defibrillator system (S-ICD) were

recently published in a landmark study (63). First, the best subcutaneous configuration, as defined by the lowest defibrillation threshold, was determined in 78 patients to be a left lateral pulse generator connected to an 8-cm coil electrode positioned at the left parasternal margin. Second, defibrillation efficiency was compared in 49 patients with both a subcutaneous and transvenous system implanted. There was no difference between the systems, but the defibrillation energy was much higher for the S-ICD (36.6 ± 19.8 J vs. 11.1 ± 8.5 J). Last, among 55 patients who received a permanent S-ICD, VF was successfully detected and defibrillated with 65-J shocks in all 137 induced episodes. During a follow-up period of 10 months, 12 episodes of spontaneous ventricular tachycardia/VF events were successfully detected and treated. In April 2012, after reviewing the results of a 330-patient (Investigational Device Exemption) IDE trial, the Food and Drug Administration Circulatory System Devices panel stated that the data demonstrated efficacy and safety of the S-ICD. While the initial data are promising and enthusiastically endorsed by the investigators, there are a number of concerns. The lack of antitachycardia pacing therapy will result in shock therapy for all detected ventricular tachycardia/VF events. There is no published data addressing the subjective discomfort of an 85-J shock applied over the chest wall compared to a 35-J shock delivered with a transvenous lead. More importantly, a higher mortality among patients who received shocks has been reported (64,65). It is claimed that a conditional discrimination zone effectively reduced inappropriate detection and shocks. Because of the large distance between the sensing electrodes (distal and proximal or either sensing electrode and the pulse generator) and their subcutaneous location, oversensing of external noises is a potentially major problem. Subcutaneous lead arrays and patches used with transvenous system have known to be susceptible to lead fracture and migration; proper positioning of the 8-cm coil electrode appeared to be critical in successful defibrillation. With time, the incidence of lead complications in the S-ICD may not be lower than the transvenous system, especially in physically active and young patients. It can be convincingly argued that subcutaneous lead replacement is much easier and less risky than transvenous lead extraction. As in any new approach to therapy, more independent and long-term follow-up data will be needed. The PRAETPRIAN (Prospective, Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter-defibrillator Therapy) trial is a randomized, multicenter, prospective study designed to compare subcutaneous to transvenous ICDs (66). A total of 700 patients are being randomized to the 2 arms. The study will last 30 months. The primary endpoint is inappropriate shock and ICD-related complications and the secondary endpoint is shock efficacy and patient mortality. Until more follow-up data are available, the S-ICD should only be considered in patients with limited vascular accesses for transvenous leads, no pacing needs for bradycardia, and for those in whom the lack of antitachycardia therapy is acceptable.

Remote Device Monitoring

ICD remote monitoring was introduced in 2002. Its validation as a standard tool for device monitoring was provided only recently by several randomized studies. The latest was the CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision Trial). It was a prospective, randomized, multicenter trial comparing wireless remote monitoring (n = 1,014) to standard in-office visits (n = 983) in patients with ICD (67). Compared to regular in-office visits, remote monitoring significantly reduced time from onset of events to clinical decisions in response to arrhythmias and device issues without increasing healthcare utilizations (hospitalizations, emergency department, and unscheduled clinic visits). The mean length of hospital stay as a result of detected problems was significantly reduced.

Although ICD remote monitoring has essentially become standard of care, pacemaker remote follow-up was introduced later and adoption has been slower. The ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) trial is a landmark study investigating the relationship between subclinical AF detected by implantable devices and stroke (68). The trial followed 2,451 new dual-chamber pacemaker and ICD recipients who were hypertensive and 65 years of age or older over a mean 2.5 years. Patients with a history of AF or atrial flutter lasting more than 5 min were excluded. In the first 3 months, at least 1 atrial tachyarrhythmia (defined as a device-detected high-rate episode of at least 190 beats/min for at least 6 min) was observed in 261 patients (10.1%). Over the remaining follow-up, subclinical atrial tachyarrhythmias occurred in an additional 633 patients (24.5%). Also over follow-up, clinical atrial tachyarrhythmias occurred in 15.7% of the 261 with subclinical tachyarrhythmias observed during the first 3 months compared with 3% of those without subclinical tachyarrhythmias during that time period (HR: 5.56, 95% CI: 3.78 to 8.17; $p < 0.001$). The rate of stroke was 1.69% per year in those with subclinical tachyarrhythmias before 3 months versus 0.69% per year in those without subclinical tachyarrhythmias before 3 months (HR: 2.49, 95% CI: 1.28 to 4.89; $p = 0.008$). The population attributable risk of ischemic stroke or systemic embolism associated with subclinical atrial tachyarrhythmias was 13%. Although there was evidence of an increased risk of stroke or systemic embolism independent of duration, a longer duration of episodes was associated with a greater risk. The increased risk of stroke and thromboembolism in those with versus those without subclinical atrial tachyarrhythmias before 3 months was also consistently observed across $CHADS_2$ scores, and as expected, the absolute risk regardless of the presence of subclinical tachyarrhythmias

increased with higher levels of $CHADS_2$ scores. This important paper confirmed the high incidence of subclinical atrial tachyarrhythmias—here observed in 34.7% of participants over 2.5 years—and provided the first evidence that these subclinical atrial tachyarrhythmias are associated with an increased risk of stroke and thromboembolism. It also provided evidence validating a critical benefit of pacemaker remote monitoring.

Cardiac Resynchronization Therapy

Available data suggest presence of reverse remodeling predicts cardiac resynchronization therapy (CRT) responders in HF patients. Factors that are associated with favorable reserve remodeling were used to predict CRT responders in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) trial (69). Using regression analysis in the CRT with ICD (CRT-D) arm of the trial, 7 factors associated with a favorable echocardiographic response (defined as a 10% reduction in left ventricular end-diastolic volume at 1 year) to CRT-D therapy were first identified—female sex, nonischemic cardiomyopathy, QRS duration ≥150 ms, the presence of left bundle branch block on baseline ECG, hospitalization for HF at any time before enrollment, baseline left ventricular end-diastolic volume ≥125 ml/m^2, and baseline left atrial volume <40 ml/m^2. Each of the 7 factors was assigned a numerical score on the basis of its relative effect in the regression model. The factor with the lowest effect, prior HF hospitalization, was assigned the lowest score of 1; the intermediate factors, which included female sex, nonischemic cardiomyopathy, left bundle branch block, QRS interval ≥150 ms, and left ventricular end-diastolic volume, were assigned a score of 2; the highest factor, left atrial volume, was assigned a score of 3. A response score was constructed by adding the number values of the factors identified in each patient. Four patient groups were created on the basis of the response scores. Group 1, the lowest score quartile, had a score of 0 to 4, Group 2 had a score of 5 to 6, Group 3 had a score of 7 to 8, and Group 4, the highest quartile, had a score of 9 to 14. Cox proportional hazards regression modeling showed that when compared to the ICD-only arm, CRT-D patients in Group 2 and higher showed a significant reduction in the risk of HF or death, whereas Group 1 patients derived no benefit. The degree of reduction was incremental between groups with a 33% ($p = 0.04$), 36% ($p = 0.03$), and 69% ($p < 0.001$) risk reduction for Groups 2, 3, and 4, respectively. This analysis provides clinicians with a very helpful algorithm in selecting HF patients with a better chance of responding to CRT.

Pacemaker Therapy

The role of pacing in patients with neutrally mediated syncope has not been well defined. The ISSUE-3 (Third International Study on Syncope of Uncertain Etiology) trial was a multicenter, double-blind, randomized placebo-controlled study to determine if pacing reduced syncope recurrence in patients with asystolic neutrally mediated syncope (70). A total of 511 patients aged ≥40 years with ≥3 neurally mediated syncopal episodes in the previous 2 years were screened with implantable loop recorders. Asystole was defined as ventricular standstill from sinus arrest or AV block. Seventy-seven of 89 patients who had 3-s asystolic episodes with syncope or asymptomatic 6-s asystole were randomized to dual-chamber pacing with rate-drop response (n = 38) or to sensing only (n = 39). Rate-drop response provides DDD pacing at a programmable rapid rate when ventricular rate drops abruptly or over a predefined window. During 2 years of follow-up, pacing significantly reduced recurrence of syncope by 57% ($p = 0.039$)—19 patients (57%) in the sensing-only arm had recurrent syncope versus 8 (25%) in the pacing arm. This important small study clearly showed that dual-chamber pacing with rate drop response is an effective treatment in patients with neurally mediated syncope with well-documented asystole events. However, for this invasive therapy to be beneficial, a large number of patients have to undergo implantable loop recorder implantation to identify a small number of suitable candidates (17% of 511 patients screened). With a relative reduction of 57%, only 10% of the original 511 patients benefited. Because rate drop response was the only pacing intervention mode used in the study, the effectiveness of conventional DDD pacing remains unknown. A recently published paper reported the efficacy of using adenosine 5'-triphosphate (ATP) to identify patients with syncope of unknown origin who would respond favorably to cardiac pacing (71). Syncope was considered to be of unknown origin when the history and physical examination, echocardiogram, ECG, and Holter diagnostic testing failed to identify a cause. Patients with positive electrophysiological studies, carotid sinus sensitivity, spontaneous, sustained or nonsustained atrial and ventricular tachyarrhythmias or AV block of any degree were excluded. An ATP test was considered abnormal when an intravenous bolus of 20 mg of the medication caused AV or sinoatrial block lasting >10 s. Eighty patients with an average age of 75.9 ± 7.7 years with a positive ATP test were randomized to either conventional DDD pacing at 70 beats/min or AAI pacing at 30 beats/min. During a mean follow-up period of 16 months, relative to AAI pacing, DDD pacing significantly reduced recurrence of syncope by 57% (HR: 0.25). When the pacing mode of the 29 patients who experienced recurrent syncope in AAI mode was changed to DDD mode, only 1 patient continued to have syncope. Adding rate drop response to the 8 DDD-mode patients who experienced syncope resulted in either a reduction in symptom severity (n = 2) or no syncope (n = 5). Despite the small number of patients, the results strongly suggested that in elderly patients with syncope of unknown origin and positive ATP tests, DDD pacing can be an effective method to reduce syncope recurrence with an acceptable number to treat (only 2.2).

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