Late-Breaking Clinical Trials III

Room 2004, Moscone West

Saturday, May 10, 2014

10:30 a.m. – noon
LBCT03 Session: 
Late-Breaking Clinical Trials III

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CHAIRS:

Anne M. Gillis, MD, FHRS. University of Calgary - Libin Cardiovascular Institute of Alberta, Calgary, AB, Canada

George F. Van Hare, MD, FHRS, CCDS, CEPS. Washington University, Saint Louis, MO

LB03-01

IS IT SAFE TO DELAY DETECTION IN ALL ICD PATIENTS? A RANDOMIZED EVALUATION OF PROLONGED ICD DETECTION INTERVALS IN SECONDARY PREVENTION PATIENTS ENROLLED IN THE PAINFREE SST TRIAL

Laurence D. Sterms, MD, Mathias Meine, MD, Edward J. Schloss, MD, Takashi Kurita, MD, PhD, Albert Meijer, MD, Angelo Auricchio, MD, PhD, Kenji Ando, Charles T. Leng, MD, Ken Okumura, MD, John L. Sapp, MD, FHRS, Bart Gerrits and Daniel R. Lexcen, PhD. Vancouver Island Arrhythmia Clinic, Victoria, BC, Canada, University Medical Center, Cardiologie, Utrecht, Netherlands, The Christ Hospital/The Ohio Heart & Vascular Center, Cincinnati, OH, Kinki University, Cardiology Division, Osaka, Japan, Catharina Ziekenhuis, Eindhoven, Netherlands, Fondazione Cardiocentro Ticino, Lugano, Switzerland, Kokura Memorial Hospital, Kitakyushu, Japan, University of Pennsylvania Health Systems, Penn- Presbyterian Medical Center, Timonium, MD, Hirosaki University Graduate School of Medicine, Aomori, Japan, QE II Health Sciences Centre, Halifax, NS, Canada, Medtronic Bakken Research Center, Maastricht, Netherlands, Medtronic, Mounds View, MN

Introduction: Extending ICD detection times for VT/VF has been shown to safely decrease inappropriate therapies and mortality in primary prevention patients. However, the safety of increasing the NID (number of intervals to detect) has not been studied prospectively in a large population with clinical VT/VF. This PainFree SST substudy is the first randomized and powered study designed to evaluate the safety of this programming strategy in secondary prevention patients.

Methods: A cohort of secondary prevention patients receiving Medtronic Protecta ICDs with SmartShock Technology were enrolled in the PainFree SST trial and randomized in a 1:1 fashion to either, a standard-interval (NID=18/24) or prolonged-interval (NID=30/40) detection of VT/VF ≥ 188 bpm (VF zone). All other programming parameters in this zone were standardized by protocol. Syncopal events were documented in patient diaries, and were classified as arrhythmic if they occurred in temporal association with a device-detected arrhythmia event. This substudy was prospectively powered to evaluate the non-inferiority (5% margin) of a prolonged-interval detection strategy using a primary endpoint of 1 yr freedom from arrhythmic syncope. Secondary endpoints included time to first all cause-syncope, appropriate therapy and inappropriate shock.

Application: The PainFree SST trial enrolled 2790 patients at 126 international centers. Of those patients, 705 had a secondary prevention indication and consented to NID randomization in this substudy. At baseline 32% of these patients had AF, and 33% had a history of syncope. Mean follow-up was 20±7 months. In the first year, 19 patients had arrhythmic syncope (8 in the standard and 11 in the prolonged group). The arrhythmic syncope-free rate was similar between groups (97.7% standard vs 96.9% prolonged, p<0.01 for non-inferiority). The all-cause syncope-free rate was also non-inferior at 1-year (96.0% standard vs 96.0% prolonged, p<0.01 for non-inferiority). There were no significant differences in appropriate VF zone therapies (1-year: 13.3% standard vs 12.3% prolonged, p=0.79). Inappropriate shocks were rare with no difference between arms (1-year: 1.0% standard vs 1.3% prolonged, p=0.93). There was a trend towards decreased mortality at 1 year in the prolonged-interval group (5.6% standard vs. 3.8% prolonged, p=0.07).

Next Steps/Future: In this large randomized trial involving high-risk secondary prevention patients, longer-detection intervals did not increase the risk of syncope, establishing the safety of this programming strategy. Prolonged-interval detection programming did not impact the rates of inappropriate shocks, which were low using advanced discrimination algorithms in both groups at 1 year.

LB03-02

SPEAR TRIAL: SMARTPHONE PEDIATRIC ELECTROCARDIOGRAM TRIAL

Hoang Nguyen, MD, Michael Rudokas, BS, Tammy M. Bowman, MSN, ACNP, George F. Van Hare, MD, FHRS and Jennifer N.A. Silva, MD. Washington University in St. Louis, St. Louis, MO, St. Louis Children's Hospital, Pediatric Cardiology, St. Louis, MO, Washington University in St. Louis, Saint Louis, MO, Washington University St. Louis, St. Louis, MO

Introduction: Smartphone-enabled ECG devices have the potential to vastly improve patient care by enabling remote ECG assessment in patients with potential and diagnosed arrhythmias. This prospective trial was initiated to assess the usefulness of pediatric ECG tracings generated by the AliveCor device (San Francisco, CA) and to assess user satisfaction.

Methods: Pediatric patients with the following inclusion criteria were consented and enrolled from 9/27/2013 to 3/7/2014: 1) age ≤21 years, 2) documented paroxysmal arrhythmia, and 3) owning an iPhone 4/4S or 5. Patients were instructed to transmit ECG tracings of concern, which were all reviewed by trained pediatric cardiac electrophysiologists. All users were
contacted by email and/or telephone with the ECG interpretations and further care instructions and were asked to complete periodic online surveys regarding their experience with the device.

**Application:** 30 patients (age 6 months–21 years) were enrolled in the 6 month study period. Diagnoses included: supraventricular tachycardia (SVT, n=15, 50%), ectopic atrial tachycardia (EAT, n=3/30, 10%), atrial fibrillation (AF, n=4/30, 13%), and ventricular tachycardia (VT, n=8/30, 27%). A total of 144 ECG tracings have been received from 20 patients. Ten patients have not sent any trips. Accurate rhythm analysis was made in 141 (98%) of the tracings transmitted, including diagnoses of sinus tachycardia, SVT, and AF. Smartphone ECG tracings facilitated intensive outpatient monitoring and management of patients with AF and SVT allowing for close follow up and patient specific directed care such as managing antiarrhythmic therapy and limiting the use of the emergency department (ED). To date, 44 patient satisfaction surveys (68% from parents) have been completed. Users record up to 14 tracings a month and transmit the tracing to the research team 45% of the time. Patient satisfaction with the device has remained high over time. 95% of the surveys' responses indicate that the device is easy to use, 98% show high level of comfort in arrhythmia management with the device, and 95% prefer to continue using the device once the study ends.

**Next Steps/Future:** Preliminary data demonstrate that a smartphone-enabled ECG device can generate tracings of diagnostic and therapeutic quality in children. The patient experience with the device has been overwhelmingly positive. Use of the device to manage certain patients with AF and SVT as demonstrated in this study showcases the future role of remote ECGs in the successful outpatient management of arrhythmias in children by limiting the need for ED visits, thereby reducing healthcare costs and improving patient care and satisfaction.

**LB03-03**

**USE OF REMOTE MONITORING IS ASSOCIATED WITH IMPROVED OUTCOMES AMONG PATIENTS WITH IMPLANTABLE CARDIOVERTER DEFIBRILLATORS**

Joseph G. Akar, MD, PhD, Haikun Bao, Paul W. Jones, MS, Yongfei Wang, Paul D. Varosy, MD, FHRs, Frederick A. Masoudi, Kenneth M. Stein, MD, FHRS, Leslie A. Saxon, Sharon-Lise Normand and Jeptha Curtis, MD. Yale University School of Medicine, New Haven, CT, Boston Scientific, St. Paul, MN, Denver VAMC - University of Colorado, Denver, CO, Univeristy of Colorado Anschutz Medical Campus, Denver, CO, USC Keck School of Medicine, Los Angeles, CA, Harvard School of Public Health, Boston, MA, Yale University, New Haven, CT

**Introduction:** Among patients with implantable cardioverter defibrillators (ICD), remote patient monitoring (RPM) improves health care utilization but its effect on clinical outcomes is less clear. We examined the association of RPM use and all-cause mortality and all-cause rehospitalization among patients undergoing first time ICD implant.

**Methods:** We constructed a limited dataset combining data from the Boston Scientific ALTITUDE® Registry and the NCDR® ICD Registry™ including first time ICD implants performed between January 2006 and March 2010. Vital status was determined using the Social Security Death Master File. All cause mortality up to 3 years was compared in patients who used RPM and those who did not use RPM. We constructed time-dependent frailty Cox models to determine the independent association between RPM use and all-cause mortality. Mortality analyses were repeated in subgroups based on age, sex, race, ICD type, indication, and cardiomyopathy etiology. In the subset of patients enrolled in Medicare fee-for-service, we used similar methodology to examine the association between RPM use and all-cause rehospitalization.

**Application:** The overall study cohort (n=37,742, age 67±13, 72% male) had a 3-year mortality of 20.9% after a median follow-up of 832 days. A total of 22,023 transmitted data using RPM within 3 years of device implantation. In multivariable analyses, patients who used RPM had lower mortality risk compared with those who did not use RPM (HR 0.67, 95% CI 0.64-0.70, p<0.0001). Findings were consistent across all subgroups (Table). The 3-year rehospitalization rate in the subset of patients enrolled in Medicare A fee-for-service (n=15,254) was 69.3% after a median follow-up of 922 days. In this population, 9150 patients transmitted data using RPM. The all-cause rehospitalization risk of patients who used RPM was significantly lower than that of patients who did not use RPM (HR 0.81, 95% CI 0.79-0.83, p<0.0001).

**Next Steps/Future:** Among patients undergoing first time ICD implantation, RPM use is associated with significantly lower risks of both all-cause mortality and re-hospitalization.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Hazard Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>0.64 (0.58-0.72)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>0.67 (0.64-0.71)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.68 (0.64-0.72)</td>
</tr>
<tr>
<td>Female</td>
<td>0.65 (0.59-0.71)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>0.66 (0.62-0.70)</td>
</tr>
<tr>
<td>Non-white</td>
<td>0.73 (0.66-0.82)</td>
</tr>
<tr>
<td>ICD Type</td>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
<td>0.60 (0.55-0.66)</td>
</tr>
<tr>
<td>CRT-0</td>
<td>0.71 (0.66-0.75)</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>0.67 (0.63-0.71)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>0.63 (0.55-0.72)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>0.69 (0.65-0.73)</td>
</tr>
<tr>
<td>Non-ischemic</td>
<td>0.62 (0.57-0.69)</td>
</tr>
</tbody>
</table>

*p for interaction for all strata not significant, except CRT-D vs ICD p = 0.02
RAFFAELLO (RANOLAZINE IN ATRIAL FIBRILLATION FOLLOWING AN ELECTRICAL CARDIOVERSION)

A. John Camm, MD, FHRS, Gaetano De Ferrari, MD, J. Lluís Mont, MD, PhD, Gregor Simonis, MD, Matthias Leschke, MD, Edoardo Gronda, MD, Niccolò Marchionni, MD, Stefano Fumagalli, MD, Laura Guillamón Torán, MD, Miguel L. Quintana Rendón, MD, Irina Savelieva, MD, Lorenzo Melani, MD, PhD, Kai Schumacher, MD, Mariangiessa Matera, PhD, Giulia Tonini, PhD, Angela Capriati, MD, PhD and Lars Maier, MD. St. George’s University of London, London, United Kingdom, IRCCS S. Matteo Hospital, Pavia, Italy, Cardiology Department, Thorax Institute Hospital Clinic, Universitat de Barcelona, Barcelona, Spain, Praxisklinik Herz und Gefäße, Dresden, Germany, Klinikum Esslingen GmbH, Abteilung Kardiologie, Esslingen, Germany, Istituto di Ricovero e Cura a Carattere Scientifico MultiMedica, Milan, Italy, Azienda Ospedaliera Universitaria Careggi di Firenze SOD Cardiologia e Medicina Geriatria, Florence, Italy, Corporacio Sanitaria Parc Taulí de Sabadell, Sabadell, Spain, Hospital de Torrevieja Servicio de Cardiología, Alicante, Spain, St George’s Hospital Medical School, London, United Kingdom, A.Menarini Industrie Farmaceutiche Riunite s.r.i, Florence, Italy, A.Menarini Research & Business Service GmbH, Berlin, Germany, Menarini Ricerche S.p.A, Florence, Italy, University of Göttingen, Goettingen, Germany

There is a great need for safe and effective drugs for treating atrial fibrillation (AF). Ranolazine is an approved antianginal drug that inhibits late sodium currents and reduces atrial excitability yet only anecdotal reports are available regarding its use in AF. The RAFFAELLO study (Ranolazine in Atrial Fibrillation Following An Electrical CardiOversion) is the first study to prospectively assess the efficacy of ranolazine in persistent AF (EudraCT no. 2011-002789-18). This was a phase 2 dose-ranging study testing 3 oral ranolazine doses (375 mg, 500 mg, 750 mg BID) vs. placebo performed in Germany, Great Britain, Italy and Spain. Patients were eligible if they suffered from persistent AF suitable for direct current cardioversion (DCC), were 18 years or older, did not have first diagnosed, paroxysmal, long-standing, permanent or secondary AF and did not take class I/III antiarrhythmics 3 days before DCC. Patients in sinus rhythm 2 hours after DCC were randomized to the 4 treatment arms. During the 16-week treatment phase, 5 study visits with 12-lead ECGs were held. If recurrent AF required medical treatment, patients exited the study. If no intervention was needed, patients could continue at the discretion of the investigator. Primary endpoint is the median time from randomization to first documented AF recurrence. Secondary endpoints assess time to first documented and confirmed (by 12-lead ECG) AF recurrence and the time to first documented AF recurrence in patients still in sinus rhythm 2 days after DCC (ranolazine steady state). Overall, 310 patients were screened and underwent DCC. Of these, 241 had sinus rhythm 2 hours after DCC and were randomized. Three randomized patients did not take the study drug. Patients had a mean age of 65.3 years. Most were male (77.3%). Almost all patients were Caucasian (98.7%). Median time since first AF diagnosis was 10 months and 91 patients (38.2%) had had previous DCC. Most common concomitant cardiovascular diseases were hypertension (69.3%), coronary artery disease (8.4%) and mitral regurgitation (6.7%). Overall, 116 patients (48.7%) sustained an AF recurrence documented by TT-ECG and 90 patients (37.8%) had documented AF recurrences later confirmed by 12-lead ECGs at the site. In total 98 patients (41.2%) completed the study after 16 weeks without AF and 24 patients (10.1%) with AF. Termination due to AF occurred in 83 patients (34.8%) while 33 patients (13.9%) discontinued the study for other reasons than AF. Most common adverse drug reactions were dizziness, fatigue, constipation, and nausea. Primary/secondary endpoint results will be available in March/April 2014.

The Effect of the Combination of Ranolazine and Low Dose Dronedarone on Atrial Fibrillation Burden in Patients with Paroxysmal Atrial Fibrillation (Harmony Trial)

Peter R. Kowey, MD, FHRS, James A. Reiffel, MD, FHRS, A. John Camm, MD, FHRS, Wojciech Zareba, MD, PhD, Ewa K. Prokopczuk, MD, Dewan Zeng, MD and Luiz Belardinelli, MD. Lankenau Medical Center and Institute for Medical Research, Wynnewood, PA, Columbia University, New York, NY, St. George University of London, London, United Kingdom, University of Rochester - Cardiology Unit, Rochester, NY, Gilead Sciences, Foster City, CA

Introduction: The increasing prevalence of atrial fibrillation (AF), and the poor safety profile and/or limited clinical efficacy of existing anti-arrhythmic drugs (AADs), has made the development of an effective and safe AAD for AF a priority. Results of nonclinical studies have shown that the combination of ranolazine (Ran) and dronedarone (Dron) suppresses AF in a synergistic manner, likely due to multichannel ion effects resulting in inhibition of peak and late I_{Na}, I_{Kr}, and I_{Ks} in atrial myocytes with a minimal effect on ventricular myocytes. This synergistic effect was observed at concentrations of Dron that are lower than those achieved by 400 mg Dron alone and do not exceed the IC_{50} value for the inhibition of L-type calcium channel.

Therefore, it was hypothesized that in patients with AF, a fixed-dose combination of Ran and Dron at doses lower than 400 mg Dron would be effective and safe in suppressing AF. Methods: HARMONY (NCT01522651) was a randomized, double-blind, placebo-controlled, parallel-arm study in 134 subjects with paroxysmal AF with dual-chamber pacemakers (PPMs) having the capability to detect AF, and record and store electrograms. HARMONY’s objective was to determine...
whether a Ran-Dron combination consisting of Ran 750 mg BID and low doses of Dron (225 mg BID or 150 mg BID) is superior to either drug alone in reducing AF burden (AFB). Patients with AFB ≥2% and ≤70% during a 4-week Run-in period (baseline) were randomized in 1:1:1:1:1 ratio to one of the following 5 parallel treatment arms: (1) placebo; (2) Ran 750 mg BID; (3) Dron 225 mg BID; (4) Ran 750 mg BID plus Dron 225 mg BID; (5) Ran 750 mg BID plus Dron 150 mg BID. Subjects were treated with study drug for 12 weeks, and PPM interrogations were repeated at weeks 4, 8 and 12. Key exclusion criteria included persistent or permanent AF, heart failure (NYHA Class III and IV or recently decompensated), concomitant use of Class I and III AADs (washout permitted), or digoxin, and recent cardiac ablation. The primary endpoint was the change in AFB from baseline over the 12 weeks of treatment. An EP Core Lab collected and read all PPM interrogation data and adjudicated electrograms in a blinded manner. 

**Application:** will be available immediately prior to the HRS meeting.

**LB03-06**

**THE EFFECTS OF REACTIVE ATRIAL ANTITACHYCARDIA PACING ON THE PROGRESSION OF ATRIAL TACHYARRHYTHMIAS: APPLICATION OF THE RANDOMIZED MINERVA TRIAL**

Luigi Padeletti, PhD, Helmut Pürerfellner, MD, Raymond Tukkie, MD, J. Lluis Mont, MD, PhD, Antonis S. Manolis, Massimo Santini, MD, Giuseppe Inama, MD, Paolo Serra, MD, Federica Gavazza, MS, Andrea Grammatico, PhD, J. Harrison Hudnall, PhD and Giuseppe Boriani, MD, PhD. Istituto di Clinica Medica I° e Cardiologia A.O.U.C. Careggi, Florence, Italy, Akademisches Lehrkrankenhaus der Elisabethinen, Linz, Austria, Kennermer Gasthuis, Haarlem, Netherlands, Cardiology Department, Thorax Institute Hospital Clinic, Universitat de Barcelona, Barcelona, Spain, Evangelismos General Hospital of Athens, Athens, Greece, Ospedale San Filippo Neri, Rome, Italy, Ospedale Maggiore, Crema, Italy, Cardiology Department, G. Mazzini Hospital, Teramo, Italy, Medtronic Clinical Research Institute, Rome, Italy, Medtronic, Inc., Minneapolis, MN, University of Bologna - Policlinico S. Orsola, Bologna, Italy

**Introduction:** Atrial tachyarrhythmias (AT/AF) are frequent in bradycardia patients. High technology pacemakers include advanced features to minimize unnecessary right ventricular pacing (MVP), atrial intervention pacing, and atrial antitachycardia pacing (DDDRP) to prevent or terminate AT/AF. The MINERVA trial evaluated whether advanced pacing (DDDRP+MVP) reduced AT/AF risk compared to standard pacing (DDDR).

**Methods:** Dual-chamber pacemaker patients with paroxysmal or persistent AT/AF history were randomly assigned to DDR (n=385), MVP alone (n=398), or DDDRP+MVP (n=383). The DDDRP+MVP arm exploited a second generation antitachycardia pacing (Reactive ATP) which attempts AT/AF termination with a re-arming logic based on AT/AF rate and regularity. Study pre-specified objectives comprised persistent AT/AF, defined as ≤7 consecutive days of AT/AF, Reactive ATP efficacy, and AT/AF rate and AT/AF regularity, defined as percentage frequency of the 2 most commonly occurring atrial intervals in the last 12 arrhythmia intervals.

**Application:** At baseline, 982 (86%) patients had atrial fibrillation history, 228 (20%) atrial flutter history and 197 (17%) atrial tachycardia history. At 2 years, persistent AT/AF incidence was 26% (95% confidence interval (CI) 22%-31%) in DDDR, 25% (CI=21%-30%) in MVP and 15% (CI=12%-20%) in DDDRP+MVP (hazard ratio (HR)=0.52 p<0.001 vs DDDR; HR=0.57, p=0.002 vs MVP). Reactive ATP median efficacy was 44% (CI=41%-48%). In a multivariable analysis, high Reactive ATP efficacy (>44%) resulted as an independent predictor of reduced persistent AT/AF (HR=0.42 (CI=0.21-0.83), p=0.013). Median AT/AF rate at detection was 244 beats per minute (bpm), 25th-75th percentile range=216-280 bpm. Reactive ATP efficacy was significantly and inversely associated with AT/AF rate (ATP success=50% for AT/AF rates <240 bpm, 47% for AT/AF rates between 240 bpm and 340 bpm and 35% for AT/AF rates >340 bpm). Preliminary analyses on the mechanisms of AT/AF termination by Reactive ATP in a subgroup of long (>6 hours duration) AT/AF episodes showed that AT/AF rate and regularity changed over time. In particular, comparing time of first unsuccessful ATP (1 minute after detection) and time of last successful therapy (>6 hours), AT/AF became slower (on average rate diminished of 41 bpm) and more regular (on average regularity increased by 31%).

**Next Steps/Futures:** In bradycardia patients, DDDRP+MVP pacing delays AT/AF disease progression, with Reactive ATP efficacy being an independent predictor of persistent AT/AF reduction. Despite most patients having documented history of atrial fibrillation, many AT/AF episodes started as atrial tachycardia or flutter or over time transitioned to slower and more regular rhythms subject to pace termination.