Late-Breaking Clinical Trials
All About AFib
D-LBCT03
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CHAIR:
Fred M. Kusumoto, MD, FHRS. Mayo Clinic Jacksonville, EP and Pacing Services, Jacksonville, FL

COMMENTATOR:
Christine M. Albert, MD, MPH, FHRS. Cedars Sinai Medical Center, Los Angeles, CA

COMMENTATOR:
Isabelle C. Van Gelder, MD, PhD. University Medical Center Groningen, Groningen, Netherlands

D-LBCT03-01

IMPROVING ESOPHAGEAL PROTECTION DURING AF ABLATION WITH ABLATION INDEX TECHNOLOGY: OUTCOMES FROM THE IMPACT STUDY

Mark M. Gallagher, MD, Lisa W.M. Leung, Abhay Baijpai, MD, Zia Zuberi, MD, Anthony Li, MD, Mark Norman, MD, Riyaz Kaba, MD, Zaki Akhtar, MBBS, Banu Evranos, MD, Hanney Gonna, MBBS, Idris Harding, MD, Manav Sohal, MD, Nawaf Subaie, MD, John Louis-Auguste, MD and Jamal Hayat, MD. St. George’s University of London, London, United Kingdom

Introduction: The IMPACT study was a single-center, prospective, double-blind randomized controlled trial studying the effect of controlled esophageal cooling for protection during AF ablation. AF ablation in the study cohort was performed using radiofrequency with Ablation Index technology. The extent of controlled esophageal cooling on the efficacy of ablation lesions created using Ablation Index technology has not been studied.

Methods: A single-center, prospective, double-blind randomized controlled trial was used to investigate the ability of a controlled method of esophageal cooling to protect the esophagus from thermal injury. This method was compared in a 1:1 randomization to a control group of standard practice utilizing a single-sensor temperature probe. In the study group, the esophageal cooling device was used to keep the luminal temperature at 4°C during radiofrequency (RF) ablation for AF. All participants received AF ablation using Ablation Index technology at posterior and anterior settings (30W at 350-400 and 40W at 450-500, respectively). Endoscopic examination was performed within 7 days post-ablation and esophageal injury was graded. The patient and the endoscopist were blinded to the randomization. Clinical follow up occurred 3 months post-ablation, with completion of structured questionnaires (GERD-Q and GCSI); both patient and follow up clinician were blinded.

Applications: We recruited 188 patients, of whom 120 underwent endoscopy. Thermal injury to the mucosa was significantly more common in the control group than in those receiving esophageal protection (12/60 versus 2/60; P=0.008). There was no difference between groups in RF time, lesion duration, force, power and ablation index (P value range= 0.2-0.9). Procedure and fluoroscopy duration were similar (P=0.97, P=0.91 respectively). The majority of those who passed through the 1st follow up evaluation (n=118) did not have gastrointestinal or chest pain symptoms post ablation and there was no difference between the randomized groups. Only 4.3% had severe symptoms and they were poorly correlated against those who sustained mucosal lesions. AF recurrence was similar in both groups (8% vs 8.8%). There were 2 cases of vascular trauma needing intervention in the control group and 1 case of conservatively managed pericardial effusion in the protected group only. Endoscopy findings did not report any cooling device-related trauma.

Next Steps/Future: Long term study population outcomes at 12 months will be reported to clarify the success of the ablation treatment with and without esophageal cooling protection. A large multi-center trial will be set up to investigate the extent of protection offered by controlled esophageal cooling and against all AF sub-types and ablation methods.

D-LBCT03-02

INCIDENCE OF SILENT BRAIN INFARCTS IN ANTICOAGULATED PATIENTS WITH ATRIAL FIBRILLATION

David Conen, MD, MPH, Philipp Krisai, MD, Nicolas Rodondi, MD, Andreas Müller, MD, Jürg H. Beer, MD, Peter Ammann, MD, Giorgio Moschovitis, MD, Angelo Auricchio, MD, PhD, Daniel Hayoz, MD, Richard Kobza, MD, Dipen Shah, MD, FHRS, Jürg Schläpfer, MD, Marcello Di Valentino, MD, Stefanie Aeschbach, PhD, Steffen Blum, MD, PhD, Ceylan Eken, PhD, Christine S. Zuern, MD, Pascal Meyre, MD, PhD, Anne Springer, PhD, Christian Sticherling, MD, Leo H. Bonati, MD, Georg Ehret, MD, Urs Fischer, MD, Andreas U. Monsch, PhD, Laurent Roten, MD, Els-avet Moutzouri, MD, Matthias Schwenkglenks, PhD (c), MPH, Tim Sinnecker, MD, Jens Wuerfel, MD, Gilles Dutilh, Michael Coslovsky, PhD, Michael Kühne, MD and Stefan Osswald, MD. Population Health Research Institute, McMaster University, ON, Canada, Cardiovascular Research Institute Basel, University Hospital Basel, Basel, Switzerland, Institute of Primary Health Care (BIHAM) and Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, Department of Cardiology, Triemli Hospital Zurich, Zurich, Switzerland, Department of Medicine, Cantonal Hospital of Baden and Molecular Cardiology, University Hospital of Zurich, Zurich, Switzerland, Department of Cardiology, Kantonsspital St. Gallen, St. Gallen, Switzerland, Department of Cardiology, Ospedale Regionale di Lugano, Lugano, Switzerland, Division of Cardiology, Fondazione Cardiocentro Ticino, Lugano, Switzerland, Department of Internal Medicine, HFR-Hôpital Cantonal Fribourg, Fribourg, Switzerland, Department of Cardiology, Luzern Cantonsspital, Luzern, Switzerland, Division of Cardiology, Department of Medical Specialties, University Hospital Geneva, Geneva, Switzerland, Division of Cardiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, Department of Cardiology, Ospedale San Giovanni, Bellinzona, Switzerland, Cardiology Division and Cardiovascular Research Institute Basel, Department of Medicine, University Hospital Basel, Basel,
Switzerland, Department of Neurology and Stroke Center, University Hospital Basel, Basel, Switzerland, Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, Memory Clinic, Universitätsklinikum Basel, Felix Platter Spital Basel, University of Basel, Basel, Switzerland, Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, Epidemiology, Biostatistics, and Prevention Institute, University of Zurich, Zurich, Switzerland, Department of Neurology and Stroke Center, University Hospital Basel, and Medical Image Analysis Center (MIAC AG) and Department of Biomedical Engineering, University of Basel, Basel, Switzerland, Medical Image Analysis Center (MIAC AG) and Department of Biomedical Engineering, University of Basel, Basel, Switzerland, Cardiovascular Research Institute Basel, Basel, Switzerland

Introduction: Oral anticoagulation greatly reduces the risk of ischemic strokes in patients with atrial fibrillation (AF). Clinically silent brain lesions are a potential reason for the increased risk of cognitive dysfunction in patients with AF. However, the incidence of silent brain infarcts in anticoagulated AF patients is currently unknown.

Methods: We enrolled patients aged ≥65 years with previously documented AF in a prospective, multicenter observational cohort study (Swiss-AF). Patients underwent brain magnetic resonance imaging (MRI) at baseline and after 2 years of follow-up according to a standardized protocol. Large noncortical or cortical infarcts (LNCCIs) as well as small noncortical infarcts (SNCIs) were quantified in a central core laboratory. New infarcts were defined as lesions present on the follow-up MRI scan but not at baseline. Clinically silent infarcts were defined as new infarcts in patients without a clinical stroke between the two MRI studies.

Applications: A total of 1,256 patients had paired brain MRI studies available at baseline and after 2 years of follow-up. Mean age at baseline was 71.5 ± 8.4 years, and 26% were women. The prevalence of hypertension, diabetes and previous stroke was 68%, 15%, and 13%, respectively. Overall, 84% of participants received oral anticoagulation during the 2-year follow-up period. There were 10 (0.8%) clinical strokes during follow-up. In the brain MRI studies obtained at 2 years of follow-up, there were 46 (3.7%) patients with at least 1 new brain infarct, 33 (2.6%) patients had at least 1 new LNCCI and 20 (1.6%) patients had at least 1 new SNCI. Of the 46 patients with new brain infarcts, 43 (93.5%) had clinically silent brain lesions, 43 (93.5%) were taking oral anticoagulation during the follow-up period, and 41 (89.1%) had clinically silent brain infarcts while taking oral anticoagulation.

Next Steps/Future: In a large contemporary cohort of patients with AF, we found a significant number of brain infarcts on systematic brain MR imaging. The great majority of these infarcts were clinically silent and occurred in patients treated with oral anticoagulation. At HRS 2020, we will present additional data on the clinical significance of these findings, including the associations of new brain infarcts with cognitive function, and an evaluation of clinical predictors for the occurrence of new brain infarcts.

D-LBCT03-03

PRIMARY OUTCOME EVALUATION OF A NEXT GENERATION LEFT ATRIAL APPENDAGE CLOSURE DEVICE: THE PINNACLE FLX TRIAL

Shephal K. Doshi, MD, Ashish Sadhu, MD, Rodney P. Horton, MD, FHRS, Jose Osorio, MD, FHRS, Christopher R. Ellis, MD, FHRS, James E. Stone, MD, Manish H. Shah, MD, Vivek Y. Reddy, MD, Srinivas R. Dukkipati, MD, FHRS, Stuart W. Adler, MD, Devi G. Nair, MD, FHRS, Jamie H. Kim, MD, Oussama M. Wazni, MD, FHRS, Matthew J. Price, MD, Federico M. Asch, MD, David R. Holmes, MD, Dominic Allocco, MD, MS, Robert Shipley, Nicole T. Gordon, BSEE and Saibal Kar. Pacific Heart Institute, Santa Monica, CA, University of Massachusetts, Worcester, MA, Texas Cardiac Arrhythmia, Austin, TX, Arrhythmia Institute at Grandview, Birmingham, AL, Vanderbilt Heart and Vascular, Nashville, TN, North Mississippi Medical Center, Tupelo, MS, MedStar Washington Hospital Center, Washington, DC, Icahn School of Medicine at Mount Sinai, New York, NY, Mount Sinai School, New York, NY, HealthEast Heart Care, Edina, MN, St. Bernard’s Heart & Vascular Center, Jonesboro, AR, New England Heart and Vascular Institute, Bedford, NH, Cleveland Clinic, Cleveland, OH, Scripps, La Jolla, CA, MedStar, Washington DC, DC, Mayo Clinic, Rochester, MN, Boston Scientific, Minneapolis, MN, Boston Scientific, Austin, TX, Boston Scientific, Maple Grove, MN, Los Robles Regional Medical Center, Thousand Oaks, CA

Introduction: The WATCHMAN Left Atrial Appendage Closure (LAAC) device is FDA-approved to reduce the risk of stroke in non-valvular atrial fibrillation (NVAF). The WATCHMAN FLX device (FLX), designed to improve implant safety and LAAD sealing, was evaluated in the PINNACLE FLX trial, a single-arm, multicenter prospective approval study (NCT 02702271).

Methods: NVAF patients (pts) were enrolled at 29 sites from April to November 2018. The post-implant medical therapy was: 45-days of a non-vitamin K oral anticoagulant (NOAC) and aspirin, then aspirin plus clopidogrel through 6 months. The primary safety endpoint was a composite of death, ischemic stroke, systemic embolism, or device/procedure-related events requiring cardiac surgery or major endovascular intervention within 7-days post-implant (performance goal ≤4.21%). The primary effectiveness endpoint was the percentage of pts with leak ≤5mm at the 1-year TEE based on core lab review (performance goal ≥97%).

Applications: Of 400 main cohort pts (age 73.8±8.6; CHA2DS2-VASc 4.2±1.5; HAS-BLED 2.0±1.0), implantation was successful in 395 (98.8%). Other baseline characteristics, post-implant therapy and primary results are shown below (Figure). All pts completed the 45-day visit, and 95.4% completed the 1-year visit (mean follow-up 12.8±3.5 months). Most pts (95.4%) discontinued OAC after 45-days. Both primary safety (0.5%, 95% upper confidence bound = 1.6, p<0.0001) and primary efficacy (100% effective seal at 12-months, 95% lower confidence bound = 98.9%, p<0.0001) endpoints met the performance goals. There were no device embolizations, pericardial effusions requiring surgery, or procedural deaths. There were 2 ischemic strokes within 7 days of the procedure and 9 ischemic
Heart Rhythm 2020

strokes not associated with the procedure. Device-related thrombus occurred in 7 pts, though none of these subjects experienced an ischemic stroke over the course of follow-up.

Next Steps/Future: The results of this study support the safety and efficacy of the FLX device. Primary endpoint results described above along with detailed clinical and echocardiographic results through 1 year will be available for presentation for the 1st time at HRS 2020.

D-LBCT03-04

ATRIAL FIBROSIS PREDICTS RECURRENT STROKE OR NEW ATRIAL FIBRILLATION IN PATIENTS WITH EMBOLIC STROKE OF UNDETERMINED SOURCE - A MULTI-CENTER STUDY

Nazem Akoum, MD, MS, FHRS, Peter Kühlein, MD, Jennifer J. Majersik, MD, Brent D. Wilson, MD, Marcel Mitlacher, MD, David Tirschwell, MD, W.T. Longstreth, MD and Christian Mahnkopf, MD. University of Washington, Seattle, WA, Regiomed Clinical Centre, Coburg, Germany, University of Utah, Salt Lake City, UT, University of Washington, Seattle, WA, Klinikum Coburg, Coburg, Germany

Introduction: Atrial disease has been implicated in embolic stroke of undetermined source (ESUS). We hypothesized that ESUS patients with advanced atrial disease are at higher risk for recurrent stroke or incident atrial fibrillation (AF).

Methods: We quantified atrial fibrosis using late-gadolinium enhancement MRI. Atrial fibrosis was reported as a percentage of the left atrial wall volume, and compared across various groups: healthy controls, lacunar stroke, ESUS and known AF with or without prior stroke. We followed ESUS patients prospectively for 30 months for recurrent ischemic stroke or new AF.

Applications: We enrolled 201 patients, 101 without AF: 35 healthy controls, 15 lacunar strokes, 51 patients with ESUS; and 100 patients with AF: 50 with prior stroke and 50 without prior stroke. Atrial fibrosis was significantly higher in ESUS compared to lacunar stroke patients (14.69±6.39% vs 10.76±8.30; p = 0.02) and to healthy controls (8.1±7.9%; <0.0001). ESUS patients had comparable fibrosis to patients with AF with or without prior stroke (16.6±9.2%; p=NS for both) (Figure 1). In prospective follow up of ESUS, 5 patients (9.8%) had recurrent stroke and 5 had incident AF (9.8%). ESUS patients with fibrosis >12% had a significantly higher proportion of the combined outcome of recurrent stroke or new AF compared to those with fibrosis <12% (5.0% vs 22.6%; p=0.045) (Figure 2).

Next Steps/Future: Patients with ESUS have atrial fibrosis comparable to that seen in AF. Atrial fibrosis >=12% may identify ESUS patients who may benefit from anticoagulation for secondary prevention.

D-LBCT03-05

ACTIVE EXTRACELLULAR MATRIX REMODELING PREPARES THE HEART FOR FUTURE ATRIAL FIBRILLATION. FIRST RESULTS OF THE PREDICT-AF TRIAL.

Joris R. de Groot, MD, PhD, Nicoline W.E. van den Berg, MD, Jolien Neefs, MD, Makiri Kawasaki, PhD, Fransiska A. Nariswari, MS, Robin Wesselinl, Aldo Jongejan, PhD, Martijn N. Klaver, MD, Hanna Havenaar, Elise L. Hulsman, Lisette Wintgens, Sarah W.E. Baalman, MD, Wim Jan van Boven, Jonas De Jong, MD, Bart P. Van Putte, Antoine H.G. Driessen, MD and Lucas V.A. Boersma, MD, PhD. Amsterdam UMC, University of Amsterdam, Heart Center, Amsterdam, Netherlands, Department of Clinical and Experimental Cardiology and Cardiothoracic Surgery, Amsterdam Cardiovascular Sciences, Amsterdam, Netherlands, Amsterdam UMC, University of Amsterdam, Bioinformatics Laboratory, Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam, Netherlands, Department of Cardiology and Cardiothoracic Surgery, St. Antonius Hospital, Nieuwegein, Netherlands, Department of Cardiology, Onze Lieve Vrouwe
Hospital, Amsterdam, Netherlands, Department of Cardiology and Cardiothoracic Surgery, St. Antonius Hospital, Nieuwegein, Utrecht, Netherlands

**Introduction:** Structural changes of the atrium may occur long before the onset of atrial fibrillation (AF).

**Methods:** Patients without a history of AF undergoing cardiothoracic surgery with a CHA2DS2-VASc score ≥2 were included and the left atrial appendage was excised (PREDICT-AF NCT03130985). Rhythm monitoring with multiple Holters was performed for 2 years. The primary endpoint was late-onset AF: any atrial tachyarrhythmia >30 sec, occurring >50 days after surgery. The expression of 25 genes related to structural or electrical remodeling was quantified with qPCR in all patients and associated with late-onset AF using Cox-regression analyses. Genes were selected based on a discovery phase (transcriptome sequencing of 22 atrial tissues). Gene panels were used to determine C-statistics.

**Applications:** We included 150 patients (age 68±7 years, 87% men, 115 CABG, 11 valve surgery, 24 combined surgeries). Median follow-up was 2.0 years [1.5-2.0]. Postoperative AF occurred in 63 (42%) patients ≤50 days post-surgery and late-onset AF in 18 (12%). Gene expression of all 25 genes was similar in patients with and without postoperative AF <50 days. Patients with late-onset AF exhibited numerical downregulation of KCNJ2 and upregulation of SCN2B. There was a marked increased expression of extracellular matrix (ECM) genes encoding collagens and matrix cellular proteins that act as structural proteins and fibrogenic mediators (Figure A). We found a strong correlation between ECM genes and the fibroblast activator Endothelin-1. The fraction of Vimentin positive cells (i.e. fibroblasts) was similar, suggesting fibroblast activation rather than proliferation. A gene panel including KCNJ2, COL8A2, and COL1A1 better discriminated late-onset AF (AUC=0.82) than a model with the most relevant clinical parameters (age≥75, LAVI and sex; AUC=0.69)(Figure B).

**Next Steps/Future:** PREDICT AF for the first time shows that extensive ECM remodeling, reaching beyond the deposition of collagens, takes place in the atria of patients long before they develop AF. The high accuracy of a gene panel to predict future AF may inspire further research to provide targets for diagnosis and primary prevention of AF.

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Differential gene expression in patients with late-onset Atrial Fibrillation

<table>
<thead>
<tr>
<th>Gene</th>
<th>Control (n=63)</th>
<th>LATE (n=18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen 1 (COL1A1)</td>
<td>1.42 (1.26-1.59)</td>
<td>0.97 (0.83-1.14)</td>
<td>0.02</td>
</tr>
<tr>
<td>Collagen 3 (COL3A1)</td>
<td>1.36 (1.20-1.53)</td>
<td>1.30 (1.07-1.61)</td>
<td>0.02</td>
</tr>
<tr>
<td>Thrombospondin-1 (THBS1)</td>
<td>1.23 (1.08-1.40)</td>
<td>1.24 (1.01-1.51)</td>
<td>0.05</td>
</tr>
<tr>
<td>Tenascin (TNC)</td>
<td>1.45 (1.29-1.62)</td>
<td>1.54 (1.30-1.80)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Left figure presents the bar chart with the mean and 95% confidence interval of the log2 fold change between the control (preoperative) and late-onset AF (postoperative) groups. Right figure presents the box and whisker plot of the fold change in gene expression.