Risk Factors for Sudden Cardiac Death in Post-Menopausal Women

Objectives The aim of this study was to estimate the annual incidence rate of sudden cardiac death (SCD) and to identify risk factors for SCD in post-menopausal women.

Background With the aging U.S. population, post-menopausal women now have the greatest population burden of cardiovascular disease including SCD.

Methods We examined 161,808 women who participated in the Women’s Health Initiative clinical trials and observational study. The women were recruited at 40 clinical sites across the United States, enrolled between 1993 and 1998, and followed until August 2009. Our primary endpoint is incident SCD, defined as death occurring within 1 h of symptom onset or within 1 h after the participant was last seen without symptoms and death that occurred in the absence of a potentially lethal non-coronary disease process.

Results Four hundred eighteen women experienced adjudicated SCD. The incidence rate of SCD was 2.4/10,000 women/year (95% confidence interval: 2.2 to 2.7). We identified the following independent risk factors for SCD: older age, African-American race, tobacco use, higher pulse, higher waist-to-hip ratio, elevated white blood cell count, history of heart failure, diabetes, history of myocardial infarction, previous carotid artery disease, and hypertension. Population-attributable fractions were greatest for hypertension, waist-to-hip ratio, and myocardial infarction.

Conclusions Besides traditional risk factors for coronary heart disease, risk factors for sudden cardiac death in post-menopausal women include African-American race, higher pulse, higher waist-to-hip ratio, elevated white blood cell count, and heart failure. Nearly one-half of women who experienced sudden cardiac death had no previous diagnosis of coronary heart disease (1).

Ventricular Arrhythmia After Cardiac Surgery: Incidence, Predictors, and Outcomes

Objectives This study sought to investigate the prevalence, predictors, and outcomes of patients with post-operative ventricular arrhythmia (POVA) in a large cohort of patients.

Background New-onset POVA after cardiac surgery (CS) is uncommon and has controversial prognostic value.

Methods A total of 14,720 consecutive patients undergoing CS at Emory University between January 2004 and July 2010 were included in the study. Data on all-cause mortality were obtained from Social Security Administration death records. Multivariable regression models were constructed to determine the risk factors for POVA and to estimate the independent impact of POVA on long-term survival after adjusting for 40 different covariates.

Results POVA occurred in 248 patients (1.7%). Patients with POVA were older (63.5 vs. 61.6 years), had lower left ventricular ejection fraction (EF) (43.7 vs. 51.3), and had greater comorbidities (Society of Thoracic Surgeons mortality risk score of 7.2% vs. 3.1%, p < 0.001). Multivariable analysis showed that older age (odds ratio [OR]: 1.018 per 1-year increase, p < 0.001), emergent surgery (OR: 1.77, p = 0.019), and the presence of PVD (OR: 1.41, p = 0.049) were associated with a higher incidence of POVA, whereas higher left ventricular EF (OR: 0.97 per 1% increase, p < 0.001), mild chronic obstructive pulmonary disease (OR: 0.37, p < 0.001), and off-pump surgery (OR: 0.41, p < 0.001) were associated with a lower incidence of POVA. POVA was associated with substantially increased adjusted long-term mortality (hazard rate: 2.53, p < 0.001) over 3.5 years of follow-up.

Conclusions POVA is associated with increased long-term mortality after CS. Older age, PVD, lower EF, and emergent surgery are associated with a higher risk of POVA, whereas off-pump surgery seems to be protective (2).

Vagal Reflexes Following an Exercise Stress Test: A Simple Clinical Tool for Gene-Specific Risk Stratification in the Long QT Syndrome

Objectives The study assessed whether heart rate (HR) reduction following an exercise stress test (ExStrT), an easily quantifiable marker of vagal reflexes, might identify high- and low-risk long QT syndrome (LQTS) type 1 (LQT1) patients.

As a service to our readers, we have compiled all the relevant manuscripts in individual subject areas of cardiology. These collections should provide a single repository of JACC publications in the specific areas. In addition, these compilations should put in perspective the recent advancements and future directions in the important disciplines of cardiovascular medicine.
Background Identification of LQTS patients more likely to be symptomatic remains elusive. We have previously shown that depressed baroreflex sensitivity, an established marker of reduced vagal reflexes, predicts low probability of symptoms among LQT1.

Methods We studied 169 LQTS genotype-positive patients < 50 years of age who performed an ExStrT with the same protocol, on and off β-blockers including 47 South African LQT1 patients all harboring the KCNQ1-A341V mutation and 122 Italian LQTS patients with impaired (IKs–, 66 LQT1) or normal (IKs+, 50 LQT2 and 6 LQT3) IKs current.

Results Despite similar maximal HR and workload, by the first minute after cessation of exercise the symptomatic patients in both IKs– groups had a greater HR reduction compared with the asymptomatic (19 ± 7 beats/min vs. 13 ± 5 beats/min and 27 ± 10 beats/min vs. 20 ± 8 beats/min, both p = 0.009). By contrast, there was no difference between the IKs+ symptomatic and asymptomatic patients (23 ± 9 beats/min vs. 26 ± 9 beats/min, p = 0.47). LQT1 patients in the upper tertile for HR reduction had a higher risk of being symptomatic (odds ratio: 3.28, 95% confidence interval: 1.3 to 8.3, p = 0.012).

Conclusions HR reduction following exercise identifies LQT1 patients at high or low arrhythmic risk, independently of β-blocker therapy, and contributes to risk stratification. Intense exercise training, which potentiates vagal reflexes, should probably be avoided by LQT1 patients (3).

Diffuse Ventricular Fibrosis in Atrial Fibrillation: Noninvasive Evaluation and Relationships With Aging and Systolic Dysfunction

Objectives The purpose of this study was to evaluate diffuse myocardial fibrosis of the left ventricle (LV) in patients with atrial fibrillation (AF).

Background Diffuse myocardial fibrosis is a hallmark of cardiomyopathy. Unlike replacement fibrosis, it is not visualized on delayed-enhancement cardiac magnetic resonance (CMR) imaging, but may be quantified with contrast-enhanced T1 mapping methods. In atrial fibrillation (AF), it may be induced by arrhythmia or reflect pre-existing cardiomyopathy.

Methods Ninety subjects underwent CMR using a clinical 1.5-T scanner: 23 controls, 40 paroxysmal AF patients, and 27 persistent AF patients. Cardiac morphology and function was evaluated from CMR cine imaging. A histologically validated T1 mapping sequence was used to calculate post-contrast T1 relaxation time (T1 time) of the LV myocardium as an index of diffuse myocardial fibrosis.

Results Age was similar across controls, paroxysmal AF patients, and persistent AF patients (54 ± 12 years, 58 ± 9 years, and 56 ± 10 years, p = NS). Persistent AF patients had larger indexed left atrium volume (55 ± 18 ml vs. 41 ± 12 ml and 47 ± 14 ml) and lower ejection fraction (54 ± 10% vs. 65 ± 6% and 61 ± 8%) than controls and paroxysmal AF patients (p < 0.05). Post-contrast ventricular T1 time differed across all groups (controls, 535 ± 86 ms; paroxysmal AF, 427 ± 95 ms; persistent AF, 360 ± 84 ms; p < 0.001). Univariate predictors of post-contrast ventricular T1 time included age, sex, AF category, ejection fraction, LV mass, congestive heart failure, and body mass index. After multivariate analysis, age, AF category, and ejection fraction remained independent predictors.

Conclusions Post-contrast ventricular T1 mapping identifies diffuse LV fibrosis in patients with AF and provides new insights into the association between AF and adverse ventricular remodeling (4).

A Novel Low-Energy Electrotherapy That Terminates Ventricular Tachycardia With Lower Energy Than a Biphasic Shock When Antitachycardia Pacing Fails

Objectives The authors sought to develop a low-energy electrotherapy that terminates ventricular tachycardia (VT) when antitachycardia pacing (ATP) fails.

Background High-energy implantable cardioverter-defibrillator (ICD) shocks are associated with device failure, significant morbidity, and increased mortality. A low-energy alternative to ICD shocks is desirable.

Methods Myocardial infarction was created in 25 dogs. Sustained, monomorphic VT was induced by programmed stimulation. Defibrillation electrodes were placed in the right ventricular apex, and coronary sinus and left ventricular epicardium. If ATP failed to terminate sustained VT, the defibrillation thresholds (DFTs) of standard versus experimental electrotherapies were measured.

Results Sustained VT ranged from 276 to 438 beats/min (mean 339 beats/min). The right ventricular–coronary sinus shock vector had lower impedance than the right ventricular–left ventricular patch (54.4 ± 18.1 Ω versus 109.8 ± 16.9 Ω; p < 0.001). A single shock required between 0.3 ± 0.2 J to 5.9 ± 2.5 J (mean 2.64 ± 3.22 J; p = 0.008) to terminate VT, and varied depending upon the phase of the VT cycle in which it was delivered. By contrast, multiple shocks delivered within 1 VT cycle length were not phase dependent and achieved lower DFT compared with a single shock (0.13 ± 0.09 J for 3 shocks, 0.08 ± 0.04 J for 5 shocks, and 0.09 ± 0.07 J for 7 shocks; p < 0.001). Finally, a multistage electrotherapy (MSE) achieved significantly lower DFT compared with a single biphasic shock (0.03 ± 0.05 J versus 2.37 ± 1.20 J; respectively, p < 0.001). At a peak shock amplitude of 20 V, MSE achieved 91.3% of terminations versus 10.5% for a biphasic shock (p < 0.001).

Conclusions MSE achieved a major reduction in DFT compared with a single biphasic shock for ATP-refractory monomorphic VT, and represents a novel electrotherapy to reduce high-energy ICD shocks (5).
Inflammation in Atrial Fibrillation

Atrial fibrillation (AF) is associated with increased risk for stroke and systemic embolism. There is plausible evidence linking inflammation to the initiation and perpetuation of AF and AF-related thrombosis. Various inflammatory markers (C-reactive protein, tumor necrosis factor-α, interleukin-2, interleukin-6, and interleukin-8) have been associated with AF. Proposed mechanisms linking inflammation and the prothrombotic AF state include endothelial activation/damage, production of tissue factor from monocytes, increased platelet activation, and increased expression of fibrinogen. The present review aims to provide an update on the association of inflammation and AF, including the impact of inflammatory markers on clinical presentation and outcome of AF patients (7).

Impact of a New Conduction Defect After Transcatheter Aortic Valve Implantation on Left Ventricular Function

Objectives This study sought to evaluate the impact of new conduction defects after transcatheter aortic valve implantation (TAVI) on the evolution of left ventricular (LV) function during 1-year follow-up.

Background New left bundle branch block (LBBB) or need for permanent pacing due to atrioventricular (AV) block are frequent after TAVI.

Methods A total of 90 consecutive patients treated with TAVI and who had 12-month echocardiographic follow-up were included in the study. In 39 patients, a new conduction defect (new LBBB or need for permanent pacemaker activity) persisted 1 month after TAVI. In 51 patients, no persistent new conduction defect was observed. Two-dimensional echocardiography using parasternal short-axis, apical 4-chamber, and apical 2-chamber views was performed before TAVI and at 1-year follow-up to determine LV volumes and ejection fraction based on Simpson’s rule. Speckle-tracking echocardiography was applied using standard LV short-axis images to assess the effect of new conduction defects on time-to-peak radial strain of different LV segments as a parameter of LV dysynchrony.

Results New conduction defects resulted in marked heterogeneity in time-to-peak strain between the 6 analyzed short-axis segments. During 1-year follow-up after TAVI, there was a significant increase in left ventricular ejection fraction (LVEF) in patients without new LBBB (53 ± 11% pre TAVI to 59 ± 10% at follow-up, p < 0.001), whereas there was no change in LVEF in patients with a new conduction defect (52 ± 11% pre TAVI to 51 ± 12% at follow-up, p = 0.740). Change in LV end-systolic volume was also significantly different between patient groups (−1.0 ± 14.2 vs. −11.2 ± 15.7 ml, p = 0.042). New conduction defect and LVEF at baseline were independent predictors of reduced LVEF at 12-month follow-up after TAVI.

Conclusions LVEF improves after TAVI for treatment of severe aortic stenosis in patients without new conduction defects. In patients with a new conduction defect after TAVI, there is no improvement in LVEF at follow-up (8).

Anatomic Localization of Rapid Repetitive Sources in Persistent Atrial Fibrillation: Fusion of Biatrial CT Images With Wave Similarity/Cycle Length Maps

Objectives The aim of this study was to investigate the anatomic distribution of critical sources in patients with atrial fibrillation (AF) by fusion of biatrial computed tomography (CT) images with cycle length (CL) and wave similarity (WS) maps.

Background Experimental and clinical studies show that atrial fibrillation (AF) may originate from rapid and repetitive (RR) sources of activation. Localization of RR sources may be crucial for an effective ablation treatment. Atrial electrograms showing rapid and repetitive activations can be identified by combining WS and CL analysis.

Methods Patients with persistent AF underwent biatrial electroanatomic mapping and pre-procedural CT cardiac imaging. WS and CL maps were constructed in 17 patients by calculating the degree of repetitiveness of activation waveforms (similarity index [S]) and the cycle length at each atrial site. WS/CL maps were then integrated with biatrial 3-dimensional CT reconstructions by a stochastic approach.

Results Repetitive sources of activation (S ≥0.5) were present in most patients with persistent AF (94%) and were mainly located at the pulmonary veins (82% of patients), at the superior caval vein (41%), on the anterior wall of the right atrium (23%), and at the left atrial appendage (23%). Potential driver sources showing both rapid and repetitive activations (CL = 140.7 ± 25.1 ms, S = 0.65 ± 0.15) were present only in a subset of patients (65%) and were confined to the pulmonary vein region (47% of patients) and left atrial appendage (12%). Differently, the repetitive activity of the superior caval vein was characterized by a slow activation rate (CL = 184.7 ± 14.6 ms).

Conclusions The identification and localization of RR sources is feasible by fusion of biatrial anatomic images with WS/CL maps. Potential driver sources are present only in a subset of patients with persistent AF and are mainly located in the pulmonary vein region (7).

In Silico Cardiac Risk Assessment in Patients With Long QT Syndrome: Type 1: Clinical Predictability of Cardiac Models

Objectives The study was designed to assess the ability of computer-simulated electrocardiography parameters to predict clinical outcomes and to risk-stratify patients with long QT syndrome type 1 (LQT1).

Background Although attempts have been made to correlate mutation-specific ion channel dysfunction with patient phenotype in long QT syndrome, these have been largely
unsuccessful. Systems-level computational models can be used to predict consequences of complex changes in channel function to the overall heart rhythm.

**Methods** A total of 633 LQT1-genotyped subjects with 34 mutations from multinational long QT syndrome registries were studied. Cellular electrophysiology function was determined for the mutations and introduced in a 1-dimensional transmural electrocardiography computer model. The mutation effect on transmural repolarization was determined for each mutation and related to the risk for cardiac events (syncope, aborted cardiac arrest, and sudden cardiac death) among patients.

**Results** Multivariate analysis showed that mutation-specific transmural repolarization prolongation (TRP) was associated with an increased risk for cardiac events (35% per 10-ms increment [p < 0.0001]; ≥ upper quartile hazard ratio: 2.80 [p < 0.0001]) and life-threatening events (aborted cardiac arrest/sudden cardiac death: 27% per 10-ms increment [p = 0.03]; ≥ upper quartile hazard ratio: 2.24 [p = 0.002]) independently of patients’ individual QT interval corrected for heart rate (QTc). Subgroup analysis showed that among patients with mild to moderate QTc duration (<500 ms), the risk associated with TRP was maintained (36% per 10 ms [p < 0.0001]), whereas the patient’s individual QTc was not associated with a significant risk increase after adjustment for TRP.

**Conclusions** These findings suggest that simulated repolarization can be used to predict clinical outcomes and to improve risk stratification in patients with LQT1, with a more pronounced effect among patients with a lower-range QTc, in whom a patient’s individual QTc may provide less incremental prognostic information (9).

**New Unipolar Electrogram Criteria to Identify Irreversibility of Nonischemic Left Ventricular Cardiomyopathy**

**Objectives** This study sought to assess the value of left ventricular (LV) endocardial unipolar electroanatomical mapping (EAM) in identifying irreversibility of LV systolic dysfunction in patients with left ventricular nonischemic cardiomyopathy (LVCM).

**Background** Identifying irreversibility of LVCM would be helpful but cannot be reliably accomplished by bipolar EAM or cardiac magnetic resonance identification of macroscopic scar.

**Methods** Detailed endocardial LV EAM was performed in 3 groups: 1) 24 patients with irreversible LVCM (I-LVCM) but with no or minimal macroscopic scar (<15% LV surface) evidenced on bipolar voltage EAM and/or cardiac magnetic resonance; 2) 14 patients with reversible ventricular premature depolarization–mediated LVCM (R-LVCM); and 3) 17 patients with structurally normal hearts. LV endocardial unipolar electrogram amplitude and area of unipolar amplitude abnormality were defined after excluding macroscopic scar.

**Results** Unipolar amplitude differed in the 3 groups: median of 7.6 (interquartile range [IQR]: 5.5 to 9.7) mV in I-LVCM group, 13.2 (IQR: 10.4 to 16.2) mV in R-LVCM group, and 16.3 (IQR: 13.6 to 19.8) mV in structurally normal hearts group (p < 0.001). Areas of unipolar abnormality represented a large proportion of total LV surface in I-LVCM, 64.7% (IQR: 47.5% to 75.9%) compared with R-LVCM, 5.2% (IQR: 0.0% to 19.1%) and structurally normal hearts, 0.1% (IQR: 0.0% to 0.9%), groups (p < 0.001). A unipolar abnormality area cutoff of 32% of total LV surface was 96% sensitive and 100% specific in identifying irreversible cardiomyopathy among patients with LV dysfunction (I-LVCM and R-LVCM), p < 0.001.

**Conclusions** Detailed unipolar voltage mapping can identify irreversible myocardial dysfunction consistent with fibrosis, even in the absence of bipolar EAM or cardiac magnetic resonance abnormalities, and may serve as valuable prognostic tool in patients presenting with LVCM to facilitate clinical decision making (10).

**Not All Beta-Blockers Are Equal in the Management of Long QT Syndrome Types 1 and 2: Higher Recurrence of Events Under Metoprolol**

**Objectives** The purpose of this study was to compare the efficacy of beta-blockers in congenital long QT syndrome (LQTS).

**Background** Beta-blockers are the mainstay in managing LQTS. Studies comparing the efficacy of commonly used beta-blockers are lacking, and clinicians generally assume they are equally effective.

**Methods** Electrocardiographic and clinical parameters of 382 LQT1/LQT2 patients initiated on propranolol (n = 134), metoprolol (n = 147), and nadolol (n = 101) were analyzed, excluding patients <1 year of age at beta-blocker initiation. Symptoms before therapy and the first breakthrough cardiac events (BCEs) were documented.

**Results** Patients (56% female, 27% symptomatic, heart rate 76 ± 16 beats/min, QTc 472 ± 46 ms) were started on beta-blocker therapy at a median age of 14 years (interquartile range: 8 to 32 years). The QTc shortening with propranolol was significantly greater than with other beta-blockers in the total cohort and in the subset with QTc >480 ms. None of the asymptomatic patients had BCEs. Among symptomatic patients (n = 101), 15 had BCEs (all synapses). The QTc shortening was significantly less pronounced among patients with BCEs. There was a greater risk of BCEs for symptomatic patients initiated on metoprolol compared to users of the other 2 beta-blockers combined, after adjustment for genotype (odds ratio: 3.95, 95% confidence interval: 1.2 to 13.1, p = 0.025). Kaplan–Meier analysis showed a significantly lower event-free survival for symptomatic patients receiving metoprolol compared to propranolol/nadolol.

**Conclusions** Propranolol has a significantly better QTc shortening effect compared to metoprolol and nadolol, especially in patients with prolonged QTc. Propranolol and
nadolol are equally effective, whereas symptomatic patients started on metoprolol are at a significantly higher risk for BCEs. Metoprolol should not be used for symptomatic LQT1 and LQT2 patients (11).

**Nonsustained Ventricular Tachycardia**

Nonsustained ventricular tachycardia (NSVT) has been recorded in a wide range of conditions, from apparently healthy individuals to patients with significant heart disease. In the absence of heart disease, the prognostic significance of NSVT is debatable. When detected during exercise, and especially at recovery, NSVT indicates increased cardiovascular mortality within the next decades. In trained athletes, NSVT is considered benign when suppressed by exercise. In patients with non-ST-segment elevation acute coronary syndrome, NSVT occurring beyond 48 h after admission indicates an increased risk of cardiac and sudden death, especially when associated with myocardial ischemia. In acute myocardial infarction, in-hospital NSVT has an adverse prognostic significance when detected beyond the first 13 to 24 h. In patients with prior myocardial infarction treated with reperfusion and beta-blockers, NSVT is not an independent predictor of long-term mortality when other covariates such as left ventricular ejection fraction are taken into account. In patients with hypertrophic cardiomyopathy, and most probably genetic channelopathies, NSVT carries prognostic significance, whereas its independent prognostic ability in ischemic heart failure and dilated cardiomyopathy has not been established. The management of patients with NSVT in those with left bundle branch conduction disturbance is debatable.

**The Entirely Subcutaneous Implantable Cardioverter-Defibrillator: Initial Clinical Experience in a Large Dutch Cohort**

**Objectives** The purpose of the study was to evaluate the efficacy and safety of the entirely subcutaneous implantable cardioverter-defibrillator (S-ICD).

**Background** A new entirely S-ICD has been introduced, that does not require lead placement in or on the heart. The authors report the largest multicenter experience to date with the S-ICD with a minimum of 1-year follow-up in the first 118 Dutch patients who were implanted with this device.

**Methods** Patients were selected if they had a class I or IIa indication for primary or secondary prevention of sudden cardiac death. All consecutive patients from 4 high-volume centers in the Netherlands with an S-ICD implanted between December 2008 and April 2011 were included.

**Results** A total of 118 patients (75% males, mean age 50 years) received the S-ICD. After 18 months of follow-up, 8 patients experienced 45 successful appropriate shocks (98% first shock conversion efficacy). No sudden deaths occurred. Fifteen patients (13%) received inappropriate shocks, mainly due to T-wave oversensing, which was mostly solved by a software upgrade and changing the sensing vector of the S-ICD. Sixteen patients (14%) experienced complications. Adverse events were more frequent in the first 15 implantations per center compared with subsequent implantations (inappropriate shocks 19% vs. 6.7%, p = 0.03; complications 17% vs. 10%, p = 0.10).

**Conclusions** This study demonstrates that the S-ICD is effective in terminating ventricular arrhythmias. There is, however, a considerable percentage of ICD related adverse events, which decreases as the therapy evolves and experience increases (13).

**Cardiac Resynchronization and Quality of Life in Patients With Minimally Symptomatic Heart Failure**

**Objectives** This study compared the quality of life (QOL) of patients with cardiac resynchronization therapy (CRT) and an implantable cardioverter-defibrillator (ICD) to patients with an ICD only.

**Background** CRT with ICD is associated with a reduction in heart failure risk among minimally symptomatic patients. It is unknown whether this improves QOL.

**Methods** This study uses the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) data. The MADIT-CRT enrolled 1,820 patients at 110 centers across 14 countries. Patients had ischemic cardiomyopathy (New York Heart Association [NYHA] functional class I or II) or non-ischemic cardiomyopathy (NYHA functional class II only), sinus rhythm, an ejection fraction of 30% or less, and prolonged intraventricular conduction with a QRS duration of 130 ms or more. QOL was evaluated on the 1,699 patients with baseline and follow-up measures using the Kansas City Cardiomyopathy Questionnaire (KCCQ). Six dimensions (Physical Limitation, Symptom Stability, Symptom Burden, Quality of Life, and Social Limitations) and 3 summary scores (Total Symptom, Clinical Summary, and Overall Summary) were analyzed.

**Results** During an average follow-up of 2.4 years, the CRT-ICD group had greater improvement than the ICD-only group on all KCCQ measures (p < 0.05 on each scale). These differences were significant among patients with left bundle branch block conduction disturbance (n = 1,204, p < 0.01 on each scale), but not among patients without left bundle branch block (n = 494).

**Conclusions** Compared with patients with ICD only, CRT-ICD is associated with greater improvement in QOL among relatively asymptomatic patients, specifically among those with left bundle branch conduction disturbance (14).

**Catheter Ablation of Long-Standing Persistent Atrial Fibrillation: 5-Year Outcomes of the Hamburg Sequential Ablation Strategy**

**Objectives** This study describes the 5-year efficacy of catheter ablation for long-standing persistent atrial fibrillation (LS-AF).
Background Long-term outcome data after catheter ablation for LS-AF are limited.

Methods Long-term follow-up of 56 months (range 49 to 67 months) was performed in 202 patients (age 61 ± 9 years) who underwent the sequential ablation strategy for symptomatic LS-AF. Initial ablation strategy was circumferential pulmonary vein isolation (PVI). Additional ablation was performed only in acute PVI nonresponder, if direct current cardioversion failed after PVI.

Results After the first ablation procedure, sinus rhythm was documented in 41 of 202 (20.3%) patients. After multiple procedures, sinus rhythm was maintained in 91 of 202 (45.0%) patients, including 24 patients receiving antiarrhythmic drugs. In 105 patients, PVI was the sole ablative therapy, 49 (46.7%) of those patients remained in sinus rhythm during follow-up. Patients with a total AF duration of <2 years had a significantly higher ablation success rate than patients whose AF duration was >2 years (76.5% vs. 42.2%, respectively; p = 0.033). Persistent AF duration (hazard ratio: 1.09 [95% confidence interval: 1.04 to 1.13]; p < 0.001) independently predicted arrhythmia recurrences, and acute PVI responders had a reduced risk of relapse (hazard ratio: 0.57 [95% confidence interval: 0.41 to 0.78]; p < 0.001) after the first ablation.

Conclusions During 5-year follow-up, single- and multiple ablation procedure success was 20% and 45%, respectively, for patients with LS-AF. For patients with a total AF duration of <2 years, the outcomes were favorable (15).

Elevated Pre-Operative Serum Peptides for Collagen I and III Synthesis Result in Post-Surgical Atrial Fibrillation

Objectives This study sought to determine if serum markers for collagen I and III synthesis, the carboxyl terminal peptide from pro-collagen I (PICP) and the amino terminal peptide from pro-collagen III (PIIINP), correlate with left atrial (LA) fibrosis and post-operative atrial fibrillation (AF).

Background AF after cardiac surgery is associated with adverse outcomes. We recently demonstrated that LA fibrosis is associated with post-operative AF in patients with no previous history of AF.

Methods Fifty-four patients having cardiac surgery without a history of AF consented to left and right atrial biopsies and a pre-operative peripheral blood draw. Picosirius red staining quantified the percentage of fibrosis, and reverse transcriptase polymerase chain reaction assessed atrial tissue messenger ribonucleic acid transcripts involved in the fibrosis pathway. PICP and PIIINP levels were measured using an enzyme immunsorbent assay.

Results Eighteen patients developed AF, whereas 36 remained in normal sinus rhythm. LA fibrosis was higher in patients who developed AF versus normal sinus rhythm (6.13 ± 2.9% vs. 2.03 ± 1.9%, p = 0.03). LA messenger ribonucleic acid transcripts for collagen I, III, transforming growth factor, and angiotensin were 1.5- to 2.0-fold higher in AF patients. Serum PICP and PIIINP levels were highest in AF versus normal sinus rhythm (PICP: 451.7 ± 200 ng/ml vs. 293.3 ± 114 ng/ml, p = 0.006; PIIINP: 379 ± 286 pg/ml vs. 191.6 ± 162 pg/ml, p = 0.01). Furthermore, there was a linear correlation between LA fibrosis and serum PICP levels (R2 = 0.2; p = 0.01), and of the markers, only PICP was independently associated with AF.

Conclusions This demonstrates that serum PICP and PIIINP levels correlate with the presence of LA fibrosis and may act as predictors for post-operative AF even in the absence of previous history of AF (16).

Effect of Cardiac Resynchronization Therapy on the Risk of First and Recurrent Ventricular Tachyarrhythmic Events in MADIT-CRT

Objectives This study aimed to evaluate the effect of cardiac resynchronization therapy with a defibrillator (CRT-D) on the risks of first and recurrent ventricular tachyarrhythmic events (VTEs) in the MADIT-CRT.

Background Reverse remodeling associated with CRT-D therapy was suggested to reduce arrhythmic risk. However, the effect of the device on the risk of recurrent VTEs among patients who experience a first arrhythmic event has not been investigated.

Methods The CRT-D versus defibrillator-only risks for first and subsequent fast VTEs (>180 beats/min) were assessed by Cox proportional hazards and Andersen-Gill proportional intensity regression modeling, respectively, in efficacy analyses recognizing active device-type during follow-up.

Results Multivariate analysis showed that CRT-D was associated with a significant 29% (p = 0.003) reduction in the risk of a first VTE, with a pronounced effect among patients with left bundle branch block (LBBB) (hazard ratio [HR]: 0.58; p < 0.001) and no significant effect among non-LBBB patients (HR: 1.05; p = 0.82, p for the difference = 0.02). Patients with LBBB who experienced a first VTE had no change in the risk of subsequent VTEs with CRT-D (HR: 0.98; p = 0.85). In contrast, the risk of recurrent VTEs with CRT-D was significantly increased among non-LBBB patients (HR: 3.62; p = 0.002, p for the difference = 0.009). Recurrent VTEs increased the risk of subsequent heart failure or death.

Conclusions In MADIT-CRT, active treatment with CRT-D was associated with a significant reduction in the risk of life-threatening VTEs. However, our findings suggest that CRT-D does not reduce the risk of subsequent VTEs in patients who experience a first arrhythmic event and may increase subsequent arrhythmic risk in non-LBBB patients. (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271)(17).
Colchicine for Prevention of Early Atrial Fibrillation Recurrence After Pulmonary Vein Isolation: A Randomized Controlled Study

Objectives The purpose of the present study was to test the potential of colchicine, an agent with potent anti-inflammatory action, to reduce atrial fibrillation (AF) recurrence after pulmonary vein isolation in patients with paroxysmal AF.

Background Proinflammatory processes induced by AF ablation therapy have been implicated in postablation arrhythmia recurrence.

Methods Patients with paroxysmal AF who received radiofrequency ablation treatment were randomized to a 3-month course of colchicine 0.5 mg twice daily or placebo. C-reactive protein (CRP) and interleukin (IL)-6 levels were measured on day 1 and on day 4 of treatment.

Results In the 3-month follow-up, recurrence of AF was observed in 27 (33.5%) of 80 patients of the placebo group versus 13 (16%) of 81 patients who received colchicine (odds ratio: 0.38, 95% confidence interval: 0.18 to 0.80). Gastrointestinal side-effects were the most common symptom among patients receiving active treatment. Diarrhea was reported in 7 patients in the colchicine group (8.6%) versus 1 patient in the placebo group (1.3%, p = 0.03). Colchicine led to higher reductions in CRP and IL-6 levels: the median difference of CRP and IL-6 levels between days 4 and 1 was −0.46 mg/l (interquartile range: −0.78 to 0.08 mg/l) and −0.10 mg/l (−0.30 to 0.10 pg/ml), respectively, in the placebo group versus −1.18 mg/l (−2.35 to −0.46 mg/l) and −0.50 pg/ml (−1.15 to −0.10 pg/ml) in the colchicine group (p < 0.01 for both comparisons).

Conclusions Colchicine is an effective and safe treatment for prevention of early AF recurrences after pulmonary vein isolation in the absence of antiarrhythmic drug treatment. This effect seems to be associated strongly with a significant decrease in inflammatory mediators, including IL-6 and CRP (18).

Predictive Factors and Long-Term Clinical Consequences of Persistent Left Bundle Branch Block Following Transcatheter Aortic Valve Implantation With a Balloon-Expandable Valve

Objectives This study evaluated the predictive factors and prognostic value of new-onset persistent left bundle branch block (LBBB) in patients undergoing transcatheter aortic valve implantation (TAVI) with a balloon-expandable valve.

Background The predictors of persistent (vs. transient or absent) LBBB after TAVI with a balloon-expandable valve and its clinical consequences are unknown.

Methods A total of 202 consecutive patients with no baseline ventricular conduction disturbances or previous permanent pacemaker implantation (PPI) who underwent TAVI with a balloon-expandable valve were included. Patients were on continuous electrocardiographic (ECG) monitoring during hospitalization and 12-lead ECG was performed daily until hospital discharge. No patient was lost at a median follow-up of 12 (range: 6 to 24) months, and ECG tracing was available in 97% of patients. The criteria for PPI were limited to the occurrence of high-degree atrioventricular block (AVB) or severe symptomatic bradycardia.

Results New-onset LBBB was observed in 61 patients (30.2%) after TAVI, and had resolved in 37.7% and 57.3% at hospital discharge and 6- to 12-month follow-up, respectively. Baseline QRS duration (p = 0.037) and ventricular depth of the prosthesis (p = 0.017) were independent predictors of persistent LBBB. Persistent LBBB at hospital discharge was associated with a decrease in left ventricular ejection fraction (p = 0.001) and poorer functional status (p = 0.034) at 1-year follow-up. Patients with persistent LBBB and no PPI at hospital discharge had a higher incidence of syncope (16.0% vs. 0.7%; p = 0.001) and complete AVB requiring PPI (20.0% vs. 0.7%; p < 0.001), but not of global mortality or cardiac mortality during the follow-up period (all, p > 0.20). New-onset LBBB was the only factor associated with PPI following TAVI (p < 0.001).

Conclusions Up to 30% of patients with no prior conduction disturbances developed new LBBB following TAVI with a balloon-expandable valve, although it was transient in more than one third. Longer baseline QRS duration and a more ventricular positioning of the prosthesis were associated with a higher rate of persistent LBBB, which in turn determined higher risks for complete AVB and PPI, but not mortality, at 1-year follow-up (19).

Antiarrhythmic Potential of Mesenchymal Stem Cell Is Modulated by Hypoxic Environment

Objectives The purpose of this study was to evaluate the antiarrhythmic potential of mesenchymal stem cells (MSC) under a different environment.

Background Little is known about how environmental status affects antiarrhythmic potential of MSCs.

Methods To investigate the effect of paracrine factors secreted from MSCs under different circumstances on arrhythmogenicity in rats with myocardial infarction, we injected paracrine media (PM) secreted under hypoxic, normoxic conditions (hypoxic PM and normoxic PM), and MSC into the border zone of infarcted myocardium in rats.

Results We found that the injection of hypoxic PM, but not normoxic PM, markedly restored conduction velocities, suppressed focal activity, and prevented sudden arrhythmic deaths in rats. Underlying this electrophysiological alteration was a decrease in fibrosis, restoration of connexin 43, alleviation of Ca2+ overload, and recovery of Ca2+-regulatory ion channels and proteins, all of which is supported by proteomic data showing that several paracrine factors including basic fibroblast growth factor, insulinlike growth factor 1, hepatocyte growth factor, and EF-hand domain-containing 2 are potential mediators. When compared with PM, MSC injection did not reduce or prevent arrhythmogenicity, suggesting that the antiarrhythmic
Objectives The aim of this study was to determine whether nonischemic cardiomyopathy (NIM) affects the type and properties of the growth factors or cytokines, and these secreted molecules determine the characteristics of the electro-anatomical substrate of the surrounding myocardium.

Conclusions A hypoxic or normoxic environment surrounding MSC affects the type and properties of the paracrine factors.

Left Ventricular Midwall Fibrosis as a Predictor of Mortality and Morbidity After Cardiac Resynchronization Therapy in Patients With Nonischemic Cardiomyopathy

Objectives The aim of this study was to determine whether left ventricular (LV) midwall fibrosis, detected by midwall hyperenhancement (MWHE) on late gadolinium enhancement cardiac magnetic resonance (CMR) imaging, predicts mortality and morbidity in patients with dilated cardiomyopathy (DCM) undergoing cardiac resynchronization therapy (CRT).

Background Midwall fibrosis predicts mortality and morbidity in patients with DCM.

Methods Patients with DCM with (+) or without (−) MWHE (n = 20 and n = 77, respectively) as well as 161 patients with ischemic cardiomyopathy (ICM) undergoing CRT (n = 258) were followed up for a maximum of 8.7 years.

Results Among patients with DCM, +MWHE predicted cardiovascular mortality (hazard ratio [HR]: 18.6; 95% confidence intervals [CI]: 3.51 to 98.5; p = 0.0008), total mortality or hospitalization for major adverse cardiovascular events (HR: 7.57; 95% CI: 2.71 to 21.2; p < 0.0001), and cardiovascular mortality or heart failure hospitalizations (HR: 9.56; 95% CI: 2.72 to 33.6; p = 0.0004), independent of New York Heart Association class, QRS duration, atrial fibrillation, LV volumes, LV ejection fraction, and a CMR-derived measure of dyssynchrony. Among patients with DCM and ICM, the risk of cardiovascular mortality for DCM +MWHE (adjusted HR: 18.5; 95% CI: 3.93 to 87.3; p = 0.0002) was similar to that for ICM (adjusted HR: 21.0; 95% CI: 5.06 to 87.2; p < 0.0001). Both DCM +MWHE and ICM were predictors of pump failure death as well as sudden cardiac death. LV reverse remodeling was observed in DCM +MWHE and in ICM but not in DCM +MWHE.

Conclusions Midwall fibrosis is an independent predictor of mortality and morbidity in patients with DCM undergoing CRT. The outcome of DCM with midwall fibrosis is similar to that of ICM. This relationship is mediated by both pump failure and sudden cardiac death.

Prediction of Mortality in Clinical Practice for Medicare Patients Undergoing Defibrillator Implantation for Primary Prevention of Sudden Cardiac Death

Objectives The aim of this study was to derive and validate a practical risk model to predict death within 4 years of primary prevention implantable cardioverter-defibrillator (ICD) implantation.

Background ICDs for the primary prevention of sudden cardiac death improve survival, but recent data suggest that a patient subset with high mortality and minimal ICD benefit may be identified.

Methods Data from a development cohort (n = 17,991) and validation cohort (n = 27,893) of Medicare beneficiaries receiving primary prevention ICDs from 2005 to 2007 were merged with outcomes data through mid-2010 to construct and validate complete and abbreviated risk models for all-cause mortality using Cox proportional hazards regression.

Results Over a median follow-up period of 4 years, 6,741 (37.5%) development and 8,595 (30.8%) validation cohort patients died. The abbreviated model was based on 7 clinically relevant predictors of mortality identified from complete model results, referred to as the “SHOCKED” predictors: 75 years of age or older (hazard ratio [HR]: 1.70; 95% confidence interval [CI]: 1.62 to 1.79), heart failure (New York Heart Association functional class III) (HR: 1.35; 95% CI: 1.29 to 1.42), out of rhythm because of atrial fibrillation (HR: 1.26; 95% CI: 1.19 to 1.33), chronic obstructive pulmonary disease (HR: 1.70; 95% CI: 1.61 to 1.80), kidney disease (chronic) (HR: 2.33; 95% CI: 2.20 to 2.47), ejection fraction (left ventricular) ≤ 20% (HR: 1.26; 95% CI: 1.20 to 1.33), and diabetes mellitus (HR: 1.43; 95% CI: 1.36 to 1.50). This model had C-statistics of 0.75 (95% CI: 0.75 to 0.76) and 0.74 (95% CI: 0.74 to 0.75) in the development and validation cohorts, respectively. Validation patients in the highest risk decile on the basis of the SHOCKED predictors had a 65% 3-year mortality rate. A nomogram is provided for survival probabilities 1 to 4 years after ICD implantation.

Conclusions This useful model, based on more than 45,000 primary prevention ICD patients, accurately identifies patients at highest risk for death after device implantation and may significantly influence clinical decision making.

Radiofrequency Ablation of Premature Ventricular Ectopy Improves the Efficacy of Cardiac Resynchronization Therapy in Nonresponders

Objectives This study sought to examine whether suppressing premature ventricular contractions (PVC) using radiofrequency ablation improves effectiveness of the cardiac resynchronization therapy (CRT) in nonresponders.

Background CRT is an effective strategy for drug refractory congestive heart failure. However, one-third of patients with CRT do not respond clinically, and the causes for nonresponse are poorly understood. Whether frequent PVC contribute to CRT nonresponse remains unknown.

Methods In this multicenter study, CRT nonresponders with >10,000 PVC in 24 h who underwent PVC ablation were enrolled from a prospective database.

Results Sixty-five subjects (age 66.6 ± 12.4 years, 78% men, QRS duration of 155 ± 18 ms) had radiofrequency ablation...
of PVC from 76 foci. Acute and long-term success rates of ablation were 91% and 88% in 12 ± 4 months of follow-up. There was significant improvement in left ventricular (LV) ejection fraction (26.2 ± 5.5% to 32.7 ± 6.7%, p < 0.001), LV end-systolic diameter (5.93 ± 0.55 cm to 5.62 ± 0.32 cm, p < 0.001), LV end-diastolic diameter (6.83 ± 0.83 cm to 6.51 ± 0.91 cm, p < 0.001), LV end-systolic volume (178 ± 72 to 145 ± 23 ml, p < 0.001), LV end-diastolic volume (242 ± 85 ml to 212 ± 63 ml, p < 0.001), and median New York Heart Association functional class (3.0 to 2.0, p < 0.001). Modeling of pre-ablation PVC burden revealed an improvement in ejection fraction when the pre-ablation PVC burden was >22% in 24 h.

Conclusions Frequent PVC is an uncommon yet significant cause of CRT nonresponse. Radiofrequency ablation of PVC foci improves LV function and New York Heart Association class and promotes reverse remodeling in CRT nonresponders. PVC ablation may be used to enhance CRT efficacy in nonresponders with significant PVC burden (23).

R222Q SCN5A Mutation Is Associated With Reversible Ventricular Ectopy and Dilated Cardiomyopathy

Objectives The goal of this study was to characterize a variant in the SCN5A gene that encodes the alpha-subunit of the cardiac sodium channel, Nav1.5, which was identified in 1 large kindred with dilated cardiomyopathy (DCM) and multiple arrhythmias, including premature ventricular complexes (PVCs).

Background Treatment guidelines for familial DCM are based on conventional heart failure therapies, and no gene-based interventions have been established.

Methods Family members underwent clinical evaluation and screening of the SCN5A and LMNA genes. Cellular electrophysiology and computational modeling were used to determine the functional consequences of the mutant Nav1.5 protein.

Results An R222Q missense variant located in a Nav1.5 voltage-sensing domain was identified in affected family members. Patch-clamp studies showed that R222Q_Nav1.5 did not alter sodium channel current density, but did left shift steady-state parameters of activation and inactivation. Using a voltage ramp protocol, normalized current responses of R222Q channels were of earlier onset and greater magnitude than wild-type channels. Action potential modeling using Purkinje fiber and ventricular cell models suggested that rate-dependent ectopy of Purkinje fiber origin is the predominant ventricular effect of the R222Q variant and a potential cause of DCM. In R222Q carriers, there were only modest responses to heart failure therapies, but PVCs and DCM were substantially reduced by amiodarone or flecainide, which are drugs that have sodium channel-blocking properties.

Conclusions The R222Q SCN5A variant has an activating effect on sodium channel function and is associated with reversible ventricular ectopy and DCM. Elucidation of the genetic basis of familial DCM can enable effective gene-targeted therapy to be implemented (24).


Objectives This study sought to define contemporary trends in permanent pacemaker use by analyzing a large national database.

Background The Medicare National Coverage Determination for permanent pacemaker, which emphasized single-chamber pacing, has not changed significantly since 1985. We sought to define contemporary trends in permanent pacemaker use by analyzing a large national database.

Methods We queried the Nationwide Inpatient Sample to identify permanent pacemaker implants between 1993 and 2009 using the International Classification of Diseases-Ninth Revision-Clinical Modification procedure codes for dual-chamber (DDD), single-ventricular (VVI), single-atrial (AAI), or biventricular (BiV) devices. Annual permanent pacemaker implantation rates and patient demographics were analyzed.

Results Between 1993 and 2009, 2.9 million patients received permanent pacemakers in the United States. Overall use increased by 55.6%. By 2009, DDD use increased from 62% to 82% (p < 0.001), whereas single-chamber ventricular pacemaker use fell from 36% to 14% (p = 0.01). Use of DDD devices was higher in urban, nonteaching hospitals (79%) compared with urban teaching hospitals (76%) and rural hospitals (72%). Patients with private insurance (83%) more commonly received DDD devices than Medicaid (79%) or Medicare (75%) recipients (p < 0.001). Patient age and Charlson comorbidity index increased over time. Hospital charges (82011) increased 45.3%, driven by the increased cost of DDD devices.

Conclusions There is a steady growth in the use of permanent pacemakers in the United States. Although DDD device use is increasing, whereas single-chamber ventricular pacemaker use is decreasing. Patients are becoming older and have more medical comorbidities. These trends have important health care policy implications (25).

Type 2 Diabetes Mellitus and Risk of Incident Atrial Fibrillation in Women

Objectives The purpose of this study was to assess whether changes of major atrial fibrillation (AF) risk factors and/or intercurrent cardiovascular events could explain the relationship between type 2 diabetes mellitus (T2D) and incident AF.

Background Previous studies found an increased risk of incident AF among individuals with T2D, but few, if any, of these studies took into account changes of AF risk factors over time.
Methods A total of 34,720 female health professionals who participated in the Women’s Health Study, and who were free of cardiovascular disease and AF at baseline were followed for a median of 16.4 years. Cox proportional-hazards models were constructed to assess the relationship between T2D and incident AF, using either information at baseline or time-varying covariates for both T2D and potential confounders.

Results At baseline, 937 (2.7 %) women had T2D. Compared with women without T2D, women with T2D had an age-adjusted hazard ratio (HR) for new-onset AF of 1.95 (95% confidence interval [CI]: 1.49 to 2.56; p < 0.0001). In multivariable analyses adjusting for baseline confounders, this HR was substantially attenuated, but baseline T2D remained a significant predictor of incident AF (HR: 1.37, 95% CI: 1.03 to 1.83; p = 0.03). In time-updated models that adjusted for changes in AF risk factors and intercurrent cardiovascular events, the HR for T2D was attenuated further and became nonsignificant (HR: 1.14; 95% CI: 0.93 to 1.40; p = 0.20).

Conclusions Although this study confirms a significant relationship between baseline T2D and incident AF, our data suggest that the increased risk associated with T2D is mainly mediated by changes of other AF risk factors (26).

Clinical Efficacy of Iprabradine in Patients With Inappropriate Sinus Tachycardia: A Prospective, Randomized, Placebo-Controlled, Double-Blind, Crossover Evaluation

Objectives The purpose of this study was to investigate the role of iprabradine in the treatment of symptomatic inappropriate sinus tachycardia using a double-blind, placebo-controlled, crossover design.

Background Due to its If blocking properties, iprabradine can selectively attenuate the high discharge rate from sinus node cells, causing inappropriate sinus tachycardia.

Methods Twenty-one patients were randomized to receive placebo (n = 10) or iprabradine 5 mg twice daily (n = 11) for 6 weeks. After a washout period, patients crossed over for an additional 6 weeks. Each patient underwent symptom evaluation and heart rate assessment at the start and finish of each phase.

Results After taking iprabradine, patients reported elimination of >70% of symptoms (relative risk: 0.25; 95% CI: 0.18 to 0.34; p < 0.001), with 47% of them experiencing complete elimination. These effects were associated with a significant reduction of heart rate at rest (from 88 ± 11 beats/min to 76 ± 11 beats/min, p = 0.011), on standing (from 108 ± 12 beats/min to 92 ± 11 beats/min, p < 0.0001), during 24 h (from 88 ± 5 beats/min to 77 ± 9 beats/min, p = 0.001), and during effort (from 176 ± 17 beats/min to 158 ± 16 beats/min, p = 0.001). Iprabradine administration was also associated with a significant increase in exercise performance. No cardiovascular side effects were observed in any patients while taking iprabradine.

Conclusions In this cohort, iprabradine significantly improved symptoms associated with inappropriate sinus tachycardia and completely eliminated them in approximately half of the patients. These findings suggest that iprabradine may be an important agent for improving symptoms in patients with inappropriate sinus tachycardia (27).

Spectrum and Prevalence of Mutations Involving BrS1–Through BrS12-Susceptibility Genes in a Cohort of Unrelated Patients Referred for Brugada Syndrome Genetic Testing: Implications for Genetic Testing

Objectives The aim of this study was to provide the spectrum and prevalence of mutations in the 12 Brugada syndrome (BrS)–susceptibility genes discovered to date in a single large cohort of unrelated BrS patients.

Background BrS is a potentially lethal heritable arrhythmia syndrome diagnosed electrocardiographically by coved-type ST-segment elevation in the right precordial leads (V1 to V3; type 1 Brugada electrocardiographic [ECG] pattern) and the presence of a personal/family history of cardiac events.

Methods Using polymerase chain reaction, denaturing high-performance liquid chromatography, and DNA sequencing, comprehensive mutational analysis of BrS1–through BrS12-susceptibility genes was performed in 129 unrelated patients with possible/probable BrS (46 with clinically diagnosed BrS [ECG pattern plus personal/family history of a cardiac event] and 83 with a type 1 BrS ECG pattern only).

Results Overall, 27 patients (21%) had a putative pathogenic mutation, absent in 1,400 Caucasian reference alleles, including 21 patients with an SCN5A mutation, 2 with a CACNB2B mutation, and 1 each with a KCNJ8 mutation, a KCND3 mutation, an SCN1Bb mutation, and an HCN4 mutation. The overall mutation yield was 23% in the type 1 BrS ECG pattern–only patients versus 17% in the clinically diagnosed BrS patients and was significantly greater among young men <20 years of age with clinically diagnosed BrS and among patients who had a prolonged PQ interval.

Conclusions We identified putative pathogenic mutations in ~20% of our BrS cohort, with BrS genes 2 through 12 accounting for <5%. Importantly, the yield was similar between patients with only a type 1 BrS ECG pattern and those with clinically established BrS. The yield approaches 40% for SCN5A-mediated BrS (BrS1) when the PQ interval exceeds 200 ms. Calcium channel–mediated BrS is extremely unlikely in the absence of a short QT interval (28).

The Limit of Plausibility for Predictors of Response: Application to Biventricular Pacing

Objectives We sought a method for any reader to quantify the limit, imposed by variability, to sustainably observable
R2 between any baseline predictor and response marker. We then apply this to echocardiographic measurements of mechanical dyssynchrony and response.

**Background** Can mechanical dyssynchrony markers strongly predict ventricular remodeling by biventricular pacing (cardiac resynchronization therapy)?

**Methods** First, we established the mathematical depression of observable R2 arising from: 1) spontaneous variability of response markers; and 2) test–retest variability of dyssynchrony measurements. Second, we contrasted published R2 values between externally monitored randomized controlled trials and highly skilled single-center studies (HSSCSs).

**Results** Inherent variability of response markers causes a contraction factor in R2 of 0.48 (change in left ventricular ejection fraction [ΔLVEF]), 0.50 (change in end-systolic volume [ΔESV]), and 0.40 (change in end-diastolic volume [ΔEDV]). Simultaneously, inherent variability of mechanical dyssynchrony markers causes a contraction factor of between 0.16 and 0.92 (average, 0.6). Therefore the combined contraction factor, that is, limit on sustainably observable R2 between mechanical dyssynchrony markers and response, is ~0.29 (ΔLVEF), ~0.24 (ΔESV), and ~0.30 (ΔEDV). Many R2 values published in HSSCSs exceeded these mathematical limits; none in externally monitored trials did so. Overall, HSSCSs overestimate R2 by 5- to 20-fold (p = 0.002). Absence of bias-resistance features in study design (formal enrollment and blinded measurements) was associated with more overstatement of R2.

**Conclusions** Reports of R2 > 0.2 in response prediction arose exclusively from studies without formally documented enrollment and blinding. The HSSCS approach overestimates R2 values, frequently breaching the mathematical ceiling on sustainably observable R2, which is far below 1.0, and can easily be calculated by readers using formulas presented here. Community awareness of this low ceiling may help resist future claims. Reliable individualized response prediction, using methods originally designed for group-mean effects, may never be possible because it has 2 currently unavailable and perhaps impossible prerequisites: 1) excellent blinded test–retest reproducibility of dyssynchrony; and 2) response markers reproducible over time within nonintervened individuals. Dispersion evaluation, and improvement, of test–retest reproducibility is required before any further claims of strong prediction. Prediction studies should be designed to resist bias (29).

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**A Randomized Comparison of Pulmonary Vein Isolation With Versus Without Concomitant Renal Artery Denervation in Patients With Refractory Symptomatic Atrial Fibrillation and Resistant Hypertension**

**Objectives** The aim of this prospective randomized study was to assess the impact of renal artery denervation in patients with a history of refractory atrial fibrillation (AF) and drug-resistant hypertension who were referred for pulmonary vein isolation (PVI).

**Background** Hypertension is the most common cardiovascular condition responsible for the development and maintenance of AF. Treating drug-resistant hypertension with renal denervation has been reported to control blood pressure, but any effect on AF is unknown.

**Methods** Patients with a history of symptomatic paroxysmal or persistent AF refractory to ≥2 antiarrhythmic drugs and drug-resistant hypertension (systolic blood pressure >160 mm Hg despite triple drug therapy) were eligible for enrolment. Consenting patients were randomized to PVI only or PVI with renal artery denervation. All patients were followed ≥1 year to assess maintenance of sinus rhythm and to monitor changes in blood pressure.

**Results** Twenty-seven patients were enrolled, and 14 were randomized to PVI only, and 13 were randomized to PVI.
with renal artery denervation. At the end of the follow-up, significant reductions in systolic (from 181 ± 7 to 156 ± 5, p < 0.001) and diastolic blood pressure (from 97 ± 6 to 87 ± 4, p < 0.001) were observed in patients treated with PVI with renal denervation without significant change in the PVI only group. Nine of the 13 patients (69%) treated with PVI with renal denervation were AF-free at the 12-month post-ablation follow-up examination versus 4 (29%) of the 14 patients in the PVI-only group (p = 0.033).

Conclusions Renal artery denervation reduces systolic and diastolic blood pressure in patients with drug-resistant hypertension and reduces AF recurrences when combined with PVI. (Combined Treatment of Resistant Hypertension and Atrial Fibrillation; NCT01117025) (31).

**Connexin43 Gene Transfer Reduces Ventricular Tachycardia Susceptibility After Myocardial Infarction**

**Objectives** The aim of this study was to evaluate the links between connexin43 (Cx43) expression, myocardial conduction velocity, and ventricular tachycardia in a model of healed myocardial infarction.

**Background** Post-infarction ventricular arrhythmias frequently cause sudden death. Impaired myocardial conduction has previously been linked to ventricular arrhythmias. Altered connexin expression is a potential source of conduction slowing identified in healed scar border tissues. The functional effect of increasing border-zone Cx43 has not been previously evaluated.

**Methods** Twenty-five Yorkshire pigs underwent anterior infarction by transient left anterior descending coronary artery occlusion, followed by weekly testing for arrhythmia inducibility. Twenty animals with reproducibly inducible monomorphic ventricular tachycardia were randomized 2:1:1 to receive AdCx43, AdC3gal, or no gene transfer. One week later, animals underwent follow-up electrophysiologic study and tissue assessment for several functional and molecular measures.

**Results** Animals receiving AdCx43 had less electrogram fractionation and faster conduction velocity in the anterior-septal border zone. Only 40% of AdCx43 animals remained inducible for ventricular tachycardia, while 100% of controls were inducible after gene transfer. AdCx43 animals had 2-fold higher Cx43 protein levels in the anterior-septal infarct border, with similar percents of phosphorylated and intercalated disk-localized Cx43 compared with controls.

**Conclusions** These data mechanistically link Cx43 expression to slow conduction and arrhythmia susceptibility in the healed scar border zone. Targeted manipulation of Cx43 levels improved conduction velocity and reduced ventricular tachycardia susceptibility. Cx43 gene transfer represents a novel treatment strategy for post-infarction arrhythmias (32).

**Clinical Evaluation of Defibrillation Testing in an Unselected Population of 2,120 Consecutive Patients Undergoing First Implantable Cardioverter-Defibrillator Implant**

**Objectives** The purpose of this study is to assess the effectiveness of defibrillation testing (DT) in patients undergoing implantable cardioverter-defibrillator (ICD) insertion.

**Background** Although DT is considered a standard procedure during ICD implantation, its usefulness has not been definitively proven.

**Methods** The SAFE-ICD (Safety of Two Strategies of ICD Management at Implantation) study is a prospective observational study designed to evaluate the outcome of 2 strategies: performing defibrillation testing (DT+) versus not performing defibrillation testing (DT−) during de novo ICD implants. No deviation from the centers’ current practice was introduced. In all, 2,120 consecutive patients (836 DT+ and 1,284 DT−) age ≥18 years were enrolled at 41 Italian centers from April 2008 to May 2009 and followed up for 24 months until June 2011. The primary endpoint was a composite of severe complications at ICD implant and sudden cardiac death or resuscitation at 2 years.

**Results** The primary endpoint occurred in 34 patients: 12 intraoperative complications (8 in DT+ group; 4 in DT− group) and 22 during follow-up (10 in DT+ group; 12 in DT− group). Overall, the estimated yearly incidence (95% confidence interval) was DT+ 1.15% (0.73 to 1.83) and DT− 0.68% (0.42 to 1.12). The difference between the 2 groups was negligible: 0.47% per year (−0.15 to 1.10). Mortality from any cause was similar at 2 years (adjusted hazard ratio: 0.97 [0.76 to 1.23], p = 0.80).

**Conclusions** In this large cohort of new ICD implants, event rates were similar and extremely low in both groups. These data indicate a limited clinical relevance for DT testing, thus supporting a strategy of omitting DT during an ICD implant. (Safety of Two Strategies of ICD Management at Implantation [SAFE-ICD]; NCT00661037) (33).

**Modeling of Catecholaminergic Polymorphic Ventricular Tachycardia With Patient-Specific Human-Induced Pluripotent Stem Cells**

**Objectives** The goal of this study was to establish a patient-specific human-induced pluripotent stem cells (hiPSCs) model of catecholaminergic polymorphic ventricular tachycardia (CPVT).

**Background** CPVT is a familial arrhythmogenic syndrome characterized by abnormal calcium (Ca2+) handling, ventricular arrhythmias, and sudden cardiac death.

**Methods** Dermal fibroblasts were obtained from a CPVT patient due to the M4109R heterozygous point RYR2 mutation and reprogrammed to generate the CPVT-hiPSCs. The patient-specific hiPSCs were coaxed to differentiate into the cardiac lineage and compared with healthy control hiPSCs-derived cardiomyocytes (hiPSCs-CMs).
Results Intracellular electrophysiological recordings demonstrated the development of delayed afterdepolarizations in 69% of the CPVT-hiPSCs-CMs compared with 11% in healthy control cardiomyocytes. Adrenergic stimulation by isoproterenol (1 μM) or forskolin (5 μM) increased the frequency and magnitude of afterdepolarizations and also led to development of triggered activity in the CPVT-hiPSCs-CMs. In contrast, flecainide (10 μM) and thapsigargin (10 μM) eliminated all afterdepolarizations in these cells. The latter finding suggests an important role for internal Ca2+ stores in the pathogenesis of delayed afterdepolarizations. Laser-confocal Ca2+ imaging revealed significant whole-cell [Ca2+] transient irregularities (frequent local and large-storage Ca2+–release events, broad and double-humped transients, and triggered activity) in the CPVT cardiomyocytes that worsened with adrenergic stimulation and Ca2+ overload and improved with beta-blockers. Store-overload–induced Ca2+ release was also identified in the hiPSCs-CMs and the threshold for such events was significantly reduced in the CPVT cells.

Conclusions This study highlights the potential of hiPSCs for studying inherited arrhythmogenic syndromes, in general, and CPVT specifically. As such, it represents a promising paradigm to study disease mechanisms, optimize patient care, and aid in the development of new therapies (34).

Familial Aggregation of Lone Atrial Fibrillation in Young Persons

Objectives This study investigated whether an individual’s risk of developing lone atrial fibrillation (AF) before age 60 years is associated with lone AF in relatives.

Background Genetic factors may play a role in the development of lone AF.

Methods Using Danish national registers, a cohort was established of ~4 million persons born between 1950 and 2008, and those with a family history of lone AF (AF without preceding cardiovascular/endocrine diagnoses) were identified. Individuals were followed up until the first diagnosis of lone AF. Poisson regression was used to estimate incidence rate ratios (IRRs).

Results In ~92 million person-years of follow-up, 9,507 persons were identified as having lone AF. The IRRs for lone AF given an affected first- or second-degree relative were 3.48 (95% confidence interval [CI]: 3.08 to 3.93) and 1.64 (95% CI: 1.04 to 2.59), respectively. IRRs were higher for men than for women but were not associated with the affected relative’s sex. IRR for lone AF was 6.24 (95% CI: 2.59 to 15.0), given at least 2 first-degree relatives affected with lone AF. The IRR for lone AF in persons aged <40 years given a first-degree relative affected at age <40 years was 5.42 (95% CI: 3.80 to 7.72), and 8.53 (95% CI: 3.82 to 19.0) in persons age <30 years given a first-degree relative affected at age <30 years.

Conclusions A family history of lone AF is associated with substantial risk of lone AF, with the strongest risks associated with young age at onset, multiple affected relatives, and in first-degree relatives. These results suggest routine evaluation of the families of at least certain types of patients with lone AF (35).

Clinical Implications of an Implantable Cardioverter-Defibrillator in Patients With Vasospastic Angina and Lethal Ventricular Arrhythmia

Objectives The present study was performed to investigate the clinical implications of an implantable cardioverter-defibrillator (ICD) in patients with vasospastic angina (VSA) resuscitated from lethal ventricular arrhythmia.

Background The prognosis of VSA is known to be good with medication; however, ventricular arrhythmia and cardiopulmonary arrest are rare but life-threatening complications of this disease. The ICD is a proven modality for patients with ventricular arrhythmia, but the clinical implications in this population remain to be elucidated.

Methods We conducted a retrospective, observational, multicenter study involving patients with an ICD due to documented ventricular arrhythmia and VSA diagnosed by acetylcholine provocation test. All patients were followed up for appropriate ICD therapy, sudden cardiac arrest, or death from all causes.

Results Twenty-three patients were included in the present study and completely followed up. All patients are still alive. During a follow-up of 2.9 years (median 2.1 years), 4 ventricular fibrillations and 1 episode of pulseless electrical activity occurred in 5 patients (21.7%). There were no statistically significant differences in patient characteristics between the recurrence and nonrecurrence groups, including medication, smoking status, and whether the patient was or was not free of symptoms after ICD implantation.

Conclusions Patients with VSA and lethal ventricular arrhythmia are a population at high risk for recurrence of cardiopulmonary arrest, and there is no reliable indicator for predicting recurrence of ventricular arrhythmia. Insertion of an ICD with medication for VSA is appropriate for this high-risk population (36).

Performance of the HEMORRH2HAGES, ATRIA, and HAS-BLED Bleeding Risk–Prediction Scores in Patients With Atrial Fibrillation Undergoing Anticoagulation: The AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) Study

Objectives The objective of this study was to compare the predictive performance of bleeding risk–estimation tools in a cohort of patients with atrial fibrillation (AF) undergoing anticoagulation.
Background Three bleeding risk–prediction schemes have been derived for and validated in patients with AF: HEMORR2HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re–Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke), ATRIA (Anti-coagulation and Risk Factors in Atrial Fibrillation), and HAS–BLEED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol). The relative predictive values of these bleeding scores have not previously been compared.

Methods We analyzed the dataset from the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) trial, a multicenter, randomized, open-label noninferiority study that compared fixed-dose idraparinux with adjustable-dose oral vitamin K antagonist therapy in patients with AF. The principal safety outcome was any clinically relevant bleeding event, which was a composite of major bleeding plus clinically relevant nonmajor bleeding.

Results The HAS–BLEED score performed best in predicting any clinically relevant bleeding, reflected both in net reclassification improvement (10.3% and 13% improvement compared with HEMORR2HAGES and ATRIA, respectively) and receiver–operating characteristic (ROC) analyses (c-indexes: 0.60 vs. 0.55 and 0.50 for HAS–BLEED vs. HEMORR2HAGES and ATRIA, respectively). Using decision-curve analysis, the HAS–BLEED score demonstrated superior performance compared with ATRIA and HEMORR2HAGES at any threshold probability for clinically relevant bleeding. HAS–BLEED was the only score that demonstrated a significant predictive performance for intracranial hemorrhage (c-index: 0.75; p = 0.03). An ATRIA score >3 was not significantly associated with the risk for any clinically relevant bleeding on Cox regression or on ROC analysis (c-index: 0.50; p = 0.87).

Conclusions All 3 tested bleeding risk–prediction scores demonstrated only modest performance in predicting any clinically relevant bleeding, although the HAS–BLEED score performed better than the HEMORR2HAGES and ATRIA scores, as reflected by ROC analysis, reclassification analysis, and decision-curve analysis. Only HAS–BLEED demonstrated a significant predictive performance for intracranial hemorrhage. Given its simplicity, the HAS–BLEED score may be an attractive method for the estimation of oral anticoagulant–related bleeding risk for use in clinical practice, supporting recommendations in international guidelines (37).

Family History of Premature Death and Risk of Early Onset Cardiovascular Disease

Objectives The purpose of this study was to examine the effect of a family history of premature death, cardiovascular death in particular, on the risk of early cardiovascular disease.

Background Studies suggest that fatal cardiovascular events and less severe cardiovascular diseases may co-occur in families. Consequently, a family history of premature death may indicate a familial cardiac frailty that predisposes to early cardiovascular disease.

Methods We ascertained family history of premature death (age <60 years) in all individuals born in Denmark from 1950 to 2008 and followed this cohort for early cardiovascular disease (age <50 years). Using Poisson regression, we estimated incidence rate ratios (IRRs) reflecting the effect of premature death in the family on early cardiovascular disease risk.

Results Among 3,985,301 persons followed up for 89,294,258 person-years, 129,825, 31,172, and 5,214 were diagnosed with any early cardiovascular disease, ischemic heart disease, and ventricular arrhythmia, respectively. IRRs for these conditions given a history of premature cardiovascular death in first-degree relatives were 1.72 (95% confidence interval [CI]: 1.68 to 1.77), 2.21 (95% CI: 2.11 to 2.31), and 1.94 (95% CI: 1.70 to 2.20), respectively. With 
≥2 cardiovascular deaths in a family, corresponding IRRs were 3.30 (95% CI: 2.77 to 3.94), 5.00 (95% CI: 3.87 to 6.45), and 6.18 (95% CI: 3.32 to 11.50). The IRR for any early cardiovascular disease given a family history of premature noncardiovascular death was significantly lower, 1.12 (95% CI: 1.10 to 1.14) (p cardiac vs. noncardiac < 0.0001).

Conclusions Family history of premature cardiovascular death was consistently and significantly associated with a risk of early cardiovascular disease, suggesting an inherited cardiac vulnerability. These results should be kept in mind when assessing cardiovascular disease risk in persons with a family history of premature cardiovascular death (38).

Common Variation in the NOS1AP Gene Is Associated With Drug-Induced QT Prolongation and Ventricular Arrhythmia

Objectives This study sought to determine whether variations in NOS1AP affect drug-induced long QT syndrome (LQTS).

Background Use of antiarrhythmic drugs is limited by the high incidence of serious adverse events including QT prolongation and torsades de pointes. NOS1AP gene variants play a role in modulating QT intervals in healthy subjects and severity of presentation in LQTS.

Methods This study carried out an association study using 167 single nucleotide polymorphisms (SNP) spanning the NOS1AP gene in 58 Caucasian patients experiencing drug-induced LQTS (dLQTS) and 87 Caucasian controls from the DARE (Drug-Induced Arrhythmia Risk Evaluation) study.

Results The rs10800397 SNP was significantly associated with dLQTS (odds ratio [OR]: 3.3, 99.95% confidence interval [CI]: 1.0 to 10.8, p = 3.7 × 10^{-4}). The associations were more pronounced in the subgroup of amiodarone users, in which 3 SNPs, including rs10800397, were significantly
associated (most significant SNP: rs10919035: OR: 5.5, 99.95% CI: 1.1 to 27.9, p = 3.0 × 10⁻⁴). We genotyped rs10919035 in an independent replication cohort of 28 amiodarone dLQTS cases versus 173 control subjects (meta-analysis of both studies: OR: 2.81, 99.95% CI: 1.62 to 4.89, p = 2.4 × 10⁻⁴). Analysis of corrected QT interval among 74 control subjects from our dataset showed a similar pattern of significance over the gene region as the case-control analysis. This pattern was confirmed in 1,480 control subjects from the BRIGHT (British Genetics of Hypertension Study) cohort (top SNP from DARE: rs12734991 in meta-analysis: increase in corrected QT interval per C allele: 9.1 ± 3.2 ms, p = 1.7 × 10⁻⁴).

**Conclusions** These results provide the first demonstration that common variations in the NOS1AP gene are associated with a significant increase in the risk of dLQTS. This study suggests that common variations in the NOS1AP gene may have relevance for future pharmacogenomic applications in clinical practice permitting safer prescription of drugs for vulnerable patients (39).

**Electrophysiological and Hemodynamic Characteristics Associated With Obesity in Patients With Atrial Fibrillation**

**Objectives** The authors sought to characterize the left atrial (LA) and pulmonary vein (PV) electrophysiological and hemodynamic features in obese patients with atrial fibrillation (AF).

**Background** Obesity is associated with increased risk for AF.

**Methods** A total of 63 consecutive patients with AF who had normal left ventricular (LV) ejection fraction and who underwent catheter ablation were studied. Atrial and PV electrophysiological studies were performed at the time of ablation with hemodynamic assessment by cardiac catheterization, and LA/LV structure and function by echocardiography. Patients were compared on the basis of body mass index (BMI): <25 kg/m² (n = 19) and BMI ≥30 kg/m² (n = 44).

**Results** At a 600-ms pacing cycle length, obese patients had shorter effective refractory period (ERP) in the left atrium (251 ± 25 ms vs. 233 ± 32 ms, p = 0.04), and in the proximal (207 ± 33 ms vs. 248 ± 34 ms, p < 0.001) and distal (193 ± 33 ms vs. 248 ± 44 ms, p < 0.001) PV than normal BMI patients. Obese patients had higher mean LA pressure (15 ± 5 mm Hg vs. 10 ± 5 mm Hg, p < 0.001) and LA volume index (28 ± 12 ml/m² vs. 21 ± 14 ml/m², p = 0.006), and lower LA strain (5.5 ± 3.1% vs. 8.8 ± 2.8%; p < 0.001) than normal BMI patients.

**Conclusions** Increased LA pressure and volume, and shortened ERP in the left atrium and PV are potential factors facilitating and perpetuating AF in obese patients with AF (40).

**Reduction in Life-Threatening Ventricular Tachyarrhythmias in Statin-Treated Patients With Nonischemic Cardiomyopathy Enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy)**

**Objectives** This study hypothesized that time-dependent statin therapy will reduce the risk of life-threatening ventricular tachyarrhythmias among patients with non-ischemic cardiomyopathy (NICM) enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy).

**Background** Prior studies suggested that statin therapy exerts antiarrhythmic properties among patients with coronary artery disease. However, data regarding the effect of statins on arrhythmic risk among patients with NICM are limited.

**Methods** Multivariate Cox proportional hazards regression modeling was used to assess the effect of statin therapy, evaluated as a time-dependent covariate, on the risk of appropriate defibrillator therapy for fast ventricular tachycardia (VT) (defined as a rate faster than 180 beats/min) or ventricular fibrillation (VF) or death (primary endpoint) and appropriate defibrillator shocks (secondary endpoint) among 821 patients with NICM enrolled in the MADIT-CRT trial.

**Results** Statin users (n = 499) were older and had a higher prevalence of diabetes and hypertension yet were less frequently smokers. Multivariate analysis showed that time-dependent statin therapy was independently associated with a significant 77% reduction in the risk of fast VT/VF or death (p < 0.001) and with a significant 46% reduction in the risk of appropriate implantable cardioverter defibrillator shocks (p = 0.01). Consistent with these findings, the cumulative probability of fast VT/VF or death at 4 years of follow-up was significantly lower among patients who were treated with statins (11%) as compared with study patients who were not treated with statins (19%; p = 0.006 for the overall difference during follow-up).

**Conclusions** Statin use was associated with a significant reduction in the risk of life-threatening ventricular tachyarrhythmias among patients with NICM (41).

**Indirect Comparisons of New Oral Anticoagulant Drugs for Efficacy and Safety When Used for Stroke Prevention in Atrial Fibrillation**

**Objectives** This study sought to perform an indirect comparison analysis of dabigatran etexilate (2 doses), rivaroxaban, and apixaban for their relative efficacy and safety against each other.

**Background** Data for warfarin compared against the new oral anticoagulants (OACs) in large phase III clinical trials of stroke prevention in atrial fibrillation (AF) are now available for the oral direct thrombin inhibitor, dabigatran etexilate, in 2 doses (150 mg twice daily [BID], 110 mg
BID), and the oral Factor Xa inhibitors, rivaroxaban and apixaban. A “head-to-head” direct comparison of drugs is the standard method for comparing different treatments, but in the absence of such head-to-head direct comparisons, another alternative to assess the relative effect of different treatment interventions would be to perform indirect comparisons, using a common comparator. Nonetheless, any inter-trial comparison is always fraught with major difficulties, and an indirect comparison analysis has many limitations, especially with the inter-trial population differences and thus, should not be overinterpreted.

Methods Indirect comparison analysis was performed using data from the published trials.

Results There was a significantly lower risk of stroke and systemic embolism (by 26%) for dabigatran (150 mg BID) compared with rivaroxaban, as well as hemorrhagic stroke and nondisabling stroke. There were no significant differences for apixaban versus dabigatran (both doses) or rivaroxaban; or rivaroxaban versus dabigatran 110 mg BID in preventing stroke and systemic embolism. For ischemic stroke, there were no significant differences between the new OACs. Major bleeding was significantly lower with apixaban compared with dabigatran 150 mg BID (by 26%) and rivaroxaban (by 34%), but not significantly different from dabigatran 110 mg BID. There were no significant differences between apixaban and dabigatran 110 mg BID in safety endpoints. Apixaban also had lower major or clinically relevant bleeding (by 34%) compared with rivaroxaban. When compared with rivaroxaban, dabigatran 110 mg BID was associated with less major bleeding (by 23%) and intracranial bleeding (by 54%). There were no significant differences in myocardial infarction events between the dabigatran (both doses) and apixaban.

Conclusions Notwithstanding the limitations of an indirect comparison study, we found no profound significant differences in efficacy between apixaban and dabigatran etexilate (both doses) or rivaroxaban. Dabigatran 150 mg BID was superior to rivaroxaban for some efficacy endpoints, whereas major bleeding was significantly lower with dabigatran 110 mg BID or apixaban. Only a head-to-head direct comparison of the different new OACs would fully answer the question of efficacy/safety differences between the new drugs for stroke prevention in AF (42).

Treatment of Atrial Fibrillation by the Ablation of Localized Sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) Trial

Objectives The goal of this study was to examine the relative impact of QRS morphology and duration in echocardiographic responses to cardiac resynchronization therapy (CRT) and clinical outcomes. These results offer a novel mechanistic framework and treatment paradigm for AF. (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation [CONFIRM]; NCT01008722) (43).

Differential Response to Cardiac Resynchronization Therapy and Clinical Outcomes According to QRS Morphology and QRS Duration

Objectives The goal of this study was to examine the relative impact of QRS morphology and duration in echocardiographic responses to cardiac resynchronization therapy (CRT) and clinical outcomes. These results offer a novel mechanistic framework and treatment paradigm for AF. (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation [CONFIRM]; NCT01008722) (43).
had LBBB and QRSd <150 ms, 92 (18.5%) had non-LBBB and a QRSd ≥150 ms, and 103 (20.8%) had non-LBBB and QRSd <150 ms. Echocardiographic response (change in ejection fraction) was better in patients with LBBB and QRSd ≥150 ms (12 ± 12%) than in those with LBBB and QRSd <150 ms (8 ± 10%), non-LBBB and QRSd ≥150 ms (5 ± 9%), and non-LBBB and QRSd <150 ms (3 ± 11%) (p < 0.0001). In a multivariate stepwise model with change in ejection fraction as the dependent variable, the presented classification was the most important independent variable (p = 0.051). Long-term survival was better in LBBB patients with QRSd ≥150 ms (p = 0.02), but this difference was not significant after adjustment for other baseline characteristics (p = 0.15).

Conclusions QRS morphology is a more important baseline electrocardiographic determinant of CRT response than QRSd (44).

**MR Cine DENSE Dyssynchrony Parameters for the Evaluation of Heart Failure: Comparison With Myocardial Tissue Tagging**

**Objectives** We sought to assess the effectiveness of automated mechanical dyssynchrony (MD) parameters based on regional heterogeneity of strain (circumferential [CURE], longitudinal [LURE], and radial uniformity ratio estimates) relative to parameters based on regional time to peak contraction with cardiac magnetic resonance (CMR) cine DENSE (Displacement Encoding with Stimulated Echoes) validated with myocardial tissue tagging (MTT) strain data.

**Background** Dyssynchrony measures based on the Fourier transformation (FT) of regional strain, such as CURE (previously evaluated in cardiac resynchronization therapy candidates), directly assess MD and yield straightforward global dyssynchrony indexes; however, performance relative to the 12-segment standard deviation of time to peak strain (SD12) or maximal regional delay in time to peak strain is unknown.

**Methods** Cine DENSE and MTT were obtained with CMR (1.5-T Siemens Avanto, Siemens, Erlangen, Germany) in 13 canines: 3 normal control subjects, 5 with bundle branch ablation (LBBB-HF), and 5 with HF and left atrial tachycardia pacing-induced heart failure (HF) and left bundle branch ablation (LBBB-HF), and 5 with HF and narrow QRS (NQRS-HF). Strain and dyssynchrony parameters were determined with both CMR methods.

**Results** Both HF groups had reduced peak strains and left ventricular ejection fraction compared with normal cases. There was strong agreement between cine DENSE and MTT on the basis of intraclass correlation coefficients (CURE: 0.99, 95% CI: 0.96 to 1.00; LURE: 0.92, 95% CI: 0.77 to 0.98; circumferential strain [ECC]: 0.95, 95% CI: 0.72 to 0.99; longitudinal strain [ELL]: 0.82, 95% CI: 0.42 to 0.97). The FT-based metrics (scale 0 to 1), in particular CURE, discriminated highly between LBBB-HF and NQRS-HF groups (median difference): CURE: 0.60, 95% CI: 0.43 to 0.76; LURE: 0.39, 95% CI: 0.19 to 0.58; radial uniformity ratio estimate: 0.22, 95% CI: 0.04 to 0.40). In contrast, relative confidence intervals for group differences in time-to-peak parameters were wide, indicating less consistent discrimination (median difference): SD12-ECC: 52.5, 95% CI: −4.0 to 109.2; SD12-ELL: 40.9, 95% CI: −5.3 to 87.1; SD12-radial strain: 42.0, 95% CI: 0.4 to 83.6). Correlations between FT-based and time-to-peak parameters were significant (CURE/SD12-ECC: r = −0.62, p = 0.03; LURE/SD12-ELL: r = −0.76, p = 0.005) but not as tight as correlations between time-to-peak parameters.

**Conclusions** Automated FT-based circumferential, radial, and longitudinal dyssynchrony measures compare favorably with time-to-peak parameters. Cine DENSE was effective for this application and validated with MTT. Further clinical evaluation in cardiac resynchronization therapy candidates with CMR or other imaging modalities is warranted (45).

**Assessment of Myocardial Scarring Improves Risk Stratification in Patients Evaluated for Cardiac Defibrillator Implantation**

**Objectives** We tested whether an assessment of myocardial scarring by cardiac magnetic resonance imaging (MRI) would improve risk stratification in patients evaluated for implantable cardioverter-defibrillator (ICD) implantation.

**Background** Current sudden cardiac death risk stratification emphasizes left ventricular ejection fraction (LVEF); however, most patients suffering sudden cardiac death have a preserved LVEF, and many with poor LVEF do not benefit from ICD prophylaxis.

**Methods** One hundred thirty-seven patients undergoing evaluation for possible ICD placement were prospectively enrolled and underwent cardiac MRI assessment of LVEF and scar. The pre-specified primary endpoint was death or appropriate ICD discharge for sustained ventricular tachyarrhythmia.

**Results** During a median follow-up of 24 months the primary endpoint occurred in 39 patients. Whereas the rate of adverse events steadily increased with decreasing LVEF, a sharp step-up was observed for scar size >5% of left ventricular mass (hazard ratio [HR]: 5.2; 95% confidence interval [CI]: 2.0 to 13.3). On multivariable Cox proportional hazards analysis, including LVEF and electrophysiological-study results, scar size (as a continuous variable or dichotomized at 5%) was an independent predictor of adverse outcome. Among patients with LVEF >30%, those with significant scarring (>5%) had higher risk than those with minimal or no (<5%) scarring (HR: 6.3; 95% CI: 1.4 to 28.0). Those with LVEF >30% and significant scarring had risk similar to patients with LVEF ≤30% (p = 0.56). Among patients with LVEF ≤30%, those with significant scarring again had higher risk than those with minimal or no scarring (HR: 3.9; 95% CI: 1.2 to 13.1). Those with LVEF ≤30% and
minimal scarring had risk similar to patients with LVEF >30% (p = 0.71).

Conclusions  Myocardial scarring detected by cardiac MRI is an independent predictor of adverse outcome in patients being considered for ICD placement. In patients with LVEF >30%, significant scarring (>5% LV) identifies a high-risk cohort similar in risk to those with LVEF ≤30%. Conversely, in patients with LVEF ≤30%, minimal or no scarring identifies a low-risk cohort similar to those with LVEF >30% (46).

Modeling Serum Biomarkers S100 Beta and Neuron-Specific Enolase as Predictors of Outcome After Out-of-Hospital Cardiac Arrest: An Aid to Clinical Decision Making

Objectives  The aim of this study was to determine the added value of the serum biomarkers S100 and neuron-specific enolase to clinical characteristics for predicting outcome after out-of-hospital cardiac arrest.

Background  Serum S100 beta (S100B) and neuron-specific enolase concentrations rise after brain injury. Methods  A prospective observational study was conducted among all adult survivors of nontraumatic out-of-hospital cardiac arrest admitted to 1 hospital (April 3, 2008 to April 3, 2011). Three blood samples (on arrival and on days 1 and 3) were drawn for biomarkers, contingent on survival. Follow-up continued until in-hospital death or discharge. Outcomes were defined as good (Cerebral Performance Category score 1 or 2) or poor (Cerebral performance category score 3 to 5).

Results  A total of 195 patients were included (65.6% men, mean age 73 ± 16 years), with presenting rhythms of asystole in 61.5% and ventricular tachycardia or ventricular fibrillation in 24.1%. Only 43 patients (22.0%) survived to hospital discharge, 26 (13.3%) with good outcomes. Patients with good outcomes had significantly lower S100B levels at all time points and lower neuron-specific enolase levels on days 1 and 3 compared with those with poor outcomes. Independent predictors at admission of a good outcome were younger age, a presenting rhythm of ventricular tachycardia or ventricular fibrillation, and lower S100B level. Predictors on day 3 were younger age and lower day 3 S100B level. The area under the receiver-operating characteristic curve of the admission-day model was 0.932 with 0.880 without biomarker data (p = 0.027 for the difference).

Conclusions  Risk stratification after out-of-hospital cardiac arrest using both clinical and biomarker data is feasible. The biomarkers, although adding an ostensibly modest 5.2% to the area under the receiver-operating characteristic curve, substantially reduced the level of uncertainty in decision making. Nevertheless, current biomarkers cannot replace societal considerations in determining acceptable levels of uncertainty. (Protein S100 Beta as a Predictor of Resuscitation Outcome; NCT00814814) (47).

Midregional Pro-Adrenomedullin as a Predictor for Therapeutic Response to Midodrine Hydrochloride in Children With Postural Orthostatic Tachycardia Syndrome

Objectives  This study was designed to explore the predictive value of the midregional fragment of pro-adrenomedullin (MR-proADM) in assessing the therapeutic efficacy of midodrine hydrochloride for children with postural orthostatic tachycardia syndrome (POTS).

Background  Midodrine hydrochloride is an important therapeutic option for children with POTS. However, there has not been any method to predict response to the drug. The MR-proADM is produced in equimolar amounts to adrenomedullin (ADM), and directly reflects levels of the rapidly degraded active peptide, ADM.

Methods  Fifty-seven children with POTS were designated as the POTS group. Twenty healthy children served as the control group. The children in the POTS group received midodrine hydrochloride treatment. The plasma concentration of MR-proADM was measured, using a sandwich immunoluminometric assay. A receiver-operating characteristic curve was used to explore the predictive value of MR-proADM.

Results  Plasma levels of MR-proADM were significantly higher in children with POTS (75.0 [62.5 to 96.0] pg/ml) than in the control group (58.5 [50.3 to 69.0] pg/ml). Plasma levels of MR-proADM in responders to midodrine hydrochloride was significantly higher than that of nonresponders (76.0 [66.0 to 91.0] pg/ml vs. 59.0 [54.0 to 65.5] pg/ml, p < 0.01). A receiver-operating characteristic curve on the predictive value of MR-proADM showed that the area under the curve was 0.879 with a 95% confidence interval of 0.761 to 0.997. Using a cutoff value for MR-proADM of 61.5 pg/ml produced both high sensitivity (71.6%) in predicting the efficacy of midodrine hydrochloride therapy for treating POTS.

Conclusions  MR-proADM can help guide midodrine hydrochloride therapy in the management of POTS in children (48).

Clinical Application of Cardiovascular Pharmacogenetics

Pharmacogenetics primarily uses genetic variation to identify subgroups of patients who may respond differently to a certain medication. Since its first description, the field of pharmacogenetics has expanded to study a broad range of cardiovascular drugs and has become a mainstream research discipline. Three principle classes of pharmacogenetic markers have emerged: 1) pharmacokinetic; 2) pharmacodynamic; and 3) underlying disease mechanism. In the realm of cardiovascular pharmacogenetics, significant advances have identified markers in each class for a variety of therapeutics, some with a potential for improving patient outcomes. While ongoing clinical trials will determine if
routine use of pharmacogenetic testing may be beneficial, the data today support pharmacogenetic testing for certain variants on an individualized, case-by-case basis. Our primary goal is to review the association data for the major pharmacogenetic variants associated with commonly used cardiovascular medications: antiplatelet agents, warfarin, statins, beta-blockers, diuretics, and antiarrhythmic drugs. In addition, we highlight which variants and in which contexts pharmacogenetic testing can be implemented by practicing clinicians. The pace of genetic discovery has outstripped the generation of the evidence justifying its clinical adoption. Until the evidentiary gaps are filled, however, clinicians may choose to target therapeutics to individual patients whose genetic background indicates that they stand to benefit the most from pharmacogenetic testing (49).

Long-Term Prognosis Following Resuscitation From Out of Hospital Cardiac Arrest: Role of Percutaneous Coronary Intervention and Therapeutic Hypothermia

Objectives The aim of the study was to assess the influence of percutaneous coronary intervention (PCI) and therapeutic hypothermia (TH) on long-term prognosis.

Background Although hospital care consisting of TH and/or PCI in particular patients resuscitated following out-of-hospital cardiac arrest (OHCA) can improve survival to hospital discharge, there is little evidence regarding how these therapies may impact long-term prognosis.

Methods We performed a cohort investigation of all persons > 18 years of age who suffered nontraumatic OHCA and were resuscitated and discharged alive from the hospital between January 1, 2001, and December 31, 2009, in a metropolitan emergency medical service (EMS) system. We reviewed EMS and hospital records, state death certificates, and the national death index to determine clinical characteristics and vital status. Survival analyses were conducted using Kaplan–Meier estimates and multivariable Cox regression. Analyses of TH were restricted to those patients who were comatose at hospital admission.

Results Of the 5,958 persons who received EMS–attempted resuscitation, 1,001 (16.8%) were discharged alive from the hospital. PCI was performed in 384 of 1,001 (38.4%), whereas TH was performed in 241 of 941 (25.6%) persons comatose at hospital admission. Five-year survival was 78.7% among those treated with PCI compared with 54.4% among those not receiving PCI and 77.5% among those treated with TH compared with 60.4% among those not receiving TH (both p < 0.001). After adjustment for confounders, PCI was associated with a lower risk of death (hazard ratio [HR]: 0.46 [95% confidence interval [CI]: 0.34 to 0.61]; p < 0.001). Likewise, TH was associated with a lower risk of death (HR: 0.70 [95% CI: 0.50 to 0.97]; p = 0.04).

Conclusions The findings suggested that effects of acute hospital interventions for post-resuscitation treatment extend beyond hospital survival and can positively influence prognosis following the arrest hospitalization (50).

Hybrid Thoracoscopic Surgical and Transvenous Catheter Ablation of Atrial Fibrillation

Objectives The purpose of this study was to evaluate the feasibility, safety, and clinical outcomes up to 1 year in patients undergoing combined simultaneous thoracoscopic surgical and transvenous catheter atrial fibrillation (AF) ablation.

Background The combination of the transvenous endocardial approach with the thoracoscopic epicardial approach in a single AF ablation procedure overcomes the limitations of both techniques and should result in better outcomes.

Methods A cohort of 26 consecutive patients with AF who underwent hybrid thoracoscopic surgical and transvenous catheter ablation were followed, with follow-up of up to 1 year.

Results Twenty-six patients (42% with persistent AF) underwent successful hybrid procedures. There were no complications. The mean follow-up period was 470 ± 154 days. In 23% of the patients, the epicardial lesions were not transmural, and endocardial touch-up was necessary. One-year success, defined according to the Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society consensus statement for the catheter and surgical ablation of AF, was 93% for patients with paroxysmal AF and 90% for patients with persistent AF. Two patients underwent catheter ablation for recurrent AF or left atrial flutter after the hybrid procedure.

Conclusions A combined transvenous endocardial and thoracoscopic epicardial ablation procedure for AF is feasible and safe, with a single-procedure success rate of 83% at 1 year (51).

Medical Device Innovation: Prospective Solutions for an Ecosystem in Crisis: Adding a Professional Society Perspective

Barriers to medical device innovation compromise timelines and costs from bench to bedside. Fragmented strategies by individual competitors are no longer sustainable. Pragmatically focused pre-competitive collaboration across stakeholders approaches innovation as an ecosystem. Desiloing experience and expertise encourages high-impact infrastructure efficiencies unique to pre-competitive constructs. Alignment of processes and objectives across the regulatory, reimbursement, clinical research, and clinical practice enterprises, with particular attention to the total product life cycle and continuous accrual of safety information, promotes more predictable equipoise for speed of access relative to residual safety concerns. Professional societies are well positioned to convene pre-competitive dialogue, facilitate alignment, and add perspective to equipoise within the innovation ecosystem (52).
Cyclic Adenosine Monophosphate Phosphodiesterase Type 4 Protects Against Atrial Arrhythmias

Objectives This study was designed to examine whether a cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE), PDE4, is expressed in human atrium and contributes to the control of electrical stability.

Background Atrial fibrillation is accompanied by a profound remodeling of membrane receptors and alterations in cAMP-dependent regulation of Ca²⁺ handling. Being responsible for cAMP hydrolysis, PDE4s are likely to play a role in this setting. In the rodent heart, PDE4 contributes up to 60% of total cAMP-hydrolytic activity. However, its role in the human heart remains controversial.

Methods L-type Ca²⁺ current and spontaneous Ca²⁺ release were recorded in isolated human atrial myocytes. Intracellular cAMP was measured by live cell imaging using a fluorescence resonance energy transfer-based sensor. Contractile force and arrhythmias were recorded in human atrial trabeculae. PDE activity was measured in human atrial tissue from patients in sinus rhythm and permanent atrial fibrillation.

Results PDE4 is expressed in human atrial myocytes and accounts for approximately 15% of total PDE activity. PDE4D represents the major PDE4 subtype. PDE4 inhibition increased intracellular cAMP and L-type Ca²⁺ current and dramatically delayed their decay after a brief β-adrenergic stimulation. PDE4 inhibition also increased the frequency of spontaneous Ca²⁺ release at baseline, as well as the contractile response and the incidence of arrhythmias in human atrial strips during β-adrenergic stimulation. Total PDE activity decreased with age, and the relative PDE4 activity was lower in patients with permanent atrial fibrillation than in age-matched sinus rhythm controls.

Conclusions PDE4 is critical in controlling cAMP levels and thereby Ca²⁺ influx and release in human atrial muscle, hence limiting the susceptibility to arrhythmias (53).

Outcome of Cardiac Surgery in Patients 50 Years of Age or Older With Ebstein Anomaly: Survival and Functional Improvement

Objectives This study sought to analyze the presentation, surgical procedures, and outcomes in patients ≥50 years of age with Ebstein anomaly (EA).

Background Data on management and surgical outcomes in older patients with EA are limited.

Methods Operative and clinical data from patients with EA ≥50 years of age undergoing cardiac surgery at our center between October 1980 and January 2010 were analyzed.

Results During the study period, 89 procedures were performed in 81 patients with EA (63% women; mean [range] age 59 [50 to 79] years). Pre-operative symptoms included palpitations (n = 69), edema (n = 30), and previous stroke/transient ischemic attack (n = 21). Seventy-six patients (85%) had functional class III or IV symptoms, and 13 (16%) had previous cardiac surgery. Tricuspid valve surgery was necessary in 87 of the 89 procedures (98%): replacement in 65 (73%) and repair in 22 (25%). Three early deaths occurred (4%). On long-term follow-up (available in 73 of 78 early survivors), 63 patients (89%) had improved functional class and 13 patients died (19%). The 20-year survival was 65% versus 74% for age- and sex-matched controls (p = 0.001). The best predictors of late death were lack of post-operative improvement and older age at surgery.

Conclusions Although cardiac surgery in patients with EA ≥50 years of age was often complex, early mortality was low (4%) when surgery was performed at an experienced center. Long-term survival was good, although less than expected. These data suggested that surgery in older patients with EA may have to be performed earlier (55).
Optimal Treatment of Patients Surviving Out-of-Hospital Cardiac Arrest

Interest in post-resuscitation care has risen with the development of treatment modalities that can affect long-term survival rates even when begun after the systematic ischemia/reperfusion insult associated with cardiac arrest. Mild therapeutic hypothermia has become the foundation for improvement of neurologically favorable survival after cardiac arrest. Reperfusion therapy, specifically early percutaneous coronary intervention, is becoming an important adjunct to therapeutic hypothermia. Identifying which post-cardiac arrest patient had an occluded or unstable coronary vessel is difficult because such events are not reliably predicted by precedent symptoms or standard electrocardiographic analysis. Increasing clinical experience suggests that resuscitated cardiac arrest victims without an obvious noncardiac etiology should undergo emergency coronary angiography and, where indicated, percutaneous coronary intervention. If comatose, they should receive concurrent therapeutic hypothermia. Such an approach can double long-term survival rates among those successfully resuscitated after out-of-hospital cardiac arrest (56).

Dynamicity of the J-Wave in Idiopathic Ventricular Fibrillation With a Special Reference to Pause-Dependent Augmentation of the J-Wave

Objectives This study evaluated the pause-dependency of the J-wave to characterize this phenomenon in idiopathic ventricular fibrillation (VF).

Background The J-wave can be found in apparently healthy subjects and in patients at risk for sudden cardiac death, and risk stratification is therefore needed.

Methods Forty patients with J-wave–associated idiopathic VF were studied for J waves with special reference concerning pause-dependent augmentation. J waves were defined as those ≥0.1 mV above the isoelectric line and were compared with 76 non-VF patients of comparable age and sex.

Results The J-wave was larger in patients with idiopathic VF than in the controls: 0.360 ± 0.181 mV versus 0.192 ± 0.064 mV (p = 0.0011). J waves were augmented during storms of VF (n = 9 [22.5%]), which was controlled by isoproterenol; they disappeared within weeks in 5 patients. In addition, sudden prolongation of the R-R interval was observed in 27 patients induced by benign arrhythmia, and 15 patients (55.6%) demonstrated pause-dependent augmentation (from 0.391 ± 0.126 mV to 0.549 ± 0.220 mV; p < 0.0001). In the other 12 experimental subjects and in the 76 control subjects, J waves remained unchanged. Pause-dependent augmentation of J waves was detected in 55.6% (sensitivity) but was specific (100%) in the patients with idiopathic VF with high positive (100%) and negative (86.4%) predictive values.

Conclusions Pause-dependent augmentation of J waves was confirmed in about one-half of the patients with idiopathic VF after sudden R-R prolongation. Such dynamicity of J waves was specific to idiopathic VF and may be used for risk stratification (57).

Sudden Cardiac Death in Patients With Human Immunodeficiency Virus Infection

Objectives The aim of this study was to determine the incidence and clinical characteristics of sudden cardiac death (SCD) in patients with human immunodeficiency virus (HIV) infection.

Background As the HIV-infected population ages, cardiovascular disease prevalence and mortality are increasing, but the incidence and features of SCD have not yet been described.

Methods The records of 2,860 consecutive patients in a public HIV clinic in San Francisco between April 2000 and August 2009 were examined. Identification of deaths, causes of death, and clinical characteristics were obtained by search of the National Death Index and/or clinic records. SCDs were determined using published retrospective criteria: 1) the International Classification of Diseases-10th Revision, code for all cardiac causes of death; and (2) circumstances of death meeting World Health Organization criteria.

Results Of 230 deaths over a median of 3.7 years of follow-up, 30 (13%) met SCD criteria, 131 (57%) were due to acquired immune deficiency syndrome (AIDS), 25 (11%) were due to other (natural) diseases, and 44 (19%) were due to overdoses, suicides, or unknown causes. SCDs accounted for 86% of all cardiac deaths (30 of 35). The mean SCD rate was 2.6 per 1,000 person-years (95% confidence interval: 1.8 to 3.8), 4.5-fold higher than expected. SCDs occurred in older patients than did AIDS deaths (mean 49.0 vs. 44.9 years, p = 0.02). Compared with AIDS and natural deaths combined, SCDs had a higher prevalence of prior myocardial infarction (17% vs. 1%, p < 0.0005), cardiomyopathy (23% vs. 3%, p < 0.0005), heart failure (30% vs. 9%, p = 0.004), and arrhythmias (20% vs. 3%, p = 0.003).

Conclusions SCDs account for most cardiac and many non-AIDS natural deaths in HIV-infected patients. Further investigation is needed to ascertain underlying mechanisms, which may include inflammation, antiretroviral therapy interruption, and concomitant medications (58).

Ventricular Arrhythmias in the Absence of Structural Heart Disease

Ventricular arrhythmia (VA) in structurally normal hearts can be broadly considered under non–life-threatening monomorphic and life-threatening polymorphic rhythms. Monomorphic VA is classified on the basis of site of origin in the heart, and the most common areas are the ventricular outflow tracts and left ventricular fascicles. The morphology of the QRS complexes on electrocardiogram is an excellent tool to identify the site of origin of the rhythm. Although these arrhythmias are common and generally carry an
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Excellent prognosis, rare sudden death events have been reported. Very frequent ventricular ectopy may also result in a cardiomyopathy in a minority of patients. Suppression of VA may be achieved using calcium-channel blockers, beta-adrenergic blockers, and class I or III antiarrhythmic drugs. Radiofrequency ablation has emerged as an excellent option to eliminate these arrhythmias, although certain foci including aortic cusps and epicardium may be technically challenging. Polymorphic ventricular tachycardia (VT) is rare and generally occurs in patients with genetic ion channel disorders including long QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT, and short QT syndrome. Unlike monomorphic VT, these arrhythmic syndromes are associated with sudden death. While the cardiac gross morphology is normal, suggesting a structurally normal heart, abnormalities exist at the molecular level and predispose them to arrhythmias. Another fascinating area, idiopathic ventricular fibrillation and early repolarization syndrome, are undergoing research for a genetic basis (59).

New Concepts in the Assessment of Syncope

Significant progress has been made in the past 3 decades in our understanding of the various causes of loss of consciousness thanks to the publication of several important studies and guidelines. In particular, the recent European Society of Cardiology guidelines provide a reference standard for optimal quality service delivery. This paper gives the reader brief guidance on how to manage a patient with syncope, with reference to the above guidelines. Despite the progress made, the management of patients with syncope remains largely unsatisfactory because of the presence of a significant gap between knowledge and its application. Two new concepts aimed at filling that gap are currently under evaluation: syncope facilities with specialist backup and interactive decision-making software. Preliminary data have shown that a standardized syncope assessment, especially when coupled with interactive decision-making software, decreases admission rate and unnecessary testing and improves diagnostic yield, thus reducing cost per diagnosis. The long-term effects of such a new health care model on the rate of diagnosis and survival await future studies (60).

Eplerenone and Atrial Fibrillation in Mild Systolic Heart Failure: Results From the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) Study

Objectives The purpose of this study was to analyze the incidence of new atrial fibrillation or flutter (AFF) in the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) database.

Background Aldosterone antagonism in heart failure might influence atrial fibrosis and remodeling and, therefore, risk of developing AFF. The development of new AFF was a prespecified secondary endpoint in the EMPHASIS-HF study.

Methods Patients in New York Heart Association functional class II and with ejection fraction ≤35% were eligible for EMPHASIS-HF. History of AFF at baseline was reported by investigators using the study case report form. New onset AFF (in those with no history of AFF at baseline) was reported using a specific endpoint form; in a sensitivity analysis we also examined the effect of eplerenone on AFF reported as an adverse event.

Results New onset AFF was significantly reduced by eplerenone: 25 of 911 (2.7%) versus 40 of 883 (4.5%) in the placebo group (hazard ratio [HR]: 0.58, 95% confidence interval [CI]: 0.35 to 0.96; p = 0.034). The reduction in the primary endpoint with eplerenone was similar among patients with and without AFF at baseline (HR: 0.60, 95% CI: 0.46 to 0.79 vs. HR: 0.70, 95% CI: 0.57 to 0.85, respectively; p for interaction = 0.41). The risk of cardiovascular (CV) death or hospital admission for worsening heart failure, the primary endpoint, was not significantly different in subjects with and without AFF at baseline (both study groups combined: HR: 1.23, 95% CI: 0.81 to 1.86; p = 0.33).

Conclusions In patients with systolic heart failure and mild symptoms, eplerenone reduced the incidence of new onset AFF. The effects of eplerenone on the reduction of major CV events were similar in patients with and without AFF at baseline (61).

Factors Predicting and Having an Impact on the Need for a Permanent Pacemaker After CoreValve Prosthesis Implantation Using the New Accutrak Delivery Catheter System

Objectives The purpose of this study was to evaluate the need for a permanent pacemaker after transcatheter aortic valve implantation with the CoreValve prosthesis (Medtronic, Inc., Minneapolis, Minnesota) using the new Accutrak delivery system (Medtronic, Inc.).

Background The need for a permanent pacemaker is a recognized complication after transcatheter aortic valve implantation with the CoreValve prosthesis.

Methods Between April 23, 2008 and May 31, 2011, 195 consecutive patients with symptomatic aortic valve stenosis underwent transcatheter aortic valve implantation using the self-expanding CoreValve prosthesis. In 124 patients, the traditional delivery system was used, and in 71 patients, the Accutrak delivery system was used.

Results There were no significant differences in baseline electrocardiographic characteristics between the traditional system and the Accutrak patients: PR interval: 153 ± 46 mm versus 165 ± 30 mm, p = 0.12; left bundle branch block: 22 (20.2%) versus 8 (12.7%), p = 0.21; right bundle branch block: 21 (19.3%) versus 8 (12.7%), p = 0.26. The depth of the prosthesis in the left ventricular outflow tract was greater with the traditional system than with the Accutrak system (9.6 ± 3.2 mm vs. 6.4 ± 3 mm, p < 0.001) and the need for a permanent pacemaker was higher with traditional system
than with Accutrak (35.1% vs. 14.3%, p = 0.003). The predictors of the need for a pacemaker were the depth of the prosthesis in the left ventricular outflow tract (hazard ratio [HR]: 1.2, 95% confidence interval [CI]: 1.08 to 1.34, p < 0.001), pre-existing right bundle branch block (HR: 3.5, 95% CI: 1.68 to 7.29, p = 0.001), and use of the traditional system (HR: 27, 95% CI: 2.81 to 257, p = 0.004).

**Conclusions** The new Accutrak delivery system was associated with less deep prosthesis implantation in the left ventricular outflow tract, which could be related to the lower rate of permanent pacemaker requirement.

### Noninvasive Programmed Ventricular Stimulation Early After Ventricular Tachycardia Ablation to Predict Risk of Late Recurrence

**Objectives** The goal of this study was to evaluate the ability of noninvasive programmed stimulation (NIPS) after ventricular tachycardia (VT) ablation to identify patients at high risk of recurrence.

**Background** Optimal endpoints for VT ablation are not well defined.

**Methods** Of 200 consecutive patients with VT and structural heart disease undergoing ablation, 11 had clinical VT inducible at the end of ablation and 11 recurred spontaneously. Of the remaining 178 patients, 132 underwent NIPS through their implantable cardioverter-defibrillator 3.1 ± 2.1 days after ablation. At 2 drive cycle lengths, single, double, and triple right ventricular extrastimuli were delivered to refractoriness. Clinical VT was defined by comparison with 12-lead electrocardiograms and stored implantable cardioverter-defibrillator electrograms from spontaneous VT episodes. Patients were followed for 1 year.

**Results** Fifty-nine patients (44.7%) had no VT inducible at NIPS; 49 (37.1%) had inducible nonclinical VT only; and 24 (18.2%) had inducible clinical VT. Patients with inducible clinical VT at NIPS had markedly decreased 1-year VT-free survival compared to those in whom no VT was inducible (<30% vs. >80%; p = 0.001), including 33% recurring with VT storm. Patients with inducible nonclinical VT only, had intermediate 1-year VT-free survival (65%).

**Conclusions** When patients with VT and structural heart disease have no VT or nonclinical VT only inducible at the end of ablation or their condition is too unstable to undergo final programmed stimulation, NIPS should be considered in the following days to further define risk of recurrence. If clinical VT is inducible at NIPS, repeat ablation may be considered because recurrence over the following year is high.

### New Oral Anticoagulants in Atrial Fibrillation and Acute Coronary Syndromes: ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease Position Paper

Until recently, vitamin K antagonists were the only available oral anticoagulants, but with numerous limitations that prompted the introduction of new oral anticoagulants targeting the single coagulation enzymes thrombin (dabigatran) or factor Xa (apixaban, rivaroxaban, and edoxaban) and given in fixed doses without coagulation monitoring. Here we review the pharmacology and the results of clinical trials with these new agents in stroke prevention in atrial fibrillation and secondary prevention after acute coronary syndromes, providing perspectives on their future incorporation into clinical practice. In phase III trials in atrial fibrillation, compared with warfarin, dabigatran etexilate 150 mg B.I.D. reduced the rates of stroke/systemic embolism without any difference in major bleeding; dabigatran etexilate 110 mg B.I.D. had similar efficacy with decreased bleeding; apixaban 5 mg B.I.D. reduced stroke, systemic embolism, and mortality as well as major bleeding; and rivaroxaban 20 mg Q.D. was noninferior to warfarin for stroke and systemic embolism without a difference in major bleeding. All these agents reduced intracranial hemorrhage. Edoxaban is currently being evaluated in a further large phase III trial. Apixaban and rivaroxaban were evaluated in phase III trials for prevention of recurrent ischemia in patients with acute coronary syndromes who were mostly receiving dual antiplatelet therapy, with conflicting results on efficacy but consistent results for increased major bleeding. Overall, the new oral anticoagulants are poised to replace vitamin K antagonists for many patients with atrial fibrillation and may have a role after acute coronary syndromes. Although convenient to administer and manage, they present challenges that need to be addressed.

### Impact of Metabolic Syndrome on Procedural Outcomes in Patients With Atrial Fibrillation Undergoing Catheter Ablation

**Objectives** The aim of this study was to investigate impact of metabolic syndrome (MS) on outcomes of catheter ablation in patients with atrial fibrillation (AF) in terms of recurrence and quality of life (QoL).

**Background** MS, a proinflammatory state with hypertension, diabetes, dyslipidemia, and obesity, is presumed to be a close associate of AF.

**Methods** In this prospective study, 1,496 consecutive patients with AF undergoing first ablation (29% with paroxysmal AF, 26% with persistent AF, and 45% with long-standing persistent AF) were classified into those with MS (group 1; n = 485) and those without MS (group 2; n = 1,011). Patients were followed for recurrence and QoL. The Medical Outcomes Study SF-36 Health Survey was used to assess QoL at baseline and 12 month after ablation.

**Results** After 21 ± 7 months of follow-up, 189 patients in group 1 (39%) and 319 in group 2 (32%) had arrhythmia recurrence (p = 0.005). When stratified by AF type, patients with nonparoxysmal AF in group 1 failed more frequently compared with those in group 2.
(150 [46%] vs. 257 [35%], p = 0.002); no difference existed in the subgroup with paroxysmal AF (39 [25%] vs. 62 [22%], p = 0.295). Group 1 patients had significantly lower baseline scores on all SF-36 Health Survey subscales. At follow-up, both mental component summary (Δ5.7 ± 2.5, p < 0.001) and physical component summary (Δ9.1 ± 3.7, p < 0.001) scores improved in group 1, whereas only mental component summary scores (Δ4.6 ± 2.8, p = 0.036) were improved in group 2. In the subgroup with nonparoxysmal AF, MS, sex, C-reactive protein ≥0.9 mg/dl, and white blood cell count were independent predictors of recurrence.

Conclusions Baseline inflammatory markers and the presence of MS predicted higher recurrence after single-catheter ablation only in patients with nonparoxysmal AF. Additionally, significant improvements in QoL were observed in the post-ablation MS population (65).

Effects of Atrial Fibrillation on Treatment of Mitral Regurgitation in the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) Randomized Trial

Objectives The purpose of this study was to characterize patients with mitral regurgitation (MR) and atrial fibrillation (AF) treated percutaneously using the MitraClip device (Abbott Vascular, Abbott Park, Illinois) and compare the results with surgery in this population.

Background The EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) randomized controlled trial compared a less invasive catheter-based treatment for MR with surgery, providing an opportunity to assess the impact of AF on the outcomes of both the MitraClip procedure and surgical repair.

Methods The study population included 264 patients with moderately severe or severe MR assessed by an anatomic imaging modality. The purpose of this study was to characterize patients with mitral regurgitation (MR) and atrial fibrillation (AF) treated percutaneously using the MitraClip device (Abbott Vascular, Abbott Park, Illinois) and compare the results with surgery in this population.

Results Pre-existing AF was present in 27% of patients. These patients were older, had more advanced disease, and were more likely to have a functional etiology. Similar reduction of MR to ≤2+ before discharge was achieved in patients with AF (83%) and in patients without AF (75%, p = 0.3). Freedom from death, mitral valve surgery for valve dysfunction, and MR >2+ was similar at 12 months for AF patients (64%) and for no-AF patients (61%, p = 0.3). At 12 months, MR reduction to <2+ was greater with surgery than with MitraClip, but there was no interaction between rhythm and MR reduction, and no difference in all-cause mortality between patients with and patients without AF.

Conclusions Atrial fibrillation is associated with more advanced valvular disease and noncardiac comorbidities. However, acute procedural success, safety, and 1-year efficacy with MitraClip therapy is similar for patients with AF and without AF (66).

The Federal Audit of Implantable Cardioverter-Defibrillator Implants: Lessons Learned

The federal government has investigated a large number of institutions regarding concerns that implantable cardioverter-defibrillator procedures were performed in violation of the criteria set forth in a National Coverage Determination. We describe our experience and responses to such an audit, as well as the complexities and nuances of practicing evidence-based medicine in the setting of heavy regulatory oversight (67).

Risk Factors and Outcomes of Post-Procedure Heart Blocks After Transcatheter Device Septal Defect

Objectives The aim of this study was to analyze the risk factors and mid-term outcomes associated with post-procedure heart blocks (PPHBs) after transcatheter closure of perimembranous ventricular septal defect (pmVSD).

Background The development of heart blocks remains a major challenge for transcatheter closure of pmVSD.

Methods Transcatheter closure of pmVSD was carried out in 228 patients. Electrocardiography and 24-h Holter monitoring were performed before the procedure, within 1 week after the procedure, then 1, 3, 6, and 12 months, and every year thereafter.

Results Thirty-three patients (14.5%) who received transcatheter closure of pmVSD developed PPHBs. PPHBs included right bundle branch block (57.6%), left bundle branch block (24.2%), and atrioventricular block (18.2%). High-degree atioventricular blocks occurred in 4 patients and recovered to normal conduction after intravenous administration of hydrocortisone. PPHBs recovered to normal conduction in 21 patients by the time of hospital discharge. Compared with the patients without PPHBs, the patients suffering PPHBs were characterized by a significantly longer distance between the aortic valve and the defect (DAVD), a shorter distance from the lower rim of the defect to the septal leaflet of the tricuspid valve (DLRD-SLTV), and a larger diameter difference between the occluder and ventricular septal defect (DDOV). The earlier the PPHBs developed after the procedure, the more difficult the recovery to normal conduction.

Conclusions The outcome of PPHBs after transcatheter closure of pmVSD was satisfactory, as most patients recovered to normal conduction. Measurements of DLRD-SLTV, DAVD, and DDOV may be useful in predicting the incidence of PPHBs (68).
Feasibility and Safety of Dabigatran Versus Warfarin for Periprocedural Anticoagulation in Patients Undergoing Radiofrequency Ablation for Atrial Fibrillation: Results From a Multicenter Prospective Registry

Objectives The purpose of this study was to evaluate the feasibility and safety of periprocedural dabigatran during atrial fibrillation (AF) ablation.

Background AF ablation requires optimal periprocedural anticoagulation for minimizing bleeding and thromboembolic complications. The safety and efficacy of dabigatran as a periprocedural anticoagulant for AF ablation are unknown.

Methods We performed a multicenter, observational study from a prospective registry including all consecutive patients undergoing AF ablation in 8 high-volume centers in the United States. All patients receiving dabigatran therapy who underwent AF ablation on periprocedural dabigatran, with the dose held on the morning of the procedure, were matched by age, sex, and type of AF with an equal number of patients undergoing AF ablation with uninterrupted warfarin therapy over the same period.

Results A total of 290 patients, including 145 taking periprocedural dabigatran and an equal number of matched patients taking uninterrupted periprocedural warfarin, were included in the study. The mean age was 60 years with 79% being male and 57% having paroxysmal AF. Both groups had a similar CHADS2 score, left atrial size, and left ventricular ejection fraction. Three thromboembolic complications (2.1%) occurred in the dabigatran group compared with none in the warfarin group (p = 0.25). The dabigatran group had a significantly higher major bleeding rate (6% vs. 1%; p = 0.019), total bleeding rate (14% vs. 6%; p = 0.031), and composite of bleeding and thromboembolic complications (16% vs. 6%; p = 0.009) compared with the warfarin group. Dabigatran use was confirmed as an independent predictor of bleeding or thromboembolic complications (odds ratio: 2.76, 95% confidence interval: 1.22 to 6.25; p = 0.01) on multivariate regression analysis.

Conclusions In patients undergoing AF ablation, periprocedural dabigatran use significantly increases the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy (69).

Impact of QRS Duration and Morphology on the Risk of Sudden Cardiac Death in Asymptomatic Patients With Aortic Stenosis: The SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) Study

Objectives The aim of the study was to examine the predictive value of QRS duration and morphology during watchful waiting in asymptomatic patients with aortic stenosis (AS).

Background QRS duration and morphology are associated with poor prognosis in many different populations, but the predictive value, particularly of the risk of sudden cardiac death (SCD), in asymptomatic patients with AS has not been well studied.

Methods Data were obtained in asymptomatic AS patients randomized to simvastatin/ezetimibe combination versus placebo in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study. The impact of QRS duration, evaluated as a categorical variable of <85 ms versus 85 to 99 ms and ≥100 ms (excluding bundle branch block [BBB]) and QRS morphology in those with BBB, on cardiovascular morbidity and mortality was assessed by adjusting for clinical and echocardiographic covariates.

Results QRS data were available in 1,542 patients who were followed for a mean of 4.3 ± 0.8 years (6,631 patient-years of follow-up). There were 68 cardiovascular deaths (4.6%), including 27 SCDs (1.8%). QRS duration was <85 ms in 900 patients (58.4%), 85 to 99 ms in 396 (25.7%), ≥100 ms in those without BBB in 144 (9.3%), and 102 (6.6%) in those with BBB. In multivariable analyses, those with QRS duration ≥100 ms had, compared with those with QRS duration <85 ms, a 5-fold higher risk of SCD (95% confidence interval: 1.8 to 13.7, p = 0.002) and a 2.5-fold higher risk of cardiovascular death (95% confidence interval: 1.2 to 5.1, p = 0.01).

Conclusions QRS duration and morphology in asymptomatic patients with AS are independently associated with a poor prognosis, particularly the risk of SCD. (Simvastatin Ezetimibe in Aortic Stenosis [SEAS]; NCT00092677) (70).

Epistatic Effects of Potassium Channel Variation on Cardiac Repolarization and Atrial Fibrillation Risk

Objectives The aim of this study was to evaluate the role of cardiac K+ channel gene variants in families with atrial fibrillation (AF).

Background The K+ channels play a major role in atrial repolarization but single mutations in cardiac K+ channel genes are infrequently present in AF families. The collective effect of background K+ channel variants of varying prevalence and effect size on the atrial substrate for AF is largely unexplored.

Methods Genes encoding the major cardiac K+ channels were resequenced in 80 AF probands. Nonsynonymous coding sequence variants identified in AF probands were evaluated in 240 control subjects. Novel variants were characterized using patch-clamp techniques and in silico modeling was performed using the Courtemanche atrial cell model.

Results Nineteen nonsynonymous variants in 9 genes were found, including 11 rare variants. Rare variants were more frequent in AF probands (18.8% vs. 4.2%, p < 0.001), and the mean number of variants was greater (0.21 vs. 0.04, p <
0.001). The majority of K\(^+\) channel variants individually had modest functional effects. Modeling simulations to evaluate combinations of K\(^+\) channel variants of varying population frequency indicated that simultaneous small perturbations of multiple current densities had nonlinear interactions and could result in substantial (>30 ms) shortening or lengthening of action potential duration as well as increased dispersion of repolarization.

**Conclusions** Families with AF show an excess of rare functional K\(^+\) channel gene variants of varying phenotypic effect size that may contribute to an atrial arrhythmogenic substrate. Atrial cell modeling is a useful tool to assess epistatic interactions between multiple variants (71).

**Histopathologic Characterization of Chronic Radiofrequency Ablation Lesions for Pulmonary Vein Isolation**

**Objectives** This study describes the histopathologic and electrophysiological findings in patients with recurrence of atrial fibrillation (AF) after pulmonary vein (PV) isolation who underwent a subsequent surgical maze procedure.

**Background** The recovery of PV conduction is commonly responsible for recurrence of AF after catheter-based PV isolation.

**Methods** Twelve patients with recurrent AF after acutely successful catheter-based antral PV isolation underwent a surgical maze procedure. Full-thickness surgical biopsy specimens were obtained from the PV antrum in areas of visible endocardial scar. Before biopsy, intraoperative epicardial electrophysiological recordings were taken from each PV using a circular mapping catheter.

**Results** Twenty-two PVs were biopsied from the 12 patients 8 ± 11 months after ablation. Eleven of the 22 specimens (50%) revealed transmural scar, and 11 (50%) showed viable myocardium with or without scar. Each biopsy specimen demonstrated evidence of injury, most commonly endocardial thickening (n = 21 [95%]) and fibrous scar (n = 18 [82%]). Seven of the 22 specimens (32%) showed conduction block at surgery. Transmural scar was more likely to be seen in the biopsy specimens from the PVs with conduction block than in specimens from the PVs showing reconnection. However, viable myocardium alone or mixed with scar was seen in 2 specimens from PVs with conduction block.

**Conclusions** PVs showing electrical reconnection after catheter-based antral ablation frequently reveal anatomic gaps or nontransmural lesions at the sites of catheter ablation. Nontransmural lesions are noted in some PVs with persistent conduction block, suggesting that lesion geometry may influence PV conduction. The histological findings show that nontransmural ablation can produce a dynamic cellular substrate with features of reversible injury. Delayed recovery from injury may explain late recurrences of AF after PV isolation (72).

**The Clinical Impact of Incomplete Left Atrial Appendage Closure With the Watchman Device in Patients With Atrial Fibrillation: A PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) Substudy**

**Objectives** The purpose of this study was to investigate the frequency and clinical impact of incomplete left atrial appendage (LAA) sealing and consequent peri-device residual blood flow in patients undergoing percutaneous LAA closure with the Watchman device (Atritech, Inc., Plymouth, Minnesota).

**Background** During percutaneous LAA closure for stroke prophylaxis, the geometric variability of the LAA ostium may result in an incomplete seal of the LAA. On the one hand, this could enhance thrombus formation and embolization of thrombi around the device into the circulation; on the other hand, the relatively small size of these leaks may preclude clinically relevant embolizations.

**Methods** Patients randomly assigned to device implantation in the PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial were analyzed. Transesophageal echocardiography was performed at 45 days, 6 months, and 12 months. Per the study protocol, patients discontinued warfarin therapy if the 45-day Transesophageal echocardiogram revealed either minimal or no peri-device flow (jet ≤5 mm width).

The impact of peri-device flow severity, defined as minor, moderate, or major (<1 mm, 1 mm to 3 mm, >3 mm, respectively) on the composite primary efficacy endpoint (stroke, systemic embolism, and cardiovascular death) was expressed as hazard ratio (HR) with 95% confidence interval (CI).

**Results** Transesophageal echocardiography follow-up revealed that 32.0% of implanted patients had at least some degree of peri-device flow at 12 months. The HR of the primary efficacy endpoint per 1 mm larger per-device flow was 0.84 (95% CI: 0.62 to 1.14; p = 0.256).

Compared to patients with no peri-device flow, the HRs were 0.85 (95% CI: 0.11 to 6.40), 0.83 (95% CI: 0.33 to 2.09), and 0.48 (95% CI: 0.11 to 2.09) for minor, moderate, and major peri-device flow, respectively (p = 0.798).

Compared to patients with no peri-device flow who discontinued warfarin, the HR for patients with any peri-device flow and continuing warfarin was 0.63 (95% CI: 0.14 to 2.71; p = 0.530).

**Conclusions** These data indicate that residual peri-device flow into the LAA after percutaneous closure with the Watchman device was common, and is not associated with an increased risk of thromboembolism. This finding should be interpreted with caution as the low event rate decreases the confidence of this conclusion (73).
Feasibility, Accuracy, and Reproducibility of Real-Time Full-Volume 3D Transthoracic Echocardiography to Measure LV Volumes and Systolic Function: A Fully Automated Endocardial Contouring Algorithm in Sinus Rhythm and Atrial Fibrillation

Objectives To assess the feasibility, accuracy, and reproducibility of real-time full-volume 3-dimensional transthoracic echocardiography (3D RT-VTTE) to measure left ventricular (LV) volumes and ejection fraction (EF) using a fully automated endocardial contouring algorithm and to identify and automatically correct the contours to obtain accurate LV volumes in sinus rhythm and atrial fibrillation (AF).

Background 3D transthoracic echocardiography is not used routinely to quantify LV volumes and EF. A fully automated workflow using RT-VTTE may improve clinical adoption.

Methods RT-VTTE was performed and 3D EF and volumes obtained using an automated trabecular endocardial contouring algorithm; an automated correction was applied to track the compacted myocardium. Cardiac magnetic resonance (CMR) and 2-dimensional biplane Simpson method were the reference standard.

Results Ninety-one patients (67 in normal sinus rhythm [NSR], 24 in AF) were included. Among all NSR patients, there was excellent correlation between RT-VTTE and CMR for end-diastolic volume (EDV), end-systolic volume (ESV), and EF (r = 0.90, 0.96, and 0.98, respectively; p < 0.001). In patients with EF ≥50% (n = 36), EDV and ESV were underestimated by 10.7 ± 17.5 ml (p = 0.001) and by 4.1 ± 6.1 ml (p < 0.001), respectively. In those with EF <50% (n = 31), EDV and ESV were underestimated by 25.7 ± 32.7 ml (p < 0.001) and by 16.2 ± 24.0 ml (p = 0.001). Automated contour correction to track the compacted myocardium eliminated mean volume differences between RT-VTTE and CMR. In patients with AF, LV volumes and EF were accurate by RT-VTTE (r = 0.94, 0.94, and 0.91 for EDV, ESV, and EF, respectively; p < 0.001). Automated 3D LV volumes and EF were highly reproducible.

Conclusions Rapid, accurate, and reproducible EF can be obtained by RT-VTTE in NSR and AF patients by using an automated trabecular edge contouring algorithm. Furthermore, automated contour correction to detect the compacted myocardium yields accurate and reproducible 3D LV volumes (74).

Bioprosthetic Tricuspid Valve Regurgitation Associated With Pacemaker or Defibrillator Lead Implantation

Objectives The goal of this study was to determine the impact of transvenous pacemaker and defibrillator leads on the incidence of bioprosthetic tricuspid valve (BTV) regurgitation compared with BTV patients without a transvalvular lead.

Background Although concern has been raised regarding the potential deleterious effect of permanent transvenous device leads on BTV function, little is known about the incidence of prosthetic tricuspid regurgitation (TR) after lead placement.

Methods A retrospective review of 58 patients who underwent BTV implantation and subsequently required endocardial pacemaker (n = 52) or defibrillator (n = 6) lead implantation across the BTV was conducted. Patient and prosthesis characteristics, lead type, and clinical events were collected. The incidence and severity of prosthetic TR, determined by Doppler echocardiography, was compared with 265 consecutive patients who underwent BTV implantation without undergoing subsequent transvalvular device lead implantation.

Results Over a mean follow-up of 25 months, in 5 patients (9%) with a transvalvular lead significant (moderate or greater) prosthetic TR developed compared with 12 patients (5%) in the control group (p = 0.20). Kaplan-Meier analysis revealed no significant difference in the incidence of TR in BTV patients with and without transvalvular leads (p = 0.45). Significant prosthetic TR in patients with and without a transvalvular lead more commonly occurred 2 years or later after lead or BTV implantation (4 of 5, 80% and 10 of 12, 83%, respectively).

Conclusions Transvalvular device lead implantation in BTV patients was not associated with an increased incidence of significant prosthetic TR (p = 0.45). Based on these data, transvalvular lead implantation appears to be an acceptable approach for patients with a BTV who require permanent pacemaker or defibrillator placement (75).

Misleading Long Post-Pacing Interval After Entrainment of Typical Atrial Flutter From the Cavotricuspid Isthmus

Objectives The purpose of this study was to evaluate the prevalence and mechanism of a misleading long post-pacing interval (PPI) upon entrainment of typical atrial flutter (AFL) from the cavotricuspid isthmus (CTI).

Background In typical AFL, the PPI from entrainment at the CTI is expected to closely match the tachycardia cycle-length (TCL).

Methods Sixty patients with confirmed CTI-dependent AFL were retrospectively analyzed and grouped into short (≤30 ms) or long (>30 ms) PPI-TCL. Thereafter, we prospectively studied 16 patients to acquire the PPI-TCL at 4 CTI sites with entrainment at pacing cycle-lengths (PCLs) 10 to 40 ms shorter than the TCL. Conduction times during AFL and entrainment were compared in 5 segments of the AFL circuit.

Results Eleven patients (18%) in the retrospective analysis had a long PPI-TCL after entrainment from the CTI. Subjects with long PPI-TCL had similar baseline characteristics but greater beat-to-beat TCL variability. In the prospective cohort, PPI-TCL was influenced by the difference between PCL and...
The aim of our study was to assess coronary vasomotion after successful revascularization of chronic total occlusion (CTO).

**Objectives**

A long PPI upon entrainment of typical AFL from the CTI is common and due to delayed conduction with entrainment. Whether these findings apply to other macro-re-entrant tachycardias warrants further investigation (76).

**Conclusions**

A long PPI upon entrainment of typical AFL from the CTI is common and due to delayed conduction with entrainment. Whether these findings apply to other macro-re-entrant tachycardias warrants further investigation (76).

**Role of AV Nodal Ablation in Cardiac Resynchronization in Patients With Coexistent Atrial Fibrillation and Heart Failure: A Systematic Review**

**Objectives**

The aim of this study was to systematically review the medical literature to evaluate the impact of AV nodal ablation in patients with heart failure and coexistent atrial fibrillation (AF) receiving cardiac resynchronization therapy (CRT).

**Background**

CRT has a substantial evidence base in patients in sinus rhythm with significant systolic dysfunction, symptomatic heart failure, and prolonged QRS duration. The role of CRT is less well established in AF patients with coexistent heart failure. AV nodal ablation has recently been suggested to improve outcomes in this group.

**Methods**

Electronic databases and reference lists through September 15, 2010, were searched. Two reviewers independently evaluated citation titles, abstracts, and articles. Studies reporting the outcomes after AV nodal ablation in patients with AF undergoing CRT for symptomatic heart failure and left ventricular dyssynchrony were selected. Data were extracted from 6 studies, including 768 CRT-AF patients, composed of 339 patients who underwent AV nodal ablation and 429 treated with medical therapy aimed at rate control alone.

**Results**

AV nodal ablation in CRT-AF patients was associated with significant reductions in all-cause mortality (risk ratio: 0.42 [95% confidence interval: 0.26 to 0.68]), cardiovascular mortality (risk ratio: 0.44 [95% confidence interval: 0.24 to 0.81]), and improvement in mean New York Heart Association functional class (risk ratio: 0.52 [95% confidence interval: 0.37 to 0.70]).

**Conclusions**

AV nodal ablation was associated with a substantial reduction in all-cause mortality and cardiovascular mortality and with improvements in New York Heart Association functional class compared with medical therapy in CRT-AF patients. Randomized controlled trials are warranted to confirm the efficacy and safety of AV nodal ablation in this patient population (77).

**Timing of the Most Recent Device Procedure Influences the Clinical Outcome of Lead-Associated Endocarditis: Results of the MEDIC (Multicenter Electrophysiologic Device Infection Cohort)**

**Objectives**

The purpose of this study was to determine whether the timing of the most recent cardiac implantable electronic device (CIED) procedure, either a permanent pacemaker or implantable cardioverter-defibrillator, influences the clinical presentation and outcome of lead-associated endocarditis (LAE).

**Background**

The CIED infection rate has increased at a time of increased device use. LAE is associated with significant morbidity and mortality.

**Methods**

The clinical presentation and course of LAE were evaluated by the MEDIC (Multicenter Electrophysiologic Device Cohort) registry, an international registry enrolling patients with CIED infection. Consecutive LAE patients enrolled in the Multicenter Electrophysiologic Device
Cohort registry between January 2009 and May 2011 were analyzed. The clinical features and outcomes of 2 groups were compared based on the time from the most recent CIED procedure (early, <6 months; late, >6 months).

**Results** The Multicenter Electrophysiologic Device Cohort registry entered 145 patients with LAE (early = 43, late = 102). Early LAE patients presented with signs and symptoms of local pocket infection, whereas a remote source of bacteremia was present in 38% of patients with late LAE but only 8% of early LAE (p < 0.01). Staphylococcal species were the most frequent pathogens in both early and late LAE. Treatment consisted of removal of all hardware and intravenous administration of antibiotics. In-hospital mortality was low (early = 7%, late = 6%).

**Conclusions** The clinical presentation of LAE is influenced by the time from the most recent CIED procedure. Although clinical manifestations of pocket infection are present in the majority of patients with early LAE, late LAE should be considered in any CIED patient who presents with fever, bloodstream infection, or signs of sepsis, even if the device pocket appears uninfected. Prompt recognition and management may improve outcomes (79).

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**Atrial Conduction Slows Immediately Before the Onset of Human Atrial Fibrillation: A Bi-Atrial Contact Mapping Study of Transitions to Atrial Fibrillation**

**Objectives** The aim of this study was to determine whether onset sites of human atrial fibrillation (AF) exhibit conduction slowing, reduced amplitude, and/or prolonged duration of signals (i.e., fractionation) immediately before AF onset.

**Background** Few studies have identified functional determinants of AF initiation. Because conduction slowing is required for reentry, we hypothesized that AF from pulmonary vein triggers might initiate at sites exhibiting rate-dependent slowing in conduction velocity (CV restitution) or local slowing evidenced by signal fractionation.

**Methods** In 28 patients with AF (left atrial size 43 ± 5 mm; n = 13 persistent) and 3 control subjects (no AF) at electrophysiological study, we measured bi-atrial conduction time (CT) electrogram fractionation at 64 or 128 electrodes with baskets in left (n = 17) or both (n = 14) atria during superior pulmonary vein pacing at cycle lengths (CL) accelerating from 500 ms (120 beats/min) to AF onset.

**Results** Atrial fibrillation initiated in 19 of 28 AF patients and no control subjects. During rate acceleration, conduction slowed in 23 of 28 AF patients (vs. no control subjects, p = 0.01) at the site of AF initiation (15 of 19) or latest activated site (20 of 28). The CT lengthened from 79 ± 23 ms to 107 ± 39 ms (p < 0.001) on acceleration, in a spectrum from persistent AF (greatest slowing) to control subjects (least slowing; p < 0.05). Three patterns of CV restitution were observed: 1) broad (gradual CT prolongation, 37% patients); 2) steep (abrupt prolongation, at CL 266 ± 62 ms, 42%); and 3) flat (no prolongation, 21% AF patients, all control subjects). The AF initiation was more prevalent in patients with CV restitution (17 of 23 vs. 2 of 8; p = 0.03) and immediately followed abrupt re-orientation of the activation vector in patients with broad but not steep CV restitution (p < 0.01). Patients with broad CV restitution had larger atria (p = 0.03) and were more likely to have persistent AF (p = 0.04). Notably, neither amplitude nor duration (fractionation) of the atrial signal at the AF initiation site were rate-dependent (both p = NS).

**Conclusions** Acceleration-dependent slowing of atrial conduction (CV restitution) precedes AF initiation, whereas absence of CV restitution identifies inability to induce AF. Conduction restitution, but not fractionated electrograms, may thus track the functional milieu enabling AF initiation.
Background \(LMNA\) mutations cause a variety of clinical phenotypes, including dilated cardiomyopathy and conduction disease. Many \(LMNA\) mutation carriers have a poor prognosis, because of a high frequency of MVA and progression to end-stage heart failure. However, it is unclear how to identify mutation carriers that are at risk for MVA.

Methods In this multicenter cohort of 269 \(LMNA\) mutation carriers, we evaluated risk factors for MVA, defined as sudden cardiac death, resuscitation, and appropriate implantable cardioverter-defibrillator (ICD) treatment.

Results In a median follow-up period of 43 months (interquartile range: 17 to 101 months), 48 (18%) persons experienced a first episode of MVA: 11 persons received successful cardiopulmonary resuscitation, 25 received appropriate ICD treatment, and 12 persons died suddenly. Independent risk factors for MVA were nonsustained ventricular tachycardia, left ventricular ejection fraction <45% at the first clinical contact, male sex, and non-missense mutations (ins-del/truncating or mutations affecting splicing). MVA occurred only in persons with at least 2 of these risk factors. There was a cumulative risk for MVA per additional risk factor.

Conclusions Carriers of \(LMNA\) mutations with a high risk of MVA can be identified using these risk factors. This facilitates selection of \(LMNA\) mutation carriers who are most likely to benefit from an ICD (82).

Hypothermia Therapy: Neurological and Cardiac Benefits

Due to its protective effect on the brain and the myocardium, hypothermia therapy (HT) has been extensively studied in cardiac arrest patients with coma as well as in patients presenting with acute myocardial infarction (MI). In the setting of cardiac arrest, randomized studies have shown that HT decreases mortality and improves neurological outcomes. Subsequent guidelines have therefore recommended cooling (32°C to 34°C) for 12 to 24 h in unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest due to ventricular fibrillation. Observational studies have also confirmed the feasibility of this therapy in clinical practice and support its early application in patients with nonventricular fibrillation cardiac arrest and in post-resuscitation circulatory shock. In patients with acute MI, available clinical evidence does not yet support HT as the standard of care, because no study to date has shown a clear net benefit in such a cohort. After a brief review of the mechanisms of action for HT, we provide a review of the clinical evidence, cooling techniques, and potential adverse effects associated with HT in the setting of post-cardiac arrest patient and acute MI (83).

Procedural Complications, Rehospitalizations, and Repeat Procedures After Catheter Ablation for Atrial Fibrillation

Objectives The purpose of this study was to estimate rates and identify predictors of inpatient complications and 30-day readmissions, as well as repeat hospitalization rates for arrhythmia recurrence following atrial fibrillation (AF) ablation.

Background AF is the most common clinically significant arrhythmia and is associated with increased morbidity and mortality. Radiofrequency or cryotherapy ablation of AF is a relatively new treatment option, and data on post-procedural outcomes in large general populations are limited.

Methods Using data from the California State Inpatient Database, we identified all adult patients who underwent their first AF ablation from 2005 to 2008. We used multivariable logistic regression to identify predictors of complications and/or 30-day readmissions and Kaplan-Meier analyses to estimate rates of all-cause and arrhythmia readmissions.

Results Among 4,156 patients who underwent an initial AF ablation, 5% had periprocedural complications, most commonly vascular, and 9% were readmitted within 30 days. Older age, female, prior AF hospitalizations, and less hospital experience with AF ablation were associated with higher adjusted risk of complications and/or 30-day readmissions. The rate of all-cause hospitalization was 38.5% by 1 year. The rate of readmission for recurrent AF, atrial flutter, and/or repeat ablation was 21.7% by 1 year and 29.6% by 2 years.

Conclusions Periprocedural complications occurred in 1 of 20 patients undergoing AF ablation, and all-cause and arrhythmia-related rehospitalizations were common. Older age, female sex, prior AF hospitalizations, and recent hospital procedure experience were associated with a higher risk of complications and/or 30-day readmission after AF ablation (84).

Home Monitoring for Heart Failure Management

With a prevalence of 5.8 million in the United States alone, heart failure (HF) is a common syndrome associated with substantial morbidity, mortality, and healthcare expenditures. Close to 1 million HF hospitalizations occur annually in the United States, with the majority of these resulting from worsening congestion in patients previously diagnosed with HF. An estimated $37.2 billion is spent each year on HF in the United States. These statistics emphasize the need to develop and implement more effective strategies to
assess, monitor, and treat HF. It has also become increasingly apparent that interventions geared toward identifying and monitoring subclinical congestion would be of value in the home management of chronic HF. Earlier identification and treatment of congestion together with improved care coordination, management of comorbid conditions, and enhanced patient self-management may help to prevent hospitalizations in patients with chronic HF. Such home monitoring extends from the promotion of self-care and home visitations to telemedicine and remote monitoring of external or implantable devices. This paper discusses the challenges in monitoring patients with HF, reviews clinical trials testing different monitoring strategies in HF, and highlights ongoing investigations into the optimal approaches to home monitoring for HF (85).

Incidence, Predictive Factors, and Prognostic Value of New-Onset Atrial Fibrillation Following Transcatheter Aortic Valve Implantation

Objectives This study sought to evaluate the incidence, predictive factors, and prognostic value of new-onset atrial fibrillation (NOAF) following transcatheter aortic valve implantation (TAVI).

Background Very few data exist on the occurrence of NOAF following TAVI.

Methods A total of 138 consecutive patients with no prior history of atrial fibrillation (AF) underwent TAVI with a balloon-expandable valve. Patients were on continuous electrocardiogram monitoring until hospital discharge, and NOAF was defined as any episode of AF lasting >30 s. All clinical, echocardiographic, procedural, and follow-up data were prospectively collected.

Results NOAF occurred in 44 patients (31.9%) at a median time of 48 h (interquartile range: 0 to 72 h) following TAVI. The predictive factors of NOAF were left atrial (LA) size (odds ratio [OR]: 1.21 for each increase in 1 mm/m², 95% confidence interval [CI]: 1.09 to 1.34, p < 0.0001) and transapical approach (OR: 4.08, 95% CI: 1.35 to 12.31, p = 0.019). At 30-day follow-up, NOAF was associated with a higher rate of stroke/systemic embolism (13.6% vs. 3.2%, p = 0.021, p = 0.047 after adjustment for baseline differences between groups), with no differences in mortality rate between groups (NOAF: 9.1%, no-NOAF: 6.4%, p = 0.57). At a median follow-up of 12 months (interquartile range: 5 to 20 months), a total of 27 patients (19.6%) had died, with no differences between the NOAF (15.9%) and no-NOAF (21.3%) groups, p = 0.58. The cumulative rate of stroke and stroke/systemic embolism at follow-up were 13.6% and 15.9%, respectively, in the NOAF group versus 3.2% in the no-NOAF group (p = 0.039, adjusted p = 0.037 for stroke; p = 0.020, adjusted p = 0.023 for stroke/systemic embolism).

Conclusions NOAF occurred in about one-third of the patients with no prior history of AF undergoing TAVI and its incidence was increased in patients with larger LA size and those undergoing transapical TAVI. NOAF was associated with a higher rate of stroke/systemic embolism, but not a higher mortality, at 30 days and at 1-year follow-up (86).

A Common β1-Adrenergic Receptor Polymorphism Predicts Favorable Response to Rate-Control Therapy in Atrial Fibrillation

Objectives In this study, we evaluated the impact of 2 common β1-adrenergic receptor (β1-AR) polymorphisms (G389R and S49G) in response to ventricular rate control therapy in patients with atrial fibrillation (AF).

Background Randomized studies have shown that ventricular rate control is an acceptable treatment strategy in patients with AF. However, identification of patients who will adequately respond to rate-control therapy remains a challenge.

Methods We studied 543 subjects (63% men; age 61.8 ± 14 years) prospectively enrolled in the Vanderbilt AF registry and managed with rate-control strategy. A “responder” displayed adequate ventricular rate control based on the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) criteria: average heart rate (HR) at rest ≤80 beats/min; and maximum HR during a 6-min walk test ≤110 beats/min or average HR during 24-h Holter ≤100 beats/min.

Results A total of 295 (54.3%) patients met the AFFIRM criteria.Baseline clinical characteristics were similar in responders and nonresponders except for mean resting HR (76 ± 20 beats/min vs. 70 ± 15 beats/min; p < 0.01) and smoking (6% vs. 1%; p < 0.01). Multiple clinical variables (age, gender, hypertension) failed to predict response to rate-control therapy. By contrast, carriers of Gly variant at 389 were more likely to respond favorably to rate-control therapy; 60% versus 51% in the Arg389Arg genotype, p = 0.04. This association persisted after correction for multiple clinical factors (odds ratio: 1.42, 95% confidence interval: 1.00 to 2.03, p < 0.05). Among responders, subjects carrying the Gly389 variant required the lowest doses of rate-control medications; atenolol: 92 mg versus 68 mg; carvedilol: 44 mg versus 20 mg; metoprolol: 80 mg versus 72 mg; diltiazem: 212 mg versus 180 mg, and verapamil: 276 mg versus 200 mg, respectively (p < 0.01 for all comparisons).

Conclusions We have identified a common β1-AR polymorphism, G389R, that is associated with adequate response to rate-control therapy in AF patients. Gly389 is a loss-of-function variant; consequently, for the same adrenergic stimulation, it produces reduced levels of adenyl cyclase, and hence, attenuates the β-adrenergic cascade. Mechanistically, the effect of rate-control drugs will be synergistic with that of the Gly389 variant, which could possibly explain our findings. These findings represent a step forward in the development of a long-term strategy of selecting treatment options in AF based on genotype (87).
Risk Stratification in Brugada Syndrome: Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) Registry

Objectives The PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) prospective registry was designed to assess the predictive accuracy of sustained ventricular tachycardia/ventricular fibrillation (VTs/VF) inducibility and to identify additional predictors of arrhythmic events in Brugada syndrome patients without history of VT/VF.

Background Brugada syndrome is a genetic disease associated with increased risk of sudden cardiac death. Even though its value has been questioned, inducibility of VTs/VF is widely used to select candidates to receive a prophylactic implantable defibrillator, and its accuracy has never been addressed in prospective studies with homogeneous enrolling criteria.

Methods Patients with a spontaneous or drug-induced type I electrocardiogram (ECG) and without history of cardiac arrest were enrolled. The registry included 308 consecutive individuals (247 men, 80%; median age 44 years, range 18 to 72 years). Programmed electrical stimulation was performed at enrollment, and patients were followed-up every 6 months.

Results During a median follow-up of 34 months, 14 arrhythmic events (4.5%) occurred (13 appropriate shocks of the implantable defibrillator, and 1 cardiac arrest). Programmed electrical stimulation performed with a uniform and pre-specified protocol induced ventricular tachycardias in 40% of patients: arrhythmia inducibility was not a predictor of events at follow-up (9 of 14 events occurred in noninducible patients). History of syncope and spontaneous type I ECG (hazard ratio [HR]: 4.20), ventricular refractory period <200 ms (HR: 3.91), and QRS fragmentation (HR: 4.94) were significant predictors of arrhythmias.

Conclusions Our data show that VT/VF inducibility is unable to identify high-risk patients, whereas the presence of a spontaneous type I ECG, history of syncope, ventricular effective refractory period <200 ms, and QRS fragmentation seem useful to identify candidates for prophylactic implantable cardioverter defibrillator.

Changes in Renal Function After Implantation of Continuous-Flow Left Ventricular Assist Devices

Objectives The aim of this study was to determine renal outcomes after left ventricular assist device (LVAD) implantation.

Background Renal dysfunction before LVAD placement is frequent, and it is unclear whether it is due to primary renal disease or to poor perfusion.

Methods A retrospective single-center analysis was conducted in 83 consecutive patients implanted with HeartMate II continuous-flow LVADs (Thoratec Corp., Pleasanton, California). Calculated glomerular filtration rate (GFR) was assessed on admission and 1, 3, and 6 months after implantation. To define predictors for improvement in GFR, clinical variables were examined in patients with decreased renal function (GFR <60 ml/min/1.73 m²) before LVAD, surviving and dialysis-free at 1 month (n = 44).

Results GFR significantly increased from admission (53.2 ± 21.4 ml/min/1.73 m²) to 1 month after LVAD implantation (87.4 ± 27.9 ml/min/1.73 m²) (p < 0.0001). Subsequently, at 3 and 6 months, GFR remained significantly (p < 0.0001) above pre-LVAD values. Of the 51 patients with GFRs <60 ml/min/1.73 m² before LVAD surviving at 1 month, 34 (67%) improved to GFRs >60 ml/min/1.73 m². Univariate pre-operative predictors for improvement in renal function at 1 month included younger age (p = 0.049), GFR improvement with optimal medical therapy (p < 0.001), intra-aortic balloon pump use (p = 0.004), kidney length above 10 cm (p = 0.023), no treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (p = 0.029), higher bilirubin (p = 0.002), higher Lietz-Miller score (p = 0.019), and atrial fibrillation (p = 0.007). Multivariate analysis indicated pre-operative improved GFR (slope = 0.5 U per unit improved; 95% confidence interval: 0.2 to 0.8; p = 0.003), atrial fibrillation (slope = 27; 95% confidence interval: 8 to 46; p = 0.006), and intra-aortic balloon pump use (slope = 14; 95% confidence interval: 2 to 26; p = 0.02) as independent predictors.

Conclusions In most patients with end-stage heart failure considered for LVAD implantation, renal dysfunction is reversible and likely related to poor renal perfusion.

Septal Involvement in Patients With Post-Infarction Ventricular Tachycardia: Implications for Mapping and Radiofrequency Ablation

Objectives The purpose of this study was to assess the prevalence of the re-entry circuit within the interventricular septum in post-infarction patients referred for ventricular tachycardia (VT) ablation.

Background Post-infarction ventricular tachycardia can involve the endocardial myocardium, the intramural myocardium, the epicardium, or the His Purkinje system.

Methods Among 74 consecutive patients with recurrent post-infarction VT, 33 patients (45%) were identified in whom the critical part of the VT involved the interventricular septum. A total of 206 VTs were induced in these 33 patients. In 46 of the 206 VTs, a critical component was identified in the interventricular septum. The critical isthmus of the re-entry circuit was identified by entrainment mapping, activation mapping, or pace-mapping.

Results In 32 of 46 VTs (70%), the critical component of the re-entry circuit was confined to the endocardium. In 9 of 46 VTs (20%), the critical component involved the Purkinje system, and in 5 of 46 VTs (11%), an intramural area was critical. Entrainment and/or pace-mapping helped to identify critical areas of endocardial VTs as well as VTs involving...
The aim of this study was to test whether c-Src

**Objectives**

- Cardiac-restricted overexpression of angiotensin-converting enzyme mediates connexin-43 (Cx43) reduction and sudden cardiac death in a transgenic mouse model of tyrosine kinase.
- The up-regulation of c-Src by angiotensin II may result in cardiac death, but the mechanism is not well understood.

**Background**

- Angiotensin II
- Inhibition of c-Src Tyrosine Kinase Prevents Mediated Connexin-43 Remodeling and Sudden Cardiac Death

**Inhibition of c-Src Tyrosine Kinase Prevents Angiotensin II–Mediated Connexin-43 Remodeling and Sudden Cardiac Death**

**Objectives**

- The aim of this study was to test whether c-Src tyrosine kinase mediates connexin-43 (Cx43) reduction and sudden cardiac death in a transgenic mouse model of cardiac–restricted overexpression of angiotensin-converting enzyme (ACE8/8 mice).

**Background**

- Renin-angiotensin system activation is associated with an increased risk for arrhythmia and sudden cardiac death, but the mechanism is not well understood.

- The up-regulation of c-Src by angiotensin II may result in the reduction of Cx43, which impairs gap junction function and provides a substrate for arrhythmia.

**Methods**

- Wild-type and ACE8/8 mice with and without treatment with the c-Src inhibitor 1-(1,1-dimethylpropyl)-1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (PP1) were studied.
- Telerecording monitoring, in vivo electrophysiologic studies, Western blot analyses for total and phosphorylated c-Src and Cx43, immunohistochemistry staining for Cx43, and functional assessment of Cx43 with fluorescent dye diffusion were performed.

**Results**

- The majority of the arrhythmic deaths resulted from ventricular tachycardia degenerating to ventricular fibrillation (83%). Levels of total and phosphorylated c-Src were increased and Cx43 reduced in ACE8/8 mice. PP1 reduced total and phosphorylated c-Src levels, increased Cx43 level by 2.1-fold (p < 0.005), increased Cx43 at the gap junctions (immunostaining), improved gap junctional communication (dye spread), and reduced ventricular tachycardia inducibility and sudden cardiac death. The survival rate increased from 11% to 86% with 4 weeks of PP1 treatment (p < 0.005). Treatment with an inactive analog did not change survival or Cx43 levels.

**Conclusions**

- Renin-angiotensin system activation is associated with c-Src up-regulation, Cx43 loss, reduced myocyte coupling, and arrhythmic sudden death, which can be prevented by c-Src inhibition. This suggests that an increase in c-Src activity may help mediate renin-angiotensin system–induced arrhythmias and that c-Src inhibitors might exert antiarrhythmic activity.

**Implantable Cardioverter-Defibrillator Patients Who Are Upgraded and Respond to Cardiac Resynchronization Therapy Have Less Ventricular Arrhythmias Compared With Nonresponders**

**Objectives**

- The purpose of this study was to evaluate the impact of upgrading implantable cardioverter-defibrillator (ICD) therapy to cardiac resynchronization therapy (CRT) combined with defibrillator (CRT-D) on the occurrence of ventricular arrhythmia (VA) and appropriate ICD therapies.

**Background**

- CRT has been shown to improve left ventricular (LV) systolic function and induce reverse LV remodeling. In addition, it has been hypothesized that CRT may reduce the incidence of VA.

**Methods**

- Heart failure patients receiving an upgrade from ICD to CRT-D were evaluated. Patients were considered responders to CRT if LV end-systolic volume reduced ≥15% at 6 months of follow-up. Episodes of VA, triggering device therapy (anti-tachycardia pacing and shocks) were recorded before and after upgrade for the overall population. In addition, these outcomes were compared between CRT responders and nonresponders during the follow-up period after CRT response was assessed.

**Results**

- One hundred fifteen patients (93 males [81%], age 65 ± 12 years) were evaluated during a mean follow-up of 54 ± 34 months before CRT-D upgrade and 37 ± 27 months after CRT-D upgrade.
after upgrade. In CRT responders (n = 70), the frequency of VA requiring appropriate device therapy demonstrated a trend toward a decrease from 0.51 ± 0.79 to 0.30 ± 0.59 per patient per year after CRT-D upgrade (p = 0.052). In CRT nonresponders (n = 45), the frequency of VA requiring appropriate device therapy significantly increased from 0.40 ± 0.69 to 1.21 ± 2.53 per patient per year after CRT-D upgrade (p = 0.014).

Conclusions After upgrade from ICD to CRT-D, nonresponders to CRT showed a significant increase in VA burden requiring appropriate device therapy (93).

New Electrocardiographic Criteria for Discriminating Between Brugada Types 2 and 3 Patterns and Incomplete Right Bundle Branch Block

Objectives The aim of this study was to evaluate new electrocardiographic (ECG) criteria for discriminating between incomplete right bundle branch block (RBBB) and the Brugada types 2 and 3 ECG patterns.

Background Brugada syndrome can manifest as either type 2 or type 3 pattern. The latter should be distinguished from incomplete RBBB, present in 3% of the population.

Methods Thirty-eight patients with either type 2 or type 3 Brugada pattern that were referred for an antiarrhythmic drug challenge (AAD) were included. Before AAD, 2 angles were measured from ECG leads V1 and/or V2 showing incomplete RBBB: 1) \( \alpha \), the angle between a vertical line and the downslope of the r’-wave, and 2) \( \beta \), the angle between the upslope of the S-wave and the downslope of the r’-wave. Baseline angle values, alone or combined with QRS duration, were compared between patients with negative and positive results on AAD. Receiver-operating characteristic curves were constructed to identify optimal discriminative cutoff values.

Results The mean \( \beta \) angle was significantly smaller in the 14 patients with negative results on AAD compared to the 24 patients with positive results on AAD (36 ± 20° vs. 62 ± 20°, p < 0.01). Its optimal cutoff value was 58°, which yielded a positive predictive value of 73% and a negative predictive value of 87% for conversion to type 1 pattern on AAD; \( \alpha \) was slightly less sensitive and specific compared with \( \beta \). When the angles were combined with QRS duration, it tended to improve discrimination.

Conclusions In patients with suspected Brugada syndrome, simple ECG criteria can enable discrimination between incomplete RBBB and types 2 and 3 Brugada patterns (94).

Structural Abnormalities in Atrial Walls Are Associated With Presence and Persistency of Atrial Fibrillation But Not With Age

Objectives The purpose of this study was to assess the association between structural changes in human atria, age, and history of atrial fibrillation (AF).

Background Development of fibrosis in atrial walls is associated with deterioration of atrial conduction and predisposes to AF in experiment. Human data, however, are scarce, and whether fibrosis is a cause or consequence of AF is not known.

Methods Medical records for consecutive autopsies were checked for AF history and duration. Atrial specimens from 30 patients (ages 64 ± 12 years) were collected in 3 equal age-matched groups as patients without AF history, with paroxysmal AF, or with permanent AF. Tissue samples were obtained at the level of superior pulmonary veins, inferior pulmonary veins, center of posterior left atrial wall, terminal crest, and Bachmann’s bundle. Histology sections were assessed for extent of fibrosis, fatty tissues, and inflammatory infiltration at each location.

Results No correlation was observed between age and fibrosis at any location. Fibrosis extent and fatty infiltration were twofold to threefold higher at all locations in patients with history of AF and correlated with lymphomononuclear infiltration. Patients with permanent AF had greater fibrosis extent than did patients with paroxysmal AF.

Conclusions In post-mortem material, structural changes in the atria were not associated with age, but were significantly correlated with presence of AF and its severity. Our findings suggest that age-related changes per se are unlikely to be the sole cause of advanced fibrosis underlying AF (95).

Transcatheter Patch Occlusion of the Left Atrial Appendage Using Surgical Adhesives in High-Risk Patients With Atrial Fibrillation

Objectives The efficacy of left atrial appendage (LAA) occlusion using the Transcatheter Patch (TP) (Custom Medical Devices, Athens, Greece) in conjunction with surgical adhesives was assessed.

Background The TP is a bioabsorbable device that can be adjusted for the shape and size of the LAA without the risk of perforation. It is attached by a surgical adhesive and is released in 45 min.

Methods Occlusion of the LAA was performed in 20 high-risk patients, 59 to 89 years of age, with atrial fibrillation. A 2-stage polyethylene glycol surgical adhesive was applied to the distal half of the device. Activation of the adhesive was achieved by direct injection of alkaline solution. Fluoroscopy and transesophageal echocardiography only were used for device placement in 17 patients. In 3 patients, angiography was used as well. Follow-up transesophageal echocardiography was performed upon discharge.

Results The procedure was successful in 17 cases. In the 3 patients in whom angiography was performed, the patch did not attach and was retrieved. In 1 case, the patch was placed beyond the mouth of the appendage, resulting in a residual opening. There was further improvement of the occlusion rate on the follow-up transesophageal echocardiography. There was 1 complication related to the procedure, namely, thrombus was released from the long sheath in the left atrium upon withdrawal and required treatment to be dissolved. No recurrent strokes were reported.
Conclusions Occlusion of the LAA by the TP is feasible and effective in most patients with atrial fibrillation at high risk for embolic stroke. Angiography before placement probably affects patch adhesion and is contraindicated (96).

Omega-3 Fatty Acids and Cardiovascular Disease: Effects on Risk Factors, Molecular Pathways, and Clinical Events

We reviewed available evidence for cardiovascular effects of n-3 polyunsaturated fatty acid (PUFA) consumption, focusing on long chain (seafood) n-3 PUFA, including their principal dietary sources, effects on physiological risk factors, potential molecular pathways and bioactive metabolites, effects on specific clinical endpoints, and existing dietary guidelines. Major dietary sources include fatty fish and other seafood. n-3 PUFA consumption lowers plasma triglycerides, resting heart rate, and blood pressure and might also improve myocardial filling and efficiency, lower inflammation, and improve vascular function. Experimental studies demonstrate direct anti-arrhythmic effects, which have been challenging to document in humans. n-3 PUFA affect a myriad of molecular pathways, including alteration of physical and chemical properties of cellular membranes, direct interaction with and modulation of membrane channels and proteins, regulation of gene expression via nuclear receptors and transcription factors, changes in eicosanoid profiles, and conversion of n-3 PUFA to bioactive metabolites. In prospective observational studies and adequately powered randomized clinical trials, benefits of n-3 PUFA seem most consistent for coronary heart disease mortality and sudden cardiac death. Potential effects on other cardiovascular outcomes are less-well-established, including conflicting evidence from observational studies and/or randomized trials for effects on nonfatal myocardial infarction, ischemic stroke, atrial fibrillation, recurrent ventricular arrhythmias, and heart failure. Research gaps include the relative importance of different physiological and molecular mechanisms, precise dose-responses of physiological and clinical effects, whether fish oil provides all the benefits of fish consumption, and clinical effects of plant-derived n-3 PUFA. Overall, current data provide strong concordant evidence that n-3 PUFA are bioactive compounds that reduce risk of cardiac death. National and international guidelines have converged on consistent recommendations for the general population to consume at least 250 mg/day of long-chain n-3 PUFA or at least 2 servings/week of oily fish (97).

Mechanical Stretch of Atrial Myocyte Monolayer Decreases Sarcoplasmic Reticulum Calcium Adenosine Triphosphatase Expression and Increases Susceptibility to Repolarization Alternans

Objectives The purpose of this study was to investigate the effect of stretch (the major risk factor for atrial fibrillation [AF]) on spatial and temporal alternations of action potential duration (APD-ALT) and calcium transient in cultured atrial myocyte monolayer.

Background How rapid firings or premature beats trigger AF is not completely understood. Discordant repolarization alternans, characterized by simultaneous prolongation and shortening of APD in different myocardial regions, is central to the genesis of ventricular fibrillation. We hypothesized that repolarization alternans also is central to the initiation of multiple re-entry circuits and AF.

Methods Confluent HL-1 atrial myocyte monolayer with spontaneous depolarization was cultured in silicone membrane and subjected to mechanical stretch. Rapid field pacing was used to induce alternans. A high-resolution dual optical mapping system was used to record action potentials and calcium transients.

Results High-rate pacing induced APD-ALT and calcium transient in atrial myocyte monolayer. Mechanical stretch significantly decreased the thresholds for APD-ALT and calcium transient. Mechanical stretch decreased the expression of sarcoplasmic reticulum adenosine triphosphatase 2, and thus slower calcium reuptake kinetics, which was responsible for the susceptibility to alternans. Mechanical stretch did not alter the APD restitution kinetics. Mechanical stretch also enhanced spatially discordant alternans. Over-expression of sarcoplasmic reticulum adenosine triphosphatase 2 reversed all the effects of stretch on susceptibility to alternans. In intact atrium, mechanical stretch also enhanced discordant alternans.

Conclusions Mechanical stretch increased the susceptibility to alternans in atrial myocytes, which may explain the susceptibility to AF in conditions of atrial stretch, such as mitral valvular heart disease, heart failure, and hypertension (98).

Cardiovascular Outcomes in the AFFIRM Trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management): An Assessment of Individual Antiarrhythmic Drug Therapies Compared With Rate Control With Propensity Score-Matched Analyses

Objectives The impact of individual antiarrhythmic drugs (AADs) on mortality and hospital stay in atrial fibrillation (AF) was evaluated.

Background Cardiovascular (CV) outcomes in AF patients receiving Pharmacologic rhythm control therapy have not been compared with rate control therapy on the basis of AAD selection.

Methods We compared CV outcomes in the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial in subgroups defined by the initial AAD selected with propensity score matched subgroups from the rate arm (Rate).

Results Seven hundred twenty-nine amiodarone patients, 606 sotalol patients, and 268 Class 1C patients were
Primary cardiac tumors in children are rare. 

**Background**

characterize associated arrhythmias, and expand knowledge experience with primary cardiac tumors in pediatric patients, 

The incidence of arrhythmias is not well-defined, and C1C HR: 1.22, 95% CI: 0.97 to 1.56, p = 0.10). There was a nonsignificant increase in mortality with amiodarone (HR: 1.20, 95% CI: 0.94 to 1.53, p = 0.15) with the risk of non-CV death being significantly higher with amiodarone versus Rate (HR: 1.11, 95% CI: 1.01 to 1.24, p = 0.04). First CVH event rates at 3 years were 47% for amiodarone, 50% for sotalol, and 44% for Class 1C versus 40%, 40%, and 36%, respectively, for Rate (amiodarone HR: 1.20, 95% CI: 1.03 to 1.40, p = 0.02, sotalol HR: 1.364, 95% CI: 1.16 to 1.611, p < 0.001, Class 1C HR: 1.24, 95% CI: 0.96 to 1.60, p = 0.09). Time to CVH with intensive care unit stay or death was shorter with amiodarone (HR: 1.22, 95% CI: 1.02 to 1.46, p = 0.03). 

**Conclusions**

In AFFIRM, composite mortality and CVH outcomes differed for Rate and AADs due to differences in CVH; CVH event rates during follow-up were high for all cohorts, but they were higher for all groups on AADs. Death, intensive care unit hospital stay, and non-CV death were more frequent with amiodarone. (Atrial Fibrillation Follow-Up Investigation of Rhythm Management; NCT00000556) (99).

**Cardiac Tumors and Associated Arrhythmias in Pediatric Patients, With Observations on Surgical Therapy for Ventricular Tachycardia**

**Objectives**

The aim of this study was to describe a large experience with primary cardiac tumors in pediatric patients, characterize associated arrhythmias, and expand knowledge of natural history and treatment options.

**Background**

Primary cardiac tumors in children are rare. The incidence of arrhythmias is not well-defined, and management plans vary widely.

**Methods**

We employed a retrospective single-center review of patients ≤21 years of age diagnosed with a primary cardiac tumor between 1968 and 2010. Clinically significant arrhythmias were defined as: 1) sudden cardiac arrest; 2) nonsustained and sustained ventricular tachycardia (VT); 3) pre-excitation; and 4) sustained supraventricular tachycardia of any mechanism.

**Results**

A total of 173 patients were identified: 106 rhabdomyoma, 25 fibroma, 14 myxoma, 6 vascular, 4 teratoma, 3 lipoma, and 15 other. Median age at diagnosis was 7 months (prenatal to 21 years). Of these, 42 (24%) had clinically significant arrhythmias. Patients with large fibromas were the highest-risk group, with VT occurring in 64%. Among rhabdomyoma patients, 10% had pre-excitation, and 6% had VT. Over a mean follow-up of 6 years (1 day to 34 years, median 4 years), surgical excision was performed in 62 cases, with rhythm treatment being 1 of the indications in 20. Post-operatively, clinically significant arrhythmias were eliminated in 18 of these 20, including all 13 fibroma patients.

**Conclusions**

Clinically significant arrhythmias occurred in 24% of pediatric patients with cardiac tumors, VT being the most common type. Surgical excision for VT associated with rhabdomyomas and fibromas in selected patients is an important and effective management strategy in these patients (100).

**The Effect of Rate Control on Quality of Life in Patients With Permanent Atrial Fibrillation: Data From the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) Study**

**Objectives**

The aim of this study was to investigate the influence of rate control on quality of life (QOL).

**Background**

The RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) trial showed that lenient rate control is not inferior to strict rate control in terms of cardiovascular morbidity and mortality. The influence of stringency of rate control on QOL is unknown.

**Methods**

In RACE II, a total of 614 patients with permanent atrial fibrillation (AF) were randomized to lenient (resting heart rate [HR] <110 beats/min) or strict (resting HR <80 beats/min, HR during moderate exercise <110 beats/min) rate control. QOL was assessed in 437 patients using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) questionnaire, AF severity scale, and Multidimensional Fatigue Inventory-20 (MFI-20) at baseline, 1 year, and end of study. QOL changes were related to patient characteristics.

**Results**

Median follow-up was 3 years. Mean age was 68 ± 8 years, and 66% were males. At the end of follow-up, all SF-36 subscales were comparable between both groups. The AF severity scale was similar at baseline and end of study. At baseline and at end of study there were no differences in the MFI-20 subscales between the 2 groups. Symptoms at baseline, younger age, and less severe underlying disease, rather than assigned therapy or heart rate, were associated with QOL improvements. Female sex and cardiovascular endpoints during the study were associated with worsening of QOL.

**Conclusions**

Stringency of heart rate control does not influence QOL. Instead, symptoms, sex, age, and severity of the underlying disease influence QOL. (Rate Control Efficacy in Permanent Atrial Fibrillation; NCT00392613) (101).

**Ambulatory External Electrocardiographic Monitoring: Focus on Atrial Fibrillation**

There has been progressive development in ambulatory external electrocardiogram (AECG) monitoring technology. AECG monitors initially consisted of 24- to 48-h Holter monitors and patient-activated event and loop recorders. More recently, several ambulatory cardiovascular telemetry monitors and a patch-type 7- to 14-day Holter monitor have
been introduced. These monitoring systems are reviewed along with their utility and limitations, with particular emphasis on their role in the diagnosis and evaluation of patients with atrial fibrillation (AF). AECG monitoring is necessary when asymptomatic AF is suspected (as in patients presenting with cryptogenic stroke) or when an ECG diagnosis of unexplained arrhythmic symptoms is warranted. In addition, AECG plays an important role in patients with known AF to guide ventricular rate control and anticoagulation therapy, and assess the efficacy of antiarrhythmic drug therapy and/or ablation procedures. Finally, we outline areas of uncertainty and provide recommendations for use of available AECG monitors in clinical practice (102).

**Cardiac Resynchronization Therapy Reduces Left Atrial Volume and the Risk of Atrial Tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy)**

**Objectives** We hypothesized that reductions in left atrial volume (LAV) with a cardiac resynchronization therapy–defibrillator (CRT-D) would translate into a subsequent reduction in the risk of atrial tachyarrhythmias (AT).

**Background** There is limited information regarding the effect of CRT-D on the risk of AT.

**Methods** Percent reduction in LAV at 1 year following CRT-D implantation (pre-specified as low [lowest quartile: <20% reduction in LAV] and high [≥20% reduction in LAV] response to CRT-D) were related to the risk of subsequent AT (comprising atrial fibrillation, atrial flutter, atrial tachycardia, and supraventricular tachyarrhythmias) among patients enrolled in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy).

**Results** The cumulative probability of AT 2.5 years after assessment of echocardiographic response was lowest among high LAV responders to CRT-D (3%) and significantly higher among both low LAV responders to CRT-D (9%) and implantable cardioverter–defibrillator–only patients (7%; p = 0.03 for the difference among the 3 groups). Consistently, multivariate analysis showed that high LAV responders to CRT-D experienced a significant 53% (p = 0.01) reduction in the risk of subsequent AT as compared with implantable cardioverter–defibrillator–only patients, whereas low LAV responders did not derive a significant risk reduction with CRT-D therapy (hazard ratio [HR]: 1.05 [95% confidence interval (CI): 0.54 to 2.00]; p = 0.89). Patients who developed in-trial AT experienced significant increases in the risk for both the combined endpoint of heart failure or death (HR: 2.28 [95% CI: 1.45 to 3.59]; p < 0.001) and the separate occurrence of all-cause mortality (HR: 1.89 [95% CI: 1.08 to 3.62]; p = 0.01).

**Conclusions** In the MADIT-CRT study, favorable reverse remodeling of the left atrium with CRT-D therapy was associated with a significant reduction in risk of subsequent AT. (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (103).

**Left Atrial Contractile Function Following a Successful Modified Maze Procedure at Surgery and the Risk for Subsequent Thromboembolic Stroke**

**Objectives** The aim of this study was to evaluate whether certain post–Maze left atrial (LA) contractile profiles may pose a risk for ischemic stroke.

**Background** The mechanical contraction of the left atrium may be modified after the Maze procedure. Whether this imposes a risk for stroke, even in the presence of sinus rhythm and after removal of the LA appendage, is not known.

**Methods** Clinical, surgery-related, and echocardiographic data from 150 patients who underwent radiofrequency and cryoablation Maze procedures without the use of atrial incisions between 2004 and 2009 and were in sustained sinus rhythm were collected and analyzed. The occurrence of stroke was evaluated by reviewing clinical records. All stroke events were adjudicated by a neurologist.

**Results** At a mean follow-up time of 24.5 months, 15 patients (10%) had experienced ischemic strokes. Forty-seven patients (31%) had no evidence of LA mechanical contraction at 3 months after surgery (baseline assessment) and on follow-up echocardiography. Multivariate analysis showed that a lack of LA mechanical contraction at baseline was associated with a 5-fold increase in the risk for stroke (p = 0.02) during follow-up. Larger atria imposed a significant risk as well; LA volume index ≥33 ml/m² was associated with a 3-fold risk increase (p = 0.03). These effects were maintained regardless of the lack of mechanical valve implantation and anticoagulation treatment.

**Conclusions** Absence of LA contraction and LA volume index ≥33 ml/m² result in a significant increase in the risk for thromboembolic stroke after the Maze procedure for patients in sinus rhythm (104).

**Effective Use of Radiation Shields to Minimize Operator Dose During Invasive Cardiology Procedures**

**Objectives** This study sought to measure the protection from scatter radiation offered to the primary physician by a variety of available shields and to provide best practice guidelines for shield use during invasive cardiology procedures.

**Background** It is accepted that exposure to radiation includes a predicted increase in cancer risk. In the cardiac interventional laboratories, radiation shields are widely available; however, proper use of the shields to optimize protection during cardiac interventional procedures is not well understood.
Methods The protection from scatter radiation offered by a variety of shields used alone and in combination was measured. Protection was assessed from air-kerma measurements of scatter radiation from a phantom performed without and with the shields. Protection was assessed for 3 patient-access locations (right jugular vein, right femoral artery, and left anterior chest) and for elevations ranging from 25 to 175 cm from the floor. The influence of precise placement of the ceiling-mounted upper body shield was specifically assessed.

Results The utility and protection of shielding varied for the 3 access points and with elevation. For femoral artery access locations, the shields can provide at least 80% protection from scatter at all elevations; however, protection depends substantially on upper body shield position. A disposable radiation-absorbing pad can provide 35% to 70% upper body protection for procedures during which the upper body shield cannot be used effectively.

Conclusions Radiation shields can provide substantial protection from radiation during cardiac interventional procedures. Shields must be thoughtfully and actively managed to provide optimum protection. Best practice guidelines for shield use are provided (105).

Effects of Increasing Doses of Intracoronary Adenosine on the Assessment of Fractional Flow Reserve

Objectives The purpose of this study was to investigate the effects of increasing dose of intracoronary adenosine on fractional flow reserve (FFR) measurement.

Backgrounds FFR is a validated method for the assessment of the severity of coronary artery stenosis. It is based on the change in the pressure gradient across the stenosis after the achievement of maximal hyperemia of the coronary microcirculation that may be obtained by either intracoronary bolus or intravenous infusion of adenosine. No study has explored so far the effects of very high doses of intracoronary adenosine on FFR.

Methods FFR was assessed in 46 patients with 50 intermediate lesions during cardiac catheterization by pressure-recording guidewire (PrimeWire, Volcano, San Diego, California). FFR was calculated as the ratio of the distal coronary pressure to the aortic pressure at hyperemia. Increasing doses of adenosine were administrated (60, 120, 180, 360, and 720 µg) as intracoronary boluses. Exclusion criteria were: 1) allergy to adenosine; 2) baseline bradycardia (heart rate <50 beats/min); 3) hypotension (blood pressure <90 mm Hg); and 4) refusal to provide signed informed consent.

Results High doses of intracoronary adenosine were well tolerated, with no major side effects. Increasing doses up to 720 µg progressively decreased FFR values and increased the percentage of patients showing an FFR <0.75. Among angiographic parameters, both percent stenosis and lesion length were independently associated with lower FFR values.

Conclusions This study shows that high doses of intracoronary adenosine (up to 720 µg) increased the sensitivity of FFR in the detection of hemodynamically relevant coronary stenoses. Furthermore, lesion length and stenosis severity were independent angiographic determinants of FFR (106).

Evidence of Atrial Functional Mitral Regurgitation Due to Atrial Fibrillation: Reversal With Arrhythmia Control

Objectives The purpose of this study was to determine whether atrial fibrillation (AF) might cause significant mitral regurgitation (MR), and to see whether MR improves with restoration of sinus rhythm.

Background MR can be classified by leaft pathology (organic/primary and functional/secondary) and by leaft motion (normal, excessive, restrictive). The existence of secondary, normal leaft motion MR remains controversial.

Methods We performed a retrospective cohort study. Patients undergoing first AF ablation at our institution (n = 828) were screened. Included patients had echocardiograms at the time of ablation and at 1-year clinical follow-up. The MR cohort (n = 53) had at least moderate MR. A reference cohort (n = 53) was randomly selected from those patients (n = 660) with mild or less MR. Baseline echocardiographic and clinical characteristics were compared, and the effect of restoration of sinus rhythm was assessed by follow-up echocardiograms.

Results MR patients were older than controls and more often had persistent AF (62% vs. 23%, p < 0.0001). MR patients had larger left atria (volume index: 32 cm³/m² vs. 26 cm³/m², p = 0.008) and annular size (3.49 cm vs. 3.23 cm, p = 0.001), but similar left ventricular size and ejection fraction. Annular size, age and persistent AF were independently associated with MR. On follow-up echocardiogram, patients in continuous sinus rhythm had greater reductions in left atrial size and annular dimension, and lower rates of significant MR (24% vs. 82%, p = 0.005) compared with those in whom sinus rhythm was not restored.

Conclusions AF can result in “atrial functional MR” that improves if sinus rhythm is restored (107).

Payment Source, Quality of Care, and Outcomes in Patients Hospitalized With Heart Failure

Objectives The aim of this study was to analyze the relationship between payment source and quality of care and outcomes in heart failure (HF).

Background HF is a major cause of morbidity and mortality. There is a lack of studies assessing the association of payment source with HF quality of care and outcomes.

Methods A total of 99,508 HF admissions from 244 sites between January 2005 and September 2009 were analyzed. Patients were grouped on the basis of payer status (private/health maintenance organization, no insurance, Medicare, or
Incidence and Predictors of Implantable Cardioverter-Defibrillator Therapy in Patients With Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Undergoing Implantable Cardioverter-Defibrillator Implantation for Primary Prevention

Objectives The purpose of this study was to define the incidence and predictors of implantable cardioverter-defibrillator (ICD) therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) after placement of an ICD for primary prevention.

Background Patients with a diagnosis of ARVD/C often receive an ICD for prevention of sudden cardiac death.

Methods Patients (n = 84) from the Johns Hopkins registry with definite or probable ARVD/C who underwent ICD implantation for primary prevention were studied. Detailed phenotypic, genotype, and ICD event information was obtained and appropriate ICD therapies were adjudicated based on intracardiac electrograms.

Results Over a mean follow-up of 4.7 ± 3.4 years, appropriate ICD therapy was seen in 40 patients (48%), of whom 16 (19%) received interventions for potentially fatal ventricular fibrillation/flutter episodes. Proband status (p < 0.001), inducibility at electrophysiologic study (p = 0.005), presence of nonsustained ventricular tachycardia (p < 0.001), and Holter premature ventricular complex count >1,000/24 h (p = 0.024) were identified as significant predictors of appropriate ICD therapy. The 5-year survival free of appropriate ICD therapy for patients with 1, 2, 3, and 4 risk factors was 100%, 83%, 21%, and 15%, respectively. Inducibility at electrophysiologic study (hazard ratio: 4.5, 95% confidence interval: 1.4 to 15, p = 0.013) and nonsustained ventricular tachycardia (hazard ratio: 10.5, 95% confidence interval: 2.4 to 46.2, p = 0.002) remained as significant predictors on multivariable analysis.

Conclusions Nearly one-half of the ARVD/C patients with primary prevention ICD implantation experience appropriate ICD interventions. Inducibility at electrophysiologic study and nonsustained ventricular tachycardia are independent strong predictors of appropriate ICD therapy. An increase in ventricular ectopy burden was associated with progressively lower event-free (appropriate ICD interventions) survival. Incremental risk of ventricular arrhythmias and ICD therapy was observed with the presence of multiple risk factors (109).

Activation and Entrainment Mapping of Hemodynamically Unstable Ventricular Tachycardia Using a Percutaneous Left Ventricular Assist Device

Objectives Our goal was to investigate the effects of percutaneous left ventricular assist device (pLVAD) support during catheter ablation of unstable ventricular tachycardia (VT).

Background Mechanical cardiac support during ablation of unstable VT is being increasingly used, but there is little available information on the potential hemodynamic benefits.

Methods Twenty-three consecutive procedures in 22 patients (ischemic, n = 11) with structural heart disease and hemodynamically unstable VT were performed with either pLVAD support (n = 10) or no pLVAD support (intra-aortic balloon pump counterpulsation, n = 6; no support, n = 7). Procedural monitoring included vital signs, left atrial pressure, arterial blood pressure, cerebral perfusion/oximetry, VT characteristics, and ablation outcomes.

Results The pLVAD group was maintained in VT significantly longer than the non-pLVAD group (66.7 min vs. 27.5 min; p = 0.03) and required fewer early terminations of sustained VT for hemodynamic instability (1.0 vs. 4.0; p = 0.001). More patients in the pLVAD group had at least 1 VT termination during ablation than non-pLVAD patients (9 of 10 [90%] vs. 5 of 13 [38%]; p = 0.03). There were no differences between groups in duration of cerebral deoxygenation, hypotension or perioperative changes in left atrial pressure, brain natriuretic peptide levels, lactic acid, or renal function.

Conclusions In patients with scar-related VT undergoing catheter ablation, pLVAD support was able to safely maintain end-organ perfusion despite extended periods of hemodynamically unstable VT. Randomized studies are necessary to determine whether this enhanced ability to perform entrainment and activation mapping will translate into a higher rate of clinical success (110).
Microvolt T-Wave Alternans: Physiological Basis, Methods of Measurement, and Clinical Utility—Consensus Guideline by International Society for Holter and Noninvasive Electrocardiology

This consensus guideline was prepared on behalf of the International Society for Holter and Noninvasive Electrocardiology and is cosponsored by the Japanese Circulation Society, the Computers in Cardiology Working Group on e-Cardiology of the European Society of Cardiology, and the European Cardiac Arrhythmia Society. It discusses the electrocardiographic phenomenon of T-wave alternans (TWA) (i.e., a beat-to-beat alternation in the morphology and amplitude of the ST-segment or T-wave). This statement focuses on its physiological basis and measurement technologies and its clinical utility in stratifying risk for life-threatening ventricular arrhythmias. Signal processing techniques including the frequency-domain Spectral Method and the time-domain Modified Moving Average method have demonstrated the utility of TWA in arrhythmia risk stratification in prospective studies in >12,000 patients. The majority of exercise-based studies using both methods have reported high relative risks for cardiovascular mortality and for sudden cardiac death in patients with preserved as well as depressed left ventricular ejection fraction. Studies with ambulatory electrocardiogram-based TWA analysis with Modified Moving Average method have yielded significant predictive capacity. However, negative studies with the Spectral Method have also appeared, including 2 interventional studies in patients with implantable defibrillators. Meta-analyses have been performed to gain insights into this issue. Frontiers of TWA research include use in arrhythmia risk stratification of individuals with preserved ejection fraction, improvements in predictivity with quantitative analysis, and utility in guiding medical as well as device-based therapy. Overall, although TWA appears to be a useful marker of risk for arrhythmic and cardiovascular death, there is as yet no definitive evidence that it can guide therapy (111).

Sudden Death in Young Adults: An Autopsy-Based Series of a Population Undergoing Active Surveillance

Objectives The purpose of this study was to define the incidence and characterization of cardiovascular cause of sudden death in the young.

Background The epidemiology of sudden cardiac death (SCD) in young adults is based on small studies and uncontrolled observations. Identifying causes of sudden death in this population is important for guiding approaches to prevention.

Methods We performed a retrospective cohort study using demographic and autopsy data from the Department of Defense Cardiovascular Death Registry over a 10-year period comprising 15.2 million person-years of active surveillance.

Results We reviewed all nontraumatic sudden deaths in persons 18 years of age and over. We identified 902 subjects in whom the adjudicated cause of death was of potential cardiac etiology, with a mean age of 38 ± 11 years. The mortality rate for SCD per 100,000 person-years for the study period was 6.7 for males and 1.4 for females (p < 0.0001). Sudden death was attributed to a cardiac condition in 715 (79.3%) and was unexplained in 187 (20.7%). The incidence of sudden unexplained death (SUD) was 1.2 per 100,000 person-years for persons <35 years of age, and 2.0 per 100,000 person-years for those ≥35 years of age (p < 0.001). The incidence of fatal atherosclerotic coronary artery disease was 0.7 per 100,000 person-years for those <35 years of age, and 13.7 per 100,000 person-years for those ≥35 years of age (p < 0.001).

Conclusions Prevention of sudden death in the young adult should focus on evaluation for causes known to be associated with SUD (e.g., primary arrhythmia) among persons <35 years of age, with an emphasis on atherosclerotic coronary disease in those ≥35 years of age (112).

16-Year Trends in the Infection Burden for Pacemakers and Implantable Cardioverter-Defibrillators in the United States 1993 to 2008

Objectives We analyzed the infection burden associated with the implantation of cardiac implantable electrophysiological devices (CIEDs) in the United States for the years 1993 to 2008.

Background Recent data suggest that the rate of infection following CIED implantation may be increasing.

Methods The Nationwide Inpatient Sample (NIS) discharge records were queried between 1993 and 2008 using the 9th Revision of the International Classification of Diseases (ICD-9-CM). CIED infection was defined as either: 1) ICD-9 code for device-related infection (996.61) and any CIED procedure or removal code; or 2) CIED procedure code along with systemic infection. Patient health profile was evaluated by coding for renal failure, heart failure, respiratory failure, and diabetes mellitus. The infection burden and patient health profile were calculated for each year, and linear regression was used to test for changes over time.

Results During the study period (1993 to 2008), the incidence of CIED infection was 1.61%. The annual rate of infections remained constant until 2004, when a marked increase was observed, which coincided with an increase in the incidence of major comorbidities. This was associated with a marked increase in mortality and in-hospital financial charges.

Conclusions The infection burden associated with CIED implantation is increasing over time and is associated with prolonged hospital stays and high financial costs (113).
Dual-Chamber Implantable Cardioverter-Defibrillator Selection Is Associated With Increased Complication Rates and Mortality Among Patients Enrolled in the NCDR Implantable Cardioverter-Defibrillator Registry

**Objectives** The aim of this study was to compare single-versus dual-chamber implantable cardioverter-defibrillator (ICD) implantation and complication rates in a large, real-world population.

**Background** The majority of patients enrolled in ICD efficacy trials received single-chamber devices. Although dual-chamber ICDs offer theoretical advantages over single-chamber defibrillators, the clinical superiority of dual-chamber models has not been conclusively proven, and they may increase complications.

**Methods** The National Cardiovascular Data Registry ICD Registry was used to examine the association between baseline characteristics and device selection in 104,049 patients receiving single- and dual-chamber ICDs between January 1, 2006, and December 31, 2007. A longitudinal cohort design was then used to determine in-hospital complication rates.

**Results** Dual-chamber devices were implanted in 64,489 patients (62%). Adverse events were more frequent with dual-chamber than with single-chamber device implantation (3.17% vs. 2.11%, p < 0.001), as was the rate of in-hospital mortality (0.40% vs. 0.23%, p < 0.001). After adjusting for demographics, medical comorbidities, diagnostic test data, and ICD indication, the odds of any complication (odds ratio: 1.40; 95% confidence interval: 1.28 to 1.52; p < 0.001) and in-hospital mortality (odds ratio: 1.45; 95% confidence interval: 1.20 to 1.74; p < 0.001) were increased with dual-chamber versus single-chamber ICD implantation.

**Conclusions** In this large, multicenter cohort of patients, dual-chamber ICD use was common. Dual-chamber device implantation was associated with increases in periprocedural complications and in-hospital mortality compared with single-chamber defibrillator selection (114).

Implantation-Related Complications of Implantable Cardioverter-Defibrillators and Cardiac Resynchronization Therapy Devices: A Systematic Review of Randomized Clinical Trials

The number of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) implantations is increasing dramatically worldwide, and hence, the number of implanting centers is also increasing. Despite abundant data on the beneficial effect of these devices, little is known regarding safety and complication rates. Eleven ICD and 7 CRT trials were systematically reviewed to provide data on the frequency of in-hospital mortality and complications related to the implementation. Average in-hospital mortality was 2.7% in trials using both thoracotomy and non-thoracotomy ICDs, 0.2% in trials using nonthoracotomy ICDs, and 0.3% in CRT trials. The pneumothorax rate was similar between the nonthoracotomy ICD and CRT trials (0.9%) Coronary sinus complications occurred in 2.0% of patients undergoing CRT. Lead dislodgement rates were higher in CRT trials (5.7%) than in nonthoracotomy ICD trials (1.8%) (115).

Effect of Lenient Versus Strict Rate Control on Cardiac Remodeling in Patients With Atrial Fibrillation: Data of the RACE II (RAte Control Efficacy in permanent atrial fibrillation II) Study

**Objectives** The aim of this study was to evaluate echocardiographic remodeling in permanent atrial fibrillation (AF) patients treated with either lenient or strict rate control.

**Background** It is unknown whether in permanent AF, lenient rate control is associated with more adverse cardiac remodeling than strict rate control.

**Methods** Echocardiography was conducted at baseline and at follow-up in 517 patients included in the RACE II trial. Echocardiographic parameters were compared between patients randomized to lenient rate control (n = 261) or strict rate control (n = 256).

**Results** Baseline echocardiographic parameters were comparable between patients randomized to lenient and strict rate control. Between baseline and follow-up, significant adverse atrial or ventricular remodeling was not observed in either group. There were also no significant differences in atrial and ventricular remodeling between patients who continuously had heart rates between 80 and 110 beats/min and patients who continuously had heart rates <80 beats/min during follow-up. Lenient rate control was not independently associated with changes in echocardiographic parameters: mean adjusted effect on left atrial size was 1.6 mm (p = 0.09) and 1.1 mm on left ventricular end-diastolic diameter (p = 0.23). Instead, female sex was independently associated with adverse remodeling: mean adjusted effect on left atrial size was 2.4 mm (p = 0.02) and 6.5 mm on left ventricular end-diastolic diameter (p < 0.0001).

**Conclusions** Female sex, not lenient rate control, seemed to be associated with significant adverse cardiac remodeling in patients with permanent AF such as those enrolled in the RACE II study. (RAte Control Efficacy in Permanent Atrial Fibrillation [RACE II]; NCT00392613) (116).

Diastolic Dysfunction in Patients Undergoing Cardiac Surgery: A Pathophysiological Mechanism Underlying the Initiation of New-Onset Post-Operative Atrial Fibrillation

**Objectives** Our goal was to investigate whether left ventricular (LV) diastolic dysfunction was an important pathophysiologic mechanism underlying the initiation of new-onset post-operative atrial fibrillation (POAF).
Background  Atrial fibrillation is a common complication after cardiac surgery. However, the precise mechanism underlying its development remains poorly understood. Pre-existing alterations of myocardial diastolic function may predispose patients to the development of POAF.

Methods  Patients were residents of Olmsted County, Minnesota, who underwent complete LV diastolic function assessment before coronary artery bypass grafting and/or valve surgery between January 1, 2000, and December 31, 2005. All were in sinus rhythm and had no history of atrial fibrillation, a pacemaker, mitral stenosis, or congenital heart disease. POAF was defined as any episode of atrial fibrillation within 30 days after surgery.

Results  POAF occurred in 135 of 351 patients (38.5%). Patients with POAF were older (mean age 72.5 ± 10.3 years vs. 63.1 ± 14.1 years, p < 0.001) and more likely to have abnormal diastolic function. The rate of POAF increased exponentially with diastolic function grade (DFG) severity (p < 0.001). By multivariate analysis, after adjusting for clinical and surgical risk factors, independent predictors of POAF were older age (odds ratio [OR]: 1.05; p < 0.001), higher body mass index (OR: 1.06; p = 0.03), and abnormal LV DFG (DFG 1, OR: 5.12 [p = 0.006]; DFG 2, OR: 9.87 [p < 0.001]; and DFG 3, OR: 28.52 [p < 0.001]).

Conclusions  LV diastolic dysfunction is a powerful, independent predisposing substrate for the initiation of POAF. Evaluation may be useful during risk stratification of patients undergoing cardiac surgery (117).

Cardiac Resynchronization Therapy in Patients With Minimal Heart Failure: A Systematic Review and Meta-Analysis

Objectives  The purpose of this study was to perform a systematic review and meta-analysis of prospective randomized clinical trials of cardiac resynchronization therapy (CRT) versus implantable cardioverter-defibrillator (ICD) in patients with reduced ejection fraction (EF), prolonged QRS interval, and New York Heart Association (NYHA) functional class I to II heart failure (HF).

Background  In patients with advanced HF, CRT improves left ventricular (LV) function and reduces mortality and hospitalizations. Recent data suggest that patients with milder HF also benefit from CRT.

Methods  A meta-analysis of 5 clinical trials including 4,317 patients with NYHA functional class I/II HF was performed.

Results  Average age of patients was 65 years, and 80% were male. Frequency of all-cause mortality for CRT versus ICD was 8% versus 11.5% (risk ratio [RR]: 0.81; 95% confidence interval [CI]: 0.65 to 0.99, p = 0.04); for HF hospitalization, it was 11.6% versus 18.2% (RR: 0.68; 95% CI: 0.59 to 0.79, p < 0.001). Patients assigned to CRT had a significantly greater improvement in LVEF (+5.9% vs. +2.2%, p < 0.001) and LV volume than ICD patients. Among mildly symptomatic (NYHA functional class II) patients, CRT was associated with significantly lower mortality and HF hospitalization (RR: 0.73; 95% CI: 0.64 to 0.83), p < 0.001). In asymptomatic (NYHA functional class I) patients, HF hospitalization risk was lower (RR: 0.57; 95% CI: 0.34 to 0.97, p = 0.04) with CRT; however, there was no difference in mortality. Twelve asymptomatic HF patients needed to be treated with CRT to prevent 1 hospitalization.

Device Therapy in Heart Failure Patients With Chronic Kidney Disease

Heart failure (HF) and chronic kidney disease (CKD) both carry significant risk for sudden cardiac death, hospitalization, and mortality; when combined, however, they markedly increase the risk of morbidity and mortality. Device therapies such as implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) are treatments proven to have significant benefit on clinical outcomes in select patients with HF. However, the majority of studies supporting the use of these devices have limited data on patients with CKD or end-stage renal disease. In this review, we discuss the intersection of HF and CKD as it relates to progressive HF and the risk of sudden death. Although these disorders are common and have a poor prognosis, the evidence available for guiding treatment decisions for the use of ICD and CRT devices in these patients is lacking. Given this lack of clear evidence, pragmatic clinical trials and comparative effectiveness studies are needed to help identify the appropriate use of ICD and CRT devices in this high-risk population of patients with HF and CKD (119).

Electrocardiographic Comparison of Ventricular Arrhythmias in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy and Right Ventricular Outflow Tract Tachycardia

Objectives  The purpose of this study was to evaluate whether electrocardiographic characteristics of ventricular arrhythmias distinguish patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) from those with right ventricular outflow tract tachycardia (RVOT-VT).

Background  Ventricular arrhythmias in RVOT-VT and ARVD/C-VT patients can share a left bundle branch block/inferior axis morphology.

Methods  We compared the electrocardiographic morphology of ventricular tachycardia or premature ventricular contractions
with left bundle branch block/inferior axis pattern in 16 ARVD/C patients with that in 42 RVOT-VT patients.

**Results** ARVD/C patients had a significantly longer mean QRS duration in lead I (150 ± 31 ms vs. 123 ± 34 ms, p = 0.006), more often exhibited a precordial transition in lead V6 (3 of 17 [18%] vs. 0 of 42 [0%] with RVOT-VT, p = 0.005), and more often had at least 1 lead with notching (11 of 17 [65%] vs. 9 of 42 [21%], p = 0.001). The most sensitive characteristics for the detection of ARVD/C were a QRS duration in lead I of ≥120 ms (88% sensitivity, 91% negative predictive value). QRS transition at V6 was most specific at 100% (100% positive predictive value, 77% negative predictive value). The presence of notching on any QRS complex had 79% sensitivity and 65% specificity of (55% positive predictive value, 85% negative predictive value). In multivariate analysis, QRS duration in lead I of ≥120 ms (odds ratio [OR]: 20.4, p = 0.034), earliest onset QRS in lead V1 (OR: 17.0, p = 0.022), QRS notching (OR: 7.7, p = 0.018), and a transition of V5 or later (OR: 7.0, p = 0.030) each predicted the presence of ARVD/C.

**Conclusions** Several electrocardiographic criteria can help distinguish right ventricular outflow tract arrhythmias originating from ARVD/C compared with RVOT-VT patients.

### Incidence of Asymptomatic Intracranial Embolic Events After Pulmonary Vein Isolation: Comparison of Different Atrial Fibrillation Ablation Technologies in a Multicenter Study

**Objectives** We compared the safety of different devices by screening for subclinical intracranial embolic events after pulmonary vein isolation with either conventional irrigated radiofrequency (RF) or cryoballoon or multielectrode phased RF pulmonary vein ablation catheter (PVAC).

**Background** New devices specifically designed to facilitate pulmonary vein isolation procedures have recently been introduced.

**Methods** This prospective, observational, multicenter study included patients with symptomatic atrial fibrillation referred for pulmonary vein isolation. Ablation was performed using 1 of the 3 catheters. Strict periprocedural anticoagulation, with intravenous heparin during ablation to achieve an activated clotting time >300 s, was ensured in all patients. Cerebral magnetic resonance imaging was performed before and after ablation.

**Results** Seventy-four patients were included in the study: 27 in the irrigated RF group, 23 in the cryoballoon group, and 24 in the PVAC group. Total procedure times were 198 ± 50 min, 174 ± 35 min, and 124 ± 32 min, respectively (p < 0.001 for PVAC vs. irrigated RF and cryoballoon). Findings on neurological examination were normal in all patients before and after ablation. Post-procedure magnetic resonance imaging detected a single new embolic lesion in 2 of 27 patients in the irrigated RF group (7.4%) and in 1 of 23 in the cryoballoon group (4.3%). However, in the PVAC group 9 of 24 patients (37.5%) demonstrated 2.7 ± 1.3 new lesions each (p = 0.003 for the presence of new embolic events among the 3 groups).

**Conclusions** The PVAC is associated with a significantly higher incidence of subclinical intracranial embolic events. Further study of the causes and significance of these emboli is required to determine the safety of the PVAC.

### Prevalence and Characteristics of Early Repolarization in the CASPER Registry: Cardiac Arrest Survivors With Preserved Ejection Fraction Registry

**Objectives** We evaluated the prevalence and characteristics of early repolarization in patients in CASPER (Cardiac Arrest Survivors With Preserved Ejection Fraction Registry).

**Background** Early repolarization has been implicated in a syndrome of polymorphic ventricular tachycardia and fibrillation in patients without organic heart disease.

**Methods** One hundred patients with apparently unexplained cardiac arrest and preserved ejection fraction underwent extensive clinical and genetic testing to unmask subclinical electrical or structural disease. A blinded independent analysis of the 12-lead electrocardiogram (ECG) was performed. Early repolarization was defined as ≥0.1 mV QRS–ST junction (J-point) elevation with terminal QRS slurring or notching in at least 2 contiguous inferior and/or lateral leads.

**Results** One hundred cardiac arrest patients were enrolled (40 females, age 43 ± 14 years). Forty-four were diagnosed with an established cause for cardiac arrest. Significant early repolarization was found in 19 patients, including 6 with a primary diagnosis that explained their cardiac arrest (14%), compared with 23% of the 56 patients with idiopathic ventricular fibrillation (IVF) (p = 0.23). J-point elevation in IVF patients had higher amplitude (0.25 ± 0.11 mV vs. 0.13 ± 0.05 mV, p = 0.02) and wider distribution (4.3 ± 1.3 leads vs. 2.8 ± 0.8 leads; p = 0.01) than those with an established cause of cardiac arrest. J-wave amplitude was fluctuant on serial ECGs; at least 1 ECG failed to demonstrate early repolarization in 58% of patients.

**Conclusions** Early repolarization is present in a significant proportion of causally diagnosed and idiopathic VF. It is often intermittent and more pronounced in IVF patients. (Registry of Unexplained Cardiac Arrest; NCT00292032)(122).

### Reduction of the Risk of Recurring Heart Failure Events With Cardiac Resynchronization Therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy)

**Objectives** The evaluation of the risk of recurring heart failure events (HFEs) was a pre-specified substudy of MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy).
Background There are limited data regarding the effect of cardiac resynchronization therapy with a defibrillator (CRT-D) on the occurrence of recurring heart failure episodes after a first post-implantation HFE.

Methods Data with regard to recurring HFEs were prospectively collected for all 1,820 MADIT-CRT participants. The CRT-D versus defibrillator-only risk for nonfatal first- and subsequent-HFEs was assessed by Cox proportional hazards and Andersen-Gill proportional intensity regression modeling, respectively, in efficacy analyses recognizing active device-type during follow-up.

Results Multivariate analysis showed that CRT-D was associated with a significant reduction in the risk of a first HFE (hazard ratio [HR]: 0.54, 95% confidence interval [CI]: 0.44 to 0.67, p<0.001) and with a similar magnitude of reduction in the risk of HFEs subsequent to a first post-enrollment event (HR: 0.62, 95% CI: 0.45 to 0.85, p=0.003). The benefit of CRT-D for the prevention of first and subsequent HFEs was pronounced among patients with left bundle branch block (HR: 0.38, 95% CI: 0.29 to 0.49, p<0.001; and HR: 0.50, 95% CI: 0.33 to 0.76, p=0.001, respectively) and nonsignificant in non-left bundle branch block patients (HR: 1.12, 95% CI: 0.77 to 1.64, p=0.55; and HR: 0.99, 95% CI: 0.58 to 1.69, p=0.96, respectively; p values for interaction: p<0.001 and p=0.06, respectively). The occurrences of first and second HFEs were associated with 7- and nearly 19-fold respective increases in the risk of subsequent mortality.

Conclusions In the MADIT-CRT trial, the benefit of cardiac resynchronization therapy for the reduction in recurring HFEs was maintained after the occurrence of a first post-enrollment event. The occurrence of HFEs greatly increased the risk of death. (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy; NCT00180271) (123).

Long-Term Follow-Up of Patients With Short QT Syndrome

Objectives The aim of this study was to investigate the clinical characteristics and the long-term course of a large cohort of patients with short QT syndrome (SQTS).

Background SQTS is a rare channelopathy characterized by an increased risk of sudden death. Data on the long-term outcome of SQTS patients are not available.

Methods Fifty-three patients from the European Short QT Registry (75% males; median age: 26 years) were followed up for 64±27 months.

Results A familial or personal history of cardiac arrest was present in 89%. Sudden death was the clinical presentation in 32%. The average QTc was 314±23 ms. A mutation in genes related to SQTS was found in 23% of the probands; most of them had a gain of function mutation in HERG (SQTS1). Twenty-four patients received an implantable cardioverter defibrillator, and 12 patients received long-term prophylaxis with hydroquinidine (HQ), which was effective in preventing the induction of ventricular arrhythmias. Patients with a HERG mutation had shorter QTc at baseline and a greater QTc prolongation after treatment with HQ. During follow-up, 2 already symptomatic patients received appropriate implantable cardioverter defibrillator shocks and 1 had syncope. Nonsustained polymorphic ventricular tachycardia was recorded in 3 patients. The event rate was 4.9% per year in the patients without antiarrhythmic therapy. No arrhythmic events occurred in patients receiving HQ.

Conclusions SQTS carries a high risk of sudden death in all age groups. Symptomatic patients have a high risk of recurrent arrhythmic events. HQ is effective in preventing ventricular tachyarrhythmia induction and arrhythmic events during long-term follow-up (124).

Radiofrequency Ablation of Atrial Fibrillation in Patients With Mechanical Mitral Valve Prostheses: Safety, Feasibility, Electrophysiologic Findings, and Outcomes

Objectives The purpose of this study was to evaluate the feasibility, safety, and outcomes of radiofrequency ablation of atrial fibrillation (AF) in patients with mechanical mitral valve replacement (MVR).

Background The role of ablative therapy in patients with MVR is not yet established, with safety concerns and very few outcome data.

Methods Between January 2003 and December 2008, we followed up 81 patients with MVR undergoing first-time AF ablation (compared with 162 age- and sex-matched controls). Arrhythmia recurrences were identified by symptoms with documentation, event monitoring, Holter monitoring, and electrocardiograms.

Results All MVR and control patients underwent ablation under therapeutic international normalized ratio. No entrapment of catheters or stroke occurred. There were no differences in terms of procedure-related complications between the groups (p=NS). Patients with MVR had larger atra (p<0.0001), lower left ventricular ejection fractions (p=0.0001), and more concomitant atrial flutter at baseline (p<0.0001). Over a 24-month follow-up, they had higher recurrence rates compared with controls (49.4% vs. 27.7% after a single ablation, p=0.0006). The creation of flutter lines significantly reduced recurrences in patients with any history of atrial flutter (16.7% vs. 60.9%, p=0.009). At last follow-up, 82.7% of MVR patients had their arrhythmia controlled (69.1% not receiving antiarrhythmic drugs).

Conclusions Radiofrequency ablation is feasible and safe for patients with MVR. It allowed restoration of sinus rhythm in a substantial proportion of patients undergoing ablation. An abnormal atrial substrate underlies recurrences in these patients. The ablation procedure needs to be further refined with a focus on extra pulmonary vein triggers and concomitant flutters to improve outcomes (125).
Pre-Operative Left Atrial Mechanical Function Predicts Risk of Atrial Fibrillation Following Cardiac Surgery

Objectives The purpose of this study was to examine whether left atrial (LA) mechanical function, as measured by LA total emptying fraction (TEF), is a predictor for the development of post-operative atrial fibrillation (POAF) following cardiac surgery.

Background POAF is an important and frequent complication of cardiac surgery. LA enlargement has been reported to be a risk factor for POAF, but the relationship between LA mechanical function and POAF is not well understood. We examined the relationship between pre-operative LA function and POAF in patients without a history of atrial fibrillation.

Methods A total of 101 subjects (mean age 64 ± 13 years) underwent pre-operative transthoracic echocardiograms and were followed for occurrence of POAF during the hospitalization for cardiac surgery. The left atrium maximum volume (LAVmax) and left atrium minimum volume (LAVmin) were measured and indexed to body surface area (LAVmaxL and LAVminL, respectively). LA TEF was calculated as: [{[(LAVmax – LAVmin)/LAVmaxL] × 100%}. Univariate and multivariate analyses examined clinical and echocardiographic predictors of POAF.

Results POAF occurred in 41% of subjects. Mean LA TEF was 49 ± 15%, mean LAVmaxL was 38 ± 15 ml/m², and mean LAVminL was 20 ± 13 ml/m². Age, LA TEF, and LAVminL were independent predictors of POAF. LA TEF was lower in patients with POAF compared with those without POAF (43 ± 15% vs. 55 ± 13%, p < 0.001), and patients with a LA TEF <50% had a high risk of POAF (odds ratio: 7.94, 95% confidence interval: 3.23 to 19.54, p < 0.001). Compared with LAVmaxL >32 ml/m², LA TEF <50% had higher discriminatory power for POAF, which remained significantly higher when adjusted for age (p = 0.04).

Conclusions LA TEF is an independent predictor of POAF and is a stronger predictor of POAF than LAVmaxL is. Impaired LA mechanical function may help to identify patients who are most likely to benefit from prophylaxis for POAF (126).

Prediction of Life-Threatening Arrhythmic Events in Patients With Chronic Myocardial Infarction by Contrast-Enhanced CMR

Objectives We hypothesized that infarct transmurality assessed with late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) predicts arrhythmic events in patients with chronic myocardial infarction.

Background Patients with decreased left ventricular function due to chronic myocardial infarction are at increased risk for life-threatening arrhythmias related to infarcted tissue. LGE-CMR accurately detects infarct morphology.

Methods We prospectively enrolled 52 patients with chronic myocardial infarction referred for primary preventive implantable cardioverter-defibrillator (ICD) implantation following MADIT (Multicenter Automatic Defibrillator Implantation Trial) study criteria. Using LGE-CMR, left ventricular volumes, function, and infarct morphology were assessed including calculation of total and relative infarct mass, infarct border, infarct border zone, and infarct transmurality.

Results Patients were followed for 1,235 ± 341 days. The primary combined endpoint including appropriate device therapy (ICD discharge or antitachycardia pacing) or death from cardiac cause occurred in 16 individuals resulting in an annual event rate of 4.7%. Six patients received an appropriate shock, 7 patients received recurrent appropriate antitachycardia pacing for sustained ventricular tachycardia, and 3 patients died of cardiac cause. There was a significant association to relative infarct mass (38 ± 8% vs. 28 ± 14%, p = 0.02), infarct transmurality (24 ± 8 g vs. 16 ± 12 g, p = 0.02), and relative infarct transmurality (RIT) (63 ± 12% vs. 48 ± 23%, p = 0.01). In separate logistic regression models, no variable emerged as significant when combined with RIT. As a single effect, RIT emerged as a predictor of the primary endpoint (p = 0.02). A RIT cutoff at 43% resulted in a sensitivity of 88%, a specificity of 50%, a positive predictive value of 44%, and a negative predictive value of 90%.

Conclusions In patients with chronic myocardial infarction scheduled for primary preventive ICD implantation, infarct transmurality as defined by LGE-CMR identifies a subgroup with increased risk for life-threatening arrhythmias and cardiac death (127).
propensity score quintiles, the rhythm-control strategy was significantly related to superior therapeutic success (odds ratio: 1.34, 95% confidence interval: 1.15 to 1.55; p = 0.0002). Clinical events occurred in 18% of patients. The arrhythmia management strategy was not predictive of clinical events. The type (persistent), presence at baseline visit, and duration (>3 months) of AF, together with age older than 75 years and the presence of heart failure, predicted progression to permanent AF. The choice of rhythm control reduced the likelihood of AF progression (odds ratio: 0.20, 95% confidence interval: 0.17 to 0.25; p < 0.0001).

**Conclusions** Clinical outcomes in AF patients were driven mainly by hospitalizations for arrhythmia/proarrhythmia and other cardiovascular causes, but not by the choice of rate or rhythm strategy. Rhythm-control patients progressed less rapidly to permanent AF (128).

### Superiority of Simulator-Based Training Compared With Conventional Training Methodologies in the Performance of Transseptal Catheterization

**Objectives** This study aims to compare the performance of electrophysiology fellows in transseptal catheterization (TSP-C) after conventional (Conv-T) or simulator training (Sim-T).

**Background** Current training for TSP-C, an increasingly used procedure, relies on performance on patients with supervision by an experienced operator. Virtual reality, a new training option, could improve post-training performance.

**Methods** Fellows inexperienced in TSP-C were enrolled and randomly assigned to Conv-T or Sim-T. The post-training performance of each fellow was evaluated and scored in 3 consecutive patient-based procedures by an experienced operator blinded to the fellow's training assignment.

**Results** Fourteen fellows were randomized to Conv-T (n = 7) or to Sim-T (n = 7) and, after training, performed 42 TSP-Cs independently. Training time was significantly longer for Conv-T than for Sim-T (median 30 days vs. 4 days; p = 0.0175). The Conv-T fellows had significantly lower post-training performance scores (median 68 vs. 95; p = 0.0001) and a higher number of recurrent errors (median 3 vs. 0; p = 0.0006) when compared with Sim-T fellows.

**Conclusions** The TSP-C training with virtual reality results in shorter training times and superior post-training performance (129).

### Impact of Implanted Recalled Sprint Fidelis Lead on Patient Mortality

**Objectives** This study sought to compare all-cause mortality in patients with Fidelis leads (Medtronic, Minneapolis, Minnesota) to those with a nonadvisory lead.

**Background** Although Fidelis leads are prone to fracture, and rare deaths due to lead failure have been reported, it is unclear whether the presence of a Fidelis lead is associated with increased mortality. This study compares all-cause mortality in a large cohort of patients with Fidelis and Quattro implantable cardioverter-defibrillator (ICD) leads.

**Methods** All patients with Fidelis (Medtronic models 6931, 6948, and 6949) and Quattro (Medtronic model 6947) leads followed at 3 tertiary care centers were identified from the medical records (implant dates: November 19, 2001, to December 23, 2008). Clinical and device-specific data were collected into a common database. Deaths were identified from medical records and the Social Security Death Index. Survival was estimated using the Kaplan-Meier method.

**Results** A total of 2,671 patients (1,030 Fidelis and 1,641 Quattro) were identified. There were 398 deaths: 147 in the Fidelis group (mean follow-up: 34.4 months) and 251 in the Quattro group (mean follow-up: 39.9 months). No deaths were associated with 85 Fidelis and 23 Quattro failures. At 4 years, survival was diminished in patients with Fidelis compared with Quattro leads (80.7% vs. 83.9%; p = 0.025). After adjustment for factors associated with mortality, survival was similar between groups. One hundred percent pacing was not associated with mortality. Elective removal of nonfailed leads was performed in 5.1% of Fidelis and 0.9% of Quattro patients.

**Conclusions** In a conservatively managed cohort, in whom observation was predominantly utilized, adjusted survival is similar between patients with Fidelis and Quattro ICD leads (130).

### Epicardial Ablation of Rotors Suppresses Inducibility of Acetylcholine-Induced Atrial Fibrillation in Left Pulmonary Vein–Left Atrium Preparations in a Beagle Heart Failure Model

**Objectives** The purpose of this study was to provide direct evidence that rotor ablation suppresses atrial fibrillation (AF) inducibility.

**Background** Micro-re-entrant wavefronts have been suggested to serve as sources of rapid activations during AF. Whether AF inducibility is suppressed by elimination of rotors remains unknown.

**Methods** We used optical mapping to study Langendorff-perfused left pulmonary vein (PV)–left atrium (LA) preparations from 13 dogs with pacing-induced heart failure. Atrial arrhythmias were induced by pacing and mapped during acetylcholine infusion (1 μmol/l). Rotors were identified from optical recordings. Epicardial ablation was performed targeting the rotor anchoring sites in preparations with sustained (>10 min) or incessant spontaneous AF. Non-rotor ablation was performed in 4 preparations. Repeated pacing was performed to test the AF inducibility after ablation.

**Results** Sustained AF (n = 12) and incessant spontaneous AF (n = 1) were induced after acetylcholine infusion.
Pulmonary vein focal discharge was found in 9 preparations (9.2 ± 4.2 beats/s), and rotor anchoring was found at the left superior PV-LA junction in 13 preparations (9.1 ± 4.6 beats/s) and at the ligament of Marshall-PV-LA junction in 1 preparation. Epicardial rotor ablation successfully inhibited the inducibility of sustained AF in 12 of 13 preparations (p < 0.01), including 4 with the maximal dominant frequency sites located on the PV-LA junctional rotor zones (direct elimination of mother rotors). The longest AF duration was shortened significantly by rotor ablation (Wilcoxon Z = 3.60, p = 0.002, n = 13), but not by non-rotor ablation (Wilcoxon Z = 1.00, p = 0.317, n = 4).

Conclusions Epicardial ablation of the rotor anchoring sites suppresses AF inducibility. The arrhythmogenicity at the maximal dominant frequency sites is directly/indirectly suppressed by the rotor ablation (131).

Tachycardia-Induced Diastolic Dysfunction and Resting Tone in Myocardium From Patients With a Normal Ejection Fraction

Objectives The purpose of this study is to evaluate tachycardia-induced relaxation abnormalities in myocardium from patients with a normal ejection fraction.

Background Diastolic dysfunction and left ventricular (LV) hypertrophy are closely linked. Tachycardia can induce heart failure symptoms in otherwise asymptomatic patients. To study the effects of tachycardia on myocardial contractility and relaxation, we evaluated the effects of increasing pacing rates in myocardial biopsy samples obtained from patients with a normal ejection fraction.

Methods LV biopsy samples were obtained during coronary bypass surgery. Myocardial strip preparations were electrically paced at rates from 60 to 180 beats/min. Diastolic resting tone was assessed by cross-bridge deactivation. Calcium transporting systems were functionally examined, and myofilament calcium sensitivity was studied.

Results Incomplete relaxation developed in 7 preparations, with increased diastolic tension development at increasing pacing rates. This was absent in the remaining 7 preparations. Incomplete relaxation was found to be associated with increased LV mass and left atrial volume. Cross-bridge deactivation showed that these preparations also had a significant resting tone. Additional functional analyses suggest that incomplete relaxation is associated with disproportionately elevated cellular calcium loads due to a reduced sarcolemmal calcium extrusion reserve.

Conclusions Tachycardia-induced incomplete relaxation was associated with increased LV mass and left atrial volumes. We also found a disproportionately increased calcium load at high rates and a substantial resting tone due to diastolic cross-bridge cycling. These observations may play a role in reduced exercise tolerance and tachycardia-induced diastolic dysfunction (132).

Syncope Due to Idiopathic Paroxysmal Atrioventricular Block: Long-Term Follow-Up of a Distinct Form of Atrioventricular Block

Objectives We present data on patients with syncope due to paroxysmal atrioventricular (AV) block unexplainable in terms of currently known mechanisms.

Background Paroxysmal AV block is known to be due to intrinsic AV conduction disease or to heightened vagal tone.

Methods We evaluated 18 patients presenting with unexplained syncope who had: 1) normal baseline standard electrocardiogram (ECG); 2) absence of structural heart disease; and 3) documentation, by means of prolonged ECG monitoring at the time of syncopal relapse, of paroxysmal third-degree AV block with abrupt onset and absence of other rhythm disturbances before or during the block.

Results The study group consisted of 9 men and 9 women, mean age 55 ± 19 years, who had recurrent unexplained syncope for 8 ± 7 years and were subsequently followed up for as long as 14 years (4 ± 4 years on average). The patients had no structural heart disease, standard ECG was normal, and electrophysiological study was negative. In all patients, prolonged ECG monitoring documented paroxysmal complete AV block with 1 or multiple consecutive pauses (mean longest pause: 9 ± 7 s at the time of syncope); AV block occurred without P-P cycle lengthening or PR interval prolongation. During the observation time, no patient had permanent AV block; on permanent cardiac pacing, no patient had further syncopal recurrences.

Conclusions Common clinical and electrophysiological features define a distinct form of syncope due to idiopathic paroxysmal AV block characterized by a long history of recurrent syncope, absence of progression to persistent forms of AV block, and efficacy of cardiac pacing therapy (133).

Feasibility and Acute Efficacy of Radiofrequency Ablation of Cavotricuspid Isthmus-Dependent Atrial Flutter Guided by Real-Time 3D TEE

Objectives The aim of this study was to evaluate the feasibility and acute efficacy of real-time 3-dimensional transesophageal echocardiography (RT3DTEE)–guided ablation of the cavotricuspid isthmus (CVTI).

Background The use of RT3DTEE to guide a transcatheter radiofrequency ablation procedure has never been systematically investigated.

Methods Seventy consecutive patients with CVTI-dependent atrial flutter underwent CVTI ablation. Procedural monitoring using RT3DTEE was assigned to patients who requested general anesthesia for the procedure (n = 21 [30%]). In the other 49 patients (the control group), the procedures were monitored using the standard fluoroscopic approach. Procedural time was considered as skin-to-skin electrophysiological procedure duration, not including anesthesia preparation; adequate radiofrequency ablation applications (with fixed temperature and power settings) were considered as lesions lasting ≥ 60 s.
Results  RT3DTEE allowed visualization of the CVTI and identified related structures in most patients (20 of 21); anatomic features such as long CVTI (n = 11), prominent Eustachian ridge (n = 9), prominent Eustachian valve (n = 6), septal recess (n = 8), and pectinate muscles (n = 10) were frequent. Also, RT3DTEE allowed continuous visualization of ablation catheter movement and contact. Compared with the control group, RT3DTEE was equally effective in achieving CVTI bidirectional block (100% in both groups), and no complications occurred. RT3DTEE shortened procedural time (median 73.0 min, interquartile range [IQR] 60.0 to 90.0 min, vs. median 115.0 min, IQR 85.0 to 133.0 min, p < 0.001), reduced radiation exposure (median fluoroscopy time 4.2 min, IQR 3.1 to 8.4 min, vs. median 19.3 min, IQR 12.9 to 36.4 min, p < 0.001; median fluoroscopy dose 575.4 cGy · cm², IQR 428.5 to 1,299.4 cGy · cm², vs. median 3,520.7 cGy · cm², IQR 1,700.0 to 6,709.0 cGy · cm², p < 0.001), and reduced the number of radiofrequency applications to achieve bidirectional block (median 7, IQR 6 to 10, vs. median 12, IQR 10 to 22, p = 0.007). A strong learning curve was detected by comparing procedural data between the first and last patients treated using RT3DTEE.

Conclusions RT3DTEE-guided ablation of CVTI was feasible, allowing real-time detailed morphological CVTI characterization as well as continuous visualization of the ablation catheter during radiofrequency ablation. This approach entailed marked reductions in procedural time, radiation exposure, and the number of radiofrequency applications (134).

Monomorphic Ventricular Tachycardia and Mediastinal Adenopathy Due to Granulomatous Infiltration in Patients With Preserved Ventricular Function

Objectives This report characterizes a syndrome of granulomatous infiltration presenting as sustained monomorphic ventricular tachycardia (SMVT) with mediastinal adenopathy in patients with preserved ventricular function.

Background Unlike truly idiopathic ventricular tachycardia, SMVT due to granulomatous infiltration responds poorly to radiofrequency ablation and has a poor prognosis.

Methods Patients without obstructive coronary artery disease and with normal ventricular function presenting with SMVT other than posterior fascicular morphology were evaluated. Computed chest tomograms, cardiac magnetic resonance imaging, and 18-fluorodeoxyglucose positron emission tomographic scans (18FDG PET-CT) were performed. Significant lymph nodes were evaluated for tuberculosis and sarcoidosis. Initial treatment included antiarrhythmic drugs ± radiofrequency ablation. Additionally, patients with evidence of tuberculosis received anti-tuberculosis therapy; the rest were treated as sarcoidosis.

Results Mediastinal adenopathy with mid-myocardial scar and/or focal myocardial inflammation was observed in 14 patients; lymph nodes revealed noncaseating granulomas in all. Evidence of tuberculosis was present in 79%. During follow-up (median duration 25 months), SMVT recurred despite initial treatment in 92%. Addition of disease-specific therapy abolished further recurrences in 64% of them. Decrease in SMVT correlated with resolution of myocardial inflammation on serial 18FDG PET-CTs. Appropriate therapies occurred in 67% of patients receiving implantable cardioverter-defibrillators.

Conclusions A subset of patients with SMVT with preserved ventricular function has a syndrome of arrhythmogenic myocarditis with granulomatous mediastinal adenopathy due to myocardial tuberculosis or cardiac sarcoidosis. This entity is optimally managed with a combination of disease-specific therapy and antiarrhythmic measures (135).

Plasma von Willebrand Factor Levels Are an Independent Risk Factor for Adverse Events Including Mortality and Major Bleeding in Anticoagulated Atrial Fibrillation Patients

Objectives The purpose of this study was to evaluate the prognostic value of plasma von Willebrand factor (vWF) levels and fibrin D-dimer in a large cohort of anticoagulated permanent atrial fibrillation (AF) patients.

Background In nonanticoagulated AF patients, plasma vWF levels have been related to stroke and vascular events. There are limited data on the prognostic role of biomarkers in anticoagulated AF patients in relation to adverse events (including thromboembolism), mortality, and major bleeding.

Methods We studied 829 patients (50% male; median age 76 years) with permanent AF who were stabilized (for at least 6 months) on oral anticoagulation therapy (international normalized ratio: 2.0 to 3.0). Plasma D-dimer and vWF levels were quantified by enzyme-linked immunosorbent assay. Patients were followed for 2 years, and adverse events (including thromboembolism, mortality, and major bleeding) were recorded.

Results Patients were followed for a median of 828 days (range 18 to 1,085 days). On multivariate analysis, age 75 years and older, previous stroke, heart failure, and high plasma vWF levels (≥221 IU/dl) were associated with future adverse cardiovascular events (all p values <0.05). High plasma vWF levels, elderly patients, diabetes, hypercholesterolemia, and current smoking were associated with mortality (all p values <0.05). High plasma vWF levels were also an independent predictor of major bleeding (hazard ratio: 4.47, 95% confidence interval: 1.86 to 10.75; p < 0.001). High plasma vWF levels were able to refine clinical risk stratification schema for stroke (CHADS2 [Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior Stroke or transient ischemic attack (doubled)], CHA2DS2-VASc [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 to 74 years, Sex category]) and...
Teamwork and Leadership in Cardiopulmonary Resuscitation

Despite substantial efforts to make cardiopulmonary resuscitation (CPR) algorithms known to healthcare workers, the outcome of CPR has remained poor during the past decades. Resuscitation teams often deviate from algorithms of CPR. Emerging evidence suggests that in addition to technical skills of individual rescuers, human factors such as teamwork and leadership affect adherence to algorithms and hence the outcome of CPR. This review describes the state of the science linking team interactions to the performance of CPR. Because logistical barriers make controlled measurement of team interaction in the earliest moments of real-life resuscitations challenging, our review focuses mainly on high-fidelity human simulator studies. This technique allows in-depth investigation of complex human interactions using precise and reproducible methods. It also removes variability in the clinical parameters of resuscitation, thus letting researchers study human factors and team interactions without confounding by clinical variability from resuscitation to resuscitation. Research has shown that a prolonged process of team building and poor leadership behavior are associated with significant shortcomings in CPR. Teamwork and leadership training have been shown to improve subsequent team performance during resuscitation and have recently been included in guidelines for advanced life support courses. We propose that further studies on the effects of team interactions on performance of complex medical emergency interventions such as resuscitation are needed. Future efforts to better understand the influence of team factors (e.g., team member status, team hierarchy, handling of human errors), individual factors (e.g., sex differences, perceived stress), and external factors (e.g., equipment, algorithms, institutional characteristics) on team performance in resuscitation situations are critical to improve CPR performance and medical outcomes of patients (136).

Reversible Remodeling and the Risk of Ventricular Tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy)

Objectives We aimed to evaluate the relationship between echocardiographic response to cardiac resynchronization therapy (CRT) and the risk of subsequent ventricular tachyarrhythmias (VTAs).

Background Current data regarding the effect of CRT on the risk of VTA are limited and conflicting.

Methods The risk of a first appropriate implantable cardioverter-defibrillator (ICD) therapy for VTA (including ventricular tachycardia, ventricular fibrillation, and ventricular flutter) was compared between high- and low-echocardiographic responders to CRT defibrillator (CRT-D) therapy (defined as ≥25% and <25% reductions, respectively, in left ventricular end-systolic volume [LVESV] at 1 year compared with baseline) and ICD-only patients enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy).

Results The cumulative probability of a first VTA at 2 years after assessment of echocardiographic response was highest among low responders to CRT-D (28%), intermediate among ICD-only patients (21%), and lowest among high responders to CRT-D (12%), with p < 0.001 for the overall difference during follow-up. Multivariate analysis showed that high responders to CRT-D experienced a significant 55% reduction in the risk of VTA compared with ICD-only patients (p < 0.001), whereas the risk of VTA was not significantly different between low responders and ICD-only patients (hazard ratio [HR]: 1.26; p = 0.21). Consistently, assessment of response to CRT-D as a continuous measure showed that incremental 10% reductions in left ventricular end-systolic volume were associated with corresponding reductions in the risk of subsequent VTA (HR: 0.80; p < 0.001), VTA/death (HR: 0.79; p < 0.001), ventricular tachycardia (HR: 0.80; p < 0.001), and ventricular fibrillation/ventricular flutter (HR: 0.75; p = 0.044).

Conclusions In patients with left ventricular dysfunction enrolled in the MADIT-CRT trial, reverse remodeling was associated with a significant reduction in the risk of subsequent life-threatening VTAs. (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (138).

Clinical Implications of Midventricular Obstruction in Patients With Hypertrophic Cardiomyopathy

Objectives We investigated the prevalence, clinical characteristics, and prognosis of hypertrophic cardiomyopathy (HCM) patients with midventricular obstruction (MVO).

Background Previous descriptions of patients with MVO have been confined to case reports or small patient series, and this subgroup of HCM patients has therefore remained underrecognized.

Methods The study population included 490 HCM patients. Left ventricular MVO was diagnosed when the peak midcavity gradient was estimated to be ≥30 mm Hg. Results MVO was identified in 46 patients (9.4%). Patients with MVO were more likely to be symptomatic than those without. MVO was found to be an independent
determinant of HCM-related death in multivariate models (hazard ratio [HR]: 2.23, p = 0.016), and this trend was especially pronounced for the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 3.19, p < 0.001). Apical aneurysm formation was identified in 28.3% of patients with MVO and strongly predicted HCM-related death (HR: 3.47, p = 0.008) and the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 5.08, p < 0.001). In addition, MVO without apical aneurysm was also identified as an independent determinant of the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 2.43, p = 0.045).

Conclusions This analysis identified MVO as an independent predictor of adverse outcomes, especially the combined endpoint of sudden death and potentially lethal arrhythmic events. Our results suggest that longer periods of exposure to MVO might lead to unfavorable consequences. They also support the principle that the presence of MVO in patients with HCM has important pathophysiological implications (139).

Low Prevalence of Risk Markers in Cases of Sudden Death Due to Brugada Syndrome: Relevance to Risk Stratification in Brugada Syndrome

Objectives The objective of this study was to determine the prevalence of conventional risk factors in sudden arrhythmic death syndrome (SADS) probands with Brugada syndrome (BrS).

Background Patients with BrS and previous aborted sudden cardiac death (SCD) are at high risk of recurrent events. Other universally accepted clinical features associated with higher risk include unheralded syncope and the presence of a spontaneous type 1 electrocardiogram (ECG).

Methods We analyzed reported symptoms and reviewed ECGs from SADS probands with familial diagnoses of BrS, established by cardiological evaluation, including ECG, 2-dimensional echocardiography, Holter monitoring, exercise tolerance testing, and ajmaline provocation. These cases underwent familial evaluation between 2003 and 2010.

Results A total of 49 consecutive families with a confirmed SADS death and a diagnosis of BrS were evaluated, comprising assessment of 202 family members in total. One family had 2 members with SADS, resulting in a total of 50 probands included. Mean age of death of probands was 29.1 ± 10.6 years, with 41 males (82%) (p < 0.05). Antemortem ECGs were available for 5 SADS probands, 1 of which demonstrated a spontaneous type 1 pattern. In 45 probands, symptoms before death were reported reliably by family members. Of these, 9 (20%) had experienced at least 1 syncopal episode before the fatal event. Importantly, 68% of probands would not have fulfilled any current criteria for consideration of implantable cardioverter-defibrillator.

Conclusions The “low-risk” asymptomatic BrS group comprises the majority of SCD in this cohort. Current risk stratification would appear to be inadequate, and new markers of risk are vital (140).

Preventing Overdiagnosis of Implantable Cardioverter-Defibrillator Lead Fractures Using Device Diagnostics

Objectives This study sought to use implantable cardioverter-defibrillator (ICD) diagnostics to discriminate ICD lead fractures from normally functioning leads with high impedance and from connection problems between the lead and header.

Background ICD diagnostics facilitate identification of fractures, but there are no accepted criteria for discriminating fractures from other causes of high impedance and/or nonphysiological “noise” oversensing.

Methods We analyzed a development set of 91 leads to construct a stepwise algorithm based on ICD diagnostics. It included 40 fractures, 30 connection problems, and 21 functioning leads that triggered high-impedance alerts. Then we applied this algorithm to an independent test set of 100 leads: 70 fractures and 30 intact leads with connection problems that were misdiagnosed clinically as fractures. In the algorithm, either extremely high maximum impedance or noise oversensing with a normal impedance trend indicated a fracture. A short interval from surgery to impedance rise or prolonged stable impedance after an abrupt rise indicated a connection problem. A gradual impedance increase or stable, high impedance indicated a functioning lead.

Results In the test set, the algorithm correctly classified 100% of fractures (95% confidence interval [CI]: 95% to 100%) and 87% of connection problems that were misdiagnosed as fractures (95% CI: 70% to 95%).

Conclusions An algorithm using only ICD diagnostics identifies leads with oversensing or high impedance as fractures or connection problems with a high degree of accuracy (141).

Flecainide Therapy Reduces Exercise-Induced Ventricular Arrhythmias in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

Objectives This study evaluated the efficacy and safety of flecainide in addition to conventional drug therapy in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT).

Background CPVT is an inherited arrhythmia syndrome caused by gene mutations that destabilize cardiac ryanodine receptor Ca2+ release channels. Sudden cardiac death is incompletely prevented by conventional drug therapy with β-blockers with or without Ca2+ channel blockers. The antiarrhythmic agent flecainide directly targets the molecular defect in CPVT by inhibiting premature Ca2+ release and triggered beats in vitro.
Methods We collected data from every consecutive genotype-positive CPVT patient started on flecainide at 8 international centers before December 2009. The primary outcome measure was the reduction of ventricular arrhythmias during exercise testing.

Results Thirty-three patients received flecainide because of exercise-induced ventricular arrhythmias despite conventional (for different reasons, not always optimal) therapy (median age 25 years; range 7 to 68 years; 73% female). Exercise tests comparing flecainide in addition to conventional therapy with conventional therapy alone were available for 29 patients. Twenty-two patients (76%) had either partial (n = 8) or complete (n = 14) suppression of exercise-induced ventricular arrhythmias with flecainide (p < 0.001). No patient experienced worsening of exercise-induced ventricular arrhythmias. The median daily flecainide dose in responders was 150 mg (range 100 to 300 mg). During a median follow-up of 20 months (range 12 to 40 months), 1 patient experienced implanted cardioverter-defibrillator shocks for polymorphic ventricular arrhythmias, which were associated with a low serum flecainide level. In 1 patient, flecainide successfully suppressed exercise-induced ventricular arrhythmias for 29 years.

Conclusions Flecainide reduced exercise-induced ventricular arrhythmias in patients with CPVT not controlled by conventional drug therapy (142).

The V2 Transition Ratio: A New Electrocardiographic Criterion for Distinguishing Left From Right Ventricular Outflow Tract Tachycardia Origin

Objectives We sought to develop electrocardiography (ECG) criteria for distinguishing left ventricular outflow tract (LVOT) from right ventricular outflow tract (RVOT) origin in patients with idiopathic outflow tract ventricular tachycardia (OTVT) and lead V3 R/S transition.

Background Several ECG criteria have been proposed for differentiating left from right OTVT origin; ventricular tachycardias (VTs) with left bundle branch block and V3 transition remain a challenge.

Methods We analyzed the surface ECG pattern of patients with OTVT with a precordial transition in lead V3 who underwent successful catheter ablation. Sinus and VT QRS morphologies were measured in limb and precordial leads with electronic calipers. The V2 and V3 transition ratios were calculated by computing the percentage R-wave during VT (R/R+S)VC21 divided by the percentage R-wave in sinus rhythm (R/R+S)SR.

Results We retrospectively analyzed ECGs from 40 patients (mean age 44 ± 14 years, 21 female) with outflow tract premature ventricular contractions (PVCs)/VT. Patients with structural heart disease, paced rhythms, and bundle branch block during sinus rhythm were excluded. The V3 transition ratio was significantly greater for LVOT PVCs compared with RVOT PVCs (1.27 ± 0.60 vs. 0.23 ± 0.16; p < 0.001) and was the only independent predictor of LVOT origin. In 21 prospective cases, a V2 transition ratio ≥0.60 predicted an LVOT origin with 91% accuracy. A PVC precordial transition occurring later than the sinus rhythm transition excluded an LVOT origin with 100% accuracy.

Conclusions The V2 transition ratio is a novel electrocardiographic measure that reliably distinguishes LVOT from RVOT origin in patients with lead V3 precordial transition. This measure might be useful for counseling patients and planning an ablation strategy (143).

The Early Repolarization Pattern in the General Population: Clinical Correlates and Heritability

Objectives This study sought to describe the clinical correlates and heritability of the early repolarization pattern (ERP) in 2 large, population-based cohorts.

Background There is growing recognition that ERP is associated with adverse outcomes.

Methods Participants of the Framingham Heart Study (FHS) (N = 3,995) and the Health 2000 Survey (H2K) (N = 5,489) were included. ERP was defined as a J-point elevation >0.1 mV in ≥2 leads in either the inferior (II, III, aVF) or lateral (I, aVL, V4–6) territory or both. We tested the association between clinical characteristics and ERP, and estimated sibling recurrence risk.

Results ERP was present in 243 of 3,955 (6.1%) of FHS and 180 of 5,489 (3.3%) of H2K subjects. Male sex, younger age, lower systolic blood pressure, higher Sokolow-Lyon index, and lower Cornell voltage were independently associated with the presence of ERP. In the FHS sample, siblings of individuals with ERP had an ERP prevalence of 11.6% (recurrence risk ratio of 1.89). Siblings of individuals with ERP had an increased unadjusted odds of ERP (odds ratio: 2.22, 95% confidence interval: 1.01 to 4.85, p = 0.047).

Conclusions ERP has strong association with clinical factors and has evidence for a heritable basis in the general population. Further assessment of the genetic determinants of ERP is warranted (144).

Congenitally Corrected Transposition of the Great Arteries: Ventricular Function at the Time of Systemic Atrioventricular Valve Replacement Predicts Long-Term Ventricular Function

Objectives The objective was to evaluate the systemic ventricular ejection fraction (SVEF) at the time of systemic atrioventricular valve (SAVV) replacement as a predictor of SVEF ≥1 year after surgery in patients with congenitally corrected transposition of the great arteries (CCTGA).

Background Progressive SAVV regurgitation causes systemic ventricular failure in CCTGA patients, who are commonly referred late for intervention. Survival after surgery is poor when the pre-operative SVEF is <44%.
Methods We retrospectively reviewed 46 patients (pre-operative SVEF ≥40% in 27 patients and <40% in 19 patients) with 2 good-sized ventricles, a morphologically right systemic ventricle, and SAVV regurgitation requiring surgery. Median follow-up was not different in patients with a pre-operative SVEF ≥40% (8.8 years) or <40% (7.7 years, p = 0.36).

Results Pre-operative SVEF was the only independent predictor of ≥1-year post-operative SVEF (p = 0.0001). The late SVEF was preserved (defined as ≥40%) in 63% of patients who underwent surgery with an SVEF ≥40% compared with 10.5% of patients who underwent surgery with an SVEF <40%. Pre-operative variables associated with late mortality were an SVEF ≤40%, a subpulmonary ventricular systolic pressure ≥50 mm Hg, atrial fibrillation, and New York Heart Association functional class III to IV.

Conclusions Post-operative systemic ventricular function after SAVV replacement can be predicted from the pre-operative SVEF. For best results, operation should be considered at an earlier stage, before the SVEF falls below 40% and the subpulmonary ventricular systolic pressure rises above 50 mm Hg (145).

Incidence, Causes, and Outcomes of Out-of-Hospital Cardiac Arrest in Children: A Comprehensive, Prospective, Population-Based Study in the Netherlands

Objectives This study sought to determine comprehensively the incidence of pediatric out-of-hospital cardiac arrest (OHCA) and its contribution to total pediatric mortality, the causes of pediatric OHCA, and the outcome of resuscitation of pediatric OHCA patients.

Background There is a paucity of complete studies on incidence, causes, and outcomes of pediatric OHCA.

Methods In this prospective, population-based study, OHCA victims younger than age 21 years in 1 province of the Netherlands were registered through both emergency medical services and coroners over a period of 4.3 years. Death certificate data on total pediatric mortality, survival status, and neurological outcome at hospital discharge also were obtained.

Results With a total mortality of 923 during the study period and 233 victims of OHCA (including 221 who died and 12 who survived), OHCA caused 24% (221 of 923) of total pediatric mortality. Natural causes of OHCA amounted to 115 (49%) cases, with cardiac causes being most prevalent (n = 90, 39%). The incidence of pediatric OHCA was 9.0 per 100,000 pediatric person-years (95% confidence interval: 7.8 to 10.3), whereas the incidence of pediatric OHCA from cardiac causes was 3.2 (95% confidence interval: 2.5 to 3.9). Of 51 resuscitated patients, 12 (24%) survived; among survivors, 10 (83%) had a neurologically intact outcome.

Conclusions Out-of-hospital cardiac arrest accounts for a significant proportion of pediatric mortality, and cardiac causes are the most prevalent causes of OHCA. The vast
majority of OHCA survivors have a neurologically intact outcome (147).

**Pericardial Fat Is Associated With Atrial Fibrillation Severity and Ablation Outcome**

**Objectives** The aim of this study was to characterize the relationship between pericardial fat and atrial fibrillation (AF).

**Background** Obesity is an important risk factor for AF. Pericardial fat has been hypothesized to exert local pathogenic effects on nearby cardiac structures above and beyond that of systemic adiposity.

**Methods** One hundred ten patients undergoing first-time AF ablation and 20 reference patients without AF underwent cardiac magnetic resonance imaging for the quantification of periatrial, periventricular, and total pericardial fat volumes using a previously validated technique. Together with body mass index and body surface area, these were examined in relation to the presence of AF, the severity of AF, left atrial volume, and long-term AF recurrence after ablation.

**Results** Pericardial fat volumes were significantly associated with the presence of AF, AF chronicity, and AF symptom burden (all p values <0.05). Pericardial fat depots were also predictive of long-term AF recurrence after ablation (p = 0.035). Finally, pericardial fat depots were also associated with left atrial volume (total pericardial fat: r = 0.46, p < 0.001). Importantly, these associations persisted after multivariate adjustment and additional adjustment for body weight. In contrast, however, systemic measures of adiposity, such as body mass index and body surface area, were not associated with these outcomes in multivariate-adjusted models.

**Conclusions** Pericardial fat is associated with the presence of AF, the severity of AF, left atrial volumes, and poorer outcomes after AF ablation. These associations are both independent of and stronger than more systemic measures of adiposity. These findings are consistent with the hypothesis of a local pathogenic effect of pericardial fat on the arrhythmogenic substrate supporting AF (148).

**Synchronicity of LV Contraction as a Determinant of LV Twist Mechanics: Serial Speckle-Tracking Analyses in WPW Syndrome Before and After Radiofrequency Catheter Ablation**

**Objectives** This study set out to investigate the isolated impact of synchronous patterns of left ventricular (LV) contraction (i.e., LV synchronicity) on LV twist behavior.

**Background** Although the relationships between LV loading status/LV contractility and twist are well-established, no data are available regarding the relation between LV twist and LV synchronicity, without any interference by changes in LV pre-load, afterload, and contractility. Serial assessment of patients with Wolff-Parkinson-White syndrome before and after radiofrequency catheter ablation (RFCA) allows this to be explored.

**Method** Of the 40 Wolff-Parkinson-White patients initially screened, 34 were enrolled. Two-dimensional and Doppler echocardiography along with speckle tracking-derived LV twist mechanics, apical-basal rotation delay, and left ventricular dyssynchrony index (LVdys) were obtained before and after RFCA. The LVdys was defined as the maximal delay in time-to-peak radial strain of different LV segments at the papillary muscle level.

**Results** Overall, no significant changes were demonstrated in LV volumes, systolic and diastolic function, and end-systolic wall stress before versus after RFCA. After RFCA, median value of LVdys was attenuated from 33.5 (interquartile range [IQR]: 14.0 to 84.3) to 14.0 (IQR: 11.5 to 21.8) (p = 0.002), which was accompanied by a reduction in apical-basal rotation delay from 9.7% (IQR: 3.5 to 23.7) to 3.3% (IQR: 1.3 to 8.0) (p = 0.004). In contrast, LV twist increased from 14.2° (IQR: 9.1° to 18.4°) before to 19.7° (IQR: 15.0° to 22.6°) after RFCA (p = 0.002). Delta LV twist pre- to post-RFCA displayed a significant inverse correlation with changes in apical-basal rotation delay (r = −0.42, p = 0.01) and Delta LVdys (r = −0.39, p = 0.02).

**Conclusions** The LV synchronous contraction is significantly related to LV twist (149).

**Prevalence and Prognostic Significance of Left Ventricular Reverse Remodeling in Dilated Cardiomyopathy Receiving Tailored Medical Treatment**

**Objectives** The purpose of this study was to determine the prevalence and prognostic role of left ventricular reverse remodeling (LVRR) in idiopathic dilated cardiomyopathy (IDCM).

**Background** Tailored medical therapy can lead to LVRR in IDCM. The prevalence and prognostic impact of LVRR remain unclear.

**Methods** We consecutively enrolled 361 IDCM patients. LVRR was defined as a left ventricular ejection fraction increase of ≥10 U or a left ventricular ejection fraction of ≥50% and a decrease in indexed left ventricular end-diastolic diameter of ≥10% or indexed left ventricular end-diastolic diameter of ≥33 mm/m² at 24 months (range 9 to 36 months). Follow-up echocardiographic data were available for 242 patients (67%), 34 (9%) died/underwent heart transplantation (HTx) before re-evaluation, and 85 (24%) did not have a complete re-evaluation. After re-evaluation, the surviving patients were followed for 110 ± 53 months; there were 55 deaths (23%) and 32 HTx (13%).

**Results** LVRR was found in 89 of 242 patients (37%). Baseline predictors of LVRR were higher systolic blood pressure (p = 0.047) and the absence of left bundle branch block (p = 0.009). When added to a prognostic baseline model including male sex, heart failure duration, New York Heart Association functional classes III to IV, LVEF,
significant mitral regurgitation, and beta-blockers, LVRR, New York Heart Association functional classes III to IV, and significant mitral regurgitation after 24 months emerged as independent predictors of death/HTx and heart failure death/HTx. The model including follow-up variables showed additional prognostic power with respect to baseline model (for death/HTx, area under the curve: 0.80 vs. 0.70, respectively, p = 0.004). Furthermore, only LVRR was significantly associated with sudden death/major ventricular arrhythmia in the long-term.

**Conclusions**
LVRR characterized approximately one-third of IDCM patients surviving 2 years while receiving optimal medical therapy and allowed a more accurate long-term prognostic stratification of the disease (150).

### Prolongation of the Atrioventricular Conduction in Fetuses Exposed to Maternal Anti-Ro/SSA and Anti-La/SSB Antibodies Did Not Predict Progressive Heart Block: A Prospective Observational Study on the Effects of Maternal Antibodies on 165 Fetuses

**Objectives**
We prospectively examined the prevalence and outcome of untreated fetal atrioventricular (AV) prolongation in the presence of maternal anti-Ro antibodies.

**Background**
It has been suggested that antibody-mediated congenital complete atrioventricular block (CAVB) may be preventable if detected and treated early when low-grade block is present. With this rationale in mind, dexamethasone has been advocated by others to treat prolonged fetal AV conduction >2 z-scores, consistent with first-degree heart block.

**Methods**
Between July 2003 and June 2009, 165 fetuses of 142 anti-Ro/La antibody–positive women were referred to our center for serial echocardiography. Our protocol included weekly evaluation of the fetal AV conduction between 19 (range 17 to 23) and 24 (range 23 to 35) gestational weeks. AV times were compared with institutional reference data and with post-natal electrocardiograms.

**Results**
Of 150 fetuses with persistently normal AV conduction throughout the observation period, a diagnosis of CAVB was subsequently made in 1 at 28 weeks, after the serial evaluation had ended. Of 15 untreated fetuses either with AV prolongation between 2 and 6 z-scores or with type 1 second-degree block, progressive heart block developed in none of them. Three of these 15 fetuses (20%) had a neonatal diagnosis of first-degree block that spontaneously resolved (n = 2) or has not progressed (n = 1) on follow-up examinations. No other cardiac complications were detected.

**Conclusions**
Fetal AV prolongation did not predict progressive heart block to birth. Our findings question the rationale of a management strategy that relies on the early identification and treatment of fetal AV prolongation to prevent CAVB (151).

### Severe Renal Impairment and Stroke Prevention in Atrial Fibrillation: Implications for Thromboprophylaxis and Bleeding Risk

The prevalence of atrial fibrillation (AF) in end-stage renal failure is high, with an increased risk of stroke among these patients with AF compared with the AF population without severe renal impairment. Many trials have shown the net clinical benefit of oral anticoagulation therapy for primary and secondary prevention of stroke in patient populations with AF. However, current stroke risk stratification schemes are based on studies that have deliberately excluded patients with severe renal impairment. Indeed, there are no large randomized controlled trials that assess the real risk/benefit of full-intensity anticoagulation in patients with severe renal impairment. Also, rates of major bleeding episodes in anticoagulated hemodialysis patients with AF are high. These data are influenced by the lack of appropriate monitoring, the difficulties in maintaining the international normalized ratio target (variable between the studies), and an inaccurate bleeding classification. Thus, the limited available data may be difficult to apply to such a heterogeneous patient population, characterized by both an increased risk of bleeding and a hypercoagulability state, as seen in the patient population with severe renal impairment (152).

### The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) Trial: The Value of Wireless Remote Monitoring With Automatic Clinician Alerts

**Objectives**
The primary objective was to determine if wireless remote monitoring with automatic clinician alerts reduces the time from a clinical event to a clinical decision in response to arrhythmias, cardiovascular (CV) disease progression, and device issues compared to patients receiving standard in-office care. A secondary objective was to compare the rates of CV health care utilization between patients in the remote and in-office arms.

**Background**
In addition to providing life-saving therapy, implantable cardioverter-defibrillators collect advanced diagnostics on the progression of the patient’s heart disease. Device technology has progressed to allow wireless remote monitoring with automatic clinician alerts to replace some scheduled in-office visits.

**Methods**
The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) study was a multicenter, prospective, randomized evaluation involving 1,997 patients from 136 clinical sites who underwent insertion of an implantable cardioverter-defibrillator (including cardiac resynchronization therapy devices) and were followed up for 15 months. Health care utilization data included all CV-related hospitalizations, emergency department visits, and clinic office visits.

**Results**
The median time from clinical event to clinical decision per patient was reduced from 22 days in the in-office arm to 4.6 days in the remote arm (p < 0.001).
Mechanisms of Fractionated Electrograms Formation in the Posterior Left Atrium During Paroxysmal Atrial Fibrillation in Humans

Objectives The aim of this paper was to study mechanisms of formation of fractionated electrograms on the posterior left atrial wall (PLAW) in human paroxysmal atrial fibrillation (AF).

Background The mechanisms responsible for complex fractionated atrial electrogram formation during AF are poorly understood.

Methods In 24 patients, we induced sustained AF by pacing from a pulmonary vein. We analyzed transitions between organized patterns and changes in electrogram morphology leading to fractionation in relation to interbeat interval duration (systolic interval [SI]) and dominant frequency. Computer simulations of rotors helped in the interpretation of the results.

Results Organized patterns were recorded 31 ± 18% of the time. In 47% of organized patterns, the electrograms and PLAW activation sequence were similar to those of incoming waves during pulmonary vein stimulation that induced AF. Transitions to fractionation were preceded by significant increases in electrogram duration, spike number, and SI shortening ($R^2 = 0.94$). Similarly, adenosine infusion during organized patterns caused significant SI shortening leading to fractionated electrograms formation. Activation maps during organization showed incoming wave patterns, with earliest activation located closest to the highest dominant frequency site. Activation maps during transitions to fragmentation showed areas of slowed conduction and unidirectional block. Simulations predicted that SI abbreviation that heralds fractionated electrograms formation might result from a Doppler effect on wave fronts preceding an approaching rotor or by acceleration of a stationary or meandering, remotely located source.

Conclusions During induced AF, SI shortening after either drift or acceleration of a source results in intermittent fibrillatory conduction and formation of fractionated electrograms at the PLAW (154).

Antiarrhythmic Effects of Simvastatin in Canine Pulmonary Vein Sleeve Preparations

Objectives The purpose of this study was to determine the electrophysiologic effects of simvastatin in canine pulmonary vein (PV) sleeve preparations.

Background Ectopic activity arising from the PV plays a prominent role in the development of atrial fibrillation.

Methods Transmembrane action potentials were recorded from canine superfused left superior or inferior PV sleeves using standard microelectrode techniques. Acetylcholine (1 μM), isoproterenol (1 μM), high calcium ([Ca$^{2+}$]o = 5.4 mM), or a combination was used to induce early afterdepolarizations or delayed afterdepolarizations and triggered activity. Voltage clamp experiments were performed in the left atrium measuring fast and late sodium currents.

Results Under steady-state conditions, simvastatin (10 nM, n = 9) induced a small increase in action potential duration measured at 85% repolarization and a significant decrease in action potential amplitude, take-off potential, and maximum rate of rise of action potential upstroke at the fastest rates. The $V_{max}$ decreased from 175.1 ± 34 V/s to 151.7 ± 28 V/s and from 142 ± 47 V/s to 97.4 ± 39 V/s at basic cycle lengths of 300 and 200 ms, respectively. Simvastatin (10 to 20 nM) eliminated delayed afterdepolarizations and delayed afterdepolarization-induced triggered activity in 7 of 7 PV sleeve preparations and eliminated or reduced late-phase 3 early afterdepolarizations in 6 of 6 PV sleeve preparations. Simvastatin (20 nM) did not affect late or fast sodium currents measured using voltage clamp techniques.

Conclusions Our data suggest that in addition to its upstream actions to reduce atrial structural remodeling, simvastatin exerts a direct antiarrhythmic effect by suppressing triggers responsible for the genesis of atrial fibrillation (155).

Impact of Lesion Sets on Mid-Term Results of Surgical Ablation Procedure for Atrial Fibrillation

Objectives The objective of this study was to evaluate the effects of different lesion sets of ablation in patients undergoing mitral surgery plus maze.

Background The role of lesion sets on outcome after maze is poorly defined.

Methods A total of 141 patients were prospectively followed up. Two different lesion sets were prepared: 32 patients underwent a radiofrequency left atrial lesion set of maze (“limited”), and 109 had combined left and right atrial lesion sets of maze ± ganglionic plexi isolation (“extensive”). A longitudinal observational study assessed the role of “extensive” versus “limited” ablation on atrial fibrillation (AF), New York Heart Association (NYHA) functional class II/III, treatment with antiarrhythmic drugs, follow-up recovery of the ratio of E- to A-wave (E/A), and survival and time to hospitalization (overall and for heart failure).

Results The prevalence of AF over time was lower in the “extensive” arm (adjusted relative risk [RR]: 0.10; 95% confidence interval [CI]: 0.03 to 0.31; p < 0.001), with significantly lower prevalence at discharge, 3 months, and 18 months. The prevalence of patients in NYHA functional...
class II/III over time was lower in the “extensive” arm (adjusted RR: 0.11; 95% CI: 0.03 to 0.34; p < 0.001), with significant differences at any assessment (except the third month). The differences in E/A recovery and use of antiarrhythmic drugs were less marked, with an RR of 1.55 (95% CI: 0.99 to 2.42; p = 0.05) and RR of 0.76 (95% CI: 0.54 to 1.06; p = 0.11), respectively, with a significantly lower prevalence of antiarrhythmic drugs in the “extensive” ablation arm at 12, 18, and 24 months. Rates of hospitalization for heart failure, overall hospitalization, and the combined event death/hospitalization were lower in the “extensive” arm (p = 0.11, p = 0.003, and p = 0.002, respectively).

Conclusions The addition of right-sided ablation improves clinical and electrophysiologic results after maze procedure (156).

Risk Factors for Recurrent Syncope and Subsequent Fatal or Near-Fatal Events in Children and Adolescents With Long QT Syndrome

Objectives We aimed to identify risk factors for recurrent syncope in children and adolescents with congenital long QT syndrome (LQTS).

Background Data regarding risk assessment in LQTS after the occurrence of the first syncope episode are limited.

Methods The Prentice-Williams-Peterson conditional gap time model was used to identify risk factors for recurrent syncope from birth through age 20 years among 1,648 patients from the International Long QT Syndrome Registry.

Results Multivariate analysis demonstrated that corrected QT interval (QTc) duration (≥500 ms) was a significant predictor of a first syncope episode (hazard ratio: 2.16), whereas QTc effect was attenuated when the end points of the second, third, and fourth syncope episodes were evaluated (hazard ratios: 1.29, 0.99, 0.90, respectively; p < 0.001 for the null hypothesis that all 4 hazard ratios are identical). A genotype-specific subanalysis showed that during childhood (0 to 12 years), males with LQTS type 1 had the highest rate of a first syncope episode (p = 0.001) but exhibited similar rates of subsequent events as other genotype-sex subsets (p = 0.63). In contrast, in the age range of 13 to 20 years, long QT syndrome type 2 females experienced the highest rate of both first and subsequent syncope events (p < 0.001 and p = 0.01, respectively). Patients who experienced ≥1 episodes of syncope had a 6- to 12-fold (p < 0.001 for all) increase in the risk of subsequent fatal/near-fatal events independently of QTc duration. Beta-blocker therapy was associated with a significant reduction in the risk of recurrent syncope and subsequent fatal/near-fatal events.

Conclusions Children and adolescents who present after an episode of syncope should be considered to be at a high risk of the development of subsequent syncope episodes and fatal/near-fatal events regardless of QTc duration (157).

Cardiac Resynchronization Therapy Is More Effective in Women Than in Men: The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) Trial

Objectives The purpose of this study was to investigate the factors related to sex-specific outcomes for death and heart failure events in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) trial.

Background In the MADIT-CRT trial, women seemed to achieve a better result from resynchronization therapy than men.

Methods All 1,820 patients (453 female and 1,367 male) enrolled in the MADIT-CRT trial were included in this sex-specific outcome analysis that compared the effect of cardiac resynchronization therapy with defibrillator (CRT-D) relative to implanted cardioverter-defibrillator (ICD) on death or heart failure (whichever came first), heart failure only, and death at any time.

Results Female patients were more likely to have nonischemic cardiomyopathy and left bundle branch block and less likely to have renal dysfunction than male patients. Overall, female patients had a better result from CRT-D therapy than male patients, with a significant 69% reduction in death or heart failure (hazard ratio: 0.31, p < 0.001) and 70% reduction in heart failure alone (hazard ratio: 0.30, p < 0.001). Women had a significant 72% reduction in all-cause mortality in the total population (hazard ratio: 0.28, p = 0.02) and significant 82% and 78% reductions in mortality in those with QRS ≥150 ms and with left bundle branch block conduction disturbance, respectively, with sex-by-treatment interactions for mortality reduction significant at p < 0.05 in each of these 3 patient groups. These beneficial CRT-D effects among women were associated with consistently greater echocardiographic evidence of reverse cardiac remodeling in women than in men.

Conclusions Women in the MADIT-CRT trial obtained significantly greater reductions in death or heart failure (whichever came first), heart failure alone, and all-cause mortality with CRT-D therapy than men, with consistently greater echocardiographic evidence of reverse cardiac remodeling in women than in men. (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (158).

Myocardial Fibrosis Predicts Appropriate Device Therapy in Patients With Implantable Cardioverter-Defibrillators for Primary Prevention of Sudden Cardiac Death

Objectives The purpose of this study was to evaluate the association between regional myocardial fibrosis and ventricular arrhythmias in patients with cardiomyopathy.

Background Patients with heart failure are at risk of sudden cardiac death (SCD). Current guidelines recommend implantable cardioverter-defibrillator (ICD) devices for
a subgroup based on impaired left ventricular function. A significant proportion of devices never discharge, hence a more accurate method for targeting those at risk is desirable.

**Methods** We prospectively enrolled 103 patients meeting criteria for ICD implantation for primary prevention of SCD. Cardiac magnetic resonance imaging was performed before device implantation. Regional fibrosis was identified with late gadolinium enhancement (LGE).

**Results** Median follow-up was 573 days (interquartile range: 379 to 863 days). The LGE identified regional fibrosis in 31 of 61 (51%) patients with nonischemic cardiomyopathy (NICM) and in all 42 patients with ischemic cardiomyopathy (ICM). There was a 29% (9 of 31) discharge rate in the NICM group with LGE compared with a 14% (6 of 42) discharge rate in the ICM group (p = NS). There were no ICD discharges in the NICM group without LGE, which was significantly lower than the rate observed in both the ICM patients (p = 0.04) and the NICM patients with LGE (p < 0.01). Left ventricular ejection fraction was similar in patients with and without device therapy (24 ± 12% vs. 26 ± 8%, p = NS) and those with or without LGE (25 ± 9% vs. 26 ± 9%, p = NS).

**Conclusions** Patients with advanced cardiomyopathy and myocardial fibrosis demonstrated by LGE on cardiac magnetic resonance imaging have a high likelihood of appropriate ICD therapy. Correspondingly, absence of LGE may indicate a lower risk for malignant ventricular arrhythmias (159).

### The Short QT Syndrome: Proposed Diagnostic Criteria

**Objectives** We aimed to develop diagnostic criteria for the short QT syndrome (SQTS) to facilitate clinical evaluation of suspected cases.

**Background** The SQTS is a cardiac channelopathy associated with atrial fibrillation and sudden cardiac death. Ten years after its original description, a consensus regarding an appropriate QT interval cutoff and specific diagnostic criteria have yet to be established.

**Methods** The MEDLINE database was searched for all reported cases of SQTS in the English language, and all relevant data were extracted. The distribution of QT intervals and electrocardiographic (ECG) features in affected cases were analyzed and compared to data derived from ECG analysis from general population studies.

**Results** A total of 61 reported cases of SQTS were identified. Index events, including sudden cardiac death, aborted cardiac arrest, syncope, and/or atrial fibrillation occurred in 35 of 61 (57.4%) cases. The cohort was predominantly male (75.4%) and had a mean QTc value of 306.7 ms with values ranging from 248 to 381 ms in symptomatic cases. In reference to the ECG characteristics of the general population, and in consideration of clinical presentation, family history, and genetic findings, a highly sensitive diagnostic scoring system was developed.

**Conclusions** Based on a comprehensive review of 61 reported cases of the SQTS, formal diagnostic criteria have been proposed that will facilitate diagnostic evaluation in suspected cases of SQTS. Diagnostic criteria may lead to a greater recognition of this condition and provoke screening of at-risk family members (160).

### Association of Left Atrial Fibrosis Detected by Delayed-Enhancement Magnetic Resonance Imaging and the Risk of Stroke in Patients With Atrial Fibrillation

**Objectives** This study tried to determine the association between left atrial (LA) fibrosis, detected using delayed-enhanced magnetic resonance imaging (DE-MRI), and the CHADS2 score (point system based on individual clinical risk factors including congestive heart failure, hypertension, age, diabetes, and prior stroke) variables, specifically stroke.

**Background** In patients with atrial fibrillation (AF), conventional markers for the risk of stroke base their higher predictive effect on clinical features, particularly previous stroke history, and not individual LA pathophysiological properties. We aimed to determine the association between LA fibrosis, detected using DE-MRI, and the CHADS2 score variables, specifically stroke.

**Methods** Patients with AF who presented to the AF clinic and received a DE-MRI of the LA were evaluated. Their risk factor profiles, including a CHADS2 score, were catalogued. The degree of LA fibrosis was determined as a percentage of the LA area. Any history of previous strokes, warfarin use, or cerebrovascular disease was recorded.

**Results** A total of 387 patients, having a mean age of 65 ± 12 years, 36.8% female, were included in this study. A history of previous stroke was present in 36 (9.3%) patients. Those patients with previous strokes had a significantly higher percentage of LA fibrosis (24.4 ± 12.4% vs. 16.2 ± 9.9%, p < 0.01). A larger amount of LA fibrosis was also seen in those patients with a higher CHADS2 score (≥2: 18.7 ± 11.4 vs. <2: 14.7 ± 9.2, p < 0.01). A logistic regression analysis of all variables except strokes (CHAD score) demonstrated that LA fibrosis independently predicted cerebrovascular events (p = 0.002) and significantly increased the predictive performance of the score (area under the curve = 0.77).

**Conclusions** Our preliminary, multicenter results suggest DE-MRI–based detection of LA fibrosis is independently associated with prior history of strokes. We propose that the amount of DE-MRI–determined LA fibrosis could represent a marker for stroke and a possible therapeutic target with potential applicability for clinical treatment for patients with AF (161).
Systematic Review of the Incidence of Sudden Cardiac Death in the United States

The need for consistent and current data describing the true incidence of sudden cardiac arrest (SCA) and/or sudden cardiac death (SCD) was highlighted during the most recent Sudden Cardiac Arrest Thought Leadership Alliance’s (SCATLA) Think Tank meeting of national experts with broad representation of key stakeholders, including thought leaders and representatives from the American College of Cardiology, American Heart Association, and the Heart Rhythm Society. As such, to evaluate the true magnitude of this public health problem, we performed a systematic literature search in MEDLINE using the MeSH headings, “death, sudden” OR the terms “sudden cardiac death” OR “sudden cardiac arrest” OR “cardiac arrest” OR “cardiac death” OR “sudden death” OR “arrhythmic death.” Study selection criteria included peer-reviewed publications of original data used to estimate SCD incidence in the U.S. We used Web of Science’s Cited Reference Search to evaluate the impact of each primary estimate on the medical literature by determining the number of times each “primary source” has been cited. The estimated U.S. annual incidence of SCD varied widely from 180,000 to >450,000 among 6 included studies. These different estimates were in part due to different data sources (with data age ranging from 1980 to 2007), definitions of SCD, case ascertainment criteria, methods of estimation/extrapolation, and sources of case ascertainment. The true incidence of SCA and/or SCD in the U.S. remains unclear, with a wide range in the available estimates that are badly dated. As reliable estimates of SCD incidence are important for improving risk stratification and prevention, future efforts are clearly needed to establish uniform definitions of SCA and SCD and then to prospectively and precisely capture cases of SCA and SCD in the overall U.S. population (162).

Use of Intravenous Gamma Globulin and Corticosteroids in the Treatment of Maternal Autoantibody-Mediated Cardiomyopathy

Objectives This study sought to evaluate the outcome of maternal autoantibody-mediated fetal cardiomyopathy/endocardial fibroelastosis following intravenous gamma globulin (IVIG) and corticosteroid therapy.

Background We have previously shown that 85% of fetuses and infants with maternal autoantibody-mediated fetal cardiomyopathy/endocardial fibroelastosis suffer demise or need for transplant. In an attempt to improve this outcome, in 1998, we began to empirically treat affected patients with IVIG and corticosteroids.

Methods We reviewed the clinical records and echocardiograms of 20 affected patients encountered in our institutions and treated with IVIG and corticosteroids from 1998 to 2009.

Results All 20 were initially referred at a median gestational age of 23 weeks (range 18 to 38 weeks). Nineteen mothers were anti-Ro antibody positive, 8 anti-La antibody positive, and 7 had clinical autoimmune disease. Endocardial fibroelastosis was seen in 16 and was not obvious in 4 others with reduced ventricular function, and 16 (80%) had reduced or borderline ventricular shortening fraction (≤30%) before or after birth. Eighteen had atrioventricular block at referral (16 in 3rd). During pregnancy, maternal IVIG was given in 9 and dexamethasone in 17. After birth, 17 infants received IVIG (n = 14) and/or corticosteroids (n = 15). Twelve underwent pacemaker implantation. Four with hydrops at presentation died perinatally, despite initial improvement in function in 3. At a median follow-up of 2.9 years (1.1 to 9.8 years), 16 (80%) patients are currently alive with normal systolic ventricular function and 6 are not paced.

Conclusions Treatment of maternal autoantibody-mediated fetal cardiomyopathy/endocardial fibroelastosis with IVIG and corticosteroids potentially improves the outcome of affected fetuses. Further studies are needed to determine the optimal dose and timing of IVIG administration (163).

Inappropriate Implantable Cardioverter-Defibrillator Shocks: Incidence, Predictors, and Impact on Mortality

Objectives The purpose of this study was to assess the incidence, predictors, and outcome of inappropriate shocks in implantable cardioverter-defibrillator (ICD) patients.

Background Despite the benefits of ICD therapy, inappropriate defibrillator shocks continue to be a significant drawback. The prognostic importance of inappropriate shocks outside the setting of a clinical trial remains unclear.

Methods From 1996 to 2006, all recipients of defibrillator devices equipped with intracardiac electrogram storage were included in the current analysis and clinically assessed at implantation. During follow-up, the occurrence of inappropriate ICD shocks and all-cause mortality was noted.

Results A total of 1,544 ICD patients (79% male, age 61 ± 13 years) were included in the analysis. During the follow-up period of 41 ± 18 months, 13% experienced ≥1 inappropriate shocks. The cumulative incidence steadily increased to 18% at 5-year follow-up. Independent predictors of the occurrence of inappropriate shocks included a history of atrial fibrillation (hazard ratio [HR]: 2.0, p < 0.01) and age younger than 70 years (HR: 1.8, p = 0.01). Experiencing a single inappropriate shock resulted in an increased risk of all-cause mortality (HR: 1.6, p = 0.01). Mortality risk increased with every subsequent shock, up to an HR of 3.7 after 5 inappropriate shocks.

Conclusions In a large cohort of ICD patients, inappropriate shocks were common. The most important finding is the association between inappropriate shocks and mortality, independent of interim appropriate shocks (164).
Prevention and Reversal of Atrial Fibrillation Inducibility and Autonomic Remodeling by Low-Level Vagosympathetic Nerve Stimulation

Objectives We hypothesized that autonomic atrial remodeling can be reversed by low-level (LL) vago-sympathetic nerve stimulation (VNS).

Background Previously, we showed that VNS can be antiarrhythmogenic.

Methods Thirty-three dogs were subjected to electrical stimulation (20 Hz) applied to both vago-sympathetic trunks at voltages 10% to 50% below the threshold that slowed sinus rate or AV conduction. Group 1 (n = 7): Programmed stimulation (PS) was performed at baseline and during 6-h rapid atrial pacing (RAP). PS allowed determination of effective refractory period (ERP) and AF inducibility measured by window of vulnerability (WOV). LL-VNS was continuously applied from the 4th to 6th hours. Group 2 (n = 4): After baseline ERP and WOV determinations, 6-h concomitant RAP+LL-VNS was applied. Sustained AF was induced by injecting acetylcholine (ACh) 10 mM into the anterior right ganglionated plexus (Group 3, n = 10) or applying ACh 10 mM to right atrial appendage (Group 4, n = 9).

Results Group 1: The ERP progressively shortened and the WOV (sum of WOV from all tested sites) progressively increased (p < 0.05) during 3-h RAP then returned toward baseline during 3-h RAP+LL-VNS (p < 0.05). Group 2: 6-h concomitant RAP+LL-VNS did not induce any significant change in ERP and WOV. Group 3 and Group 4: AF duration (AF-D) and cycle length (AF-CL) were markedly altered by 3-h LL-VNS (Group 3: baseline: AF-D = 389 ± 90 s, AF-CL = 45.1 ± 7.8 ms; LL-VNS: AF-D = 50 ± 15 s, AF-CL = 82.0 ± 13.7 ms [both p < 0.001]; Group 4: baseline: AF-D = 505 ± 162 s, AF-CL = 48.8 ± 6.6 ms; LL-VNS: AF-D = 71 ± 21 s, AF-CL = 101.3 ± 20.9 ms [both p < 0.001]).

Conclusions LL-VNS can prevent and reverse atrial remodeling induced by RAP as well as suppress AF induced by strong cholinergic stimulation. Inhibition of the intrinsic cardiac autonomic nervous system by LL-VNS may be responsible for these salutary results (165).

Long-Term Cardiovascular Mortality After Radiotherapy for Breast Cancer

Objectives This study sought to investigate long-term cardiovascular mortality and its relationship to the use of radiotherapy for breast cancer.

Background Cardiovascular diseases are among the main long-term complications of radiotherapy, but knowledge is limited regarding long-term risks because published studies have, on average, <20 years of follow-up.

Methods A total of 4,456 women who survived at least 5 years after treatment of a breast cancer at the Institut Gustave Roussy between 1954 and 1984 were followed up for mortality until the end of 2003, for over 28 years on average.

Results A total of 421 deaths due to cardiovascular diseases were observed, of which 236 were due to cardiac disease. Women who had received radiotherapy had a 1.76-fold (95% confidence interval [CI]: 1.34 to 2.31) higher risk of dying of cardiac disease and a 1.33-fold (95% CI: 0.99 to 1.80) higher risk of dying of vascular disease than those who had not received radiotherapy. Among women who had received radiotherapy, those who had been treated for a left-sided breast cancer had a 1.56-fold (95% CI: 1.27 to 1.90) higher risk of dying of cardiac disease than those treated for a right-sided breast cancer. This relative risk increased with time since the breast cancer diagnosis (p = 0.05).

Conclusions This study confirmed that radiotherapy, as delivered until the mid-1980s, increased the long-term risk of dying of cardiovascular diseases. The long-term risk of dying of cardiac disease is a particular concern for women treated for a left-sided breast cancer with contemporary tangential breast or chest wall radiotherapy. This risk may increase with a longer follow-up, even after 20 years following radiotherapy (166).

Overexpression of CaMKIIΔc in RyR2R4496C +/- Knock-In Mice Leads to Altered Intracellular Ca2+ Handling and Increased Mortality

Objectives We investigated whether increased Ca2+/calmodulin-dependent kinase II (CaMKII) activity aggravates defective excitation-contraction coupling and proarhythmic activity in mice expressing R4496C mutated cardiac ryanodine receptors (RyR2).

Background RyR2 dysfunction is associated with arrhythmic events in inherited and acquired cardiac disease.

Methods CaMKIIΔc transgenic mice were crossbred with RyR2ΔR4496C+/− knock-in mice.

Results Heart weight-to-body weight ratio in CaMKIIΔc/RyR2R4496C and CaMKIIΔc mice was similarly increased approximately 3-fold versus wild-type mice (p < 0.05). Echocardiographic data showed comparable cardiac dilation and impaired contractility in CaMKIIΔc/RyR2R4496C and CaMKIIΔc mice. Sarcoplasmic reticulum Ca2+ content in isolated myocytes was decreased to a similar extent in CaMKIIΔc/RyR2R4496C and CaMKIIΔc mice. However, relaxation parameters and Ca2+ decay at 1 Hz were prolonged significantly in CaMKIIΔc mice versus CaMKIIΔc/RyR2R4496C. Sarcoplasmic reticulum Ca2+ spark frequency and characteristics indicated increased sarcoplasmic reticulum Ca2+ leak in CaMKIIΔc/RyR2R4496C versus CaMKIIΔc myocytes (p < 0.05), most likely because of increased RyR2 phosphorylation. Delayed after-depolarizations were significantly more frequent with increased amplitudes in CaMKIIΔc/RyR2R4496C versus CaMKIIΔc mice. Increased arrhythmias in vivo (67% vs. 25%; p < 0.05) may explain the increased mortality in CaMKIIΔc/RyR2R4496C mice, which died prematurely with...
only 30% alive (vs. 60% for CaMKIIΔc, p < 0.05) after 14 weeks. **Conclusions** CaMKIIΔc overexpression in RyR2^{R4496C+/-} knock-in mice increases the propensity toward triggered arrhythmias, which may impair survival. CaMKII contributes to further destabilization of a mutated RyR2 receptor (167).

**Alcohol Consumption and Risk of Atrial Fibrillation: A Meta-Analysis**

**Objectives** The purpose of this meta-analysis is to summarize the estimated risk of atrial fibrillation (AF) related to alcohol consumption.

**Background** Results from observational studies examining the relationship between alcohol consumption and AF are inconsistent.

**Methods** A systematic electronic search of Medline (January 1966 to December 2009) and Embase (January 1974 to December 2009) databases was conducted for studies using key words related to alcohol and AF. Studies were included if data on effect measures for AF associated with habitual alcohol intake were reported or could be calculated. The effect measures for AF for the highest versus lowest alcohol intake in individual studies were pooled with a variance-based method. Linear and spline regression analyses were conducted to quantify the relationship between alcohol intake and AF risk.

**Results** Fourteen eligible studies were included in this meta-analysis. The pooled estimate of AF for the highest versus the lowest alcohol intake was 1.51 (95% confidence interval: 1.31 to 1.74). A linear regression model showed that the pooled estimate for an increment of 10 g per day alcohol intake was 1.08 (95% confidence interval: 1.05 to 1.10; R² = 0.43, p < 0.001). A spline regression model also indicated that the AF risk increased with increasing levels of alcohol consumption.

**Conclusions** Results of this meta-analysis suggest that not consuming alcohol is most favorable in terms of AF risk reduction (168).

**Left Atrial Strain Predicts Reverse Remodeling After Catheter Ablation for Atrial Fibrillation**

**Objectives** The purpose of this study was to assess left atrial (LA) strain during long-term follow-up after catheter ablation for atrial fibrillation and to find predictors for LA reverse remodeling.

**Background** The association between LA reverse remodeling and improvement in LA strain after catheter ablation has not been investigated thus far.

**Methods** In 148 patients undergoing catheter ablation for atrial fibrillation, LA volumes and LA strain were assessed with echocardiography at baseline and after a mean of 13.2 ± 6.7 months of follow-up. The study population was divided according to LA reverse remodeling at follow-up: responders were defined as patients who exhibited 15% or more reduction in maximum LA volume at long-term follow-up. Left atrial systolic (LAs) strain was assessed with tissue Doppler imaging.

**Results** At follow-up, 93 patients (63%) were classified as responders, whereas 55 patients (37%) were nonresponders. At baseline, LAs strain was significantly higher in the responders as compared with the nonresponders (19 ± 8% vs. 14 ± 6%; p = 0.001). Among the responders, a significant increase in LAs strain was noted from baseline to follow-up (from 19 ± 8% to 22 ± 9%; p < 0.05), whereas no change was noted among the nonresponders. LAs strain at baseline was an independent predictor of LA reverse remodeling (odds ratio: 1.813; 95% confidence interval: 1.102 to 2.982; p = 0.019).

**Conclusions** In the present study, 63% of the patients exhibited LA reverse remodeling after catheter ablation for atrial fibrillation, with a concomitant improvement in LA strain. LA strain at baseline was an independent predictor of LA reverse remodeling (169).

**Suppression of Re-Entrant and Multifocal Ventricular Fibrillation by the Late Sodium Current Blocker Ranolazine**

**Objectives** The purpose of this study was to test the hypothesis that the late Na current blocker ranolazine suppresses re-entrant and multifocal ventricular fibrillation (VF).

**Background** VF can be caused by either re-entrant or focal mechanism.

**Methods** Simultaneous voltage and intracellular Ca²⁺ optical mapping of the left ventricular epicardial surface along with microelectrode recordings was performed in 24 isolated-perfused aged rat hearts. Re-entrant VF was induced by rapid pacing and multifocal VF by exposure to oxidative stress with 0.1 mM hydrogen peroxide (H₂O₂).

**Results** Rapid pacing induced sustained VF in 7 of 8 aged rat hearts, characterized by 2 to 4 broad propagating wavefronts. Ranolazine significantly (p < 0.05) reduced the maximum slope of action potential duration restitution curve and converted sustained to nonsustained VF lasting 24 ± 8 s in all 7 hearts. Exposure to H₂O₂ initiated early afterdepolarization (EAD)-mediated triggered activity that led to sustained VF in 8 out of 8 aged hearts. VF was characterized by multiple foci, appearing at an average of 6.8 ± 3.2 every 100 ms, which remained confined to a small area averaging 2.8 ± 0.85 mm² and became extinct after a mean of 43 ± 16 ms. Ranolazine prevented (when given before H₂O₂) and suppressed H₂O₂-mediated EADs by reducing the number of foci, causing VF to terminate in 8 out of 8 hearts. Simulations in 2-dimensional tissue with EAD-mediated multifocal VF showed progressive reduction in the number of foci and VF termination by blocking the late Na current. Simulations in 2-dimensional tissue with EAD-mediated multifocal VF showed progressive reduction in the number of foci and VF termination by blocking the late Na current.
A Randomized Active-Controlled Study Comparing the Efficacy and Safety of Vernakalant to Amiodarone in Recent-Onset Atrial Fibrillation

**Objectives** This randomized double-blind study compared the efficacy and safety of intravenous vernakalant and amiodarone for the acute conversion of recent-onset atrial fibrillation (AF).

**Background** Intravenous vernakalant has effectively converted recent-onset AF and was well tolerated in placebo-controlled studies.

**Methods** A total of 254 adult patients with AF (3 to 48 h duration) eligible for cardioversion were enrolled in the study. Patients received either a 10-min infusion of vernakalant (3 mg/kg) followed by a 15-min observation period and a second 10-min infusion (2 mg/kg) if still in AF, plus a sham amiodarone infusion, or a 60-min infusion of amiodarone (5 mg/kg) followed by a maintenance infusion (50 mg) over an additional 60 min, plus a sham vernakalant infusion.

**Results** Conversion from AF to sinus rhythm within the first 90 min (primary end point) was achieved in 60 of 116 (51.7%) vernakalant patients compared with 6 of 116 (5.2%) amiodarone patients (p < 0.0001). Vernakalant resulted in rapid conversion (median time of 11 min in responders) and was associated with a higher rate of symptom relief compared with amiodarone (53.4% of vernakalant patients reported no AF symptoms at 90 min compared with 32.8% of amiodarone patients; p = 0.0012). Serious adverse events or events leading to discontinuation of study drug were uncommon. There were no cases of torsades de pointes, ventricular fibrillation, or polymorphic or sustained ventricular tachycardia.

**Conclusions** Vernakalant demonstrated efficacy superior to amiodarone for acute conversion of recent-onset AF. Both vernakalant and amiodarone were safe and well tolerated in this study. (A Phase III Superiority Study of Vernakalant vs Amiodarone in Subjects With Recent Onset Atrial Fibrillation [AVRO]; NCT00668759) (171).

Catheter Ablation for Atrial Fibrillation: Are Results Maintained at 5 Years of Follow-Up?

**Objectives** This study describes 5-year follow-up results of catheter ablation for atrial fibrillation (AF).

**Background** Long-term efficacy following catheter ablation of AF remains unknown.

**Methods** A total of 100 patients (86 men, 14 women), age 55.7 ± 9.6 years, referred to our center for a first AF ablation (63% paroxysmal; 35 ± 1.4 prior ineffective antiarrhythmic agents) were followed for 5 years. Complete success was defined as absence of any AF or atrial tachycardia recurrence (clinical or by 24-h Holter monitoring) lasting ≥30 s.

**Results** Arrhythmia-free survival rates after a single catheter ablation procedure were 40%, 37%, and 29% at 1, 2, and 5 years, respectively, with most recurrences over the first 6 months. Patients with long-standing persistent AF experienced a higher recurrence rate than those with paroxysmal or persistent forms (hazard ratio [HR]: 1.9, 95% confidence interval [CI]: 1.0 to 3.5; p = 0.0462). In all, 175 procedures were performed, with a median of 2 per patient. Arrhythmia-free survival following the last catheter ablation procedure was 87%, 81%, and 63% at 1, 2, and 5 years, respectively. Valvular heart disease (HR: 6.0, 95% CI: 2.0 to 17.6; p = 0.0012) and nons ischemic dilated cardiomyopathy (HR: 34.0, 95% CI: 6.3 to 182.1; p < 0.0001) independently predicted recurrences. Major complications (cardiac tamponade requiring drainage) occurred in 3 patients (3%).

**Conclusions** In selected patients with AF, a catheter ablation strategy with repeat intervention as necessary provides acceptable long-term relief. Although most recurrences transpire over the first 6 to 12 months, a slow but steady decline in arrhythmia-free survival is noted thereafter (172).

Noninvasive Identification of Ventricular Tachycardia-Related Conducting Channels Using Contrast-Enhanced Magnetic Resonance Imaging in Patients With Chronic Myocardial Infarction: Comparison of Signal Intensity Scar Mapping and Endocardial Voltage Mapping

**Objectives** We performed noninvasive identification of post-infarction sustained monomorphic ventricular tachycardia (SMVT)-related slow conduction channels (CC) by contrast-enhanced magnetic resonance imaging (cEMRI).

**Background** Conduction channels identified by voltage mapping are the critical isthmuses of most SMVT. We hypothesized that CC are formed by heterogeneous tissue (HT) within the scar that can be detected by cEMRI.

**Methods** We studied 18 consecutive VT patients (SMVT group) and 18 patients matched for age, sex, infarct location, and left ventricular ejection fraction (control group). We used cEMRI to quantify the infarct size and differentiate it into scar core and HT based on signal-intensity (SI) thresholds (>3 SD and 2 to 3 SD greater than remote normal myocardium, respectively). Consecutive left ventricle slices were analyzed to determine the presence of continuous corridors of HT (channels) in the scar. In the SMVT group, color-coded shells displaying cEMRI subendocardial SI were generated (3-dimensional SI mapping) and compared with endocardial voltage maps.

**Results** No differences were observed between the 2 groups in myocardial, necrotic, or heterogeneous mass. The HT channels were more frequently observed in the SMVT group (88%) than in the control group (33%, p < 0.001). In the SMVT group, voltage mapping identified 26 CC in 17 of 18 patients. All CC corresponded, in location and orientation, to a similar channel detected by 3-dimensional SI mapping; 15 CC were related to 15 VT critical isthmuses.

**Conclusions** SMVT substrate can be identified by cEMRI scar heterogeneity analysis. This information could help identify patients at risk of VT and facilitate VT ablation (173).
Device-Detected Atrial Tachyarrhythmias Predict Adverse Outcome in Real-World Patients With Implantable Biventricular Defibrillators

Objectives The purpose of this analysis was to evaluate the correlation between atrial tachycardia (AT) or atrial fibrillation (AF) and clinical outcomes in heart failure (HF) patients implanted with a cardiac resynchronization therapy defibrillator (CRT-D).

Background In HF patients, AT and AF have high prevalence and are associated with compromised hemodynamic function.

Methods Forty-four Italian cardiological centers followed up 1,193 patients who received a CRT-D according to current guidelines for advanced HF, New York Heart Association functional class ≥II, left ventricular ejection fraction ≤35%, and QRS complex ≥120 ms. All patients were in sinus rhythm at implant.

Results During a median follow-up period of 13 months, AT/AF > 10 min occurred in 361 of 1,193 (30%) patients. The composite end point (deaths or HF hospitalizations) occurred in 174 of 1,193 (14.6%). Multivariate time-dependent Cox regression analyses showed that composite end point risk was higher among patients with device-detected AT/AF (hazard ratio [HR]: 2.16, p = 0.032), New York Heart Association functional class III or IV compared with II (HR: 2.09, p = 0.002), and absence of beta-blockers (HR: 1.36, p = 0.036). Furthermore, the composite end point risk was inversely associated with left ventricular ejection fraction (HR: 1.04, p = 0.045), increasing by a factor of 4% for each 1% decrease in left ventricular ejection fraction.

Conclusions In HF patients with CRT-D, device-detected AT/AF is associated with a worse prognosis. Continuous device diagnostics monitoring and Web-based alerts may inform the physician of AT/AF occurrences and identify patients at risk of cardiac deterioration or patients with suboptimal rate or rhythm control. (Italian ClinicalService Project; NCT01007474) (174).

The Effect of Air Pollution on Spatial Dispersion of Myocardial Repolarization in Healthy Human Volunteers

Objectives We tested the hypothesis that exposure to concentrated ambient particles (CAP) and/or ozone (O3) would increase dispersion of ventricular repolarization.

Background Elevated levels of air pollution are associated with cardiac arrhythmias through mechanisms yet to be elucidated.

Methods Each of 25 volunteers (18 to 50 years of age) had four 2-h exposures to 150 μg/m³ CAP; 120 parts per billion O3; CAP + O3; and filtered air (FA). Exposure-induced changes (Δ = 5-min epochs at end-start) in spatial dispersion of repolarization were determined from continuous 12-lead electrocardiographic recording.

Results Spatial dispersion of repolarization assessed by corrected ΔT-wave peak to T-wave end interval increased significantly for CAP + O3 (0.17 ± 0.03, p < 0.0001) exposure only, remaining significant when factoring FA (CAP + O3 − FA) as control (0.11 ± 0.04, p = 0.013). The influence on repolarization was further verified by a significant increase in ΔQT dispersion (for CAP + O3 compared with FA (5.7 ± 1.4, p = 0.0002). When the low-frequency to high-frequency ratio of heart rate variability (a conventional representation of sympathetic-parasympathetic balances) was included as a covariate, the effect estimate was positive for both corrected ΔT-wave peak to T-wave end interval (p = 0.002) and ΔQT dispersion (p = 0.038). When the high-frequency component (parasympathetic heart rate modulation) was included as a covariate with corrected ΔT-wave peak to T-wave end interval, the effect estimate for high frequency was inverse (p = 0.02).

Conclusions CAP + O3 exposure alters dispersion of ventricular repolarization in part by increasing sympathetic and decreasing parasympathetic heart rate modulation. Detection of changes in repolarization parameters, even in this small cohort of healthy individuals, suggests an underappreciated role for air pollutants in urban arrhythmogenesis (175).

Comparative Validation of a Novel Risk Score for Predicting Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation: The HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) Score

Objectives The purpose of this study was to investigate predictors of bleeding in a cohort of anticoagulated patients and to evaluate the predictive value of several bleeding risk stratification schemas.

Background The risk of bleeding during antithrombotic therapy in patients with atrial fibrillation (AF) is not homogeneous, and several clinical risk factors have been incorporated into clinical bleeding risk stratification schemas. Current risk stratification schemas for bleeding during anticoagulation therapy have been based on complex scoring systems that are difficult to apply in clinical practice, and few have been derived and validated in AF cohorts.

Methods We investigated predictors of bleeding in a cohort of 7,329 patients with AF participating in the SPORTIF (Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation) III and V clinical trials and evaluated the predictive value of several risk stratification schemas by multivariate analysis. Patients were anticoagulated orally with either adjusted-dose warfarin (target international normalized ratio 2 to 3) or fixed-dose ximelagatran 36 mg twice daily. Major bleeding was centrally adjudicated, and concurrent aspirin therapy was allowed in patients with clinical atherosclerosis.
Results By multivariate analyses, significant predictors of bleeding were concurrent aspirin use (hazard ratio [HR]: 2.10; 95% confidence interval [CI]: 1.59 to 2.77; p < 0.001); renal impairment (HR: 1.98; 95% CI: 1.42 to 2.76; p < 0.001); age 75 years or older (HR: 1.63; 95% CI: 1.23 to 2.17; p = 0.0008); diabetes (HR: 1.47; 95% CI: 1.10 to 1.97; p = 0.009), and heart failure or left ventricular dysfunction (HR: 1.32; 95% CI: 1.01 to 1.73; p = 0.041). Of the tested schemas, the new HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score performed best, with a stepwise increase in rates of major bleeding with increasing HAS-BLED score ($p_{\text{trend}} < 0.0001$). The $c$ statistic for bleeding varied between 0.50 and 0.67 in the overall entire cohort and 0.68 among patients naïve to warfarin at baseline ($n = 769$).

Conclusions This analysis identifies diabetes and heart failure or left ventricular dysfunction as potential risk factors for bleeding in AF beyond those previously recognized. Of the contemporary bleeding risk stratification schemas, the new HAS-BLED scheme offers useful predictive capacity for bleeding over previously published schemas and may be simpler to apply (176).

**Risk for Life-Threatening Cardiac Events in Patients With Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals**

**Objectives** This study was designed to assess the clinical course and to identify risk factors for life-threatening events in patients with long-QT syndrome (LQTS) with normal corrected QT (QTc) intervals.

**Background** Current data regarding the outcome of patients with concealed LQTS are limited.

**Methods** Clinical and genetic risk factors for aborted cardiac arrest (ACA) or sudden cardiac death (SCD) from birth through age 40 years were examined in 3,386 probands, the frequency of copy number variants (CNVs) in LQTS genes. Of the tested schemas, the new HAS-BLED scheme offers useful predictive capacity for bleeding over previously published schemas and may be simpler to apply (176).

**Conclusions** Genotype-confirmed patients with concealed LQTS make up about 25% of the at-risk LQTS population. Genetic data, including information regarding mutation characteristics and the LQTS genotype, identify increased risk for ACA or SCD in this overall lower risk LQTS subgroup (177).

**Screening for Copy Number Variation in Genes Associated With the Long QT Syndrome: Clinical Relevance**

**Objectives** The aim of this study was to investigate, in a set of 93 mutation-negative long QT syndrome (LQTS) probands, the frequency of copy number variants (CNVs) in LQTS genes.

**Background** LQTS is an inherited cardiac arrhythmia characterized by a prolonged heart rate–corrected QT (QTc) interval associated with sudden cardiac death. Recent studies suggested the involvement of duplications or deletions in the occurrence of LQTS. However, their frequency remains unknown in LQTS patients.

**Methods** Point mutations in KCNQ1, KCNH2, and SCN5A genes were excluded by denaturing high-performance liquid chromatography or direct sequencing. We applied Multiplex Ligation-dependent Probe Amplification (MLPA) to detect CNVs in exons of these 3 genes. Abnormal exon copy numbers were confirmed by quantitative multiplex PCR of short fluorescent fragment (QMFPSF). Array-based comparative genomic hybridization (array CGH) analysis was performed using Agilent Human Genome 244K Microarrays to further map the genomic rearrangements.

**Results** We identified 3 different deletions in 3 unrelated families: 1 in KCNQ1 and 2 involving KCNH2. We showed in the largest family that the deletion involving KCNH2 is fully penetrant and segregates with the long QT phenotype in 7 affected members.

**Conclusions** Our study demonstrates that CNVs in KCNQ1 and KCNH2 explain around 3% of LQTS in patients with no point mutation in these genes. This percentage is likely higher than the frequency of point mutations in ANKB, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, and SNTAI together. Thus, we propose that CNV screening in KCNQ1 and KCNH2 may be performed routinely in LQTS patients (178).

**Iodine-123 mIBG Imaging for Predicting the Development of Atrial Fibrillation**

**Objectives** We investigated whether cardiac sympathetic nervous system (SNS) activity measured by iodine-123 meta-iodobenzylguanidine ($^{123}$I-mIBG) imaging would be associated with both the occurrence of heart failure (HF)
and the transit to permanent atrial fibrillation (AF) in patients with paroxysmal AF.

**Background**

Atrial fibrillation occurs suddenly and transiently and can persist, and results in the occurrence of HF. An important feature of AF and HF is their propensity to coexist not only because they share antecedent risk factors, but also because the one may directly predispose the heart to the other. However, a useful modality for predicting the occurrences of both those has not been established in patients with paroxysmal AF.

**Methods**

The $^{123}$I-mIBG scintigraphy was performed to evaluate cardiac SNS activity presented as the heart/mediastinum ratio in 98 consecutive patients (age 66 ± 13 years, 63.3% male) with idiopathic paroxysmal AF and preserved left ventricular ejection fraction ($\geq$50%).

**Results**

During 4 ± 3.6 years of follow-up, the transit to permanent AF was associated with the occurrence of HF (34.3% in 12 of 35 patients with permanent AF vs. 6.3% in 4 of 63 patients without, $p < 0.0001$). Lower heart/mediastinum ratio and lower left ventricular ejection fraction were the independent predictors of the transit to permanent AF with adjusted hazard ratios of 3.44 (95% confidence interval [CI]: 1.9 to 6.2, $p < 0.0001$) and 1.04 (95% CI: 1.01 to 1.08, $p = 0.014$). Further, these factors and higher plasma brain natriuretic peptide concentration were the independent predictors of the occurrence of HF with permanent AF, with adjusted hazard ratios of 5.08 (95% CI: 1.5 to 17.5, $p = 0.011$), 1.11 (95% CI: 1.03 to 1.19, $p = 0.004$), and 1.004 (95% CI: 1.001 to 1.008, $p = 0.014$).

**Conclusions**

Cardiac SNS abnormality was associated with the occurrence of both HF and permanent AF in paroxysmal AF patients, and $^{123}$I-mIBG imaging may be a useful modality for predicting the development of AF (179).

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