HIGHLIGHTS OF THE YEAR

Editor-in-Chief’s Picks From 2014: Part Two

Valentin Fuster, MD, PhD

As I spent countless hours pouring over hundreds of manuscripts to select those that rose to the top over the past year, I became incredibly excited about being part of a Journal that produces such wonderfully rich and diverse content each year. I have personally selected the papers (both original investigations and review articles) from 13 distinct specialties for your review. There are approximately 150 articles selected across this 2-part series, which represents less than 3% of the papers submitted to JACC in 2014. In order to present the full breadth of this important research in a consumable fashion, we will present these manuscripts over the course of 2 issues of JACC.

Part One includes the sections: Congenital Heart Disease, Coronary Disease & Interventions, Genetics, Omics, & Tissue Regeneration, CV Prevention & Health Promotion, Cardiac Failure, and Cardiomyopathies. Part Two includes the sections: Hypertension, Imaging, Metabolic Disorders & Lipids, Neurovascular & Neurodegenerative Disorders, Rhythm Disorders, Valvular Heart Disease, and Vascular Medicine.

HYPERTENSION

2014 Hypertension Recommendations From the Eighth Joint National Committee Panel Members Raise Concerns for Elderly Black and Female Populations

L.R. Krakoff, et al.

A report from panel members appointed to the Eighth Joint National Committee titled “2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults” has garnered much attention due to its major change in recommendations for hypertension treatment for patients ≥60 years of age and for their treatment goal. In response, certain groups have opposed the decision to initiate pharmacologic treatment to lower blood pressure (BP) at systolic BP ≥150 mm Hg and treat to a goal systolic BP of <150 mm Hg in the general population age ≥60 years. This paper contains 3 sections— an introduction followed by the opinions of 2 writing groups—outlining objections to or support of maintaining this proposed strategy in certain at-risk populations, namely African Americans, women, and the elderly. Several authors argue for maintaining current targets, as opposed to adopting the new recommendations, to allow for optimal treatment for older women and African Americans, helping to close sex and race/ethnicity gaps in cardiovascular disease morbidity and mortality.

Impact of the 2014 Expert Panel Recommendations for Management of High Blood Pressure on Contemporary Cardiovascular Practice: Insights From the NCDR PINNACLE Registry

W.B. Borden, et al.

BACKGROUND Since 2003, the Seventh Report of the Joint National Committee (JNC-7) has been the predominant guideline for blood pressure management. A 2014 expert panel recommended increasing the blood pressure targets for patients age 60 years and older, as well as those with diabetes or chronic kidney disease.

OBJECTIVES The purpose of this study was to examine the effect of the 2014 expert panel blood pressure management recommendations on patients managed in U.S. ambulatory cardiovascular practices.

METHODS Using the National Cardiovascular Data Registry PINNACLE Registry, we assessed the proportion of patients who met the 2003 and 2014 panel recommendations, highlighting the populations of patients for whom the blood pressure goals changed.

RESULTS Of 1,185,253 patients in the study cohort, 706,859 (59.6%) achieved the 2003 JNC-7 goals. Using the 2014 recommendations, 880,378 (74.3%) patients were at goal. Among the 173,519 (14.6%) for whom goal achievement changed, 40,323 (23.2%) had a...
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Fuster

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19.5%.
and baseline systolic BP

CONCLUSIONS Among U.S. ambulatory cardiology

RESULTS

OBJECTIVES

METHODS

RESULTS

BACKGROUND

OBJECTIVES

METHODS

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BACKGROUND

BACKGROUND

OBJECTIVES

METHODS

RESULTS

Effects of Cardiorespiratory Fitness on Blood Pressure Trajectory With Aging in a Cohort of Healthy Men

J. Liu, et al.
heart rate, glucose level, triglyceride level, cholesterol level, current smoking, heavy alcohol consumption, and parental history of hypertension. DBP had a yearly increase of 0.14 mm Hg (95% confidence interval: 0.13 to 0.15) before age 60 years. Overall, abnormal SBP (>120 mm Hg) began to occur at approximately 50 years of age and abnormal DBP (>80 mm Hg) began to occur at 60 years of age. Men with higher fitness levels experienced abnormal SBP later than those with low fitness levels.

**CONCLUSIONS** Our findings underscore the potential modifying effect of fitness on BP trajectory with aging over the male adult life span. Improving fitness levels might extend the normal SBP and DBP ranges, delaying the development of hypertension (4).

**Anatomic Assessment of Sympathetic Peri-Arterial Renal Nerves in Man**

K. Sakakura, et al.

**BACKGROUND** Although renal sympathetic denervation therapy has shown promising results in patients with resistant hypertension, the human anatomy of peri-arterial renal nerves is poorly understood.

**OBJECTIVES** The aim of our study was to investigate the anatomic distribution of peri-arterial sympathetic nerves around human renal arteries.

**METHODS** Bilateral renal arteries were collected from human autopsy subjects, and peri-arterial renal nerve anatomy was examined by using morphometric software. The ratio of afferent to efferent nerve fibers was investigated by dual immunofluorescence staining using antibodies targeted for anti-tyrosine hydroxylase and anti-calcitonin gene-related peptide.

**RESULTS** A total of 10,329 nerves were identified from 20 (12 hypertensive and 8 nonhypertensive) patients. The mean individual number of nerves in the proximal and middle segments was similar (39.6 ± 16.7 per section and 39.9 ± 1 3.9 per section), whereas the distal segment showed fewer nerves (33.6 ± 13.1 per section) (p = 0.01). Mean subject-specific nerve distance to arterial lumen was greatest in proximal segments (3.40 ± 0.78 mm), followed by middle segments (3.10 ± 0.69 mm), and least in distal segments (2.60 ± 0.77 mm) (p < 0.001). The mean number of nerves in the ventral region (11.0 ± 3.5 per section) was greater compared with the dorsal region (6.2 ± 3.0 per section) (p < 0.001). Efferent nerve fibers were predominant (tyrosine hydroxylase/calcitonin gene-related peptide ratio 25.1 ± 33.4; p < 0.0001). Nerve anatomy in hypertensive patients was not considerably different compared with nonhypertensive patients.

**CONCLUSIONS** The density of peri-arterial renal sympathetic nerve fibers is lower in distal segments and dorsal locations. There is a clear predominance of efferent nerve fibers, with decreasing prevalence of afferent nerves from proximal to distal peri-arterial and renal parenchyma. Understanding these anatomic patterns is important for refinement of renal denervation procedures (5).

**Innervation Patterns May Limit Response to Endovascular Renal Denervation**


**BACKGROUND** Renal denervation is a new interventional approach to treat hypertension with variable results.

**OBJECTIVES** The purpose of this study was to correlate response to endovascular radiofrequency ablation of renal arteries with nerve and ganglia distributions. We examined how renal neural network anatomy affected treatment efficacy.

**METHODS** A multielectrode radiofrequency catheter (15 W/60 s) treated 8 renal arteries (group 1). Arteries and kidneys were harvested 7 days post-treatment. Renal norepinephrine (NEPI) levels were correlated with ablation zone geometries and neural injury. Nerve and ganglion distributions and sizes were quantified at discrete distances from the aorta and were compared with 16 control arteries (group 2).

**RESULTS** Nerve and ganglia distributions varied with distance from the aorta (p < 0.001). A total of 75% of nerves fell within a circumferential area of 9.3, 6.3, and 3.4 mm of the lumen and 0.3, 3.0, and 6.0 mm from the aorta. Efficacy (NEPI 37 ng/g) was observed in only 1 of 8 treated arteries where ablation involved all 4 quadrants, reached a depth of 9.1 mm, and affected 50% of nerves. In 7 treated arteries, NEPI levels remained at baseline values (620 to 991 ng/g), ≤20% of the nerves were affected, and the ablation areas were smaller (16.2 ± 10.9 mm²) and present in only 1 to 2 quadrants at maximal depths of 3.8 ± 2.7 mm.

**CONCLUSIONS** Renal denervation procedures that do not account for asymmetries in renal periarterial nerve and ganglia distribution may miss targets and fall below the critical threshold for effect. This phenomenon is most acute in the ostium but holds throughout the renal artery, which requires further definition (6).
IMAGING

Left Atrial Size and Function: Role in Prognosis
B.D. Hoit, et al.

The author examines the ability of left atrial size and function to predict cardiovascular outcomes. Data are sufficient to recommend evaluation of left atrial volume in certain populations, and although analysis of atrial reservoir, conduit, and booster pump function trails in that regard, the gap is rapidly closing. In this state-of-the-art paper, the author reviews the methods used to assess left atrial size and function and discusses their role in predicting cardiovascular events in general and referral populations and in patients with atrial fibrillation, cardiomyopathy, ischemic heart disease, and valvular heart disease (7).

Short-Term Rosuvastatin Therapy for Prevention of Contrast-Induced Acute Kidney Injury in Patients With Diabetes and Chronic Kidney Disease
Y. Han, et al.

OBJECTIVES This study sought to evaluate the safety and efficacy of rosuvastatin in preventing contrast-induced acute kidney injury (CI-AKI) in patients with diabetes mellitus (DM) and chronic kidney disease (CKD).

BACKGROUND CI-AKI is an important complication after contrast medium injection. While small studies have shown positive results with statin therapy, the role of statin therapy in prevention of CI-AKI remains unknown.

METHODS We randomized 2,998 patients with type 2 DM and concomitant CKD who were undergoing coronary/ peripheral arterial angiography with or without percutaneous intervention to receive rosuvastatin, 10 mg/day (n = 1,498), for 5 days (2 days before, and 3 days after procedure) or standard-of-care (n = 1,500). Patients’ renal function was assessed at baseline, 48 h, and 72 h after exposure to contrast medium. The primary endpoint of the study was the development of CI-AKI, which was defined as an increase in serum creatinine concentration ≥0.5 mg/dl (44.2 μmol/l) or 0.25% above baseline at 72 h after exposure to contrast medium.

RESULTS Patients randomized to the rosuvastatin group had a significantly lower incidence of CI-AKI than controls (2.3% vs. 3.9%, respectively; p = 0.01). During 30 days’ follow-up, the rate of worsening heart failure was significantly lower in the patients treated with rosuvastatin than that in the control group (2.6% vs. 4.3%, respectively; p = 0.02).

CONCLUSIONS Rosuvastatin significantly reduced the risk of CI-AKI in patients with DM and CKD undergoing arterial contrast medium injection. (Rosuvastatin Prevent Contrast Induced Acute Kidney Injury in Patients With Diabetes [TRACK-D]; NCT00786136) (8).

Coronary Artery Calcification: Pathogenesis and Prognostic Implications
M.V. Madhavan, et al.

Coronary artery calcification (CAC) is a risk factor for adverse outcomes in the general population and in patients with coronary artery disease. The pathogenesis of CAC and bone formation share common pathways, and risk factors have been identified that contribute to the initiation and progression of CAC. Efforts to control CAC with medical therapy have not been successful. Event-free survival is also reduced in patients with coronary calcification after both percutaneous coronary intervention (PCI) and bypass graft surgery. Although drug-eluting stents and devices for plaque modification have modestly improved outcomes in calcified vessels, adverse event rates are still high. Innovative pharmacologic and device-based approaches are needed to improve the poor prognosis of patients with CAC (9).

Coronary Computed Tomography Angiography for the Detection of Cardiac Allograft Vasculopathy: A Meta-Analysis of Prospective Trials
O. Wever-Pinzon, et al.

OBJECTIVES This study aimed to evaluate the diagnostic accuracy of coronary computed tomography angiography (CCTA) for detecting cardiac allograft vasculopathy (CAV) in comparison with conventional coronary angiography (CCAG) alone or with intravascular ultrasound (IVUS).

BACKGROUND CAV limits long-term survival after heart transplantation, and screening for CAV is performed on annual basis. CCTA is currently not recommended for CAV screening due to the limited accuracy reported by early studies. Technological advances, however, might have resulted in improved test performance and might justify re-evaluation of this recommendation.

METHODS A systematic review of Medline, Cochrane, and Embase for all prospective trials assessing CAV using CCTA was performed using a standard approach for meta-analysis for diagnostic test and a bivariate analysis.

RESULTS Thirteen studies evaluating 615 patients (mean age 52 years, 83% male) and 9,481 segments fulfilled inclusion criteria. Patient-based analyses comparing CCTA versus CCAG for the detection of any
CAV (> luminal irregularities) and significant CAV (stenosis ≥50%), showed mean weighted sensitivities of 97% and 94%, specificities of 81% and 92%, a negative predictive value (NPV) of 97% and 99%, a positive predictive value (PPV) of 78% and 67%, and diagnostic accuracies of 88% and 94%, respectively. There was a strong trend toward improved sensitivity (97% vs. 91%; p = 0.06) and NPV (99% vs. 97%; p = 0.06) to detect significant CAV with 64-slice compared with 16-slice CCTA. A patient-based analysis of 64-slice CCTA versus IVUS showed a mean weighted sensitivity and specificity of 81% and 75% to detect CAV (intimal thickening >0.5 mm), whereas the PPV and NPV were 93% and 50%, respectively.

CONCLUSIONS CCTA using currently available technology is a reliable noninvasive imaging alternative to coronary angiography with an excellent sensitivity, specificity, and NPV for the detection of CAV (10).

Cardiac Positron Emission Tomography Enhances Prognostic Assessments of Patients With Suspected Cardiac Sarcoidosis

R. Blankstein, et al.

OBJECTIVES This study sought to relate imaging findings on positron emission tomography (PET) to adverse cardiac events in patients referred for evaluation of known or suspected cardiac sarcoidosis.

BACKGROUND Although cardiac PET is commonly used to evaluate patients with suspected cardiac sarcoidosis, the relationship between PET findings and clinical outcomes has not been reported.

METHODS We studied 118 consecutive patients with no history of coronary artery disease, who were referred for PET, using [18F]fluorodeoxyglucose (FDG) to assess for inflammation and rubidium-82 to evaluate for perfusion defects (PD), following a high-fat/low-carbohydrate diet to suppress normal myocardial glucose uptake. Blind readings of PET data categorized cardiac findings as normal, positive PD or FDG, positive PD and FDG. Images were also used to identify whether findings of extra-cardiac sarcoidosis were present. Adverse events (AE)—death or sustained ventricular tachycardia (VT)—were ascertained by electronic medical records, defibrillator interrogation, patient questionnaires, and telephone interviews.

RESULTS Among the 118 patients (age 52 ± 11 years; 57% males; mean ejection fraction: 47 ± 16%), 47 (40%) had normal and 71 (60%) had abnormal cardiac PET findings. Over a median follow-up of 1.5 years, there were 31 (26%) adverse events (27 VT and 8 deaths). Cardiac PET findings were predictive of AE, and the presence of both a PD and abnormal FDG (29% of patients) was associated with hazard ratio of 3.9 (p < 0.01) and remained significant after adjusting for left ventricular ejection fraction (LVEF) and clinical criteria. Extra-cardiac FDG uptake (26% of patients) was not associated with AE.

CONCLUSIONS The presence of focal PD and FDG uptake on cardiac PET identifies patients at higher risk of death or VT. These findings offer prognostic value beyond Japanese Ministry of Health and Welfare clinical criteria, the presence of extra-cardiac sarcoidosis and LVEF (11).

Distinct Morphological Features of Ruptured Culprit Plaque for Acute Coronary Events Compared to Those With Silent Rupture and Thin-Cap Fibroatheroma: A Combined Optical Coherence Tomography and Intravascular Ultrasound Study

J. Tian, et al.

OBJECTIVES The study sought to identify specific morphological characteristics of ruptured culprit plaques (RCP) responsible for acute events, and compare them with ruptured nonculprit plaques (RNCP) and non-ruptured thin-cap fibroatheroma (TCFA) in patients presenting with acute coronary syndromes (ACS).

BACKGROUND Nonruptured TCFA and multiple ruptured plaques are detected in the same patients with ACS. It remains unknown whether certain morphological characteristics determine rupture of TCFA and subsequently result in ACS.

METHODS We analyzed 126 plaques (RCP = 49, RNCP = 19, TCFA = 58) from 82 ACS patients using optical coherence tomography (OCT) and intravascular ultrasound (IVUS). Fibrous cap thickness was determined by OCT. Plaque burden and lumen area were measured with IVUS.

RESULTS Fibrous cap was thinner in RCP (43 ± 11 μm) and RNCP (41 ± 10 μm) than in TCFA (56 ± 9 μm; p < 0.001 and p < 0.001, respectively). Plaque burden was greater in RCP (82 ± 7.2%), compared with RNCP (64 ± 7.2%; p < 0.001) and TCFA (62 ± 12.5%; p < 0.001). Lumen area was smaller in RCP (2.1 ± 0.9 mm²), compared with RNCP (4.6 ± 2.3 mm²; p = 0.001) and TCFA (5.1 ± 2.7 mm²; p < 0.001). The fibrous cap thickness <52 μm had good performance in discriminating ruptured plaque from TCFA (area under the curve [AUC] = 0.857; p < 0.001), and plaque burden >76% and lumen area <2.6 mm² had good performance in discriminating RCP from RNCP and TCFA (AUC = 0.923, p < 0.001; and AUC = 0.881, p < 0.001, respectively).

CONCLUSIONS Fibrous cap thickness is a critical morphological discriminator between ruptured plaques...
and nonruptured TCFA, while plaque burden and lumen area appear to be important morphological features of RCP. These findings suggest that plaque rupture is determined by fibrous cap thickness, and a combination of large plaque burden and luminal narrowing result in ACS (12).

Prevalence and Characteristics of TCFA and Degree of Coronary Artery Stenosis: An OCT, IVUS, and Angiographic Study

J. Tian, et al.

BACKGROUND The relationship between features of vulnerable plaque and angiographic coronary stenosis is unknown.

OBJECTIVES The purpose of this study was to systematically investigate the absolute number, relative prevalence, and characteristics of thin-cap fibroatheroma (TCFA) at different degrees of stenosis using optical coherence tomography (OCT), intravascular ultrasound, and coronary angiography.

METHODS We identified 643 plaques from 255 subjects who underwent OCT imaging in all 3 coronary arteries. They were divided into 3 groups on the basis of angiographic diameter stenosis: Group A (30% to 49%, n = 325), Group B (50% to 69%, n = 227), and Group C (>70%, n = 91).

RESULTS OCT showed that the absolute number of TCFA was greatest in Group A (n = 58), followed by Groups B (n = 40) and C (n = 33). However, the relative prevalence of TCFA was higher in Group C (36%) than in Groups A (18%) or B (18%) (p = 0.002). Fibrous cap of TCFA was thinner in Group C than in Groups A (p < 0.001) or B (p = 0.001). Intravascular ultrasound showed that the plaque burden of TCFA was largest in Group C (80.1 ± 7.4%), compared with Groups B (67.5 ± 9.4%) and A (58.1 ± 8.4%). TCFA in Group C had a higher remodeling index than those in Group A (p = 0.002).

CONCLUSIONS The absolute number of TCFA is 3 times greater in nonsevere stenosis than in severe stenosis. It is, however, twice as likely for a lesion to be TCFA in cases of severe stenosis than in nonsevere stenosis. Moreover, TCFA in severely-stenotic areas had more features of plaque vulnerability (13).

OCT Assessment of the Long-Term Vascular Healing Response 5 Years After Everolimus-Eluting Bioresorbable Vascular Scaffold

A. Karanasos, et al.

BACKGROUND Although recent observations suggest a favorable initial healing process of the everolimus-eluting bioresorbable vascular scaffold (BVS), little is known regarding long-term healing response.

OBJECTIVES This study assessed the in vivo vascular healing response using optical coherence tomography (OCT) 5 years after elective first-in-man BVS implantation.

METHODS Of the 14 living patients enrolled in the Thoraxcenter Rotterdam cohort of the ABSORB A study, 8 patients underwent invasive follow-up, including OCT, 5 years after implantation. Advanced OCT image analysis included luminal morphometry, assessment of the adluminal signal-rich layer separating the lumen from other plaque components, visual and quantitative tissue characterization, and assessment of side-branch ostia “jailed” at baseline.

RESULTS In all patients, BVS struts were integrated in the vessel and were not discernible. Both minimum and mean luminal area increased from 2 to 5 years, whereas lumen eccentricity decreased over time. In most patients, plaques were covered by a signal-rich, low-attenuating layer. Minimum cap thickness over necrotic core was 155 ± 90 μm. One patient showed plaque progression and discontinuity of this layer. Side-branch ostia were preserved with tissue bridge thinning that had developed in the place of side-branch struts, creating a neo-carina.

CONCLUSIONS At long-term BVS follow-up, we observed a favorable tissue response, with late luminal enlargement, side-branch patency, and development of a signal-rich, low-attenuating tissue layer that covered thrombogenic plaque components. The small size of the study and the observation of a different tissue response in 1 patient warrant judicious interpretation of our results and confirmation in larger studies (14).

METABOLIC DISORDERS & LIPIDS

Body Mass Index and Mortality in Acutely Decompensated Heart Failure Across the World: A Global Obesity Paradox

R. Shah, et al.

OBJECTIVES This study sought to define the relationship between body mass index (BMI) and mortality in heart failure (HF) across the world and to identify specific groups in whom BMI may differentially mediate risk.

BACKGROUND Obesity is associated with incident HF, but it is paradoxically associated with better prognosis during chronic HF.
METHODS We studied 6,142 patients with acute decompensated HF from 12 prospective observational cohorts followed-up across 4 continents. Primary outcome was all-cause mortality. Cox proportional hazards models and net reclassification index described associations of BMI with all-cause mortality.

RESULTS Normal-weight patients (BMI 18.5 to 25 kg/m²) were older with more advanced HF and lower cardiometabolic risk. Despite worldwide heterogeneity in clinical features across obesity categories, a higher BMI remained associated with decreased 30-day and 1-year mortality (11% decrease at 30 days; 9% decrease at 1 year per 5 kg/m²; p < 0.05), after adjustment for clinical risk. The BMI obtained at index admission provided effective 1-year risk reclassification beyond current markers of clinical risk (net reclassification index 0.119; p < 0.001). Notably, the “protective” association of BMI with mortality was confined to persons with older age (>75 years; hazard ratio [HR]: 0.82; p = 0.006), decreased cardiac function (ejection fraction <50%; HR: 0.85; p < 0.001), no diabetes (HR: 0.86; p < 0.001), and de novo HF (HR: 0.89; p = 0.004).

CONCLUSIONS A lower BMI is associated with age, disease severity, and a higher risk of death in acute decompensated HF. The “obesity paradox” is confined to older persons, with decreased cardiac function, less cardiometabolic illness, and recent-onset HF, suggesting that aging, HF severity/chronicity, and metabolism may explain the obesity paradox (15).

Obesity and Cardiovascular Diseases: Implications Regarding Fitness, Fatness, and Severity in the Obesity Paradox

C.J. Lavie, et al.

Obesity has been increasing in epidemic proportions, with a disproportionately higher increase in morbid or class III obesity, and obesity adversely affects cardiovascular (CV) hemodynamics, structure, and function, as well as increases the prevalence of most CV diseases. Progressive declines in physical activity over 5 decades have occurred and have primarily caused the obesity epidemic. Despite the potential adverse impact of overweight and obesity, recent epidemiological data have demonstrated an association of mild obesity and, particularly, overweight on improved survival. We review in detail the obesity paradox in CV diseases where overweight and at least mildly obese patients with most CV diseases seem to have a better prognosis than do their leaner counterparts. The implications of cardiorespiratory fitness with prognosis are discussed, along with the joint impact of fitness and adiposity on the obesity paradox. Finally, in light of the obesity paradox, the potential value of purposeful weight loss and increased physical activity to affect levels of fitness is reviewed (16).

Early High-Dose Rosuvastatin for Contrast-Induced Nephropathy Prevention in Acute Coronary Syndrome: Results From the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On Contrast-Induced Acute Kidney Injury and Myocardial Damage in Patients With Acute Coronary Syndrome)

M. Leoncini, et al.

OBJECTIVES This study sought to determine if in addition to standard preventive measures on-admission, high-dose rosuvastatin exerts a protective effect against contrast-induced acute kidney injury (CI-AKI).

BACKGROUND Patients with acute coronary syndrome (ACS) are at high risk for CI-AKI, and the role of statin pre-treatment in preventing renal damage remains uncertain.

METHODS Consecutive statin-naïve non-ST elevation ACS patients scheduled to undergo early invasive strategy were randomly assigned to receive rosuvastatin (40 mg on admission, followed by 20 mg/day; statin group n = 252) or no statin treatment (control group n = 252). CI-AKI was defined as an increase in creatinine concentration of ≥0.5 mg/dl or ≥25% above baseline within 72 h after contrast administration.

RESULTS The incidence of CI-AKI was significantly lower in the statin group than in controls (6.7% vs. 15.1%; adjusted odds ratio: 0.38; 95% confidence interval [CI]: 0.20 to 0.71; p = 0.003). The benefits against CI-AKI were consistent, even applying different CI-AKI definition criteria and in all the prespecified risk categories. The 30-day incidence of adverse cardiovascular and renal events (death, dialysis, myocardial infarction, stroke, or persistent renal damage) was significantly lower in the statin group (3.6% vs. 7.9%, respectively; p = 0.036). Moreover, statin treatment given on admission was associated with a lower rate of death or nonfatal myocardial infarction at 6 month follow-up (3.6% vs. 7.2%, respectively; p = 0.07).

CONCLUSIONS High-dose rosuvastatin given on admission to statin-naïve patients with ACS who are scheduled for an early invasive procedure can prevent CI-AKI and improve short-term clinical outcome. (Statin Contrast Induced Nephropathy Prevention [PRATO-ACS]; NCT01185938) (17).
Implications of the 2013 ACC/AHA Cholesterol Guidelines for Adults in Contemporary Cardiovascular Practice: Insights From the NCDR PINNACLE Registry

T.M. Maddox, et al.

BACKGROUND In a significant update, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines recommend fixed-dose statin therapy for those at risk and do not recommend nonstatin therapies or treatment to target low-density lipoprotein cholesterol (LDL-C) levels, limiting the need for repeated LDL-C testing.

OBJECTIVES The goal of this study was to examine the impact of the 2013 ACC/AHA cholesterol guidelines on current U.S. cardiovascular practice.

METHODS Using the NCDR PINNACLE (National Cardiovascular Data Registry Practice Innovation and Clinical Excellence) registry data from 2008 to 2012, we assessed current practice patterns as a function of the 2013 cholesterol guidelines. Lipid-lowering therapies and LDL-C testing patterns by patient risk group (atherosclerotic cardiovascular disease [ASCVD]), diabetes, LDL-C ≥190 mg/dl, or an estimated 10-year ASCVD risk ≥7.5%) were described.

RESULTS Among a cohort of 1,174,545 patients, 1,129,205 (96.1%) were statin-eligible (91.2% ASCVD, 6.6% diabetes, 0.3% off-treatment LDL-C ≥190 mg/dl, 1.9% estimated 10-year ASCVD risk ≥7.5%). There were 377,311 patients (32.4%) not receiving statin therapy and 259,143 (22.6%) receiving nonstatin therapies. During the study period, 20.8% of patients had 2 or more LDL-C assessments, and 7.0% had more than 4.

CONCLUSIONS In U.S. cardiovascular practices, 32.4% of statin-eligible patients, as defined by the 2013 ACC/AHA cholesterol guidelines, were not currently receiving statins. In addition, 22.6% were receiving nonstatin lipid-lowering therapies and 20.8% had repeated LDL-C testing. Achieving concordance with the new cholesterol guidelines in patients treated in U.S. cardiovascular practices would result in significant increases in statin use, as well as significant reductions in nonstatin therapies and laboratory testing (18).

The Severe Hypercholesterolemia Phenotype: Clinical Diagnosis, Management, and Emerging Therapies

A.D. Sniderman, et al.

The severe hypercholesterolemia phenotype includes all patients with marked elevation of low-density lipoprotein cholesterol (LDL-C) levels. The most common cause is autosomal dominant hypercholesterolemia, an inherited disorder caused by mutations either in LDL receptor, apolipoprotein B (APOB), or proprotein convertase subtilisin kexin type 9 (PCSK9) genes. However, it is now known that many subjects with severe inherited hypercholesterolemia have no defects in these genes. These cases are caused either by mutations in genes yet to be identified or are
consequences of polygenic, epigenetic, or acquired defects. Because the clinical consequences of extreme hypercholesterolemia are the same no matter the cause, the focus should be on the identification of subjects with severe hypercholesterolemia, followed by phenotypic screening of family members. Genetic screening is not necessary to diagnose or initiate treatment for the severe hypercholesterolemia phenotype. Management of severe hypercholesterolemia is based on risk factor modification and use of multiple lipid-lowering medications. Lipoprotein apheresis is indicated for coronary artery disease (CAD) patients taking maximally tolerated therapy and with LDL-C levels >200 mg/dl (>300 mg/dl if without CAD). A microsomal triglyceride transfer protein inhibitor and an antisense oligonucleotide against APOB have recently been approved for use in subjects with clinically diagnosed homozygous familial hypercholesterolemia. PCSK9 inhibitors, currently in phase II and III trials, lower LDL-C up to an additional 70% in the setting of maximally tolerated medical therapy and have the potential to reduce LDL-C to <70 mg/dl in most patients. Early identification of affected individuals and aggressive treatment should significantly reduce the burden of cardiovascular disease in society (20).

**Nonpharmacological Lipoprotein Apheresis Reduces Arterial Inflammation in Familial Hypercholesterolemia**

D.F. van Wijk, et al.

**BACKGROUND** Patients with familial hypercholesterolemia (FH) are characterized by elevated atherogenic lipoprotein particles, predominantly low-density lipoprotein cholesterol (LDL-C), which is associated with accelerated atherogenesis and increased cardiovascular risk.

**OBJECTIVES** This study used 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) to investigate whether arterial inflammation is higher in patients with FH and, moreover, whether lipoprotein apheresis attenuates arterial wall inflammation in FH patients.

**METHODS** In total, 38 subjects were recruited: 24 FH patients and 14 normolipidemic controls. All subjects underwent FDG-PET imaging at baseline. Twelve FH patients who met the criteria for lipoprotein apheresis underwent apheresis procedures followed by a second FDG-PET imaging 3 days (range 1 to 4 days) after apheresis. Subsequently, the target-to-background ratio (TBR) of FDG uptake within the arterial wall was assessed.

**RESULTS** In FH patients, the mean arterial TBR was higher compared with healthy controls (2.12 ± 0.27 vs. 1.92 ± 0.19; p = 0.03). A significant correlation was observed between baseline arterial TBR and LDL-C (R = 0.37; p = 0.03) that remained significant after adjusting for statin use (β = 0.001; p = 0.02) and atherosclerosis risk factors (β = 0.001; p = 0.03). LDL-C levels were significantly reduced after lipoprotein apheresis (284 ± 118 mg/dl vs. 127 ± 50 mg/dl; p < 0.001). There was a significant reduction of arterial inflammation after lipoprotein apheresis (TBR: 2.05 ± 0.31 vs. 1.91 ± 0.33; p < 0.02).

**CONCLUSIONS** The arterial wall of FH patients is characterized by increased inflammation, which is markedly reduced after lipoprotein apheresis. This lends support to a causal role of apoprotein B-containing lipoproteins in arterial wall inflammation and supports the concept that lipoprotein-lowering therapies may impart anti-inflammatory effects by reducing atherogenic lipoproteins (21).

**Elevated Plasma PCSK9 Level Is Equally Detrimental for Patients With Nonfamilial Hypercholesterolemia and Heterozygous Familial Hypercholesterolemia, Irrespective of Low-Density Lipoprotein Receptor Defects**

G. Lambert, et al.

**OBJECTIVES** Do elevated proprotein convertase subtilisin/kexin type 9 (PCSK9) levels constitute an even greater risk for patients who already have reduced low-density lipoprotein receptor (LDLR) levels, such as those with heterozygous familial hypercholesterolemia (HeFH)?

**BACKGROUND** As a circulating inhibitor of LDLR, PCSK9 is an attractive target for lowering LDL-cholesterol (LDL-C) levels.

**METHODS** Circulating PCSK9 levels were measured by enzyme-linked immunosorbent assay in nontreated patients with HeFH carrying a D206E (n = 237), V408M (n = 117), or D154N (n = 38) LDLR missense mutation and in normolipidemic controls (n = 152). Skin fibroblasts and lymphocytes were isolated from a subset of patients and grown in 0.5% serum and mevastatin with increasing amounts of recombinant PCSK9. LDLR abundance at the cell surface was determined by flow cytometry.

**RESULTS** PCSK9 reduced LDLR expression in a dose-dependent manner in control and FH fibroblasts to similar extents, by up to 77 ± 8% and 82 ± 7%, respectively. Likewise, PCSK9 reduced LDLR abundance by 39 ± 8% in nonfamilial hypercholesterolemia (non-FH) and by 45 ± 10% in HeFH lymphocytes, irrespective of their LDLR mutation status. We found...
positive correlations of the same magnitude between PCSK9 and LDL-C levels in controls ($\beta = 0.22$; $p = 0.0003$), D206E ($\beta = 0.20$; $p = 0.0002$), V408M ($\beta = 0.24$; $p = 0.0002$), and D154N ($\beta = 0.25$; $p = 0.048$) patients with HeFH. The strengths of these associations were all similar.

CONCLUSIONS Elevated PCSK9 levels are equally detrimental for patients with HeFH or non-FH: a 100-ng/ml increase in PCSK9 will lead to an increase in LDL-C of 0.20 to 0.25 mmol/l in controls and HeFH alike, irrespective of their LDLR mutation. This explains why patients with non-FH or HeFH respond equally well to monoclonal antibodies targeting PCSK9 (22).

AMG 145, a Monoclonal Antibody Against PCSK9, Facilitates Achievement of National Cholesterol Education Program—Adult Treatment Panel III Low-Density Lipoprotein Cholesterol Goals Among High-Risk Patients: An Analysis From the LAPLACE-TIMI 57 Trial (LDL-C Assessment with PCSK9 monoclonal Antibody Inhibition Combined With Statin therapy—Thrombolysis In Myocardial Infarction 57)

N.R. Desai, et al.

OBJECTIVES This study sought to define the ability of AMG 145, a monoclonal antibody directed against proprotein convertase subtilisin kexin type 9 (PCSK9), to enable subjects at high risk for major adverse cardiovascular events to achieve National Cholesterol Education Program—Adult Treatment Panel III (NCEP-ATP III) parameters for low-density lipoprotein cholesterol (LDL-C) and other lipid goals.

BACKGROUND Many patients at high risk for adverse cardiovascular events are unable to achieve the NCEP-ATP III LDL-C goal of <70 mg/dl, even with high-potency statin therapy.

METHODS In 282 subjects from the LAPLACE-TIMI 57 (LDL-C Assessment with PCSK9 monoclonal Antibody Inhibition Combined With Statin therapy—Thrombolysis In Myocardial Infarction 57) trial at high risk according to NCEP-ATP III criteria, we compared the proportion of subjects achieving the NCEP-ATP III recommended LDL-C goal of <70 mg/dl across treatment arms. Other outcomes included the triple goals of LDL-C <70 mg/dl, non-high-density lipoprotein cholesterol (HDL-C) <100 mg/dl, and apolipoprotein B (ApoB) <80 mg/dl.

RESULTS During the dosing interval, more than 90% of subjects in both of the top dose groups every 2 weeks and every 4 weeks attained this lipid target over the dosing interval, with similar success rates for the triple lipid goal.

CONCLUSIONS PCSK9 inhibition with AMG 145 enables high-risk patients to achieve established lipid goals. If this therapy demonstrates efficacy for reducing cardiovascular events with a favorable safety profile in ongoing phase 3 trials, we believe it will have major public health implications (23).

Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients With Statin Intolerance: The GAUSS-2 Randomized, Placebo-Controlled Phase 3 Clinical Trial of Evolocumab

E. Stroes, et al.

OBJECTIVES This study sought to evaluate the efficacy and safety of subcutaneous evolocumab compared with oral ezetimibe in hypercholesterolemic patients who are unable to tolerate effective statin doses.

BACKGROUND Statin intolerance, which is predominantly due to muscle-related side effects, is reported in up to 10% to 20% of patients. Evolocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), demonstrated marked reductions in plasma low-density lipoprotein cholesterol (LDL-C) in a phase 2 study in statin-intolerant patients.

METHODS The GAUSS-2 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects) trial was a 12-week, double-blind study of randomized patients (2:2:1:1) to evolocumab 140 mg every 2 weeks (Q2W) or evolocumab 420 mg once monthly (QM) both with daily oral placebo or subcutaneous placebo Q2W or QM both with daily oral ezetimibe 10 mg. Co-primary endpoints were percent change from baseline in LDL-C at the mean of weeks 10 and 12, and at week 12.

RESULTS Three hundred seven patients (age 62 ± 10 years; LDL-C 193 ± 59 mg/dl) were randomized. Evolocumab reduced LDL-C from baseline by 53% to 56%, corresponding to treatment differences versus ezetimibe of 37% to 39% (p <0.001). Muscle adverse events occurred in 12% of evolocumab-treated patients and 23% of ezetimibe-treated patients. Treatment-emergent adverse events and laboratory abnormalities were comparable across treatment groups.

CONCLUSIONS Robust efficacy combined with favorable tolerability makes evolocumab a promising therapy for addressing the largely unmet clinical need in high-risk patients with elevated cholesterol who are statin intolerant. (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-2; NCT01763905) (24).
Anti-PCSK9 Monotherapy for Hypercholesterolemia: The MENDEL-2 Randomized, Controlled Phase III Clinical Trial of Evolocumab

M.J. Koren, et al.

OBJECTIVES The aim of this study was to compare biweekly and monthly evolocumab with placebo and oral ezetimibe in patients with hypercholesterolemia in a phase III trial.

BACKGROUND Evolocumab, a fully human monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9), significantly reduced LDL-C in phase II trials.

METHODS Patients 18 to 80 years of age with fasting low-density lipoprotein cholesterol (LDL-C) ≥100 and <190 mg/dl and Framingham risk scores ≤10% were randomized in a 1:1:1:2:2 ratio to oral placebo and subcutaneous (SC) placebo biweekly; oral placebo and SC placebo monthly; ezetimibe and SC placebo biweekly; ezetimibe and SC placebo monthly; oral placebo and evolocumab 140 mg biweekly; or oral placebo and evolocumab 420 mg monthly.

RESULTS A total of 614 patients were randomized and administered doses. Evolocumab treatment reduced LDL-C from baseline, on average, by 55% to 57% more than placebo and 38% to 40% more than ezetimibe (p < 0.001 for all comparisons). Evolocumab treatment also favorably altered other lipoprotein levels. Treatment-emergent adverse events (AEs), muscle-related AEs, and laboratory abnormalities were comparable across treatment groups.

CONCLUSIONS In the largest monotherapy trial using a PCSK9 inhibitor to date, evolocumab yielded significant LDL-C reductions compared with placebo or ezetimibe and was well tolerated in patients with hypercholesterolemia. (Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2 [MENDEL-2]; NCT01765827) (25).

Lipoprotein(a) for Risk Assessment in Patients With Established Coronary Artery Disease

M.L. O’Donoghue, et al.

OBJECTIVES The purpose of this study was to determine the relationship between lipoprotein(a) (Lp(a)) and cardiovascular disease (CVD) in a large cohort of patients with heterozygous familial hypercholesterolemia (FH).

BACKGROUND Lp(a) is considered a cardiovascular risk factor. Nevertheless, the role of Lp(a) as a predictor of CVD in patients with FH has been a controversial issue.

METHODS A cross-sectional analysis of 1,960 patients with FH and 957 non-FH relatives recruited for SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study), a long-term observational cohort study of a molecularly well-defined FH study group, was performed. Lp(a) concentrations were measured in plasma using an immunoturbidimetric method.

RESULTS Patients with FH, especially those with CVD, had higher Lp(a) plasma levels compared with their unaffected relatives (p < 0.001). A significant
CONCLUSIONS \( \text{Lp(a)} \) is an independent predictor of CVD in men and women with FH. The risk of CVD is higher in those patients with an \( \text{Lp(a)} \) level >50 mg/dl and carrying a receptor-negative mutation in the \( \text{LDLR} \) gene compared with other less severe mutations (27).

Reduction in Lipoprotein(a) With PCSK9 Monoclonal Antibody Evolocumab (AMG 145): A Pooled Analysis of More Than 1,300 Patients in 4 Phase II Trials

F.J. Raal, et al.

OBJECTIVES The purpose of this study was assess the effect of evolocumab (AMG 145) on lipoprotein (\( \text{Lp(a)} \)) from a pooled analysis of 4 phase II trials.

BACKGROUND \( \text{Lp(a)} \), a low-density lipoprotein (LDL) particle linked to the plasminogen-like glycoprotein apolipoprotein(a), shows a consistent and independent positive association with cardiovascular disease risk in epidemiological studies. Current therapeutic options to reduce \( \text{Lp(a)} \) are limited.

METHODS A pooled analysis of data from 1,359 patients in 4 phase II trials assessed the effects of evolocumab, a fully human monoclonal antibody to PCSK9, on \( \text{Lp(a)} \), the relationship between \( \text{Lp(a)} \) and lowering of low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B, and the influence of background statin therapy. \( \text{Lp(a)} \) was measured using a standardized isoform-independent method.

RESULTS Evolocumab treatment for 12 weeks resulted in significant (\( p < 0.001 \)) mean (95% confidence interval) dose-related reductions in \( \text{Lp(a)} \) compared to control: 29.5% (23.3% to 35.7%) and 24.5% (20.4% to 28.7%) with 140 mg and 420 mg, dosed every 2 and 4 weeks, respectively, with no plateau of effect. \( \text{Lp(a)} \) reductions were significantly correlated with percentages of reductions in LDL-C (Spearman correlation coefficient, 0.5134; \( p < 0.001 \)) and apolipoprotein B (Spearman correlation coefficient, 0.5203; \( p < 0.001 \)). Mean percentage reductions did not differ based on age or sex but the trend was greater in those patients taking statins.

CONCLUSIONS Inhibition of PCSK9 with evolocumab resulted in significant dose-related reductions in \( \text{Lp(a)} \). While the mean percentage of reduction was significantly greater in those patients with baseline \( \text{Lp(a)} \) of ≤125 nmol/l, the absolute reduction was substantially larger in those with levels >125 nmol/l (28).

Genetics and Causality of Triglyceride-Rich Lipoproteins in Atherosclerotic Cardiovascular Disease

R.S. Rosenson, et al.

Triglycerides represent 1 component of a heterogeneous pool of triglyceride-rich lipoproteins (TGRLs). The reliance on triglycerides or TGRLs as cardiovascular disease (CVD) risk biomarkers prompted investigations into therapies that lower plasma triglycerides as a means to reduce CVD events. Genetic studies identified TGRL components and pathways involved in their synthesis and metabolism. We advocate that only a subset of genetic mechanisms regulating TGRLs contribute to the risk of CVD events. This “omic” approach recently resulted in new targets for reducing CVD events (29).

Atrial Autonomic Innervation: A Target for Interventional Antiarrhythmic Therapy?

D. Linz, et al.

Atrial fibrillation is the most common arrhythmia and is associated with significant morbidity and mortality. The autonomic nervous system contributes to the creation of atrial fibrillation substrates. Atrial electrophysiology is influenced differently by sympathetic and parasympathetic activation. Several strategies are available to modulate the complex interaction between the autonomic nervous system and the heart. However, different approaches target the problem differently making the prediction of arrhythmogenic and/or antiarrhythmic effects difficult. We discuss the role of the autonomic nervous system on the development of a substrate for atrial fibrillation and explore the potential antiarrhythmic and/or arrhythmogenic effect of modulation of the autonomic nervous system by renal sympathetic denervation, ganglionic plexi ablation, ganglion stellatum ablation, high thoracic epidural anesthesia, low-level vagal nerve stimulation, and baroreflex stimulation (30).

Regional Myocardial Sympathetic Denervation Predicts the Risk of Sudden Cardiac Arrest in Ischemic Cardiomyopathy

J.A. Fallavollita, et al.

OBJECTIVES The PAREPET (Prediction of ARrhythmic Events with Positron Emission Tomography) study
sought to test the hypothesis that quantifying inhomogeneity in myocardial sympathetic innervation could identify patients at highest risk for sudden cardiac arrest (SCA).

**BACKGROUND** Left ventricular ejection fraction (LVEF) is the only parameter identifying patients at risk of SCA who benefit from an implantable cardiac defibrillator (ICD).

**METHODS** We prospectively enrolled 204 subjects with ischemic cardiomyopathy (LVEF ≤35%) eligible for primary prevention ICDs. Positron emission tomography (PET) was used to quantify myocardial sympathetic denervation ([11C-meta-hydroxyephedrine ([11C-HED]), perfusion ([13N-ammonia) and viability (insulin-stimulated [18F-2-deoxyglucose). The primary endpoint was SCA defined as arrhythmic death or ICD discharge for ventricular fibrillation or ventricular tachycardia >240 beats/min.

**RESULTS** After 4.1 years follow-up, cause-specific SCA was 16.2%. Infarct volume (22 ± 7% vs. 19 ± 9% of left ventricle [LV]) and LVEF (24 ± 8% vs. 28 ± 9%) were not predictors of SCA. In contrast, patients developing SCA had greater amounts of sympathetic denervation (33 ± 10% vs. 26 ± 11% of LV; p = 0.001) reflecting viable, denervated myocardium. The lower tertiles of sympathetic denervation had SCA rates of 1.2%/year and 2.2%/year, whereas the highest tertile had a rate of 6.7%/year. Multivariate predictors of SCA were PET imaging with quantification of sympathetic denervation (3% vs. 9% of left ventricle; p = 0.001), LVEF, and left ventricular ejection fraction (LVEF) <35%.

**CONCLUSIONS** PET imaging may be a useful tool for identifying patients at highest risk for primary prevention ICDs. Further studies are needed to evaluate the utility of PET imaging for primary prevention ICDs.

**A Molecular Mechanism for Adrenergic-Induced Long QT Syndrome**

J. Wu, et al.

**OBJECTIVES** This study sought to explore molecular mechanisms underlying the adrenergic-induced QT prolongation associated with KCNQ1 mutations.

**BACKGROUND** The most frequent type of congenital long QT syndrome is LQT1, which is caused by mutations in the gene (KCNQ1) that encodes the alpha subunit of the slow component of delayed rectifier K+ current (I_Ks) channel. We identified 11 patients from 4 unrelated families that are heterozygous for KCNQ1-G269S. Most patients remained asymptomatic, and their resting corrected QT intervals ranged from normal to borderline but were prolonged significantly during exercise.

**METHODS** Wild-type (WT) KCNQ1 and/or KCNQ1-G269S (G269S) were expressed in mammalian cells with KCNE1. I_Ks-like currents were measured in control conditions or after isoproterenol or protein kinase A (PKA) stimulation using the patch-clamp technique. Additionally, experiments that incorporated the phosphomimetic KCNQ1 substitution, S27D, in WT or KCNQ1-G269S were also performed.

**RESULTS** The coexpression of WT-KCNQ1 with varying amounts of G269S decreased I_Ks, shifted the current-voltage I-V relation of I_Ks to more positive potentials, and accelerated the I_Ks deactivation rates in a concentration-dependent manner. In addition, the coexpression of G269S and WT blunted the activation of I_Ks in response to isoproterenol or PKA stimulation. Lastly, a phosphomimetic substitution in G269S did not show an increased I_Ks.

**CONCLUSIONS** G269S modestly affected I_Ks in control conditions, but it almost completely blunted I_Ks responsiveness in conditions that simulate or mimic PKA phosphorylation of KCNQ1. This insensitivity to PKA stimulation may explain why patients with G269S mutation showed an excessive prolongation of QT intervals on exercise.

**Engineered Electrical Conduction Tract Restores Conduction in Complete Heart Block: From In Vitro to In Vivo Proof of Concept**

E. Cingolani, et al.

**BACKGROUND** Cardiac electrical conduction delays and blocks cause rhythm disturbances such as complete heart block, which can be fatal. Standard of care relies on electronic devices to artificially restore synchrony. We sought to create a new modality for treating these disorders by engineering electrical conduction tracts designed to propagate electrical impulses.

**OBJECTIVES** This study sought to create a new approach for treating cardiac conduction disorders by using engineered electrical conduction tracts (EECTs).

**METHODS** Paramagnetic beads were conjugated with an antibody to gamma-sarcoglycan, a cardiomyocyte cell surface antigen, and mixed with freshly isolated
neonatal rat ventricular cardiomyocytes. A magnetic field was used to pattern a linear EECT.

**RESULTS** In an in vitro model of conduction block, the EECT was patterned so that it connected 2 independently beating neonatal rat ventricular cardiomyocyte monolayers; it achieved coordinated electrical activity, with action potentials propagating from 1 region to the other via EECT. Spiking the EECT with heart-derived stromal cells yielded stable structures with highly reproducible conduction velocities. Transplantation of EECTs in vivo restored atrioventricular conduction in a rat model of complete heart block.

**CONCLUSIONS** An EECT can re-establish electrical conduction in the heart. This novel approach could, in principle, be used not only to treat cardiac arrhythmias but also to repair other organs (33).

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**RHYTHM DISORDERS**

*Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation: The ARREST-AF Cohort Study*


**BACKGROUND** The long-term outcome of atrial fibrillation (AF) ablation demonstrates attrition. This outcome may be due to failure to attenuate the progressive substrate promoted by cardiovascular risk factors.

**OBJECTIVES** The goal of this study was to evaluate the impact of risk factor and weight management on AF ablation outcomes.

**METHODS** Of 281 consecutive patients undergoing AF ablation, 149 with a body mass index \( \leq 27 \text{ kg/m}^2 \) and \( \geq 1 \) cardiac risk factor were offered risk factor management (RFM) according to American Heart Association/American College of Cardiology guidelines. After AF ablation, all 61 patients who opted for RFM and 88 control subjects were assessed every 3 to 6 months by clinic review and 7-day Holter monitoring. Changes in the Atrial Fibrillation Severity Scale scores were determined.

**RESULTS** There were no differences in baseline characteristics, number of procedures, or follow-up duration between the groups (p = NS). RFM resulted in greater reductions in weight (p = 0.002) and blood pressure (p = 0.006), and better glycemic control (p = 0.001) and lipid profiles (p = 0.01). At follow-up, AF frequency, duration, symptoms, and symptom severity decreased more in the RFM group compared with the control group (all p < 0.001).

Single-procedure drug-unassisted arrhythmia-free survival was greater in RFM patients compared with control subjects (p < 0.001). Multiple-procedure arrhythmia-free survival was markedly better in RFM patients compared with control subjects (p < 0.001), with 16% and 42.4%, respectively, using antiarrhythmic drugs (p = 0.004). On multivariate analysis, type of AF (p < 0.001) and RFM (hazard ratio 4.8 [95% confidence interval: 2.04 to 11.4]; p < 0.001) were independent predictors of arrhythmia-free survival.

**CONCLUSIONS** Aggressive RFM improved the long-term success of AF ablation. This study underscores the importance of therapy directed at the primary promoters of the AF substrate to facilitate rhythm control strategies (34).

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*Atrial Remodeling and Atrial Fibrillation: Recent Advances and Translational Perspectives*

S. Nattel, et al.

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. AF and its complications are responsible for important population morbidity and mortality. Presently available therapeutic approaches have limited efficacy and nontrivial potential to cause adverse effects. Thus, new mechanistic knowledge is essential for therapeutic innovation. Atrial arrhythmogenic remodeling, defined as any change in atrial structure or function that promotes atrial arrhythmias, is central to AF. Remodeling can be due to underlying cardiac conditions, systemic processes and conditions such as aging, or AF itself. Recent work has underlined the importance of remodeling in AF, provided new insights into basic mechanisms, and identified new biomarker/imaging approaches to follow remodeling processes. The importance of intracellular Ca\(^{2+}\) handling abnormalities has been highlighted, both for the induction of triggered ectopic activity and for the activation of Ca\(^{2+}\)-related cell signaling that mediates proarrhythmic remodeling. The importance of microRNAs, which are a new class of small noncoding sequences that regulate gene expression, has emerged in both electrical and structural remodeling. Remodeling related to aging, cardiac disease, and AF itself is believed to underlie the progressive nature of the arrhythmia, which contributes to the complexities of long-term management. New tools that are being developed to quantify remodeling processes and monitor their progression include novel biomarkers, imaging modalities to quantify/localize fibrosis, and noninvasive monitoring/mapping to better characterize the burden of AF and identify arrhythmic sources. This
Lone Atrial Fibrillation: Does it Exist?
D.G. Wyse, et al.

The historical origin of the term “lone atrial fibrillation” (AF) predates by 60 years our current understanding of the pathophysiology of AF, the multitude of known etiologies for AF, and our ability to image and diagnose heart disease. The term was meant to indicate AF in patients for whom subsequent investigations could not demonstrate heart disease, but for many practitioners has become synonymous with “idiopathic AF.” As the list of heart diseases has expanded and diagnostic techniques have improved, the prevalence of lone AF has fallen. The legacy of the intervening years is that definitions of lone AF in the literature are inconsistent so that studies of lone AF are not comparable. Guidelines provide a vague definition of lone AF but do not provide direction about how much or what kind of imaging and other testing are necessary to exclude heart disease. There has been an explosion in the understanding of the pathophysiology of AF in the last 20 years in particular. Nevertheless, there are no apparently unique mechanisms for AF in patients categorized as having lone AF. In addition, the term “lone AF” is not invariably useful in making treatment decisions, and other tools for doing so have been more thoroughly and carefully validated. It is, therefore, recommended that use of the term “lone AF” be avoided.

Alcohol Consumption and Risk of Atrial Fibrillation: A Prospective Study and Dose-Response Meta-Analysis
S.C. Larsson, et al.

BACKGROUND Although high alcohol consumption has been associated with increased risk of atrial fibrillation (AF), the role of light to moderate drinking remains unclear.

OBJECTIVES The study sought to investigate the association between alcohol consumption and AF risk in a prospective study of Swedish men and women and to conduct a meta-analysis of prospective studies to summarize available evidence.

METHODS We followed 79,019 men and women who, at baseline, were free from AF and had completed a questionnaire about alcohol consumption and other risk factors for chronic diseases. Incident AF cases were ascertained by linkage to the Swedish Inpatient Register. For the meta-analysis, studies were identified by searching PubMed through January 10, 2014, and by reviewing references of pertinent publications. Study-specific relative risks (RRs) were combined using a random effects model.

RESULTS Over 859,420 person-years of follow-up (1998 to 2009), 7,245 incident AF cases were identified in our own cohort study. The association between alcohol consumption and AF did not differ by sex (p for interaction = 0.74). Compared with current drinkers of <1 drink/week (12 g alcohol/week), the multivariable RRs of AF were 1.01 (95% confidence interval [CI]: 0.94 to 1.09) for 1 to 6 drinks/week, 1.07 (95% CI: 0.98 to 1.17) for 7 to 14 drinks/week, 1.14 (95% CI: 1.01 to 1.28) for 15 to 21 drinks/week, and 1.39 (95% CI: 1.22 to 1.58) for >21 drinks/week. Results were similar after excluding binge drinkers. In a meta-analysis of 7 prospective studies, including 12,554 AF cases, the RRs were 1.08 (95% CI: 1.06 to 1.10) for 1 drink/day, 1.17 (95% CI: 1.13 to 1.21) for 2 drinks/day, 1.26 (95% CI: 1.19 to 1.33) for 3 drinks/day, 1.36 (95% CI: 1.27 to 1.46) for 4 drinks/day, and 1.47 (95% CI: 1.34 to 1.61) for 5 drinks/day, compared with nondrinkers.

CONCLUSIONS These findings indicate that alcohol consumption, even at moderate intakes, is a risk factor for atrial fibrillation.

Insights Into Onco-Cardiology: Atrial Fibrillation in Cancer
D. Farmakis, et al.

Atrial fibrillation (AF) has been found to occur with an increased frequency in patients with malignancies, particularly in those undergoing cancer surgery. The occurrence of AF in cancer may be related to comorbid states or a direct tumor effect or may represent a complication of cancer surgical or medical therapy, whereas inflammation may be a common denominator for both conditions. Treating AF in patients with malignancies is a challenge, especially in terms of antithrombotic therapy, because cancer may result in an increased risk of either thrombosis or hemorrhage and an unpredictable anticoagulation response, whereas thromboembolic risk prediction scores such as CHADS2 (Cardiac Failure, Hypertension, Age, Diabetes, and Stroke [doubled]) may not be applicable. The general lack of evidence imposes an individualized approach to the management of AF in those patients, although some general recommendations based on current guidelines in noncancer patients and the existing evidence in cancer patients, where available, may be outlined.
**Increased Mortality Associated With Digoxin in Contemporary Patients With Atrial Fibrillation: Findings From the TREAT-AF Study**

M.P. Turakhia, et al.

**BACKGROUND** Despite endorsement of digoxin in clinical practice guidelines, there exist limited data on its safety in atrial fibrillation/flutter (AF).

**OBJECTIVES** The goal of this study was to evaluate the association of digoxin with mortality in AF.

**METHODS** Using complete data of the TREAT-AF (The Retrospective Evaluation and Assessment of Therapies in AF) study from the U.S. Department of Veterans Affairs (VA) healthcare system, we identified patients with newly diagnosed, nonvalvular AF seen within 90 days in an outpatient setting between VA fiscal years 2004 and 2008. We used multivariate and propensity-matched Cox proportional hazards to evaluate the association of digoxin use with death. Residual confounding was assessed by sensitivity analysis.

**RESULTS** Of 122,465 patients with 353,168 person-years of follow-up (age 72.1 ± 10.3 years, 98.4% male), 28,679 (23.4%) patients received digoxin. Cumulative mortality rates were higher for digoxin-treated patients than for untreated patients (95 vs. 67 per 1,000 person-years; p < 0.001). Digoxin use was independently associated with mortality after multivariate adjustment (hazard ratio [HR]: 1.26, 95% confidence interval [CI]: 1.23 to 1.29; p < 0.001) and propensity matching (HR: 1.21, 95% CI: 1.17 to 1.25; p < 0.001), even after adjustment for drug adherence. The risk of death was not modified by age, sex, heart failure, kidney function, or concomitant use of beta-blockers, amiodarone, or warfarin.

**CONCLUSIONS** Digoxin was associated with increased risk of death in patients with newly diagnosed AF, independent of drug adherence, kidney function, cardiovascular comorbidities, and concomitant therapies. These findings challenge current cardiovascular society recommendations on use of digoxin in AF (39).

**Clinical Classifications of Atrial Fibrillation Poorly Reflect Its Temporal Persistence: Insights From 1,195 Patients Continuously Monitored With Implantable Devices**

E.I. Charitos, et al.

**OBJECTIVES** This study aimed to identify how accurately the current clinical atrial fibrillation (AF) classifications reflect its temporal persistence.

**BACKGROUND** Clinical classification of AF is employed to communicate its persistence, to select appropriate therapies, and as inclusion criterion for clinical trials.

**METHODS** Cardiac rhythm histories of 1,195 patients (age 73.0 ± 10.1 years, follow-up: 349 ± 40 days) with implantable devices were reconstructed and analyzed. Patients were classified as having paroxysmal or persistent AF by physicians at baseline in accordance with current guidelines. AF burden, measured as the proportion of time spent in AF, was obtained from the device. Additionally we evaluated the agreement between clinical and device-derived AF classifications.

**RESULTS** Patients within the same clinical class were highly heterogeneous with regards to AF temporal persistence. Agreement between the clinical AF classification and the objective device-derived assessments of AF temporal persistence was poor (Cohen’s kappa: 0.12 [95% CI: 0.05 to 0.18]). Patient characteristics influenced the clinical decision to classify AF as paroxysmal or persistent. Higher ejection fraction (odds ratio: 0.97/per unit [95% CI: 0.95 to 0.98/per unit]; p < 0.0001) and presence of coronary artery disease (odds ratio: 0.53 [95% CI: 0.32 to 0.88]; p = 0.01) were independently associated with a lower probability of being classified as persistent AF for the same AF burden level.

**CONCLUSIONS** The currently used clinical AF classifications poorly reflect AF temporal persistence. Patient characteristics significantly influence the physician’s classification of AF. Patients classified in identical clinical categories may be inherently heterogeneous with regard to AF temporal persistence. Further study is required to determine if patient selection on the basis of objective criteria derived from rigorous AF monitoring can improve reported outcomes and better identify responders and non-responders to treatments. (OMNI Study-Assessing Therapies in Medtronic Pacemaker, Defibrillator, and Cardiac Resynchronization Therapy Devices; NCT00277524; TRENDS: A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics; NCT00279981) (40).

**Amiodarone, Anticoagulation, and Clinical Events in Patients With Atrial Fibrillation: Insights From the ARISTOTLE Trial**

G. Flaker, et al.

**BACKGROUND** Amiodarone is an effective medication in preventing atrial fibrillation (AF), but it interferes with the metabolism of warfarin.

**OBJECTIVES** This study sought to examine the association of major thrombotic clinical events and bleeding with the use of amiodarone in the ARISTOTLE
(Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.

**METHODS** Baseline characteristics of patients who received amiodarone at randomization were compared with those who did not receive amiodarone. The interaction between randomized treatment and amiodarone was tested using a Cox model, with main effects for randomized treatment and amiodarone and their interaction. Matching on the basis of a propensity score was used to compare patients who received and who did not receive amiodarone at the time of randomization.

**RESULTS** In ARISTOTLE, 2,051 (11.4%) patients received amiodarone at randomization. Patients on warfarin and amiodarone had time in the therapeutic range that was lower than patients not on amiodarone (56.5% vs. 63.0%; p < 0.0001). More amiodarone-treated patients had a stroke or a systemic embolism (1.58%/year vs. 1.19%/year; adjusted hazard ratio [HR]: 1.47, 95% confidence interval [CI]: 1.03 to 2.10; p = 0.0322). Overall mortality and major bleeding rates were elevated, but were not significantly different in amiodarone-treated patients and patients not on amiodarone. When comparing apixaban with warfarin, patients who received amiodarone had a stroke or a systemic embolism rate of 1.24%/year versus 1.85%/year (HR: 0.68, 95% CI: 0.40 to 1.15), death of 4.15%/year versus 5.65%/year (HR: 0.74, 95% CI: 0.55 to 0.98), and major bleeding of 1.86%/year versus 3.06%/year (HR: 0.61, 95% CI: 0.39 to 0.96). In patients who did not receive amiodarone, the stroke or systemic embolism rate was 1.29%/year versus 1.57%/year (HR: 0.82, 95% CI: 0.68 to 1.00), death was 3.43%/year versus 3.68%/year (HR: 0.93, 95% CI: 0.83 to 1.05), and major bleeding was 2.18%/year versus 3.03%/year (HR: 0.72, 95% CI: 0.62 to 0.84). The interaction p values for amiodarone use by apixaban treatment effects were not significant.

**CONCLUSIONS** Amiodarone use was associated with significantly increased stroke and systemic embolism risk and a lower time in the therapeutic range when used with warfarin. Apixaban consistently reduced the rate of stroke and systemic embolism, death, and major bleeding compared with warfarin in amiodarone-treated patients and patients who were not on amiodarone (41).

**Net Clinical Benefit of Antithrombotic Therapy in Patients With Atrial Fibrillation and Chronic Kidney Disease: A Nationwide Observational Cohort Study**  
A.N. Bonde, et al.

**BACKGROUND** The balance between stroke reduction and increased bleeding associated with antithrombotic therapy among patients with atrial fibrillation (AF) and chronic kidney disease (CKD) is controversial.

**OBJECTIVES** This study assessed the risk associated with CKD in individual CHA2DS2-VASc (Congestive heart failure; Hypertension; Age ≥75 years; Diabetes mellitus; previous Stroke, transient ischemic attack, or thromboembolism; Vascular disease; Age 65 to 74 years; Sex category) strata and the net clinical benefit of warfarin in patients with AF and CKD in a nationwide cohort.

**METHODS** By individual-level linkage of nationwide Danish registries, we identified all patients discharged with nonvalvular AF from 1997 to 2011. The stroke risk associated with non-end-stage CKD and end-stage CKD (e.g., patients on renal replacement therapy [RRT]) was estimated using Cox regression analyses. The net clinical benefit of warfarin was assessed using 4 endpoints: a composite endpoint of death/hospitalization from stroke/bleeding; a composite endpoint of fatal stroke/fatal bleeding; cardiovascular death; and all-cause death.

**RESULTS** From nonvalvular AF patients (n = 154,259), we identified 11,128 patients (7.2%) with non-end-stage CKD and 1,728 (1.1%) receiving RRT. In all CHA2DS2-VASc risk groups, RRT was independently associated with a higher risk of stroke/thromboembolism, from a 5.5-fold higher risk in patients with CHA2DS2-VASc score = 0 to a 1.6-fold higher risk in patients with CHA2DS2-VASc score ≥2. In patients receiving RRT with CHA2DS2-VASc score ≥2, warfarin was associated with lower risk of all-cause death (hazard ratio [HR]: 0.85, 95% confidence interval [CI]: 0.72 to 0.99). In non-end-stage CKD patients with CHA2DS2-VASc score ≥2, warfarin was associated with a lower risk of a composite outcome of fatal stroke/fatal bleeding (HR: 0.71, 95% CI: 0.57 to 0.88), a lower risk of cardiovascular death (HR: 0.80, 95% CI: 0.74 to 0.88), and a lower risk of all-cause death (HR: 0.64, 95% CI: 0.60 to 0.69).

**CONCLUSIONS** CKD is associated with a higher risk of stroke/thromboembolism across stroke risk strata in AF patients. High-risk CKD patients (CHA2DS2-VASc ≥2) with AF benefit from warfarin treatment for stroke prevention (42).

**Triple Therapy for Atrial Fibrillation and Percutaneous Coronary Intervention: A Contemporary Review**  
W.J.M. Dewilde, et al.

Chronic oral anticoagulant therapy is recommended (class I) in patients with mechanical heart valves and in
patients with atrial fibrillation with a CHA2DS2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65 to 74 years, Sex category) score ≥1. When these patients undergo percutaneous coronary intervention with stenting, treatment with aspirin and a P2Y12 receptor inhibitor also becomes indicated. Before 2014, guidelines recommended the use of triple therapy (vitamin K antagonists, aspirin, and clopidogrel) for these patients. However, major bleeding is increasingly recognized as the Achilles’ heel of the triple therapy regimen. Lately, various studies have investigated this topic, including a prospective randomized trial, and the evidence for adding aspirin to the regimen of vitamin K antagonists and clopidogrel seems to be weakened. In this group of patients, the challenge is finding the optimal equilibrium to prevent thromboembolic events, such as stent thrombosis and thromboembolic stroke, without increasing bleeding risk (43).

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

P.A. Reilly, et al.

OBJECTIVES The goal of this study was to analyze the impact of dabigatran plasma concentrations, patient demographics, and aspirin (ASA) use on frequencies of ischemic strokes/systemic emboli and major bleeds in atrial fibrillation patients.

BACKGROUND The efficacy and safety of dabigatran etexilate were demonstrated in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, but a therapeutic concentration range has not been defined.

METHODS In a pre-specified analysis of RE-LY, plasma concentrations of dabigatran were determined in patients treated with dabigatran etexilate 110 mg twice daily (bid) or 150 mg bid and correlated with the clinical outcomes of ischemic stroke/systemic embolism and major bleeding using univariate and multivariate logistic regression and Cox regression models. Patient demographics and ASA use were assessed descriptively and as covariates.

RESULTS Plasma concentrations were obtained from 9,183 patients, with 112 ischemic strokes/systemic emboli (1.3%) and 323 major bleeds (3.8%) recorded. Dabigatran levels were dependent on renal function, age, weight, and female sex, but not ethnicity, geographic region, ASA use, or clopidogrel use. A multiple logistic regression model (c-statistic 0.657, 95% confidence interval [CI]: 0.61 to 0.71) showed that the risk of ischemic events was inversely related to trough dabigatran concentrations (p = 0.045), with age and previous stroke (both p < 0.0001) as significant covariates. Multiple logistic regression (c-statistic 0.715, 95% CI: 0.69 to 0.74) showed major bleeding risk increased with dabigatran exposure (p < 0.0001), age (p < 0.0001), ASA use (p < 0.0003), and diabetes (p = 0.018) as significant covariates.

CONCLUSIONS Ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations. Age was the most important covariate. Individual benefit-risk might be improved by tailoring dabigatran dose after considering selected patient characteristics. (Randomized Evaluation of Long Term Anticoagulant Therapy [RE-LY] With Dabigatran Etexilate; NCT00262600) (44).

Factors Associated With Major Bleeding Events: Insights From the ROCKET AF Trial (Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)

S.G. Goodman, et al.

OBJECTIVES This study sought to report additional safety results from the ROCKET AF (Rivaroxaban Once-daily oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation).

BACKGROUND The ROCKET AF trial demonstrated similar risks of stroke/systemic embolism and major/nonmajor clinically relevant bleeding (principal safety endpoint) with rivaroxaban and warfarin.

METHODS The risk of the principal safety and component bleeding endpoints with rivaroxaban versus warfarin were compared, and factors associated with major bleeding were examined in a multivariable model.

RESULTS The principal safety endpoint was similar in the rivaroxaban and warfarin groups (14.9 vs. 14.5 events/100 patient-years; hazard ratio: 1.03; 95% confidence interval: 0.96 to 1.11). Major bleeding risk increased with age, but there were no differences between treatments in each age category (<65, 65 to 74, ≥75 years; PInteraction = 0.59). Compared with those without (n = 13,455), patients with a major bleed (n = 781) were more likely to be older, current/prior smokers, have prior gastrointestinal (GI) bleeding, mild anemia, and a lower calculated creatinine clearance and less likely to be female or have a prior stroke/transient
ischemic attack. Increasing age, baseline diastolic blood pressure (DBP) \( \geq 90 \) mm Hg, history of chronic obstructive pulmonary disease or GI bleeding, prior acetylsalicylic acid use, and anemia were independently associated with major bleeding risk; female sex and DBP <90 mm Hg were associated with a decreased risk.

**CONCLUSIONS** Rivaroxaban and warfarin had similar risk for major/nonmajor clinically relevant bleeding. Age, sex, DBP, prior GI bleeding, prior acetylsalicylic acid use, and anemia were associated with the risk of major bleeding. (An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation; NCT00403767) (45).

**Feasibility and Safety of Uninterrupted Rivaroxaban for Periprocedural Anticoagulation in Patients Undergoing Radiofrequency Ablation for Atrial Fibrillation: Results From a Multicenter Prospective Registry**

D. Lakkireddy, et al.

**OBJECTIVES** The purpose of this study was to evaluate the feasibility and safety of uninterrupted rivaroxaban therapy during atrial fibrillation (AF) ablation.

**BACKGROUND** Optimal periprocedural anticoagulation strategy is essential for minimizing bleeding and thromboembolic complications during and after AF ablation. The safety and efficacy of uninterrupted rivaroxaban therapy as a periprocedural anticoagulant for AF ablation are unknown.

**METHODS** We performed a multicenter, observational, prospective study of a registry of patients undergoing AF ablation in 8 centers in North America. Patients taking uninterrupted periprocedural rivaroxaban were matched by age, sex, and type of AF with an equal number of patients taking uninterrupted warfarin therapy who were undergoing AF ablation during the same period.

**RESULTS** A total of 642 patients were included in the study, with 321 in each group. Mean age was 63 ± 10 years, with 442 (69%) males and 328 (51%) patients with paroxysmal AF equally distributed between the 2 groups. Patients in the warfarin group had a slightly higher mean HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score (1.70 ± 1.0 vs. 1.47 ± 0.9, respectively; \( p = 0.032 \)). Bleeding and embolic complications occurred in 47 (7.3%) and 2 (0.3%) patients (both had transient ischemic attacks) respectively. There were no differences in the number of major bleeding complications (5 [1.6%] vs. 7 [1.9%], respectively; \( p = 0.772 \)), minor bleeding complications (16 [5.0%] vs. 19 [5.9%], respectively; \( p = 0.602 \)), or embolic complications (1 [0.3%] vs. 1 [0.3%], respectively; \( p = 1.0 \)) between the rivaroxaban and warfarin groups in the first 30 days.

**CONCLUSIONS** Uninterrupted rivaroxaban therapy appears to be as safe and efficacious in preventing bleeding and thromboembolic events in patients undergoing AF ablation as uninterrupted warfarin therapy (46).

**Efficacy and Safety of Apixaban in Patients After Cardioversion for Atrial Fibrillation: Insights From the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)**

G. Flaker, et al.

**OBJECTIVES** The aim of this study was to determine the risk of major clinical and thromboembolic events after cardioversion for atrial fibrillation in subjects treated with apixaban, an oral factor Xa inhibitor, compared with warfarin.

**BACKGROUND** In patients with atrial fibrillation, thromboembolic events may occur after cardioversion. This risk is lowered with vitamin K antagonists and dabigatran.

**METHODS** Using data from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, we conducted a post-hoc analysis of patients undergoing cardioversion.

**RESULTS** A total of 743 cardioversions were performed in 540 patients: 265 first cardioversions in patients assigned to apixaban and 275 in those assigned to warfarin. The mean time to the first cardioversion for patients assigned to warfarin and apixaban was 243 ± 231 days and 251 ± 248 days, respectively; 75% of the cardioversions occurred by 1 year. Baseline characteristics were similar between groups. In patients undergoing cardioversion, no stroke or systemic emboli occurred in the 30-day follow-up period. Myocardial infarction occurred in 1 patient (0.2%) receiving warfarin and 1 patient receiving apixaban (0.3%). Major bleeding occurred in 1 patient (0.2%) receiving warfarin and 1 patient receiving apixaban (0.3%). Death occurred in 2 patients (0.5%) receiving warfarin and 2 patients receiving apixaban (0.6%).

**CONCLUSIONS** Major cardiovascular events after cardioversion of atrial fibrillation are rare and comparable between warfarin and apixaban. (Apixaban...
**Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes**

E.M. Hylek, et al.

**OBJECTIVES** This study sought to characterize major bleeding on the basis of the components of the major bleeding definition, to explore major bleeding by location, to define 30-day mortality after a major bleeding event, and to identify factors associated with major bleeding.

**BACKGROUND** Apixaban was shown to reduce the risk of major hemorrhage among patients with atrial fibrillation in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.

**METHODS** All patients who received at least 1 dose of a study drug were included. Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis. Factors associated with major hemorrhage were identified using a multivariable Cox model.

**RESULTS** The on-treatment safety population included 18,140 patients. The rate of major hemorrhage among patients in the apixaban group was 2.13% per year compared with 3.09% per year in the warfarin group (hazard ratio [HR] 0.69, 95% confidence interval [CI]: 0.60 to 0.80; p < 0.001). Compared with warfarin, major extracranial hemorrhage associated with apixaban led to reduced hospitalization, medical or surgical intervention, transfusion, or change in antithrombotic therapy. Major hemorrhage followed by mortality within 30 days occurred half as often in apixaban-treated patients than in those receiving warfarin (HR 0.50, 95% CI: 0.33 to 0.74; p < 0.001). Older age, prior hemorrhage, prior stroke or transient ischemic attack, diabetes, lower creatinine clearance, decreased hematocrit, aspirin therapy, and nonsteroidal anti-inflammatory drugs were independently associated with an increased risk.

**CONCLUSIONS** Apixaban, compared with warfarin, was associated with fewer intracranial hemorrhages, less adverse consequences following extracranial hemorrhage, and a 50% reduction in fatal consequences at 30 days in cases of major hemorrhage (48).

**Atrial Fibrillation Ablation: Translating Basic Mechanistic Insights to the Patient**

K. Nishida, et al.

Atrial fibrillation (AF) ablation is widely performed and is progressively supplanting drug therapy. Catheter-based AF ablation modalities have evolved progressively in parallel to our understanding of underlying mechanisms. Initial attempts to mimic the surgical maze procedure, which were based on the multiple wavelet model, failed because of adverse outcomes and insufficient effectiveness. A major advance was the targeting of pulmonary veins, which is highly effective for paroxysmal AF. Active research on the underlying mechanisms continues. The main challenge is reconnection, but procedures to minimize this are being developed. Ablation procedures for persistent AF are presently limited by suboptimal success rates and long-term disease progression that causes recurrences. Basic research into the underlying mechanisms has led to promising driver mechanism-directed clinical approaches along with pathways toward the prevention of atrial remodeling. Here, we review the role of basic research in the development of presently used AF-ablation procedures and look toward future contributions in improving outcomes (49).

**Ablation of Rotor and Focal Sources Reduces Late Recurrence of Atrial Fibrillation Compared With Trigger Ablation Alone: Extended Follow-Up of the CONFIRM Trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation)**

S.M. Narayan, et al.

**OBJECTIVES** The aim of this study was to determine if ablation that targets patient-specific atrial fibrillation (AF)-sustaining substrates (rotors or focal sources) is more durable than trigger ablation alone at preventing late AF recurrence.

**BACKGROUND** Late recurrence substantially limits the efficacy of pulmonary vein isolation for AF and is associated with pulmonary vein reconnection and the emergence of new triggers.

**METHODS** Three-year follow-up was performed of the CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial, in which 92 consecutive patients with AF (70.7% persistent) underwent novel computational mapping. Ablation comprised source (focal impulse and rotor modulation [FIRM]) and then conventional ablation in 27 patients (FIRM guided) and conventional ablation alone in 65
patients (FIRM blinded). Patients were followed with implanted electrocardiographic monitors when possible (85.2% of FIRM-guided patients, 23.1% of FIRM-blinded patients).

RESULTS FIRM mapping revealed a median of 2 (interquartile range: 1 to 2) rotors or focal sources in 97.7% of patients during AF. During a median follow-up period of 890 days (interquartile range: 224 to 1,563 days), compared to FIRM-blinded therapy, patients receiving FIRM-guided ablation maintained higher freedom from AF after 1.2 ± 0.4 procedures (median 1; interquartile range: 1 to 1) (77.8% vs. 38.5%; p = 0.001) and a single procedure (p < 0.001) and higher freedom from all atrial arrhythmias (p = 0.003). Freedom from AF was higher when ablation directly or coincidentally passed through sources than when it missed sources (p < 0.001).

CONCLUSIONS FIRM-guided ablation is more durable than conventional trigger-based ablation in preventing 3-year AF recurrence. Future studies should investigate how ablation of patient-specific AF-sustaining rotors and focal sources alters the natural history of arrhythmia recurrence. (The Dynamics of Human Atrial Fibrillation; NCT01008722) (50).

Incidence and Risk Factors for Sick Sinus Syndrome in the General Population
P.N. Jensen, et al.

BACKGROUND Little is known about the incidence of and risk factors for sick sinus syndrome (SSS), a common indication for pacemaker implantation.

OBJECTIVES This study sought to describe the epidemiology of SSS.

METHODS This analysis included 20,572 participants (mean baseline age 59 years, 43% male) in the ARIC (Atherosclerosis Risk In Communities) study and the CHS (Cardiovascular Health Study), who at baseline (mean baseline age 59 years, 43% male) in the ARIC study and the (Atherosclerosis Risk In Communities) study and the (mean baseline age 59 years, 43% male) in the ARIC study and the (mean baseline age 59 years, 43% male) in the ARIC study and the (mean baseline age 59 years, 43% male) in the ARIC study and the (mean baseline age 59 years, 43% male) in the ARIC study and the. We assessed databases (including autopsy reports) from both the U.S. National Registry of Sudden Death in Athletes and the National Collegiate Athletic Association (2002 to 2011).

RESULTS Over the 10-year study period, 182 sudden deaths occurred (age 20 ± 1.7 years; 85% white, 64% male), 52 resulting from suicide (n = 31) or drug abuse (n = 21) and 64 probably or likely attributable to cardiovascular causes (6/year). Of these 64 athletes, 47 had a confirmed post-mortem diagnosis; the most common were hypertrophic cardiomyopathy in 21 and congenital coronary anomalies in 8. The 4,052,369 athlete participations (in 30 sports over 10 years) incurred mortality risks as follows: suicide and drugs combined, 1.3/100,000 athlete participation-years (5 deaths/year); and documented cardiovascular disease, 1.2/100,000 athlete participation-years (4 deaths/year). Notably, cardiovascular deaths were 5-fold more common in African-American athletes than in white athletes (3.8 vs. 0.7/100,000 athlete participation-years; p < 0.01) but did not differ from the general population of the same age and race (p = 0.6).

CONCLUSIONS In college student-athletes, risk of sudden death due to cardiovascular disease is relatively low, with mortality rates similar to suicide and drug abuse, but less than expected in the general population, although highest in African-American
athletes. A substantial minority of confirmed cardiovascular deaths would not likely have been reliably detected by pre-participation screening with 12-lead electrocardiograms (52).

**Sudden Cardiac Death Risk Stratification in Patients With Nonischemic Dilated Cardiomyopathy**

J.J. Goldberger, et al.

**OBJECTIVES** The purpose of this study was to provide a meta-analysis to estimate the performance of 12 commonly reported risk stratification tests as predictors of arrhythmic events in patients with nonischemic dilated cardiomyopathy.

**BACKGROUND** Multiple techniques have been assessed as predictors of death due to ventricular tachyarrhythmias/sudden death in patients with nonischemic dilated cardiomyopathy.

**METHODS** Forty-five studies enrolling 6,088 patients evaluating the association between arrhythmic events and predictive tests (baroreflex sensitivity, heart rate turbulence, heart rate variability, left ventricular end-diastolic dimension, left ventricular ejection fraction, electrophysiology study, nonsustained ventricular tachycardia, left bundle branch block, signal-averaged electrocardiogram, fragmented QRS, QRS-T angle, and T-wave alternans) were included. Raw event rates were extracted, and meta-analysis was performed using mixed effects methodology. We also used the trim-and-fill method to estimate the influence of missing studies on the results.

**RESULTS** Patients were 52.8 ± 14.5 years of age, and 77% were male. Left ventricular ejection fraction was 30.6 ± 11.4%. Test sensitivities ranged from 28.8% to 91.0%, specificities from 36.2% to 87.1%, and odds ratios from 1.5 to 6.7. Odds ratio was highest for fragmented QRS and TWA (odds ratios: 6.73 and 4.66, 95% confidence intervals: 3.85 to 11.76 and 2.55 to 8.53, respectively) and lowest for QRS duration (odds ratio: 1.51, 95% confidence interval: 1.13 to 2.01). None of the autonomic tests (heart rate variability, heart rate turbulence, baroreflex sensitivity) were significant predictors of arrhythmic outcomes. Accounting for publication bias reduced the odds ratios for the various predictors but did not eliminate the predictive association.

**CONCLUSIONS** Techniques incorporating functional parameters, depolarization abnormalities, repolarization abnormalities, and arrhythmic markers provide only modest risk stratification for sudden cardiac death in patients with nonischemic dilated cardiomyopathy. It is likely that combinations of tests will be required to optimize risk stratification in this population (53).

**Ventricular Arrhythmias in the North American Multidisciplinary Study of ARVC: Predictors, Characteristics, and Treatment**

M.S. Link, et al.

**BACKGROUND** Arrhythmogenic right ventricular cardiomyopathy (ARVC) is associated with sudden cardiac death. However, the selection of patients for implanted cardioverter-defibrillators (ICDs), as well as programming of the ICD, is unclear.

**OBJECTIVES** The objective of this study was to identify predictors, characteristics, and treatment of ventricular arrhythmias in patients with ARVC.

**METHODS** The Multidisciplinary Study of Right Ventricular Cardiomyopathy established the North American ARVC Registry and enrolled patients with a diagnosis of ARVC. Patients were followed prospectively.

**RESULTS** Of 137 patients enrolled, 108 received ICDs. Forty-eight patients had 502 sustained episodes of ventricular arrhythmias, including 489 that were monomorphic and 13 that were polymorphic. In the patients with ICDs, independent predictors of ventricular arrhythmias in follow-up included spontaneous sustained ventricular arrhythmias before ICD implantation and T-wave inversions inferiorly. The only independent predictor for life-threatening arrhythmias, defined as sustained ventricular tachycardia (VT) ≥240 beats/min or ventricular fibrillation, was a younger age at enrollment. Anti-tachycardia pacing (ATP), independent of the cycle length of the VT, was successful in terminating 92% of VT episodes.

**CONCLUSIONS** In the North American ARVC Registry, the majority of ventricular arrhythmias in follow-up are monomorphic. Risk factors for ventricular arrhythmias were spontaneous ventricular arrhythmias before enrollment and a younger age at ICD implantation. ATP is highly successful in terminating VT, and all ICDs should be programmed for ATP, even for rapid VT (54).

**Clinical Effectiveness of CRT and ICD Therapy in Heart Failure Patients by Racial/Ethnic Classification: Insights From the IMPROVE HF Registry**

B. Ziaeian, et al.

**BACKGROUND** Clinical trials have demonstrated benefit for cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD) therapies in patients with heart failure with reduced
ejection fraction (HFrEF); yet, questions have been raised with regard to the benefit of device therapy for minorities.

**OBJECTIVES** The purpose of this study was to determine the clinical effectiveness of CRT and ICD therapies as a function of race/ethnicity in outpatients with HFrEF (ejection fraction ≤35%).

**METHODS** Data from IMPROVE HF (Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting) were analyzed by device status and race/ethnicity among guideline-eligible patients for mortality at 24 months. Multivariate Generalized Estimating Equations analyses were conducted, adjusting for patient and practice characteristics.

**RESULTS** The ICD/cardiac resynchronization defibrillator (CRT-D)-eligible cohort (n = 7,748) included 3,391 (44%) non-Hispanic white, 719 (9%) non-Hispanic black, and 3,638 (47%) other racial/ethnic minorities or race-not-documented patients. The cardiac resynchronization pacemaker (CRT-P)/CRT-D-eligible cohort (n = 1,188) included 596 (50%) non-Hispanic white, 99 (8%) non-Hispanic black, and 493 (41%) other/not-documented patients. There was clinical benefit associated with ICD/CRT-D therapy (adjusted odds ratio: 0.64, 95% confidence interval: 0.52 to 0.79; p = 0.0002 for 24-month mortality), which was of similar proportion in white, black, and other minority/not-documented patients (device-race/ethnicity interaction p = 0.7861). For CRT-P/CRT-D therapy, there were also associated mortality benefits (adjusted odds ratio: 0.55, 95% confidence interval: 0.33 to 0.91; p = 0.0222), and the device-race/ethnicity interaction was not significant (p = 0.5413).

**CONCLUSIONS** The use of guideline-directed CRT and ICD therapy was associated with reduced 24-month mortality without significant interaction by racial/ethnic group. Device therapies should be offered to eligible heart failure patients, without modification based on race/ethnicity (55).

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**The Subcutaneous Defibrillator: A Review of the Literature**

S. Aziz, et al.

The recently commercially available subcutaneous implantable cardioverter-defibrillator (S-ICD) uses a completely subcutaneous electrode configuration to treat potentially lethal ventricular tachyarrhythmia. Clinical trials have proven its effectiveness in detecting and treating ventricular fibrillation and tachycardia. The S-ICD offers the advantage of eliminating the need for intravenous and intracardiac leads and their associated risks and shortcomings. However, its major disadvantage is its inability to provide bradycardia rate support and antitachycardia pacing to terminate ventricular tachycardia. This paper discusses the S-ICD clinical trials and advantages and disadvantages of this novel technology to help the physician identify its role and select candidate patients who will benefit from this device (56).

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**Rotor Stability Separates Sustained Ventricular Fibrillation From Self-Terminating Episodes in Humans**

D.E. Krummen, et al.

**OBJECTIVES** This study mapped human ventricular fibrillation (VF) to define mechanistic differences between episodes requiring defibrillation versus those that spontaneously terminate.

**BACKGROUND** VF is a leading cause of mortality; yet, episodes may also self-terminate. We hypothesized that the initial maintenance of human VF is dependent upon the formation and stability of VF rotors.

**METHODS** We enrolled 26 consecutive patients (age 64 ± 10 years, n = 13 with left ventricular dysfunction) during ablation procedures for ventricular arrhythmias, using 64-electrode basket catheters in both ventricles to map VF prior to prompt defibrillation per the institutional review board-approved protocol. A total of 52 inductions were attempted, and 36 VF episodes were observed. Phase analysis was applied to identify biventricular rotors in the first 10 s or until VF terminated, whichever came first (11.4 ± 2.9 s to defibrillator charging).

**RESULTS** Rotors were present in 16 of 19 patients with VF and in all patients with sustained VF. Sustained, but not self-limiting VF, was characterized by greater rotor stability: 1) rotors were present in 17% of cycles in sustained VF versus 11 ± 18% of cycles in self-limiting VF (p < 0.001); and 2) maximum continuous rotations were greater in sustained (17 ± 11, range 7 to 48) versus self-limiting VF (1.1 ± 1.4, range 0 to 4; p < 0.001). Additionally, biventricular rotor locations in sustained VF were conserved across multiple inductions (7 of 7 patients; p = 0.025).

**CONCLUSIONS** In patients with and without structural heart disease, the formation of stable rotors identifies individuals whose VF requires defibrillation from those in whom VF spontaneously self-terminates. Future work should define the
mechanisms that stabilize rotors and evaluate whether rotor modulation may reduce subsequent VF risk (57).

**Electrocardiographic Parameters and Fatal Arrhythmic Events in Patients With Brugada Syndrome: Combination of Depolarization and Repolarization Abnormalities**

K. Tokioka, et al.

**OBJECTIVES** This study aimed to determine the usefulness of the combination of several electrocardiographic markers on risk assessment of ventricular fibrillation (VF) in patients with Brugada syndrome (BrS).

**BACKGROUND** Detection of high-/low-risk BrS patients using a noninvasive method is an important issue in the clinical setting. Several electrocardiographic markers related to depolarization and repolarization abnormalities have been reported, but the relationship and usefulness of these parameters in VF events are unclear.

**METHODS** Baseline characteristics of 246 consecutive patients (236 men; mean age, 47.6 ± 13.6 years) with a Brugada-type electrocardiogram, including 13 patients with a history of VF and 40 patients with a history of syncope episodes, were retrospectively analyzed. During the mean follow-up period of 45.1 months, VF in 23 patients and sudden cardiac death (SCD) in 1 patient were observed. Clinical/genetic and electrocardiographic parameters were compared with VF/SCD events.

**RESULTS** On univariate analysis, a history of VF and syncope episodes, paroxysmal atrial fibrillation, spontaneous type 1 pattern in the precordial leads, and electrocardiographic markers of depolarization abnormalities (QRS duration ≥120 ms, and fragmented QRS [f-QRS]) and those of repolarization abnormalities (inferolateral early repolarization [ER] pattern and QT prolongation) were associated with later cardiac events. On multivariable analysis, a history of VF and syncope episodes, inferolateral ER pattern, and f-QRS were independent predictors of documented VF and SCD (odds ratios: 19.61, 28.57, 2.87, and 5.21, respectively; p < 0.05). Kaplan-Meier curves showed that the presence/absence of inferolateral ER and f-QRS predicted a worse/better prognosis (log-rank test, p < 0.01).

**CONCLUSIONS** The combination of depolarization and repolarization abnormalities in BrS is associated with later VF events. The combination of these abnormalities is useful for detecting high- and low-risk BrS patients (58).

**Drug-Induced Brugada Syndrome in Children: Clinical Features, Device-Based Management, and Long-Term Follow-Up**

G. Conte, et al.

**OBJECTIVES** The goal of this study was to investigate the clinical features, management, and long-term follow-up of children with drug-induced Brugada syndrome (BS).

**BACKGROUND** Patients with BS <12 years of age with a spontaneous type I electrocardiogram have a higher risk of arrhythmic events. Data on drug-induced BS in patients <12 years of age are lacking.

**METHODS** Among 505 patients with ajmaline-induced BS, subjects ≥12 years of age at the time of diagnosis were considered as children and eligible for this study.

**RESULTS** Forty children (60% male; age 8 ± 2.8 years) were included. Twenty-four children (60%) had a family history of sudden death. Two (5%) had a previous episode of aborted sudden death, and 8 (20%) had syncope. Children experienced more frequent episodes of sinus node dysfunction (SND) compared with older subjects (7.5% vs. 1.5%; p = 0.04) and had a comparable incidence of atrial tachyarrhythmias. Children more frequently experienced episodes of ajmaline-induced sustained ventricular arrhythmias (VAs) compared with older patients (10.0% vs. 1.3%; p = 0.005). Twelve children (30%) received an implantable cardioverter-defibrillator (ICD). After a mean follow-up time of 83 ± 51 months, none of the children died suddenly. Spontaneous sustained VAs were documented in 1 child (2%). Among children with ICD, 1 (8%) experienced an appropriate shock, 4 (33%) had inappropriate ICD shocks, and 4 (33%) experienced device-related complications.

**CONCLUSIONS** Drug-induced BS is associated with atrial arrhythmias and SND. Children are at higher risk of ajmaline-induced VAs. The rate of device-related complications, leading to lead replacement or inappropriate shocks, is considerable and even higher than with appropriate interventions. Based on these findings, the optimal management of BS in childhood should remain individualized, taking into consideration the patient’s clinical history and family’s wishes (59).
recommendations, none had Level of Evidence: A. There were 28 Class I recommendations with Level of Evidence: B in 6 and C in 22. There were 31 Class IIa recommendations with Level of Evidence: B in 1 and C in 30. There are 7 Class IIb recommendations; all were with Level of Evidence: C (60).

**B-Type Natriuretic Peptide Clinical Activation in Aortic Stenosis: Impact on Long-Term Survival**

M.-A. Clavel, et al.

**OBJECTIVES** This study was conducted to define the association between serum B-type natriuretic peptide (BNP) activation and survival after the diagnosis of aortic stenosis (AS).

**BACKGROUND** In AS, the link between BNP levels and clinical outcome is in dispute. Failure to account for the normal shifting of BNP ranges with aging in men and women, not using hard endpoints (survival), and not enrolling large series of patients have contributed to the uncertainty.

**METHODS** A program of prospective measurement of BNP levels with Doppler echocardiographic AS assessment during the same episode of care was conducted. BNP ratio (measured BNP/maximal normal BNP levels with Doppler echocardiographic AS) was independently predicted mortality after diagnosis (p < 0.0001; hazard ratio [HR]: 1.17; 95% CI: 1.07 to 1.27) and provided incremental power to the survival predictive model (p < 0.0001). Eight-year survival was 62.3% with normal BNP levels, 44.3% with BNP ratio of 1 to 2 (adjusted HR: 1.49; 95% CI: 1.17 to 1.90), 25.4% with BNP ratio of 2 to 3 (adjusted HR: 2.12; 95% CI: 1.63 to 2.76), and 15.2% with BNP ratio of ≥3 (adjusted HR: 2.43; 95% CI: 1.94 to 3.05). This strong link to survival was confirmed in asymptomatic patients with normal EF (adjusted HR: 2.35 [95% CI: 1.57 to 3.46] for BNP clinical activation and 2.10 [95% CI: 1.32 to 3.35] for BNP ratio of 1 to 2, 2.25 [95% CI: 1.31 to 3.87] for BNP ratio of 2 to 3, 3.93 [95% CI: 2.40 to 6.43] for BNP ratio of ≥3). Aortic valve replacement was associated with survival improved by a similarly high margin (p = 0.54) with BNP ratio of <2 (HR: 0.68; 95% CI: 0.52 to 0.89; p = 0.003) or BNP ratio of ≥2 (HR: 0.56; 95% CI: 0.47 to 0.66; p < 0.0001).

**CONCLUSIONS** In this large series of patients with AS, BNP clinical activation was associated with excess long-term mortality incrementally and independently of all baseline characteristics. Higher mortality with higher BNP clinical activation, even in asymptomatic patients, emphasizes the importance of appropriate clinical interpretation of BNP levels in managing patients with AS (61).

**Highlights of the Year**

**Early Surgery Versus Conventional Treatment for Asymptomatic Severe Mitral Regurgitation: A Propensity Analysis**


**OBJECTIVES** This study sought to compare long-term outcomes of early surgery with a conventional treatment strategy in asymptomatic patients with severe mitral regurgitation (MR).

**BACKGROUND** The timing of surgery in asymptomatic severe MR remains controversial.

**METHODS** From 1996 to 2009, 610 consecutive asymptomatic patients (364 men, 50 ± 14 years of age) with severe degenerative MR and preserved left ventricular function were evaluated prospectively. Early surgery was performed on 235 patients, and the conventional treatment strategy was chosen for 375 patients. We compared overall mortality, cardiac mortality, and cardiac events (operative mortality, cardiac mortality, repeat surgery, and urgent admission due to heart failure) between the 2 treatment strategies in the propensity score-matched cohort.

**RESULTS** For the 207 propensity score-matched pairs, early surgery had a lower risk of cardiac mortality (hazard ratio [HR]: 0.109; 95% confidence interval [CI]: 0.014 to 0.836; p = 0.033) and cardiac events (HR: 0.216; 95% CI: 0.083 to 0.558; p = 0.002) than conventional treatment. On Cox proportional hazard model analysis, the risk of cardiac events was significantly lower in the early surgery group than in the conventional treatment group in patients aged 50 years of age and older (HR: 0.221; 95% CI: 0.086 to 0.567; p = 0.002), but not significantly different in those younger than 50 years of age (p = 0.20).

**CONCLUSIONS** Compared with conservative management, early surgery is associated with significant long-term reductions of cardiac mortality and cardiac events in asymptomatic severe MR. These benefits were evident among patients age 50 years of age and older (62).
Transcatheter Aortic Valve Replacement Using a Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis at Extreme Risk for Surgery

J.J. Popma, et al.

OBJECTIVES This study sought to evaluate the safety and efficacy of the CoreValve transcatheter heart valve (THV) for the treatment of severe aortic stenosis in patients at extreme risk for surgery.

BACKGROUND Untreated severe aortic stenosis is a progressive disease with a poor prognosis. Transcatheter aortic valve replacement (TAVR) with a self-expanding bioprosthesis is a potentially effective therapy.

METHODS We performed a prospective, multicenter, nonrandomized investigation evaluating the safety and efficacy of self-expanding TAVR in patients with symptomatic severe aortic stenosis with prohibitive risks for surgery. The primary endpoint was a composite of all-cause mortality or major stroke at 12 months, which was compared with a pre-specified objective performance goal (OPG).

RESULTS A total of 41 sites in the United States recruited 506 patients, of whom 489 underwent attempted treatment with the CoreValve THV. The rate of all-cause mortality or major stroke at 12 months was 26.0% (upper 2-sided 95% confidence bound: 29.9%) versus 43.0% with the OPG (p < 0.0001). Individual 30-day and 12-month events included all-cause mortality (8.4% and 24.3%, respectively) and major stroke (2.3% and 4.3%, respectively). Procedural events at 30 days included life-threatening/disabling bleeding (12.7%), major vascular complications (8.2%), and need for permanent pacemaker placement (21.6%). The frequency of moderate or severe paravalvular aortic regurgitation was lower 12 months after self-expanding TAVR (4.2%) than at discharge (10.7%; p = 0.004 for paired analysis).

CONCLUSIONS TAVR with a self-expanding bioprosthesis was safe and effective in patients with symptomatic severe aortic stenosis at prohibitive risk for surgical valve replacement. (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Symptomatic Severe Aortic Stenosis in High Risk and Very High Risk Subjects Who Need Aortic Valve Replacement; NCT01240902) (63).

Comprehensive Analysis of Mortality Among Patients Undergoing TAVR: Results of the PARTNER Trial

L.G. Svensson, et al.

BACKGROUND Patients with severe aortic stenosis (AS) who were deemed too high risk or inoperable for conventional aortic valve replacement (AVR) in the PARTNER (Placement of Aortic Transcatheter Valves) trial were randomized to transcatheter aortic valve replacement (TAVR) versus AVR (PARTNER-A arm) or standard therapy (PARTNER-B arm).

OBJECTIVES This study compared when and how deaths occurred after TAVR versus surgical AVR or standard therapy.

METHODS The PARTNER-A arm included 244 transfemoral (TF) and 104 transapical (TA) TAVR patients, and 351 AVR patients; the PARTNER-B arm included 179 TF-TAVR patients and 179 standard therapy patients. Deaths were categorized as cardiovascular, noncardiovascular, or uncategorizable, and were characterized by multiphase hazard modelling.

RESULTS In the PARTNER-A arm, the risk of death peaked after randomization in the TA-TAVR and AVR groups, falling to low levels commensurate with the U.S. population within 3 months. Early risk was less in TF-TAVR patients, resulting in initial superior survival; between 12 and 18 months, risk increased, such that within 2 years, TF-TAVR and AVR patients had similar survival rates. Cardiovascular, noncardiovascular, and uncategorizable deaths for TF-TAVR were 37%, 43%, and 20%, respectively, versus 22%, 41%, and 37%, respectively, for TA-TAVR and 33%, 43%, and 24%, respectively, for AVR. In the PARTNER-B arm, risk with standard therapy was 60% per year; TF-TAVR reduced risk to 20% per year, resulting in 0.5 years of life added within 2.5 years.

CONCLUSIONS In inoperable AS patients, TAVR substantially reduced the risk of cardiovascular death. In high-risk patients, TA-TAVR and AVR were associated with elevated peri-procedural risk more than with TF-TAVR, although cardiovascular death was higher after TF-TAVR. Therefore, TF-TAVR should be considered the standard of care for severely symptomatic inoperable patients or those at high risk of noncardiovascular mortality after conventional surgery. (THE PARTNER TRIAL: Placement of AoRTic TraNs catheterER Valve Trial; NCT00530894) (64).

Predictors of Permanent Pacemaker Implantation in Patients With Severe Aortic Stenosis Undergoing TAVR: A Meta-Analysis

G.C.M. Siontis, et al.

BACKGROUND Atrioventricular (AV) conduction disturbances requiring permanent pacemaker (PPM) implantation may complicate transcatheter aortic valve replacement (TAVR). Available evidence on predictors of PPM is sparse and derived from small studies.
OBJECTIVES The objective of this study was to provide summary effect estimates for clinically useful predictors of PPM implantation after TAVR.

METHODS We performed a systematic search for studies that reported the incidence of PPM implantation after TAVR and that provided raw data for the predictors of interest. Data on study, patient, and procedural characteristics were abstracted. Crude risk ratios (RRs) and 95% confidence intervals for each predictor were calculated by use of random effects models. Stratified analyses by type of implanted valve were performed.

RESULTS We obtained data from 41 studies that included 11,210 TAVR patients, of whom 17% required PPM implantation after intervention. The rate of PPM ranged from 2% to 51% in individual studies (with a median of 28% for the Medtronic CoreValve Revalving System [MCRS] and 6% for the Edwards SAPIEN valve [ESV]). The summary estimates indicated increased risk of PPM after TAVR for men (RR: 1.23; p < 0.01); for patients with first-degree AV block (RR: 1.52; p < 0.01), left anterior hemiblock (RR: 1.62; p < 0.01), or right bundle branch block (RR: 2.89; p < 0.01) at baseline; and for patients with intraprocedural AV block (RR: 3.49; p < 0.01). These variables remained significant predictors when only patients treated with the MCRS bioprosthesis were considered. The data for ESV were limited. Unadjusted estimates indicated a 2.5-fold higher risk for PPM implantation for patients who received the MCRS than for those who received the ESV.

CONCLUSIONS Male sex, baseline conduction disturbances, and intraprocedural AV block emerged as predictors of PPM implantation after TAVR. This study provides useful tools to identify high-risk patients and to guide clinical decision making before and after intervention (65).

Incidence, Predictors, and Prognostic Impact of Late Bleeding Complications After Transcatheter Aortic Valve Replacement

P. Généreux, et al.

BACKGROUND The incidence and prognostic impact of late bleeding complications after transcatheter aortic valve replacement (TAVR) are unknown.

OBJECTIVES The aim of this study was to identify the incidence, predictors, and prognostic impact of major late bleeding complications (MLBCs) (≥30 days) after TAVR.

METHODS Clinical and echocardiographic outcomes of patients who underwent TAVR within the randomized cohorts and continued access registries in the PARTNER (Placement of Aortic Transcatheter Valves) trial were analyzed after stratifying by the occurrence of MLBCs. Predictors of MLBCs and their association with 30-day to 1-year mortality were assessed.

RESULTS Among 2,401 patients who underwent TAVR and survived to 30 days, MLBCs occurred in 142 (5.9%) at a median time of 132 days (interquartile range: 71 to 230 days) after the index procedure. Gastrointestinal complications (n = 58 [40.8%]), neurological complications (n = 22 [15.5%]), and traumatic falls (n = 11 [7.8%]) were identified as the most frequent types of MLBCs. Independent predictors of MLBCs were the presence of low hemoglobin at baseline, atrial fibrillation or flutter at baseline or 30 days, the presence of moderate or severe paravalvular leak at 30 days, and greater left ventricular mass at 30 days. MLBCs were identified as a strong independent predictor of mortality between 30 days and 1 year (adjusted hazard ratio: 3.91; 95% confidence interval: 2.67 to 5.71; p < 0.001).

CONCLUSIONS MLBCs after TAVR were frequent and associated with increased mortality. Better individualized and risk-adjusted antithrombotic therapy after TAVR is urgently needed in this high-risk population. (THE PARTNER TRIAL: Placement of AoRTic TraNscatheter Valve Trial; NCT00530894) (66).

Bleeding Complications After Surgical Aortic Valve Replacement Compared With Transcatheter Aortic Valve Replacement: Insights From the PARTNER I Trial (Placement of Aortic Transcatheter Valve)

P. Généreux, et al.

OBJECTIVES This study sought to identify the incidence, predictors, and prognostic impact of bleeding complications (BC) after surgical aortic valve replacement (SAVR) compared with transcatheter aortic valve replacement (TAVR).

BACKGROUND Bleeding complications after SAVR and TAVR are frequent and may be associated with an unfavorable prognosis.

METHODS In the randomized controlled PARTNER (Placement of Aortic Transcatheter Valve) I trial, 657 patients from cohort A (operative high risk) were randomly assigned to SAVR or TAVR (transfemoral [TF] if iliofemoral access was suitable or transapical [TA] if not) and received the designated treatment. First-generation Edwards SAPIEN valves and delivery systems (Edwards Lifesciences, Irvine, California) were used for TAVR, through a 22- or 24-F sheath. The 30-day rates of major BC (modified Valve Academic Research Consortium definitions),
predictors of BC, and their association with 1-year mortality were assessed.

**RESULTS** A total of 71 (22.7%), 27 (11.3%), and 9 (8.8%) patients had major BC within 30 days of the procedure after SAVR, TF-TAVR, and TA-TAVR, respectively (p < 0.0001). SAVR was associated with a significantly higher 30-day rate of transfusion (17.9%) than either TF-TAVR (7.1%) or TA-TAVR (4.8%; p < 0.0001).

Independent predictors of major BC were the occurrence of major vascular complications and use of intra-procedural hemodynamic support among TF-TAVR patients, severe procedural complications requiring conversion to open surgery among TA-TAVR patients, and the presence of low hemoglobin at baseline among SAVR patients. Major BC was identified as the strongest independent predictor of 1-year mortality among the full cohort. However, risk-adjusted analyses demonstrated a significant interaction between BC and treatment strategy with respect to mortality, suggesting that BC after SAVR have a greater impact on prognosis than after TAVR.

**CONCLUSIONS** Among high-risk aortic stenosis patients enrolled in the PARTNER I randomized trial, BC were more common after SAVR than after TAVR and were also associated with a worse long-term prognosis. (THE PARTNER TRIAL: Placement of AoRTic TranScatheT ER Valve Trial; NCT00530894) (67).

**Temporal Changes in Interpapillary Muscle Dynamics as an Active Indicator of Mitral Valve and Left Ventricular Interaction in Ischemic Mitral Regurgitation**

K. Kalra, et al.

**BACKGROUND** Regional subpapillary myocardial hypokinesis may impair lateral reduction in the interpapillary muscle distance (IPMD) from diastole to systole, and adversely affect mitral valve geometry and tethering.

**OBJECTIVES** The goal of this study was to investigate the impact of impaired lateral shortening in the interpapillary muscle distance on mitral valve geometry and function in ischemic heart disease.

**METHODS** To quantify ventricular size/shape, regional myocardial contraction, lateral shortening of the IPMD, mitral valve geometry, and severity of mitral regurgitation, 67 patients with ischemic heart disease underwent cardiac magnetic resonance imaging, and a correlation analysis of measured parameters was performed. The impact of reduced IPMD shortening on mitral valve (dys) function was confirmed in swine and in a physiological computational mitral valve model.
Mitral regurgitation (MR) is the most common valve disease in the United States. However, a significant number of patients are denied surgery due to increased age, poor ventricular function, or associated comorbidities, putting them at high risk for adverse events. Moreover, the benefit of surgery for MR is unclear in patients with functional (secondary) MR. Recently, percutaneous repair of the mitral valve with a particular device (MitraClip, Abbott, Menlo Park, California) has emerged as a novel therapeutic option for patients with secondary MR or those deemed to be high risk for surgery. We review data from its initial concept through clinical trials and current data available from several registries. We focused on lessons learned regarding adequate patient selection, along with current and future perspectives on the use of device therapy for the treatment of MR.

Percutaneous Approaches to Valve Repair for Mitral Regurgitation

T. Feldman, et al.

Percutaneous therapy has emerged as an option for treatment of mitral regurgitation for selected, predominantly high-risk patients. Most of the percutaneous approaches are modifications of existing surgical approaches. Catheter-based devices mimic these surgical approaches with less procedural risk, due to their less-invasive nature. Percutaneous annuloplasty can be achieved indirectly via the coronary sinus or directly from retrograde left ventricular access. Catheter-based leaflet repair with the MitraClip (Abbott Laboratories, Abbott Park, Illinois) is accomplished with an implantable clip to mimic the surgical edge-to-edge leaflet repair technique. A large experience with MitraClip has been reported, and several other percutaneous approaches have been successfully used in smaller numbers of patients to demonstrate proof of concept, whereas others have failed and are no longer under development. There is increasing experience in both trials and practice to begin to define the clinical utility of percutaneous leaflet repair, and annuloplasty approaches are undergoing significant development. Transcatheter mitral valve replacement is still in early development.

The Evolution of Percutaneous Mitral Valve Repair Therapy: Lessons Learned and Implications for Patient Selection

R. Beigel, et al.

Percutaneous Mitral Valve Repair for Mitral Regurgitation in High-Risk Patients: Results of the EVEREST II Study


BACKGROUND

The EVEREST II (Endovascular Valve Edge-to-Edge REpair StuStudy) High-Risk registry and REALISM Continued Access Study High-Risk registry are prospective registries of patients who received the MitraClip device (Abbott Vascular, Santa Clara, California) for mitral regurgitation (MR) in the United States.

OBJECTIVES

The purpose of this study was to report 12-month outcomes in high-risk patients treated with the percutaneous mitral valve edge-to-edge repair.

METHODS

Patients with grades 3 to 4+ MR and a surgical mortality risk of ≥12%, based on the Society of Thoracic Surgeons risk calculator or the estimate of a surgeon coinvestigator following pre-specified protocol criteria, were enrolled.

RESULTS

In the studies, 327 of 351 patients completed 12 months of follow-up. Patients were elderly (76 ± 11 years of age), with 70% having functional MR and 60% having prior cardiac surgery. The mitral valve device reduced MR to ≤2+ in 86% of patients at discharge (n = 325; p < 0.0001). Major adverse events at 30 days included death in 4.8%, myocardial infarction in 1.1%, and stroke in 2.6%. At 12 months, MR was ≤2+ in 84% of patients (n = 225; p < 0.0001). From baseline to 12 months, left ventricular (LV) end-diastolic volume improved from 161 ± 56 ml to 143 ± 53 ml (n = 203; p < 0.0001) and LV
end-systolic volume improved from 87 ± 47 ml to 79 ± 44 ml (n = 202; p < 0.0001). New York Heart Association functional class improved from 82% in class III/IV at baseline to 83% in class I/II at 12 months (n = 234; p < 0.0001). The 36-item Short Form Health Survey physical and mental quality-of-life scores improved from baseline to 12 months (n = 191; p < 0.0001). Annual hospitalization rate for heart failure fell from 0.79% pre-procedure to 0.41% post-procedure (n = 338; p < 0.0001). Kaplan-Meier survival estimate at 12 months was 77.2%.

**CONCLUSIONS** The percutaneous mitral valve device significantly reduced MR, improved clinical symptoms, and decreased LV dimensions at 12 months in this high-surgical-risk cohort. (Endovascular Valve Edge-to-Edge REpair Study [EVERESTIIIRCT]; NCT00209274) (72).

**Percutaneous Mitral Valve Edge-to-Edge Repair: In-Hospital Results and 1-Year Follow-Up of 628 Patients of the 2011–2012 Pilot European Sentinel Registry**

G. Nickenig, et al.

**BACKGROUND** The use of transcatheter mitral valve repair (TMVR) has gained widespread acceptance in Europe, but data on immediate success, safety, and long-term echocardiographic follow-up in real-world patients are still limited.

**OBJECTIVES** The aim of this multinational registry is to present a real-world overview of TMVR use in Europe.

**METHODS** The Transcatheter Valve Treatment Sentinel Pilot Registry is a prospective, independent, consecutive collection of individual patient data.

**RESULTS** A total of 628 patients (mean age 74.2 ± 9.7 years, 63.1% men) underwent TMVR between January 2011 and December 2012 in 25 centers in 8 European countries. The prevalent pathogenesis was functional mitral regurgitation (FMR) (n = 452 [72.0%]). The majority of patients (85.5%) were highly symptomatic (New York Heart Association functional class III or higher), with a high logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) (20.4 ± 16.7%). Acute procedural success was high (95.4%) and similar in FMR and degenerative mitral regurgitation (p = 0.662). One clip was implanted in 61.4% of patients. In-hospital mortality was low (2.9%), without significant differences between groups. The estimated 1-year mortality was 15.3%, which was similar for FMR and degenerative mitral regurgitation. The estimated 1-year rate of rehospitalization because of heart failure was 22.8%, significantly higher in the FMR group (25.8% vs. 12.0%, p[log-rank] = 0.009). Paired echo-cardiographic data from the 1-year follow-up, available for 368 consecutive patients in 15 centers, showed a persistent reduction in the degree of mitral regurgitation at 1 year (6.0% of patients with severe mitral regurgitation).

**CONCLUSIONS** This independent, contemporary registry shows that TMVR is associated with high immediate success, low complication rates, and sustained 1-year reduction of the severity of mitral regurgitation and improvement of clinical symptoms (73).

**Percutaneous Mitral Valve Repair With the MitraClip System for Severe Mitral Regurgitation in Patients With Surgical Mitral Valve Repair Failure**

C. Grasso, et al.

Surgical mitral valve repair (SMVR) is the preferred intervention for patients with either symptomatic severe mitral regurgitation (MR) or asymptomatic severe MR and left ventricular dysfunction. The rate of freedom from severe MR 10 years after SMVR, however, is reported to be 70%, leading to a considerable number of mitral valve reinterventions, which carry substantial risk, particularly in elderly patients and in those with significant comorbidities (74).

**Improved Functional Status and Quality of Life in Prohibitive Surgical Risk Patients With Degenerative Mitral Regurgitation After Transcatheter Mitral Valve Repair**

D.S. Lim, et al.

**BACKGROUND** Surgical mitral valve repair (SMVR) remains the gold standard for severe degenerative mitral regurgitation (DMR). However, the results with transcatheter mitral valve repair (TMVR) in prohibitive-risk DMR patients have not been previously reported.

**OBJECTIVES** This study aimed to evaluate treatment of mitral regurgitation (MR) in patients with severe DMR at prohibitive surgical risk undergoing TMVR.

**METHODS** A prohibitive-risk DMR cohort was identified by a multidisciplinary heart team that retrospectively evaluated high-risk DMR patients enrolled in the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II studies.

**RESULTS** A total of 141 high-risk DMR patients were consecutively enrolled; 127 of these patients were retrospectively identified as meeting the definition of prohibitive risk and had 1-year follow-up (median: 1.47 years) available. Patients were elderly (mean
age: 82.4 years), severely symptomatic (87% New York Heart Association class III/IV), and at prohibitive surgical risk (STS score: 13.2 ± 7.3%). TMVR (MitraClip) was successfully performed in 95.3%; hospital stay was 2.9 ± 3.1 days. Major adverse events at 30 days included death in 6.3%, myocardial infarction in 0.8%, and stroke in 2.4%. Through 1 year, there were a total of 30 deaths (23.6%), with no survival difference between patients discharged with MR =1+ or MR 2+. At 1 year, the majority of surviving patients (82.9%) remained MR =2+ at 1 year, and 86.9% were in New York Heart Association functional class I or II. Left ventricular end-diastolic volume decreased (from 125.1 ± 40.1 ml to 108.5 ± 37.9 ml; p < 0.0001 [n = 69 survivors with paired data]). SF-36 quality-of-life scores improved and hospitalizations for heart failure were reduced in patients whose MR was reduced.

CONCLUSIONS TMVR in prohibitive surgical risk patients is associated with safety and good clinical outcomes, including decreases in rehospitalization, functional improvements, and favorable ventricular remodeling, at 1 year. (Real World Expanded Multicenter Study of the MitraClip System [REALISM]; NCT01931956) (75).

Off-Pump Transapical Implantation of Artificial Neo-Chordae to Correct Mitral Regurgitation: The TACT Trial (Transapical Artificial Chordae Tendineae) Proof of Concept
J. Seeburger, et al.

OBJECTIVES The goal of this study was to evaluate the safety and performance of the NeoChord DS1000 system (NeoChord, Inc., Minneapolis, Minnesota).

BACKGROUND There is an increasing interest in transcatheter mitral valve (MV) treatment. The NeoChord DS 1000 system enables off-pump beating heart transapical MV repair with implantation of artificial neo-chordae.

METHODS Patients with severe mitral regurgitation (MR) due to isolated posterior prolapse were included in this TACT (Transapical Artificial Chordae Tendineae) trial. All patients were scheduled for off-pump transapical implantation of neo-chordae.

RESULTS Thirty patients at 7 centers were enrolled. Major adverse events included 1 death due to post-cardiomyotomy syndrome and concomitant sepsis and 1 minor stroke with the patient fully recovered at the 30-day follow-up visit. Additional patients experienced procedural major adverse events related to a reoperation or conversion to standard of care. Acute procedural success (placement of at least 1 neo-chord and reduction of MR from 3+ or 4+ to ≤2+) was achieved in 26 patients (86.7%). In 4 patients neo-chordae were not placed for technical and/or patient-specific reasons. These patients underwent intraoperative (3 patients) or post-operative (1 patient) standard MV repair. At 30 days, 17 patients maintained an MR grade ≤2+. Four patients who developed recurrent MR were successfully treated with open MV repair during 30-day follow-up. Results improved with experience: durable reduction in MR to ≤2+ at 30 days was achieved in 5 (33.3%) of the first 15 patients and 12 (85.7%) of the last 14 patients.

CONCLUSIONS Off-pump transapical implantation of artificial chordae to correct MR is technically safe and feasible; however, it yields further potential for improvement of efficacy and durability. (Safety and Performance Study of the NeoChord Device [TACT]; NCT01777819) (76).

Proximal Aortic Distensibility Is an Independent Predictor of All-Cause Mortality and Incident CV Events: The MESA Study
A. Redheuil, et al.

BACKGROUND The predictive value of ascending aortic distensibility (AAD) for mortality and hard cardiovascular disease (CVD) events has not been fully established.

OBJECTIVES This study sought to assess the utility of AAD to predict mortality and incident CVD events beyond conventional risk factors in MESA (Multi-Ethnic Study of Atherosclerosis).

METHODS AAD was measured with magnetic resonance imaging at baseline in 3,675 MESA participants free of overt CVD. Cox proportional hazards regression was used to evaluate risk of death, heart failure (HF), and incident CVD in relation to AAD, CVD risk factors, indexes of subclinical atherosclerosis, and Framingham risk score.

RESULTS There were 246 deaths, 171 hard CVD events (myocardial infarction, resuscitated cardiac arrest, stroke and CV death), and 88 HF events over a median 8.5-year follow-up. Decreased AAD was associated with increased all-cause mortality with a hazard ratio (HR) for the first versus fifth quintile of AAD of 2.7 (p = 0.008) independent of age, sex, ethnicity, other CVD risk factors, and indexes of subclinical atherosclerosis. Overall, patients with the lowest AAD had an independent 2-fold higher risk of hard CVD events. Decreased AAD was associated with CV events in low to intermediate- CVD risk individuals.
with an HR for the first quintile of AAD of 5.3 (p = 0.03) as well as with incident HF but not after full adjustment.

**CONCLUSIONS** Decreased proximal aorta distensibility significantly predicted all-cause mortality and hard CV events among individuals without overt CVD. AAD may help refine risk stratification, especially among asymptomatic, low- to intermediate-risk individuals (77).

**Transcatheter Implantation of Homologous “Off-the-Shelf” Tissue-Engineered Heart Valves With Self-Repair Capacity: Long-Term Functionality and Rapid In Vivo Remodeling in Sheep**

A. Driessen-Mol, et al.

**OBJECTIVES** This study sought to evaluate long-term in vivo functionality, host cell repopulation, and remodeling of “off-the-shelf” tissue engineered transcatheter homologous heart valves.

**BACKGROUND** Transcatheter valve implantation has emerged as a valid alternative to conventional surgery, in particular for elderly high-risk patients. However, currently used bioprosthetic transcatheter valves are prone to progressive dysfunctional degeneration, limiting their use in younger patients. To overcome these limitations, the concept of tissue engineered heart valves with self-repair capacity has been introduced as next-generation technology.

**METHODS** In vivo functionality, host cell repopulation, and matrix remodeling of homologous transcatheter tissue-engineered heart valves (TEHVs) was evaluated up to 24 weeks as pulmonary valve replacements (transapical access) in sheep (n = 12). As a control, tissue composition and structure were analyzed in identical not implanted TEHVs (n = 5).

**RESULTS** Transcatheter implantation was successful in all animals. Valve functionality was excellent displaying sufficient leaflet motion and coaptation with only minor paravalvular leakage in some animals. Mild central regurgitation was detected after 8 weeks, increasing to moderate after 24 weeks, correlating to a compromised leaflet coaptation. Mean and peak transvalvular pressure gradients were 4.4 ± 1.6 mm Hg and 9.7 ± 3.0 mm Hg, respectively. Significant matrix remodeling was observed in the entire valve and corresponded with the rate of host cell repopulation.

**CONCLUSIONS** For the first time, the feasibility and long-term functionality of transcatheter tissue engineered heart valves are demonstrated in a relevant pre-clinical model. Such engineered heart valves may represent an interesting alternative to current prostheses because of their rapid cellular repopulation, tissue remodeling, and therewith self-repair capacity. The concept of homologous off-the-shelf tissue engineered heart valves may therefore substantially simplify previous tissue engineering concepts toward clinical translation (78).

**VASCULAR MEDICINE**

Local Stiffness of the Carotid and Femoral Artery Is Associated With Incident Cardiovascular Events and All-Cause Mortality: The Hoorn Study

T.T. van Sloten, et al.

**OBJECTIVES** This study sought to investigate the association of local and segmental arterial stiffness with incident cardiovascular events and all-cause mortality.

**BACKGROUND** The association of different stiffness indices, in particular of carotid, brachial, and femoral stiffness, with cardiovascular disease and mortality is currently unknown.

**METHODS** In a population-based cohort (n = 579, mean age 67 years, 50% women, 23% with type 2 diabetes [by design]), we assessed local stiffness of carotid, femoral, and brachial arteries (by ultrasonography), carotid-femoral pulse wave velocity (cfPWV), aortic augmentation index, and systemic arterial compliance.

**RESULTS** After a median follow-up of 7.6 years, 130 participants had a cardiovascular event and 96 had died. The hazard ratios (HRs) (95% confidence intervals [CIs]) per 1 SD for cardiovascular events and all-cause mortality, respectively, were HR: 1.22 (95% CI: 0.95 to 1.56) and 1.51 (95% CI: 1.11 to 2.06) for lower carotid distensibility; HR: 1.19 (95% CI: 1.00 to 1.41) and 1.28 (95% CI: 1.07 to 1.53) for higher carotid elastic modulus; HR: 1.08 (95% CI: 0.88 to 1.31) and 1.43 (95% CI: 1.10 to 1.86) for lower carotid compliance; HR: 1.39 (95% CI: 1.06 to 1.83) and 1.27 (95% CI: 0.90 to 1.79) for lower femoral distensibility; HR: 1.25 (95% CI: 0.96 to 1.63) and 1.47 (95% CI: 1.01 to 2.13) for lower femoral compliance; and HR: 1.56 (95% CI: 1.23 to 1.98) and 1.13 (95% CI: 0.83 to 1.54) for higher cfPWV. These results were adjusted for age, sex, mean arterial pressure, and cardiovascular risk factors. Mutual adjustments for each of the other stiffness indices did not materially change these results. Brachial stiffness, augmentation index, and systemic arterial compliance were not associated with cardiovascular events or mortality.
Aortic dissection is the most devastating complication of thoracic aortic disease. In the more than 250 years since thoracic aortic dissection was first described, much has been learned about diseases of the thoracic aorta. In this review, we describe normal thoracic aortic size; risk factors for dissection, including genetic and inflammatory conditions; the underpinnings of genetic diseases associated with aneurysm and dissection, including Marfan syndrome and the role of transforming growth factor beta signaling; data on the role for medical therapies in aneurysmal disease, including beta-blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors; prophylactic surgery for aneurysm; surgical techniques for the aortic root; and surgical and endovascular management of aneurysm and dissection for different aortic segments.

**Outcomes of Acute Type A Dissection Repair Before and After Implementation of a Multidisciplinary Thoracic Aortic Surgery Program**

N.D. Andersen, et al.

**OBJECTIVES** The purpose of this study was to compare the results of acute type A aortic dissection (ATAAD) repair before and after implementation of a multidisciplinary thoracic aortic surgery program (TASP) at our institution, with dedicated high-volume thoracic aortic surgeons, a multidisciplinary approach to thoracic aortic disease management, and a standardized protocol for ATAAD repair.

**BACKGROUND** Outcomes of ATAAD repair may be improved when operations are performed at specialized high-volume thoracic aortic surgical centers.

**METHODS** Between 1999 and 2011, 128 patients underwent ATAAD repair at our institution. Records of patients who underwent ATAAD repair 6 years before (n = 56) and 6 years after (n = 72) implementation of the TASP were retrospectively compared. Expected operative mortality rates were calculated using the International Registry of Acute Aortic Dissection pre-operative prediction model.

**RESULTS** Baseline risk profiles and expected operative mortality rates were comparable between patients who underwent surgery before and after implementation of the TASP. Operative mortality before TASP implementation was 33.9% and was statistically equivalent to the expected operative mortality rate of 26.0% (observed-to-expected mortality ratio 1.30; p = 0.54). Operative mortality after TASP implementation fell to 2.8% and was statistically improved compared with the expected operative mortality rate of 18.2% (observed-to-expected mortality ratio 0.15; p = 0.005). Differences in survival persisted over long-term follow-up, with 5-year survival rates of 85% observed for TASP patients compared with 55% for pre-TASP patients (p = 0.002).

**CONCLUSIONS** ATAAD repair can be performed with results approximating those of elective proximal aortic surgery when operations are performed by a high-volume multidisciplinary thoracic aortic surgery team. Efforts to standardize or centralize care of patients undergoing ATAAD are warranted.

**How Does the Ascending Aorta Geometry Change When It Dissects?**

B. Rylski, et al.

**OBJECTIVES** The purpose of this study is to delineate changes in aortic geometry and diameter due to dissection.

**BACKGROUND** Aortic diameter is the major criterion for elective ascending aortic replacement for dilated ascending aortas to prevent aortic dissection. However, recommendations are made on the basis of clinical experience and observation of diameters of previously dissected aortas.

**METHODS** Six tertiary centers on 2 continents reviewed their acute aortic dissection type A databases, which contained 1,821 patients. Included were all non-Marfan patients with nonbicuspid aortic valves who had undergone computed tomography angiography <2 years before and within 12 h after aortic dissection onset. Aortic geometry before and after dissection onset were compared.

**RESULTS** Altogether, 63 patients were included (27 spontaneous and 36 retrograde dissections, median age 68 [57; 77] years; 54% were men). In all but 1 patient, maximum ascending aortic diameter was <55 mm before aortic dissection onset. The largest increase in diameter and volume induced by the dissection were observed in the ascending aorta (40.1 [36.6; 45.3] mm vs. 52.9 [46.1; 58.6] mm, +12.8 mm; p < 0.001; 124.0 [90.8; 162.5] cm³ vs. 171.0 [147.0; 197.0] cm³, +47 cm³; p < 0.001). Mean aortic arch diameter increased from 39.8 (30.5; 42.6) mm to 46.4 (42.0; 51.6) mm (+6.6 mm; p < 0.001) and descending
thoracic aorta diameter from 31.2 (27.0; 33.3) mm to 34.9 (30.9; 39.5) mm (+3.7 mm; p < 0.001). Changes in thoracic aorta geometry were similar for spontaneous and retrograde etiology.

CONCLUSIONS Geometry of the thoracic aorta is affected by aortic dissection, leading to an increase in diameter that is most pronounced in the ascending aorta. Both spontaneous and retrograde dissection result in similar aortic geometry changes (82).

Coronary Artery Manifestations of Fibromuscular Dysplasia
K.C. Michelis, et al.

Fibromuscular dysplasia (FMD) involving the coronary arteries is an uncommon but important condition that can present as acute coronary syndrome, left ventricular dysfunction, or potentially sudden cardiac death. Although the classic angiographic “string of beads” that may be observed in renal artery FMD does not occur in coronary arteries, potential manifestations include spontaneous coronary artery dissection, distal tapering or long, smooth narrowing that may represent dissection, intramural hematoma, spasm, or tortuosity. Importantly, FMD must be identified in at least one other noncoronary arterial territory to attribute any coronary findings to FMD. Although there is limited evidence to guide treatment, many lesions heal spontaneously; thus, a conservative approach is generally preferred. The etiology is poorly understood, but there are ongoing efforts to better characterize FMD and define its genetic and molecular basis. This report reviews the clinical course of FMD involving the coronary arteries and provides guidance for diagnosis and treatment strategies (83).

Paradoxical Embolism
S. Windecker, et al.

Paradoxical embolism is an important clinical entity among patients with venous thromboembolism in the presence of intracardiac or pulmonary shunts. The clinical presentation is diverse and potentially life-threatening. Although the serious nature and complications of paradoxical embolism are recognized, the disease entity is still rarely considered and remains under-reported. This paper provides an overview on the different clinical manifestations of paradoxical embolism, describes the diagnostic tools for the detection of intracardiac and pulmonary shunts, reviews therapeutic options, and summarizes guideline recommendations for the secondary prevention of paradoxical embolism (84).

Cor Pulmonale Parvus in Chronic Obstructive Pulmonary Disease and Emphysema: The MESA COPD Study
S.M. Kawut, et al.

BACKGROUND The classic cardiovascular complication of chronic obstructive pulmonary disease (COPD) is cor pulmonale or right ventricular (RV) enlargement. Most studies of cor pulmonale were conducted decades ago.

OBJECTIVES This study sought to examine RV changes in contemporary COPD and emphysema using cardiac magnetic resonance (CMR) imaging.

METHODS We performed a case-control study nested predominantly in 2 general population studies of 310 participants with COPD and control subjects 50 to 79 years of age with ≧10 pack-years of smoking who were free of clinical cardiovascular disease. RV volumes and mass were assessed using magnetic resonance imaging. COPD and COPD severity were defined according to standard spirometric criteria. The percentage of emphysema was defined as the percentage of lung regions < −950 Hounsfield units on full-lung computed tomography; emphysema subtypes were scored by radiologists. Results were adjusted for age, race/ethnicity, sex, height, weight, smoking status, pack-years, systemic hypertension, and sleep apnea.

RESULTS Right ventricular end-diastolic volume (RVEDV) was reduced in COPD compared with control subjects (−7.8 ml; 95% confidence interval: −15.0 to −0.5 ml; p = 0.04). Increasing severity of COPD was associated with lower RVEDV (p = 0.004) and lower RV stroke volume (p < 0.001). RV mass and ejection fraction were similar between the groups. A greater percentage of emphysema also was associated with lower RVEDV (p = 0.005) and stroke volume (p < 0.001), as was the presence of centrilobular and paraseptal emphysema.

CONCLUSIONS RV volumes are lower without significant alterations in RV mass and ejection fraction in contemporary COPD, and this reduction is related to the greater percentage of emphysema on computed tomography (85).

Multiparametric Cardiovascular Magnetic Resonance Assessment of Cardiac Allograft Vasculopathy
C.A. Miller, et al.

OBJECTIVES This study sought to evaluate the diagnostic performance of multiparametric cardiovascular magnetic resonance (CMR) for detecting cardiac allograft vasculopathy (CAV) using contemporary invasive
epicardial artery and microvascular assessment techniques as reference standards, and to compare the performance of CMR with that of angiography.

**BACKGROUND** CAV continues to limit the long-term survival of heart transplant recipients. Coronary angiography has a Class I recommendation for CMR surveillance and annual or biannual surveillance angiography is performed routinely in most centers.

**METHODS** All transplant recipients referred for surveillance angiography at a single UK center over a 2-year period prospectively underwent coronary angiography followed by coronary intravascular ultrasound. Female Populations.

**RESULTS** Forty-eight patients were recruited, median 7.1 years (interquartile range: 4.6 to 10.3 years) since transplantation. The CMR myocardial perfusion reserve was the only independent predictor of both epicardial ($\beta = -0.57; p < 0.001$) and microvascular disease ($\beta = -0.60; p < 0.001$) on stepwise multivariable regression. The CMR myocardial perfusion reserve significantly outperformed angiography for detecting moderate CAV (area under the curve, 0.89 [95% confidence interval (CI): 0.79 to 1.00] vs. 0.59 [95% CI: 0.42 to 0.77]; $p = 0.01$) and severe CAV (area under the curve, 0.88 [95% CI: 0.78 to 0.98] vs. 0.67 [95% CI: 0.52 to 0.82]; $p = 0.05$).

**CONCLUSIONS** CAV, including epicardial and microvascular components, can be detected more accurately using noninvasive CMR-based absolute myocardial blood flow assessment than with invasive coronary angiography, the current clinical surveillance technique (86).

**REFERENCES**


Highlights of the Year


