

## HIGHLIGHTS OF THE YEAR

# Editor-in-Chief's Top Picks From 2018



Valentin Fuster, MD, PhD

Each week, I record audio summaries for every article in *JACC*, as well as an issue summary. Although this process is quite time-consuming, I have become familiar with every paper that we publish. Thus, I have personally selected the top 100 papers (both Original Investigations and Review Articles) from 15 distinct specialties each year. In addition to my personal choices, I have included papers that have been the most accessed or downloaded on our websites, as well as those selected by the *JACC* Editorial Board members. In order to present the full breadth of this important research in a consumable fashion, we will present these abstracts in this issue of *JACC*.

The highlights comprise the following sections: Basic & Translational Research, Cardiac Failure, Cardiomyopathies/Myocardial & Pericardial Diseases, Cardio-oncology, Congenital Heart Disease, Coronary Disease & Interventions, CVD Prevention & Health Promotion, CV Medicine & Society, Hypertension, Imaging, Metabolic & Lipid Disorders, Rhythm Disorders, Valvular Heart Disease, and Vascular Medicine (1-100).

### BASIC & TRANSLATIONAL RESEARCH

#### Myocardial Interstitial Fibrosis in Heart Failure: Biological and Translational Perspectives

A. González, et al.

Myocardial interstitial fibrosis contributes to left ventricular dysfunction leading to the development of heart failure. Basic research has provided abundant evidence for the cellular and molecular mechanisms behind this lesion and the pathways by which it imparts a detrimental impact on cardiac function. Translation of this knowledge, however, to improved diagnostics and therapeutics for patients with heart failure has not been as robust. This is partly related to the paucity of biomarkers to accurately identify myocardial interstitial fibrosis and to the lack of personalized antifibrotic strategies to treat it in an effective manner. This paper summarizes current knowledge of the mechanisms and detrimental consequences of myocardial interstitial fibrosis, discusses the potential of circulating and imaging biomarkers available to recognize different phenotypes of this lesion and track their clinical evolution, and reviews the currently available and potential future therapies that allow its individualized management in heart failure patients (1).

#### Genome Editing of Induced Pluripotent Stem Cells to Decipher Cardiac Channelopathy Variant

P. Garg, et al.

**BACKGROUND** The long QT syndrome (LQTS) is an arrhythmogenic disorder of QT interval prolongation that predisposes patients to life-threatening ventricular arrhythmias such as Torsades de pointes and sudden cardiac death. Clinical genetic testing has emerged as the standard of care to identify genetic variants in patients suspected of having LQTS. However, these results are often confounded by the discovery of variants of uncertain significance (VUS), for which there is insufficient evidence of pathogenicity.

**OBJECTIVES** The purpose of this study was to demonstrate that genome editing of patient-specific induced pluripotent stem cells (iPSCs) can be a valuable approach to delineate the pathogenicity of VUS in cardiac channelopathy.

**METHODS** Peripheral blood mononuclear cells were isolated from a carrier with a novel missense variant (T983I) in the *KCNH2* (LQT2) gene and an unrelated healthy control subject. iPSCs were generated using an integration-free Sendai virus and differentiated to iPSC-derived cardiomyocytes (CMs).

**RESULTS** Whole-cell patch clamp recordings revealed significant prolongation of the action potential duration (APD) and reduced rapidly activating delayed rectifier  $K^+$  current ( $I_{Kr}$ ) density in VUS iPSC-CMs compared with healthy control iPSC-CMs. ICA-105574, a potent  $I_{Kr}$  activator, enhanced  $I_{Kr}$  magnitude and restored normal action potential duration in VUS iPSC-CMs. Notably, VUS iPSC-CMs exhibited greater propensity to proarrhythmia than healthy control cells in response to high-risk torsadogenic drugs (dofetilide, ibutilide, and azimilide), suggesting a compromised repolarization reserve. Finally, the selective correction of the causal variant in iPSC-CMs using CRISPR/Cas9 gene editing (isogenic control) normalized the aberrant cellular phenotype, whereas the introduction of the homozygous variant in healthy control cells recapitulated hallmark features of the LQTS disorder.

**CONCLUSIONS** The results suggest that the  $KCNH2^{T983I}$  VUS may be classified as potentially pathogenic (2).

### Deficiency of GATA3-Positive Macrophages Improves Cardiac Function Following Myocardial Infarction or Pressure Overload Hypertrophy

M. Yang, et al.

**BACKGROUND** Macrophages are highly plastic cells that play an important role in the pathogenesis of cardiovascular disease.

**OBJECTIVES** This study investigated the role of GATA3-positive macrophages in modulating cardiac function after myocardial infarction (MI) or in response to pressure overload hypertrophy.

**METHODS** Myeloid-specific GATA3-deficient (mGATA3KO) mice were generated, MI or pressure overload was induced, and cardiac function was determined by echocardiography. GATA3-sufficient Cre mice were used as a control. Immunohistochemical staining, flow cytometry, MILLIPLEX Mouse Cytokine/Chemokine Assay, cultured macrophages, quantitative real-time polymerase chain reaction, and western blot were used to determine the role of GATA3 in macrophages.

**RESULTS** GATA3-positive macrophages rapidly accumulated in the infarcted region of the myocardium after acute MI. Deficiency of GATA3-positive macrophages led to a significant improvement of cardiac function in response to acute MI or pressure overload hypertrophy compared

with the control mice. This improvement was associated with the presence of a large number of proinflammatory  $Ly6C^{hi}$  monocytes/macrophages and fewer reparative  $Ly6C^{lo}$  macrophages in the myocardium of mGATA3KO mice compared with control mice. Analysis of serum proteins from the 2 mouse genotypes revealed no major changes in the profile of serum growth factors and cytokines between the 2 mice genotypes before and after MI. GATA3 was found to be specifically and transiently induced by interleukin 4 in cultured macrophages through activity of the proximal promoter, whereas the distal promoter remained silent. In addition, the absence of GATA3 in macrophages markedly attenuated arginase-1 expression in cultured macrophages.

**CONCLUSIONS** We demonstrated that the presence of GATA3-positive macrophages adversely affects remodeling of the myocardium in response to ischemia or pressure overload, whereas the absence of these macrophages led to a significant improvement in cardiac function. Targeting of signaling pathways that lead to the expression of GATA3 in macrophages may have favorable cardiac outcomes (3).

### Telomere Length as Cardiovascular Aging Biomarker: JACC Review Topic of the Week

T. De Meyer, et al.

Telomeres shorten with age, the major risk factor for atherosclerotic cardiovascular disease (aCVD). The observation of shorter telomeres in aCVD patients thus suggested that critical telomere shortening may contribute to premature biological aging and aCVD. Therefore, telomere length often is suggested as a causal aCVD risk factor, a proposal supported by recent Mendelian randomization studies; however, epidemiological research has shown disappointingly low effect sizes. It therefore remains uncertain whether telomere shortening is a cause of aCVD or merely a consequence. The authors argue that elucidating the mechanistic foundation of these findings is essential for any possible translation of telomere biology to the clinic. Here, they critically evaluate evidence for causality in animal models and human studies, and review popular hypotheses and discuss their clinical implications. The authors identify 4 key questions that any successful mechanistic theory should address, and they discuss how atherosclerosis-associated local telomere attrition may provide the answers (4).

### Alterations of Hyaluronan Metabolism in Acute Coronary Syndrome: Implications for Plaque Erosion

D. Pedicino, et al.

**BACKGROUND** Superficial erosion currently causes at least one-third of acute coronary syndromes (ACS), and its incidence is increasing. Yet, the underlying mechanisms in humans are still largely unknown.

**OBJECTIVES** The authors sought to assess the role of hyaluronan (HA) metabolism in ACS.

**METHODS** Peripheral blood mononuclear cells were collected from ACS (n = 66), stable angina (SA) (n = 55), and control (CTRL) patients (n = 45). The authors evaluated: 1) gene expression of hyaluronidase 2 (HYAL2) (enzyme degrading high-molecular-weight HA to its proinflammatory 20-kDa isoform) and of CD44v1, CD44v4, and CD44v6 splicing variants of HA receptor; and 2) HYAL2 and CD44 protein expression. Moreover, they compared HYAL2 and CD44 gene expression in ACS patients with plaque erosion (intact fibrous cap and thrombus) and in ACS patients with plaque rupture, identified by optical coherence tomography analysis.

**RESULTS** Gene expression of HYAL2, CD44v1, and CD44v6 were significantly higher in ACS as compared with SA (p = 0.003, p < 0.001, and p = 0.033, respectively) and CTRL subjects (p < 0.001, p < 0.001, and p = 0.009, respectively). HYAL2 protein expression was significantly higher in ACS than in SA (p = 0.017) and CTRL (p = 0.032), whereas no differences were found in CD44 protein expression. HYAL2 and CD44v6 gene expression was significantly higher in patients with plaque erosion than in those with plaque rupture (p = 0.015 and p = 0.029, respectively).

**CONCLUSIONS** HYAL2 and CD44v6 splicing variants seem to play an important role in ACS, in particular when associated with plaque erosion. After further validation, HYAL2 might represent a potentially useful biomarker for the noninvasive identification of this mechanism of coronary instability (5).

### Macrophage Biology, Classification, and Phenotype in Cardiovascular Disease: JACC Macrophage in CVD Series (Part 1)

J.W. Williams, et al.

Macrophages represent one of the most numerous and diverse leukocyte types in the body. Furthermore, they are important regulators and promoters of many cardiovascular disease programs. Their functions range

from sensing pathogens to digesting cell debris, modulating inflammation, and producing key cytokines and other regulatory factors throughout the body. Macrophage research has undergone a renaissance in recent years, which has propelled a newfound interest in their heterogeneity as well as a new understanding of ontological differences in their development. In addition, recent technological advances such as single-cell mass-cytometry by time-of-flight have enabled phenotype and functional analyses of individual immune myeloid cells, including macrophages, at unprecedented resolution. In this Part 1 of a 4-part review series covering the macrophage in cardiovascular disease, we focus on the basic principles of macrophage development, heterogeneity, phenotype, tissue-specific differentiation, and functionality as a basis to understand their role in cardiovascular disease (6).

### Long Noncoding RNAs in Atherosclerosis: JACC Review Topic of the Week

Z. Zhang, et al.

Atherosclerosis is a complex and chronic disease characterized by lipid deposition in the vessel wall that leads to an inflammatory and proliferative cascade involving smooth muscle, endothelial, and immune cells. Despite substantial improvements in our understanding of mechanisms contributing to atherosclerosis and overall reduction in cardiovascular mortality, the absolute disease burden remains substantially high. The recent discovery of a new group of mediators known as long noncoding ribonucleic acids (lncRNAs) offers a unique opportunity for the development of novel diagnostic and therapeutic tools in atherothrombotic disease. A number of studies suggest that lncRNAs are important mediators in health and disease, and rapidly accumulating evidence implicates lncRNAs in regulatory circuits controlling atherosclerosis. In this review, the authors outline important contributions of lncRNAs to atherosclerosis and its associated risk factors, including hypercholesterolemia, diabetes, hypertension, and obesity (7).

### A Targeting Nanotherapy for Abdominal Aortic Aneurysms

J. Cheng, et al.

**BACKGROUND** Abdominal aortic aneurysm (AAA) is a leading cause of mortality and morbidity in the elderly. Currently, there remain no effective drugs that can prevent the growth of aneurysms and delay aneurysm rupture in the clinical setting.

**OBJECTIVES** The aim of this study was to develop a nanotherapy that can target aneurysms and release drug molecules in response to the inflammatory microenvironment.

**METHODS** Using a reactive oxygen species (ROS)-responsive nanoparticle and a candidate drug rapamycin, in combination with a peptide ligand for integrin and biomimetic cloaking with macrophage cell membrane, a nanotherapy was developed. Its effectiveness was demonstrated by in vitro and in vivo studies.

**RESULTS** Based on a facile and translational method, a rapamycin-loaded responsive nanotherapy was successfully prepared, which could release drug molecules upon triggering by the high level of ROS. In cells associated with the development of AAAs, the nanotherapy significantly inhibited calcification and attenuated ROS-mediated oxidative stress and apoptosis. By passively targeting aneurysms and releasing drug molecules in response to the inflammatory microenvironment, the intravenously injected ROS-responsive nanotherapy more effectively prevented aneurysm expansion in AAA rats than a nonresponsive control nanotherapy. After decoration with a peptide ligand cRGDfK and macrophage cell membrane, the aneurysmal targeting capability and therapeutic effects of a ROS-responsive nanotherapy with a mean diameter of 190 nm were further enhanced. Moreover, the nanotherapy showed a good safety profile in a preliminary safety test.

**CONCLUSIONS** The multifunctional nanotherapy can be further studied as a promising targeted drug for treatment of aneurysms. The underlying design principles enable the development of a broad range of nanomedicines for targeted therapy of other vascular diseases (8).

### Genetic Etiology for Alcohol-Induced Cardiac Toxicity

J.S. Ware, et al.

**BACKGROUND** Alcoholic cardiomyopathy (ACM) is defined by a dilated and impaired left ventricle due to chronic excess alcohol consumption. It is largely unknown which factors determine cardiac toxicity on exposure to alcohol.

**OBJECTIVES** This study sought to evaluate the role of variation in cardiomyopathy-associated genes in the pathophysiology of ACM, and to examine the effects of alcohol intake and genotype on dilated cardiomyopathy (DCM) severity.

**METHODS** The authors characterized 141 ACM cases, 716 DCM cases, and 445 healthy volunteers. The authors compared the prevalence of rare, protein-altering variants in 9 genes associated with inherited DCM. They evaluated the effect of genotype and alcohol consumption on phenotype in DCM.

**RESULTS** Variants in well-characterized DCM-causing genes were more prevalent in patients with ACM than control subjects (13.5% vs. 2.9%;  $p = 1.2 \times 10^{-5}$ ), but similar between patients with ACM and DCM (19.4%;  $p = 0.12$ ) and with a predominant burden of titin truncating variants (TTNtv) (9.9%). Separately, we identified an interaction between *TTN* genotype and excess alcohol consumption in a cohort of DCM patients not meeting ACM criteria. On multivariate analysis, DCM patients with a TTNtv who consumed excess alcohol had an 8.7% absolute reduction in ejection fraction (95% confidence interval:  $-2.3\%$  to  $-15.1\%$ ;  $p < 0.007$ ) compared with those without TTNtv and excess alcohol consumption. The presence of TTNtv did not predict phenotype, outcome, or functional recovery on treatment in ACM patients.

**CONCLUSIONS** TTNtv represent a prevalent genetic predisposition for ACM, and are also associated with a worse left ventricular ejection fraction in DCM patients who consume alcohol above recommended levels. Familial evaluation and genetic testing should be considered in patients presenting with ACM (9).

### Clinician's Guide to Reducing Inflammation to Reduce Atherothrombotic Risk: JACC Review Topic of the Week

P.M. Ridker, et al.

Life-threatening cardiovascular events occur despite control of conventional risk factors. Inflammation, as measured by high-sensitivity C-reactive protein (hsCRP) concentration, is associated with future vascular events in both primary and secondary prevention, independent of usual risk markers. Statins are powerful lipid-lowering agents with clinically relevant anti-inflammatory effects. Recent data support targeting the interleukin (IL)-1-to-IL-6-to-CRP signaling pathway as an adjunctive method for atheroprotection. The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial showed that reducing inflammation through IL-1 $\beta$  inhibition significantly reduced vascular risk, beyond that achievable with lipid lowering. CANTOS further demonstrated a 31% reduction in cardiovascular mortality and all-cause mortality among patients treated with canakinumab who achieved the largest

reductions in hsCRP, as well as efficacy in high-risk patients with chronic kidney disease and diabetes. This review outlines the clinical implications of CANTOS for patients with “residual inflammatory risk,” the potential benefits and risks associated with anti-inflammatory therapy, and the importance of CANTOS for future drug development (10).

## CARDIAC FAILURE

### Myocardial Injury and Cardiac Reserve in Patients With Heart Failure and Preserved Ejection Fraction

M. Obokata, et al.

**BACKGROUND** Cardiac reserve is depressed in patients with heart failure and preserved ejection fraction (HFpEF). The mechanisms causing this are poorly understood.

**OBJECTIVES** The authors hypothesized that myocardial injury might contribute to the hemodynamic derangements and cardiac reserve limitations that are present in HFpEF. Markers of cardiomyocyte injury, central hemodynamics, ventricular function, and determinants of cardiac oxygen supply-demand balance were measured.

**METHODS** Subjects with HFpEF ( $n = 38$ ) and control subjects without heart failure ( $n = 20$ ) underwent cardiac catheterization, echocardiography, and expired gas analysis at rest and during exercise. Central venous blood was sampled to measure plasma high-sensitivity troponin T levels as an index of cardiomyocyte injury.

**RESULTS** Compared with control subjects, troponins were more than 2-fold higher in subjects with HFpEF at rest and during exercise ( $p < 0.0001$ ). Troponin levels were directly correlated with left ventricular (LV) filling pressures ( $r = 0.52$ ;  $p < 0.0001$ ) and diastolic dysfunction ( $r = -0.43$ ;  $p = 0.002$ ). Although myocardial oxygen demand was similar, myocardial oxygen supply was depressed in HFpEF, particularly during exercise (coronary perfusion pressure-time integral;  $44 \pm 9$  mm Hg  $\times$  s  $\times$  min<sup>-1</sup>  $\times$  l  $\times$  dl<sup>-1</sup> vs.  $30 \pm 9$  mm Hg  $\times$  s  $\times$  min<sup>-1</sup>  $\times$  l  $\times$  dl<sup>-1</sup>;  $p < 0.0001$ ), and reduced indices of supply were correlated with greater myocyte injury during exercise ( $r = -0.44$ ;  $p = 0.0008$ ). Elevation in troponin with exercise was directly correlated with an inability to augment LV diastolic ( $r = -0.40$ ;  $p = 0.02$ ) and systolic reserve ( $r = -0.57$ ;  $p = 0.0003$ ), greater increases in LV filling pressures ( $r = 0.55$ ;  $p < 0.0001$ ), blunted cardiac output response

( $r = -0.44$ ;  $p = 0.002$ ), and more severely depressed aerobic capacity in HFpEF.

**CONCLUSIONS** Limitations in LV functional reserve and the hemodynamic derangements that develop secondary to these limitations during exercise in HFpEF are correlated with the severity of cardiac injury, assessed by plasma levels of troponin T. Further study is warranted to determine the mechanisms causing myocyte injury in HFpEF and the potential role of ischemia, and to identify and test novel interventions targeted to these mechanisms. (EXEC [Study of Exercise and Heart Function in Patients With Heart Failure and Pulmonary Vascular Disease]; NCT01418248) (11).

### Identifying Pathophysiological Mechanisms in Heart Failure With Reduced Versus Preserved Ejection Fraction

J. Tromp, et al.

**BACKGROUND** Information on the pathophysiological differences between heart failure with reduced ejection fraction (HFrEF) versus heart failure with preserved ejection fraction (HFpEF) is needed

**OBJECTIVES** The purpose of this study was to establish biological pathways specifically related to HFrEF and HFpEF.

**METHODS** The authors performed a network analysis to identify unique biomarker correlations in HFrEF and HFpEF using 92 biomarkers from different pathophysiological domains in a cohort of 1,544 heart failure (HF) patients. Data were independently validated in 804 patients with HF. Networks were enriched with existing knowledge on protein-protein interactions and translated into biological pathways uniquely related to HFrEF, HF with a midrange ejection fraction, and HFpEF.

**RESULTS** In the index cohort (mean age 74 years; 34% female), 718 (47%) patients had HFrEF (left ventricular ejection fraction [LVEF]  $<40\%$ ) and 431 (27%) patients had HFpEF (LVEF  $\geq 50\%$ ). A total of 8 (12%) correlations were unique for HFrEF and 6 (9%) were unique to HFpEF. Central proteins in HFrEF were N-terminal B-type natriuretic peptide, growth differentiation factor-15, interleukin-1 receptor type 1, and activating transcription factor 2, while central proteins in HFpEF were integrin subunit beta-2 and catenin beta-1. Biological pathways in HFrEF were related to DNA binding transcription factor activity, cellular protein metabolism, and regulation of nitric oxide biosynthesis. Unique pathways in patients with



HFpEF were related to cytokine response, extracellular matrix organization, and inflammation. Biological pathways of patients with HF with a midrange ejection fraction were in between HFrEF and HFpEF.

**CONCLUSIONS** Network analysis showed that biomarker profiles specific for HFrEF are related to cellular proliferation and metabolism, whereas biomarker profiles specific for HFpEF are related to inflammation and extracellular matrix reorganization. (The BIOlogy Study to Tailored Treatment in Chronic Heart Failure [BIOSAT-CHF]; EudraCT 2010-020808-29) (12).

### Ejection Fraction Pros and Cons: JACC State-of-the-Art Review

T.H. Marwick

Ejection fraction (EF) reflects both cardiac function and remodeling, and is widely recognized as a valuable diagnostic and prognostic tool. Its use in a variety of settings, ranging from heart failure and myocardial infarction to valvular heart disease, has made it a cornerstone of modern cardiology, pervading guidelines and practice. However, the development of the test was in another era, with younger patients and a lower prevalence of heart failure with preserved EF. The performance expectations of EF in the current era are also demanding—in relation to detection of subclinical LV dysfunction, and especially relating to recognition of changes in LV function on sequential testing—for example in patients taking cardiotoxic drugs. This review discusses whether the impressive evidence base for EF justifies its ongoing use in the context of newer markers of LV function, and the sophisticated questions posed by modern cardiology (13).

### Renal Denervation Prevents Heart Failure Progression Via Inhibition of the Renin-Angiotensin System

T.E. Sharp III, et al.

**BACKGROUND** Previously, we have shown that radiofrequency (RF) renal denervation (RDN) reduces myocardial infarct size in a rat model of acute myocardial infarction (MI) and improves left ventricular (LV) function and vascular reactivity in the setting of heart failure following MI.

**OBJECTIVES** The authors investigated the therapeutic efficacy of RF-RDN in a clinically relevant

normotensive swine model of heart failure with reduced ejection fraction (HFrEF).

**METHODS** Yucatan miniswine underwent 75 min of left anterior descending coronary artery balloon occlusion to induce MI followed by reperfusion (R) for 18 weeks. Cardiac function was assessed pre- and post-MI/R by transthoracic echocardiography and every 3 weeks for 18 weeks. HFrEF was classified by an LV ejection fraction <40%. Animals who met inclusion criteria were randomized to receive bilateral RF-RDN (n = 10) treatment or sham-RDN (n = 11) at 6 weeks post-MI/R using an RF-RDN catheter.

**RESULTS** RF-RDN therapy resulted in significant reductions in renal norepinephrine content and circulating angiotensin I and II. RF-RDN significantly increased circulating B-type natriuretic peptide levels. Following RF-RDN, LV end-systolic volume was significantly reduced when compared with sham-treated animals, leading to a marked and sustained improvement in LV ejection fraction. Furthermore, RF-RDN improved LV longitudinal strain. Simultaneously, RF-RDN reduced LV fibrosis and improved coronary artery responses to vasodilators.

**CONCLUSIONS** RF-RDN provides a novel therapeutic strategy to reduce renal sympathetic activity, inhibit the renin-angiotensin system, increase circulating B-type natriuretic peptide levels, attenuate LV fibrosis, and improve left ventricular performance and coronary vascular function. These cardioprotective mechanisms synergize to halt the progression of HFrEF following MI/R in a clinically relevant model system (14).

### CARDIOMYOPATHIES/MYOCARDIAL & PERICARDIAL DISEASES

#### Genetics, Clinical Features, and Long-Term Outcome of Noncompaction Cardiomyopathy

J.I. van Waning, et al.

**BACKGROUND** The clinical outcomes of non-compaction cardiomyopathy (NCCM) range from asymptomatic to heart failure, arrhythmias, and sudden cardiac death. Genetics play an important role in NCCM.

**OBJECTIVES** This study investigated the correlations among genetics, clinical features, and outcomes in adults and children diagnosed with NCCM.

**METHODS** A retrospective multicenter study from 4 cardiogenetic centers in the Netherlands classified 327 unrelated NCCM patients into 3 categories: 1) genetic,

with a mutation in 32% (81 adults; 23 children) of patients; 2) probably genetic, familial cardiomyopathy without a mutation in 16% (45 adults; 8 children) of patients; or 3) sporadic, no family history, without mutation in 52% (149 adults; 21 children) of patients. Clinical features and major adverse cardiac events (MACE) during follow-up were compared across the children and adults.

**RESULTS** *MYH7*, *MYBPC3*, and *TTN* mutations were the most common mutations (71%) found in genetic NCCM. The risk of having reduced left ventricular (LV) systolic dysfunction was higher for genetic patients compared with the probably genetic and sporadic cases ( $p = 0.024$ ), with the highest risk in patients with multiple mutations and *TTN* mutations. Mutations were more frequent in children ( $p = 0.04$ ) and were associated with MACE ( $p = 0.025$ ). Adults were more likely to have sporadic NCCM. High risk for cardiac events in children and adults was related to LV systolic dysfunction in mutation carriers, but not in sporadic cases. Patients with *MYH7* mutations had low risk for MACE ( $p = 0.03$ ).

**CONCLUSIONS** NCCM is a heterogeneous condition, and genetic stratification has a role in clinical care. Distinguishing genetic from nongenetic NCCM complements prediction of outcome and may lead to management and follow-up tailored to genetic status (15).

### Elevated Cardiac Troponin T in Patients With Skeletal Myopathies

J. Schmid, et al.

**BACKGROUND** Cardiac troponins are often elevated in patients with skeletal muscle disease who have no evidence of cardiac disease.

**OBJECTIVES** The goal of this study was to characterize cardiac troponin concentrations in patients with myopathies and derive insights regarding the source of elevated troponin T measurements.

**METHODS** Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) concentrations were determined by using high sensitivity assays in 74 patients with hereditary and acquired skeletal myopathies. Patients underwent comprehensive cardiac evaluation, including 12-lead electrocardiogram, 24-h electrocardiogram, cardiac magnetic resonance imaging, and coronary artery computed tomography. cTnT and cTnI protein expression was determined in skeletal muscle samples of 9 patients and in control tissues derived from autopsy using antibodies that are used in commercial assays. Relevant Western

blot bands were subjected to liquid chromatography tandem mass spectrometry for protein identification.

**RESULTS** Levels of cTnT (median: 24 ng/l; interquartile range: 11 to 54 ng/l) were elevated ( $>14$  ng/l) in 68.9% of patients; cTnI was elevated ( $>26$  ng/l) in 4.1% of patients. Serum cTnT levels significantly correlated with creatine kinase and myoglobin ( $r = 0.679$  and  $0.786$ , respectively; both  $p < 0.001$ ). Based on cTnT serial testing, 30.1% would have fulfilled current rule-in criteria for myocardial infarction. Noncoronary cardiac disease was present in 23%. Using cTnT antibodies, positive bands were found in both diseased and healthy skeletal muscle at molecular weights approximately 5 kDa below cTnT. Liquid chromatography tandem mass spectrometry identified the presence of skeletal troponin T isoforms in these bands.

**CONCLUSIONS** Measured cTnT concentrations were chronically elevated in the majority of patients with skeletal myopathies, whereas cTnI elevation was rare. Our data indicate that cross-reaction of the cTnT immunoassay with skeletal muscle troponin isoforms was the likely cause (16).

### Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

S.S. Mahmood, et al.

**BACKGROUND** Myocarditis is an uncommon, but potentially fatal, toxicity of immune checkpoint inhibitors (ICI). Myocarditis after ICI has not been well characterized.

**OBJECTIVES** The authors sought to understand the presentation and clinical course of ICI-associated myocarditis.

**METHODS** After observation of sporadic ICI-associated myocarditis cases, the authors created a multicenter registry with 8 sites. From November 2013 to July 2017, there were 35 patients with ICI-associated myocarditis, who were compared to a random sample of 105 ICI-treated patients without myocarditis. Covariates of interest were extracted from medical records including the occurrence of major adverse cardiac events (MACE), defined as the composite of cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block.

**RESULTS** The prevalence of myocarditis was 1.14% with a median time of onset of 34 days after starting ICI (interquartile range: 21 to 75 days). Cases were  $65 \pm 13$  years of age, 29% were female, and 54% had no other immune-related side effects. Relative to controls, combination ICI (34% vs. 2%;  $p < 0.001$ ) and diabetes

(34% vs. 13%;  $p = 0.01$ ) were more common in cases. Over 102 days (interquartile range: 62 to 214 days) of median follow-up, 16 (46%) developed MACE; 38% of MACE occurred with normal ejection fraction. There was a 4-fold increased risk of MACE with troponin T of  $\geq 1.5$  ng/ml (hazard ratio: 4.0; 95% confidence interval: 1.5 to 10.9;  $p = 0.003$ ). Steroids were administered in 89%, and lower steroid doses were associated with higher residual troponin and higher MACE rates.

**CONCLUSIONS** Myocarditis after ICI therapy may be more common than appreciated, occurs early after starting treatment, has a malignant course, and responds to higher steroid doses (17).

### Long-Term Prognosis of Patients With Takotsubo Syndrome

J.R. Ghadri, et al.

**BACKGROUND** Prognosis of Takotsubo syndrome (TTS) remains controversial due to scarcity of available data. Additionally, the effect of the triggering factors remains elusive.

**OBJECTIVES** This study compared prognosis between TTS and acute coronary syndrome (ACS) patients and investigated short- and long-term outcomes in TTS based on different triggers.

**METHODS** Patients with TTS were enrolled from the International Takotsubo Registry. Long-term mortality of patients with TTS was compared to an age- and sex-matched cohort of patients with ACS. In addition, short- and long-term outcomes were compared between different groups according to triggering conditions.

**RESULTS** Overall, TTS patients had a comparable long-term mortality risk with ACS patients. Of 1,613 TTS patients, an emotional trigger was detected in 485 patients (30%). Of 630 patients (39%) related to physical triggers, 98 patients (6%) had acute neurologic disorders, while in the other 532 patients (33%), physical activities, medical conditions, or procedures were the triggering conditions. The remaining 498 patients (31%) had no identifiable trigger. TTS patients related to physical stress showed higher mortality rates than ACS patients during long-term follow-up, whereas patients related to emotional stress had better outcomes compared with ACS patients.

**CONCLUSIONS** Overall, TTS patients had long-term outcomes comparable to age- and sex-matched ACS patients. Also, we demonstrated that TTS can either be benign or a life-threatening condition depending on

the inciting stress factor. We propose a new classification based on triggers, which can serve as a clinical tool to predict short- and long-term outcomes of TTS. (International Takotsubo Registry [InterTAK Registry]; [NCT01947621](#)) (18).

### Percutaneous Intramyocardial Septal Radiofrequency Ablation for Hypertrophic Obstructive Cardiomyopathy

L. Liu, et al.

**BACKGROUND** In patients with disabling symptoms caused by hypertrophic obstructive cardiomyopathy (HOCM), echocardiography-guided percutaneous intramyocardial septal radiofrequency ablation (PIMSRA) could be a less invasive treatment option.

**OBJECTIVES** This study aimed to investigate the safety and efficacy of the PIMSRA for left ventricular outflow tract (LVOT) gradient reduction in HOCM.

**METHODS** The study enrolled 15 patients with HOCM. These patients underwent electrocardiography, imaging, and blood biochemistry examination over 6 months of follow-up.

**RESULTS** At 6 months of follow-up, patients showed significant reductions in peak LVOT gradients (resting gradient: from 88.00 [66.00] mm Hg to 11.00 [6.00] mm Hg;  $p = 0.001$ ; stress-induced gradient: from 117.00 [81.00] mm Hg to 25.00 [20.00] mm Hg;  $p = 0.005$ ) and interventricular septum (IVS) thickness (anterior IVS: from 25.00 [21.00] mm to 14.00 [12.00] mm;  $p = 0.001$ ; posterior IVS: from 24.00 [21.00] mm to 14.00 [11.50] mm;  $p = 0.001$ ). The reductions in IVS thickness and LVOT gradients were associated with improvement in New York Heart Association functional classification (from 3.00 [2.00] to 1.00 [1.00];  $p < 0.001$ ), total exercise time (from 6.00 [5.50] min to 9.00 [8.00] min;  $p = 0.007$ ), and pro B-type natriuretic peptide levels (from 924.00 [370.45] pg/ml to 137.45 [75.73] pg/ml;  $p = 0.028$ ). No patient had bundle branch block or complete heart block.

**CONCLUSIONS** PIMSRA is a safe and effective treatment approach for severe, symptomatic HOCM and results in sustained improvement in exercise capacity, persistent reduction in LVOT gradient, and sustained improvement in cardiac function (19).

### Cardiac Phenotypes in Hereditary Muscle Disorders: JACC State-of-the-Art Review

E. Arbustini, et al.

Hereditary muscular diseases commonly involve the heart. Cardiac manifestations encompass a spectrum



of phenotypes, including both cardiomyopathies and rhythm disorders. Common biomarkers suggesting cardiomyopathies include increased circulating creatine kinase and/or lactic acid levels or disease-specific metabolic indicators. Cardiac and extra-cardiac traits, imaging tests, family studies, and genetic testing provide precise diagnoses. Cardiac phenotypes are mainly dilated and hypokinetic in dystrophinopathies, Emery-Dreifuss muscular dystrophies, and limb girdle muscular dystrophies; hypertrophic in Friedreich ataxia, mitochondrial diseases, glycogen storage diseases, and fatty acid oxidation disorders; and restrictive in myofibrillar myopathies. Left ventricular noncompaction is variably associated with the different myopathies. Conduction defects and arrhythmias constitute a major phenotype in myotonic dystrophies and skeletal muscle channelopathies. Although the actual cardiac management is rarely based on the cause, the cardiac phenotypes need precise characterization because they are often the only or the predominant manifestations and the prognostic determinants of many hereditary muscle disorders (20).

### Left Ventricular Scar and Prognosis in Chronic Chagas Cardiomyopathy

G.J. Volpe, et al.

**BACKGROUND** Patients with chronic Chagas cardiomyopathy (CCC) have pronounced myocardial fibrosis, which may predispose to sudden cardiac death, despite well-preserved global left ventricular (LV) systolic function. Cardiac magnetic resonance can assess myocardial fibrosis by late gadolinium enhancement (LGE) sequences.

**OBJECTIVES** This prospective study evaluated if the presence of scar by LGE predicted hard adverse outcomes in a cohort of patients with CCC.

**METHODS** A prospective cohort of 140 patients with CCC (52.1% female; median age 57 years [interquartile range: 45 to 67 years]) were included. Cardiac magnetic resonance cine and LGE imaging were performed at enrollment with a 1.5-T scanner. The primary endpoint was the combination of cardiovascular death and sustained ventricular tachycardia. The secondary endpoint was the combination of cardiovascular death, sustained ventricular tachycardia, or cardiovascular hospitalization during follow-up.

**RESULTS** After a median of 34 months (interquartile range: 24 to 49 months) of follow-up, 11 cardiovascular deaths, 3 episodes of sustained ventricular tachycardia, and 20 cardiovascular hospitalizations

were recorded. LGE scar was present in 71.4% of the patients, with the lateral, inferolateral, and inferior walls most commonly affected. Patients with positive LGE had lower LV ejection fraction and higher LV end-diastolic volume and LV mass than patients without LGE. No difference in other cardiovascular risk factors was noted. Patients with scar had higher event rates compared with those without scar for the primary ( $p = 0.043$ ) and the secondary ( $p = 0.016$ ) endpoint. In multivariable analysis, age and LGE area were related to primary outcome; age and lower LV ejection fraction were related to the secondary outcome. The pattern of LGE myocardial fibrosis was transmural, focal, or diffuse scar in approximately one-third of patients with positive LGE, and no pattern was specifically related to outcomes.

**CONCLUSIONS** In patients with CCC, presence of scar by LGE is common and is strongly associated with major adverse outcomes (21).

### Long-Term Prognostic Value of Myocardial Fibrosis in Patients With Chagas Cardiomyopathy

T. Senra, et al.

**BACKGROUND** Myocardial fibrosis (MF) according to cardiac magnetic resonance (CMR) is a frequent finding in Chagas cardiomyopathy and has been associated with risk factors of poor outcome.

**OBJECTIVES** The goal of this study was to determine the prognostic value of MF in predicting combined hard events or all-cause mortality.

**METHODS** Patients with Chagas cardiomyopathy who had a previous CMR evaluation were included, and clinical follow-up was retrospectively obtained. The primary outcome was a combination of all-cause mortality, heart transplantation, antitachycardia pacing or appropriate shock from an implantable cardioverter-defibrillator, and aborted sudden cardiac death; the secondary outcome was all-cause mortality.

**RESULTS** A total of 130 patients were included; mean age was  $53.6 \pm 11.5$  years, and 53.9% were female. The majority of patients reported no symptoms of heart failure or arrhythmia, but electrocardiographic and echocardiographic abnormalities were common. On CMR, left ventricular dilatation and dysfunction were frequent, and MF was found in 76.1%, with a mean mass of  $15.2 \pm 16.5$  g. Over a median follow-up of 5.05 years, 58 (44.6%) patients reached the combined endpoint, and 45 (34.6%) patients died. MF was

associated with the primary outcome as a continuous variable (adjusted hazard ratio: 1.031; 95% CI: 1.013 to 1.049;  $p = 0.001$ ) and as a categorical variable (MF  $\geq 12.3$  g) (adjusted hazard ratio: 2.107; 95% CI: 1.111 to 3.994;  $p = 0.022$ ), independently from the Rassi risk score. MF expressed as a continuous variable was also associated with all-cause mortality (adjusted hazard ratio: 1.028; 95% CI: 1.005 to 1.051;  $p = 0.017$ ) independently from the Rassi risk score.

**CONCLUSIONS** MF is an independent predictor of adverse outcome in Chagas cardiomyopathy. Our data may support the use of CMR in better risk-stratifying this population and possibly guiding therapy (22).

### Survival After Alcohol Septal Ablation in Patients With Hypertrophic Obstructive Cardiomyopathy

A. Batzner, et al.

**BACKGROUND** Alcohol-induced infarction for treatment of symptomatic hypertrophic obstructive cardiomyopathy (HOCM) was discussed as a risk factor for increased cardiac mortality during follow-up.

**OBJECTIVES** This study sought to report on long-term survival after echo-guided alcohol septal ablation (percutaneous transluminal septal myocardial ablation [PTSMA]) in symptomatic patients with HOCM.

**METHODS** Between May 2000 and June 2017, PTSMA with alcohol injection was performed in 952 patients (age  $55.7 \pm 14.9$  years; 59.2% men; 73.3% New York Heart Association functional class III or IV; 50.3% syncope; 10.3% sudden cardiac death in family). Clinical follow-up after  $6.0 \pm 5.0$  years was achieved in all patients.

**RESULTS** We injected  $2.1 \pm 0.4$  cc of alcohol. Maximal creatine kinase rise was  $872 \pm 489$  U/l. Two (0.21%) patients died 3 and 33 days after ablation. Permanent pacemaker was implanted in 100 (10.50%) patients. Echo gradients were acutely reduced from  $63.9 \pm 38.2$  mm Hg to  $33.6 \pm 29.8$  mm Hg at rest and from  $104.6 \pm 44.0$  mm Hg to  $56.5 \pm 41.0$  mm Hg at Valsalva ( $p < 0.0001$ , each). During follow-up, 164 (17.2%) patients underwent reablation due to the planned staged procedure, 18 (1.9%) patients underwent surgical myectomy, and 49 (5.10%) patients underwent cardioverter-defibrillator implantation. Seventy patients died: causes of death were identified as noncardiovascular in 50, stroke related in 6, and cardiac in 14 patients. Estimated 5-year survival was 95.8%, estimated 5-year survival free of cardiovascular events was 98.6%, and an estimated 5-year survival free of cardiac events was 98.9%.

Corresponding values at 10 years were 88.3%, 96.5%, and 97.0%, and at 15 years were 79.7%, 92.3%, and 96.5%.

**CONCLUSIONS** In this study, PTSMA could be proofed as a safe procedure with ongoing symptomatic improvement and excellent long-term survival. Therefore, PTSMA is a reasonable alternative to surgical myectomy in HOCM (23).

## CARDIO-ONCOLOGY

### Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial

M.S. Avila, et al.

**BACKGROUND** Anthracycline (ANT) chemotherapy is associated with cardiotoxicity. Prevention with  $\beta$ -blockers remains controversial.

**OBJECTIVES** This prospective, randomized, double-blind, placebo-controlled study sought to evaluate the role of carvedilol in preventing ANT cardiotoxicity.

**METHODS** The authors randomized 200 patients with HER2-negative breast cancer tumor status and normal left ventricular ejection fraction (LVEF) referred for ANT ( $240 \text{ mg/m}^2$ ) to receive carvedilol or placebo until chemotherapy completion. The primary endpoint was prevention of a  $\geq 10\%$  reduction in LVEF at 6 months. Secondary outcomes were effects of carvedilol on troponin I, B-type natriuretic peptide, and diastolic dysfunction.

**RESULTS** Primary endpoint occurred in 14 patients (14.5%) in the carvedilol group and 13 patients (13.5%) in the placebo group ( $p = 1.0$ ). No differences in changes of LVEF or B-type natriuretic peptide were noted between groups. A significant difference existed between groups in troponin I levels over time, with lower levels in the carvedilol group ( $p = 0.003$ ). Additionally, a lower incidence of diastolic dysfunction was noted in the carvedilol group ( $p = 0.039$ ). A nonsignificant trend toward a less-pronounced increase in LV end-diastolic diameter during the follow-up was noted in the carvedilol group ( $44.1 \pm 3.64$  mm to  $45.2 \pm 3.2$  mm vs.  $44.9 \pm 3.6$  mm to  $46.4 \pm 4.0$  mm;  $p = 0.057$ ).

**CONCLUSIONS** In this largest clinical trial of  $\beta$ -blockers for prevention of cardiotoxicity under contemporary ANT dosage, the authors noted a 13.5% to 14.5% incidence of cardiotoxicity. In this scenario, carvedilol had no impact on the incidence of early onset of LVEF reduction. However, the use of carvedilol resulted in a significant reduction in troponin

levels and diastolic dysfunction. (Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity [CECCY]; [NCT01724450](#)) (24).

### Neoplasia and the Heart: Pathological Review of Effects With Clinical and Radiological Correlation

J.J. Maleszewski, et al.

The intersection of oncological and cardiovascular diseases is an increasingly recognized phenomenon. This recognition has led to the emergence of cardio-oncology as a true subspecialty. This field is not simply limited to primary cardiac tumors or complications of chemotherapeutic medications. Rather, it also encompasses metastatic cardiovascular complications and secondary cardiovascular effects of the underlying neoplasia. This review will broadly cover primary and metastatic cardiac neoplasms, as well as secondary cardiovascular effects of extracardiac neoplasia (e.g., amyloidosis, carcinoid valvulopathy, and chemotherapeutic cardiotoxicities) (25).

### CONGENITAL HEART DISEASE

#### Clinical Outcomes in Adolescents and Adults After the Fontan Procedure

M. Dennis, et al.

**BACKGROUND** Long-term outcomes of Fontan patients who survive to age  $\geq 16$  years have not been well characterized. The Australian and New Zealand Fontan Registry (ANZFR) provides a unique opportunity to understand survival and complication rates in Fontan patients who transition to adult congenital heart disease centers.

**OBJECTIVES** This study sought to describe the survival and complications of adult patients who have had a Fontan procedure.

**METHODS** The study analyzed outcomes in patients  $\geq 16$  years of age who were prospectively enrolled in the ANZFR.

**RESULTS** Data from all 683 adult survivors from the ANZFR were analyzed. Mortality status was confirmed from the National Death Index. There were 201 atrio-pulmonary (AP) connections and 482 total cavopulmonary connections (249 lateral tunnels and 233 extracardiac conduits). For these subjects, the survival rate at age 30 years was 90% (95% CI: 87% to 93%), and it was 80% (95% CI: 75% to 87%) at 40 years of age. Survival at age 30 years was significantly worse for the patients with AP connections ( $p = 0.03$ ). At latest follow-up, only 53% of patients were in New

York Heart Association functional class I. After the age of 16 years, 136 (20%) had experienced at least 1 new arrhythmia, 42 (6%) required a permanent pacemaker, 45 (7%) had a thromboembolic event, and 135 (21%) required a surgical reintervention. Only 41% (95% CI: 33% to 51%) of Fontan patients were free of serious adverse events at 40 years of age.

**CONCLUSIONS** This comprehensively followed cohort showed that a variety of morbid complications is common in Fontan adults, and that there is a substantial incidence of premature death, particularly in patients with AP connections (26).

### CORONARY DISEASE & INTERVENTIONS

#### Multivessel Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction With Cardiogenic Shock

J.M. Lee, et al.

**BACKGROUND** Recent trials demonstrated a benefit of multivessel percutaneous coronary intervention (PCI) for noninfarct-related artery (non-IRA) stenosis over IRA-only PCI in patients with ST-segment elevation myocardial infarction (STEMI) multivessel disease. However, evidence is limited in patients with cardiogenic shock.

**OBJECTIVES** This study investigated the prognostic impact of multivessel PCI in patients with STEMI multivessel disease presenting with cardiogenic shock, using the nationwide, multicenter, prospective KAMIR-NIH (Korea Acute Myocardial Infarction-National Institutes of Health) registry.

**METHODS** Among 13,104 consecutive patients enrolled in the KAMIR-NIH registry, we selected patients with STEMI with multivessel disease presenting with cardiogenic shock and who underwent primary PCI. Primary outcome was 1-year all-cause death, and secondary outcomes included patient-oriented composite outcome (a composite of all-cause death, any myocardial infarction, and any repeat revascularization) and its individual components.

**RESULTS** A total of 659 patients were treated by multivessel PCI ( $n = 260$ ) or IRA-only PCI ( $n = 399$ ) strategy. The risk of all-cause death and non-IRA repeat revascularization was significantly lower in the multivessel PCI group than in the IRA-only PCI group (21.3% vs. 31.7%; hazard ratio: 0.59; 95% confidence interval: 0.43 to 0.82;  $p = 0.001$ ; and 6.7% vs. 8.2%; hazard ratio: 0.39; 95% confidence interval: 0.17 to 0.90;  $p = 0.028$ , respectively). Results were consistent after multivariable regression, propensity-score matching, and inverse

probability weighting to adjust for baseline differences. In a multivariable model, multivessel PCI was independently associated with reduced risk of 1-year all-cause death and patient-oriented composite outcome.

**CONCLUSIONS** Of patients with STEMI and multivessel disease with cardiogenic shock, multivessel PCI was associated with a significantly lower risk of all-cause death and non-IRA repeat revascularization. Our data suggest that multivessel PCI for complete revascularization is a reasonable strategy to improve outcomes in patients with STEMI with cardiogenic shock (27).

### Long-Term Outcomes of On- Versus Off-Pump Coronary Artery Bypass Grafting

N.A. Smart, et al.

**BACKGROUND** When comparing effects of on- versus off-pump coronary artery bypass grafting (CABG), it is important to assess the long-term clinical outcomes. However, most research conducted thus far has concentrated on short-term outcomes and ignored the long-term clinical outcomes, especially the 5-year outcomes of the largest randomized controlled trials.

**OBJECTIVES** The aim of this systematic review and meta-analysis was to investigate the long-term clinical outcomes of on- versus off-pump CABG.

**METHODS** To identify potential studies systematic searches were carried out using various databases. The search strategy included the key concepts of *cardiopulmonary bypass AND off-pump AND long term OR 5-year outcomes*. This was followed by a meta-analysis investigating mortality, incidence of myocardial infarction, incidence of angina, need for revascularization, and incidence of stroke.

**RESULTS** Six studies totaling 8,145 participants were analyzed. In the on-pump group mortality was 12.3%, compared with 13.9% in the off-pump group. The odds ratio (OR) for this comparison was 1.16 (95% confidence interval [CI]: 1.02 to 1.32;  $p = 0.03$ ; 13.9% vs. 12.3%). In contrast, there were no differences in the incidence of myocardial infarction (OR: 1.06; 95% CI: 0.91 to 1.25;  $p = 0.45$ ; 8.4% vs. 7.9%), incidence of angina (OR: 1.09; 95% CI: 0.75 to 1.57;  $p = 0.65$ ; 2.3% vs. 2.1%), need for revascularization (OR: 1.15; 95% CI: 0.95 to 1.40;  $p = 0.16$ ; 5.9% vs. 5.1%), and the incidence of stroke (OR: 0.78; 95% CI: 0.56 to 1.10;  $p = 0.16$ ; 2.2% vs. 2.8%).

**CONCLUSIONS** Statistically, on-pump CABG appeared to offer superior long-term survival,

although the clinical significance of this may be more uncertain (28).

### Neoatherosclerosis 5 Years After Bioresorbable Vascular Scaffold Implantation

N. Moriyama, et al.

**BACKGROUND** Data regarding neoatherosclerosis after everolimus-eluting bioresorbable vascular scaffold (BVS) (ABSORB BVS Rev. 1.1, Abbott Vascular, Santa Clara, California) implantation are limited.

**OBJECTIVES** This study investigated the findings of neoatherosclerosis at 5 years after BVS 1.1 implantation by using multi-imaging modalities, including optical coherence tomography (OCT).

**METHODS** Patients included in the ABSORB EXTEND (ABSORB EXTEND Clinical Investigation) trial at Shonan Kamakura General Hospital underwent OCT at baseline after the index procedure and at 1 and 5 years. Intimal plaque distributions in the in-scaffold and out-scaffold segments were analyzed.

**RESULTS** Twenty patients (22 lesions) with stable angina pectoris were enrolled. The median follow-up duration was 67 months (interquartile range: 65 to 69 months), and the mean age was  $69 \pm 8$  years. Patients with diabetes mellitus (25%) were included. Based on the baseline angiogram, 10 (46%) lesions were type B2/C lesions. At 1 and 5 years of follow-up, significant differences in the prevalence of in-scaffold lipid-laden neointima (17% vs. 61%;  $p = 0.04$ ), calcification (28% vs. 94%;  $p < 0.01$ ), neovascularization (6% vs. 78%;  $p < 0.01$ ), and thin-cap fibroatheroma (0% vs. 22%;  $p = 0.02$ ) were found. In the out-scaffold segments, no significant difference in the plaque prevalence between 1 and 5 years was noted.

**CONCLUSIONS** The occurrence and progression of in-scaffold neoatherosclerosis with luminal narrowing was observed at 5 years after BVS 1.1 implantation. The small size of the current study warrants confirmation in larger study. (ABSORB EXTEND Clinical Investigation [ABSORB EXTEND]; NCT01023789) (29).

### Local Low Shear Stress and Endothelial Dysfunction in Patients With Nonobstructive Coronary Atherosclerosis

G. Siasos, et al.

**BACKGROUND** Local hemodynamic factors are important determinants of atherosclerotic plaque development and progression.

**OBJECTIVES** The goal of this study was to determine the association between low endothelial shear stress (ESS) and microvascular and epicardial endothelial dysfunction in patients with early atherosclerosis.

**METHODS** Sixty-five patients (mean age  $52 \pm 11$  years) with nonobstructive coronary atherosclerosis (luminal diameter stenosis  $<30\%$ ) were included. Microvascular and epicardial coronary endothelial function was assessed by using intracoronary acetylcholine infusion. Vascular profiling, using 2-plane coronary angiography and intravascular ultrasound, was used to reconstruct the three-dimensional anatomy of the left anterior descending artery. Each reconstructed artery was divided into sequential 3-mm segments and analyzed for local ESS with computational fluid dynamics; that is, lower ESS levels at both a 3-mm regional level (average ESS and low ESS) and at a vessel level (lowest ESS per artery) and for plaque characteristics (plaque area, plaque thickness, and plaque burden).

**RESULTS** Coronary segments in arteries with abnormal microvascular function exhibited lower ESS compared with segments in arteries with normal microvascular function (average ESS:  $1.67 \pm 1.04$  Pa vs.  $2.03 \pm 1.72$  Pa [ $p = 0.050$ ]; lowest ESS:  $0.54 \pm 0.25$  Pa vs.  $0.72 \pm 0.32$  Pa [ $p = 0.014$ ]). Coronary segments in arteries with abnormal epicardial endothelial function also exhibited significantly lower ESS compared with segments in arteries with normal epicardial function (average ESS:  $1.49 \pm 0.89$  Pa vs.  $1.93 \pm 1.50$  Pa [ $p < 0.0001$ ]; low ESS:  $1.26 \pm 0.81$  Pa vs.  $1.56 \pm 1.30$  Pa [ $p = 0.001$ ]; lowest ESS:  $0.51 \pm 0.27$  Pa vs.  $0.65 \pm 0.29$  Pa [ $p = 0.080$ ]). Patients with abnormal microvascular endothelial function exhibited a progressive decrease in average and low ESS, starting from patients with normal epicardial endothelial function to those with both microvascular and epicardial endothelial dysfunction ( $p < 0.0001$  and  $p = 0.004$ , respectively).

**CONCLUSIONS** These data indicate an association between dysfunction of the microvascular and epicardial endothelium and local ESS at the early stages of coronary atherosclerosis in humans (30).

### Arterial Pulsatility and Circulating von Willebrand Factor in Patients on Mechanical Circulatory Support

F. Vincent, et al.

**BACKGROUND** The main risk factor for bleeding in patients with continuous-flow mechanical circulatory support (CF-MCS) is the acquired von Willebrand factor (VWF) defect related to the high shear-stress forces developed by these devices. Although a higher

bleeding rate has been reported in CF-MCS recipients who had reduced pulsatility, the relation between pulsatility and the VWF defect has never been studied.

**OBJECTIVES** The purpose of this study was to investigate the relation between pulsatility and VWF under CF-MCS.

**METHODS** We assessed the effect of 2 CF-MCS on VWF multimer degradation in a mock circulatory loop (model 1). Using these devices, we investigated in a dose-effect model (model 2) 3 levels of pulsatility in 3 groups of swine. In a cross-over model (model 3), we studied the effects of sequential changes of pulsatility on VWF. We reported the evolution of VWF multimerization in a patient undergoing serial CF-MCS and/or pulsatile-MCS.

**RESULTS** We demonstrated the proteolytic degradation of VWF multimers by high shear CF-MCS in a circulatory loop without pulsatility. We observed both in swine models and in a patient that the magnitude of the VWF degradation is modulated by the pulsatility level in the high shear-stress level condition, and that the restoration of pulsatility is a trigger for the endothelial release of VWF.

**CONCLUSIONS** We demonstrated that the VWF defect reflects the balance between degradation induced by the shear stress and the endothelial release of new VWF triggered by the pulsatility. This modulation of VWF levels could explain the relationship between pulsatility and bleeding observed in CF-MCS recipients. Preservation of pulsatility may be a new target to improve clinical outcomes of patients (31).

### Fractional Flow Reserve Derived From Computed Tomographic Angiography in Patients With Multivessel CAD

C. Collet, et al.

**BACKGROUND** The functional SYNTAX score (FSS) has been shown to improve the discrimination for major adverse cardiac events compared with the anatomic SYNTAX score (SS) while reducing interobserver variability. However, evidence supporting the noninvasive FSS in patients with multivessel coronary artery disease (CAD) is scarce.

**OBJECTIVES** The purpose of this study was to assess the feasibility of and validate the noninvasive FSS derived from coronary computed tomography angiography (CTA) with fractional flow reserve (FFR<sub>CT</sub>) in patients with 3-vessel CAD.

**METHODS** The CTA-SS was calculated in patients with 3-vessel CAD included in the SYNTAX II (SYnergy between percutaneous coronary intervention with



TAXus and cardiac surgery II) study. The noninvasive FSS was determined by including only ischemia-producing lesions ( $FFR_{CT} \leq 0.80$ ). SS derived from different imaging modalities were compared using the Bland-Altman and Passing-Bablok method, and the agreement on the SS tertiles was investigated with Cohen's Kappa. The risk reclassification was compared between the noninvasive and invasive physiological assessment, and the diagnostic accuracy of  $FFR_{CT}$  was assessed by the area under the receiver-operating characteristic curve using instantaneous wave-free ratio as a reference.

**RESULTS** The CTA-SS was feasible in 86% of patients (66 of 77), whereas the noninvasive FSS was feasible in 80% (53 of 66). The anatomic SS was overestimated by CTA compared with conventional angiography ( $27.6 \pm 6.4$  vs.  $25.3 \pm 6.9$ ;  $p < 0.0001$ ) whereas the calculation of the FSS yielded similar results between the noninvasive and invasive imaging modalities ( $21.6 \pm 7.8$  vs.  $21.2 \pm 8.8$ ;  $p = 0.589$ ). The noninvasive FSS reclassified 30% of patients from the high- and intermediate-SS tertiles to the low-risk tertile, whereas invasive FSS reclassified 23% of patients from the high- and intermediate-SS tertiles to the low-risk tertile. The agreement on the classic SS tertiles based on Kappa statistics was slight for the anatomic SS (Kappa = 0.19) and fair for the FSS (Kappa = 0.32). The diagnostic accuracy of  $FFR_{CT}$  to detect functional significant stenosis based on an instantaneous wave-free ratio  $\leq 0.89$  revealed an area under the receiver-operating characteristics curve of 0.85 (95% CI: 0.79 to 0.90) with a sensitivity of 95% (95% CI: 89% to 98%), specificity of 61% (95% CI: 48% to 73%), positive predictive value of 81% (95% CI: 76% to 86%), and negative predictive value of 87% (95% CI: 74% to 94%).

**CONCLUSIONS** Calculation of the noninvasive FSS is feasible and yielded similar results to those obtained with invasive pressure-wire assessment. The agreement on the SYNTAX score tertile classification improved with the inclusion of the functional component from slight to fair agreement.  $FFR_{CT}$  has good accuracy in detecting functionally significant lesions in patients with 3-vessel CAD. (A Trial to Evaluate a New Strategy in the Functional Assessment of 3-Vessel Disease Using SYNTAX II Score in Patients Treated With PCI; [NCT02015832](#)) (32).

### 21-Year Survival of Left Internal Mammary Artery–Radial Artery–Y Graft

A.G. Royle, et al.

**BACKGROUND** In 1999, Royle et al. reported on the left internal mammary artery, radial artery, Y-graft

technique (LIMA-RA-Y), which achieves total arterial revascularization (TAR). However, the most common coronary reconstruction remains LIMA and supplementary saphenous vein grafts (LIMA + SVG).

**OBJECTIVES** The goal of this study was to conduct a survival comparison of LIMA-RA-Y versus the conventional LIMA + SVG.

**METHODS** Of the original 464 LIMA-RA-Y patients reported (1996 to 1998), 346 were from the Royal Melbourne Hospital. Survival at June 2017 was compared with a group of 534 patients from 1996 to 2003 from the same institution who received LIMA + SVG, or 5,800 patients who received TAR with different grafting configurations. Propensity score matching (PSM) was performed with 1:1 matching using 26 variables. Comparisons used Kaplan-Meier (KM) and Cox proportional hazards methods. LIMA-RA-Y was compared with LIMA + SVG in which all non-left anterior descending artery grafts were performed with either composite RA or aorta-coronary SVG with no use of right internal mammary artery. We also conducted a comparison of LIMA-RA-Y versus TAR.

**RESULTS** Baseline characteristics of the LIMA-RA-Y group ( $n = 346$ ) compared with LIMA + SVG ( $n = 534$ ) after PSM ( $n = 232$  pairs) did not differ ( $3.3 \pm 0.8$  grafts per patient). Survival was worse for LIMA + SVG in the unmatched groups (KM,  $p < 0.001$ ) and for PSM groups (KM,  $p = 0.043$ ; Cox proportional hazards ratio: 1.3; 95% confidence interval: 1.0 to 1.6;  $p = 0.038$ ). Survival did not differ between LIMA-RA-Y and other TAR ( $n = 5,800$ ) patients before, or after, PSM ( $n = 332$  pairs).

**CONCLUSIONS** Use of LIMA + SVG has worse survival than LIMA-RA-Y in achieving total arterial revascularization (33).

### High Coronary Shear Stress in Patients With Coronary Artery Disease Predicts Myocardial Infarction

A. Kumar, et al.

**BACKGROUND** Coronary lesions with low fractional flow reserve (FFR) that are treated medically are associated with higher revascularization rates. High wall shear stress (WSS) has been linked with increased plaque vulnerability.

**OBJECTIVES** This study investigated the prognostic value of WSS measured in the proximal segments of lesions ( $WSS_{prox}$ ) to predict myocardial infarction (MI) in patients with stable coronary artery disease (CAD) and hemodynamically significant lesions. The authors

hypothesized that in patients with low FFR and stable CAD, higher  $WSS_{prox}$  would predict MI.

**METHODS** Among 441 patients in the FAME II (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation II) trial with  $FFR \leq 0.80$  who were randomized to medical therapy alone, 34 (8%) had subsequent MI within 3 years. Patients with vessel-related MI and adequate angiograms for 3-dimensional reconstruction ( $n = 29$ ) were propensity matched to a control group with no MI ( $n = 29$ ) by using demographic and clinical variables. Coronary lesions were divided into proximal, middle, and distal, along with 5-mm upstream and downstream segments.  $WSS$  was calculated for each segment.

**RESULTS** Median age was 62 years, and 46 (79%) were male. In the marginal Cox model, whereas lower FFR showed a trend (hazard ratio: 0.084;  $p = 0.064$ ), higher  $WSS_{prox}$  (hazard ratio: 1.234;  $p = 0.002$ , C-index = 0.65) predicted MI. Adding  $WSS_{prox}$  to FFR resulted in a significant increase in global chi-square for predicting MI ( $p = 0.045$ ), a net reclassification improvement of 0.69 ( $p = 0.005$ ), and an integrated discrimination index of 0.11 ( $p = 0.010$ ).

**CONCLUSIONS** In patients with stable CAD and hemodynamically significant lesions, higher  $WSS$  in the proximal segments of atherosclerotic lesions is predictive of MI and has incremental prognostic value over FFR (34).

### 10-Year Outcomes of Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease

Duk-Woo Park et al.

**BACKGROUND** Comparative outcomes of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) for left main coronary artery (LMCA) disease were previously reported. However, data on very long-term (>10 years) outcomes are limited.

**OBJECTIVES** The authors compare 10-year outcomes after PCI and CABG for LMCA disease.

**METHODS** In this observational study of the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization) registry, the authors evaluated 2,240 patients with unprotected LMCA disease who underwent PCI ( $n = 1,102$ ) or underwent CABG ( $n = 1,138$ ) between January 2000 and June 2006. Adverse outcomes (death; a composite outcome of death, Q-wave myocardial infarction, or stroke; and target-vessel revascularization) were compared with the use of

propensity scores and inverse-probability-weighting adjustment. The follow-up was extended to at least 10 years of all patients (median 12.0 years).

**RESULTS** In the overall cohort, there was no significant difference in adjusted risks of death and the composite outcome between the groups up to 10 years. The risk of target-vessel revascularization was significantly higher in the PCI group. In the cohort comparing drug-eluting stents and concurrent CABG, the 2 study groups did not differ significantly in the risks of death and the composite outcome at 5 years. However, after 5 years, drug-eluting stents were associated with higher risks of death (hazard ratio: 1.35; 95% confidence interval: 1.00 to 1.81) and the composite outcome (hazard ratio: 1.46; 95% confidence interval: 1.10 to 1.94) compared with CABG.

**CONCLUSIONS** In patients with significant LMCA disease, as compared with CABG, PCI showed similar rates of death and serious composite outcomes, but a higher rate of target-vessel revascularization at 10 years. However, CABG showed lower mortality and serious composite outcome rates compared with PCI with drug-eluting stents after 5 years. (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization [MAIN-COMPARE]; [NCT02791412](#)) (35).

### CVD PREVENTION & HEALTH PROMOTION

#### Sustained Physical Activity, Not Weight Loss, Associated With Improved Survival in Coronary Heart Disease

T. Moholdt, et al.

**BACKGROUND** Individuals with coronary heart disease (CHD) are recommended to be physically active and to maintain a healthy weight. There is a lack of data on how long-term changes in body mass index (BMI) and physical activity (PA) relate to mortality in this population.

**OBJECTIVES** This study sought to determine the associations among changes in BMI, PA, and mortality in individuals with CHD.

**METHODS** The authors studied 3,307 individuals (1,038 women) with CHD from the HUNT (Nord-Trøndelag Health Study) with examinations in 1985, 1996, and 2007, followed until the end of 2014. They calculated the hazard ratio (HR) for all-cause and cardiovascular disease (CVD) mortality according to changes in BMI and PA, and estimated using Cox proportional hazards regression models adjusted for

age, smoking, blood pressure, diabetes, alcohol, and self-reported health.

**RESULTS** There were 1,493 deaths during 30 years of follow-up (55% from CVD, median 15.7 years). Weight loss, classified as change in BMI  $<-0.10$  kg/m<sup>2</sup>/year, associated with increased all-cause mortality (adjusted HR: 1.30; 95% confidence interval [CI]: 1.12 to 1.50). Weight gain, classified as change in BMI  $\geq 0.10$  kg/m<sup>2</sup>/year, was not associated with increased mortality (adjusted HR: 0.97; 95% CI: 0.87 to 1.09). Weight loss only associated with increased risk in those who were normal weight at baseline (adjusted HR: 1.38; 95% CI: 1.11 to 1.72). There was a lower risk for all-cause mortality in participants who maintained low PA (adjusted HR: 0.81; 95% CI: 0.67 to 0.97) or high PA (adjusted HR: 0.64; 95% CI: 0.50 to 0.83), compared with participants who were inactive over time. CVD mortality associations were similar as for all-cause mortality.

**CONCLUSIONS** The study observed no mortality risk reductions associated with weight loss in individuals with CHD, and reduced mortality risk associated with weight gain in individuals who were normal weight at baseline. Sustained PA, however, was associated with substantial risk reduction (36).

### Cardiovascular Health Promotion: An Issue That Can No Longer Wait

J.V. Turco, et al.

There are 3 critical pathways for preventing the development and progression of cardiovascular disease (CVD): 1) primordial prevention, wherein the goal is to prevent the development of cardiovascular risk factors; 2) primary prevention, wherein the goal is to prevent the onset of CVD in persons with cardiovascular risk factors and no known disease; and 3) secondary prevention, wherein the goal is to prevent the recurrence of cardiovascular events or complications of CVD in persons diagnosed with CVD, and health promotion efforts can still be applied during this stage. The concept of primordial prevention was first introduced as a complementary approach to primary prevention of CVD in the late 1970s (1,2), and it was more recently reinforced by the American Heart Association's (AHA's) national goals for cardiovascular health (CVH) promotion and disease reduction. This document recommended 7 health factors or goals, including body mass index  $<25$  kg/m<sup>2</sup>, nonsmoking, diet with low salt and sugar intake, participating in  $\geq 30$  min of moderate to vigorous physical activity daily (on average),

untreated total cholesterol  $<200$  mg/dl, untreated blood pressure  $<120/<80$  mm Hg, and fasting blood glucose  $<100$  mg/dl (2,3). The committee members who compiled these AHA goals took into account 3 key concepts in health promotion and disease prevention: 1) the power of primordial prevention; 2) the evidence that CVD and its risk factors often develop early in life; and 3) the balance between population-level approaches for health promotion and disease prevention and individualized high-risk approaches (3). Using a range that spans the 7 goals of primordial approach (listed in the previous text), metrics were proposed for CVH status for the whole population as poor, intermediate, or ideal (3)—thus, providing a framework for the clinical community (37).

### Cardiovascular Disease Prevention by Diet Modification: JACC Health Promotion Series

E. Yu, et al.

Reduction in excess calories and improvement in dietary composition may prevent many primary and secondary cardiovascular events. Current guidelines recommend diets high in fruits, vegetables, whole grains, nuts, and legumes; moderate in low-fat dairy and seafood; and low in processed meats, sugar-sweetened beverages, refined grains, and sodium. Supplementation can be useful for some people but cannot replace a good diet. Factors that influence individuals to consume a low-quality diet are myriad and include lack of knowledge, lack of availability, high cost, time scarcity, social and cultural norms, marketing of poor-quality foods, and palatability. Governments should focus on cardiovascular disease as a global threat and enact policies that will reach all levels of society and create a food environment wherein healthy foods are accessible, affordable, and desirable. Health professionals should be proficient in basic nutritional knowledge to promote a sustainable pattern of healthful eating for cardiovascular disease prevention for both healthy individuals and those at higher risk (38).

### Midlife Cardiorespiratory Fitness and the Long-Term Risk of Mortality: 46 Years of Follow-Up

J.S.R. Clausen, et al.

**BACKGROUND** A high cardiorespiratory fitness (CRF) level is recommended to promote healthy aging. However, the association between CRF and very-long-term prognosis is unclear, and reverse causation may bias results in studies with shorter follow-up.

**OBJECTIVES** This study investigated the association between CRF and mortality in middle-aged, employed men free of cardiovascular disease (CVD).

**METHODS** Participants from the Copenhagen Male Study, established in 1970 to 1971, were included and stratified into 4 age-adjusted maximal oxygen consumption ( $V_{O_2max}$ ) categories: below the lower limit of normal (lowest 5%); low normal (45%); high normal (45%); and above the upper limit of normal (top 5%).  $V_{O_2max}$  was estimated by using a bicycle ergometer. Multivariable restricted mean survival time models were performed for all-cause and cardiovascular mortality using Danish national registers.

**RESULTS** A total of 5,107 men with a mean age of  $48.8 \pm 5.4$  years were included in the study. During the 46 years of follow-up, 4,700 (92%) men died; 2,149 (42.1%) of the men died of CVD. Compared with below the lower limit of normal CRF, low normal CRF was associated with 2.1 years (95% confidence interval [CI]: 0.7 to 3.4;  $p = 0.002$ ), high normal with 2.9 years (95% CI: 1.5 to 4.2;  $p < 0.001$ ), and above upper limit of normal with 4.9 years (95% CI: 3.1 to 6.7;  $p < 0.001$ ) longer mean life expectancy. Each unit increase in  $V_{O_2max}$  was associated with a 45-day (95% CI: 30 to 61;  $p < 0.001$ ) increase in longevity. Estimates for cardiovascular mortality were similar to all-cause mortality. Results were essentially unchanged when excluding individuals who died within the first 10 years of follow-up, suggesting a minimal role of reverse causation.

**CONCLUSIONS** CRF was significantly related to longevity over the course of 4 decades in middle-aged, employed men free of CVD. The benefits of higher midlife CRF extend well into the later part of life (39).

### Prevention and Treatment of Tobacco Use: JACC Health Promotion Series

S. Kalkhoran, et al.

Tobacco use is the leading preventable cause of death worldwide and is a major risk factor for cardiovascular disease (CVD). Both prevention of smoking initiation among youth and smoking cessation among established smokers are key for reducing smoking prevalence and the associated negative health consequences. Proven tobacco cessation treatment includes pharmacotherapy and behavioral support, which are most effective when provided together. First-line medications (varenicline, bupropion, and nicotine replacement) are effective and safe for patients with CVD. Clinicians who care

for patients with CVD should give as high a priority to treating tobacco use as to managing other CVD risk factors. Broader tobacco control efforts to raise tobacco taxes, adopt smoke-free laws, conduct mass media campaigns, and restrict tobacco marketing enhance clinicians' actions working with individual smokers (40).

### Impact of Lipids on Cardiovascular Health: JACC Health Promotion Series

B.A. Ference, et al.

People who maintain ideal cardiovascular health have a low lifetime risk of cardiovascular disease. Therefore, encouraging people to achieve ideal cardiovascular health represents an important opportunity to improve the prevention of cardiovascular disease. However, preventing cardiovascular disease by promoting ideal cardiovascular health requires shifting the focus from treating disease after it develops to preventing cardiovascular events before they happen by slowing the progression of atherosclerosis. Because atherogenic lipoproteins play a central causal role in the initiation and progression of atherosclerosis, maintaining optimal lipid levels is necessary to achieve ideal cardiovascular health. This review describes the cumulative effect of lipid-carrying lipoproteins on the risk of cardiovascular disease, estimates the magnitude of the clinical benefit that can be achieved by maintaining optimal lipid levels, identifies the most effective timing for implementing strategies designed to achieve optimal lipid levels, and provides a clinical pathway to help people achieve the lipid levels necessary for ideal cardiovascular health (41).

### Prevention and Control of Hypertension: JACC Health Promotion Series

R.M. Carey, et al.

Hypertension, the leading risk factor for cardiovascular disease, originates from combined genetic, environmental, and social determinants. Environmental factors include overweight/obesity, unhealthy diet, excessive dietary sodium, inadequate dietary potassium, insufficient physical activity, and consumption of alcohol. Prevention and control of hypertension can be achieved through targeted and/or population-based strategies. For control of hypertension, the targeted strategy involves interventions to increase awareness, treatment, and control in individuals. Corresponding population-based strategies involve interventions designed to

achieve a small reduction in blood pressure (BP) in the entire population. Having a usual source of care, optimizing adherence, and minimizing therapeutic inertia are associated with higher rates of BP control. The Chronic Care Model, a collaborative partnership among the patient, provider, and health system, incorporates a multilevel approach for control of hypertension. Optimizing the prevention, recognition, and care of hypertension requires a paradigm shift to team-based care and the use of strategies known to control BP (42).

### **Positive Psychological Well-Being and Cardiovascular Disease: JACC Health Promotion Series**

L.D. Kubzansky, et al.

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Facets of positive psychological well-being, such as optimism, have been identified as positive health assets because they are prospectively associated with the 7 metrics of cardiovascular health (CVH) and improved outcomes related to cardiovascular disease. Connections between psychological well-being and cardiovascular conditions may be mediated through biological, behavioral, and psychosocial pathways. Individual-level interventions, such as mindfulness-based programs and positive psychological interventions, have shown promise for modifying psychological well-being. Further, workplaces are using well-being-focused interventions to promote employee CVH, and these interventions represent a potential model for expanding psychological well-being programs to communities and societies. Given the relevance of psychological well-being to promoting CVH, this review outlines clinical recommendations to assess and promote well-being in encounters with patients. Finally, a research agenda is proposed. Additional prospective observational studies are needed to understand mechanisms underlying the connection between psychological well-being and cardiovascular outcomes. Moreover, rigorous intervention trials are needed to assess whether psychological well-being-promoting programs can improve cardiovascular outcomes (43).

### **Healthy Weight and Obesity Prevention: JACC Health Promotion Series**

C.J. Lavie, et al.

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Overweight and obesity have reached epidemic levels in the United States and worldwide, and this has contributed to substantial cardiovascular and other health risks. However, controversy exists concerning

the causes of obesity and effective modalities for its prevention and treatment. There is also controversy related to the concept of metabolically healthy obesity phenotype, the “obesity paradox,” and on the importance of fitness to protect individuals who are overweight or obese from cardiovascular diseases. In this state-of-the-art review, the authors focus on “healthy weight” with the emphasis on the pathophysiologic effects of weight gain on the cardiovascular system; mechanistic/triggering factors; and the role of preventive actions through personal, education/environment, and societal/authoritative factors, as well as factors to provide guidance for caregivers of health promotion. Additionally, the authors briefly review metabolically healthy obesity, the obesity paradox, and issues beyond lifestyle consideration for weight loss with medications and bariatric surgery (44).

### **Cardiorespiratory Fitness and Mortality in Healthy Men and Women**

M.T. Imboden, et al.

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**BACKGROUND** There is a well-established inverse relationship between cardiorespiratory fitness (CRF) and mortality. However, this relationship has almost exclusively been studied using estimated CRF.

**OBJECTIVES** This study aimed to assess the association of directly measured CRF, obtained using cardiopulmonary exercise (CPX) testing with all-cause, cardiovascular disease (CVD), and cancer mortality in apparently healthy men and women.

**METHODS** Participants included 4,137 self-referred apparently healthy adults (2,326 men, 1,811 women; mean age:  $42.8 \pm 12.2$  years) who underwent CPX testing to determine baseline CRF. Participants were followed for  $24.2 \pm 11.7$  years (1.1 to 49.3 years) for mortality. Cox-proportional hazard models were performed to determine the relationship of CRF ( $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and CRF level (low, moderate, and high) with mortality outcomes.

**RESULTS** During follow-up, 727 participants died (524 men, 203 women). CPX-derived CRF was inversely related to all-cause, CVD, and cancer mortality. Low CRF was associated with higher risk for all-cause (hazard ratio [HR]: 1.73; 95% confidence interval [CI]: 1.20 to 3.50), CVD (HR: 2.27; 95% CI: 1.20 to 3.49), and cancer (HR: 2.07; 95% CI: 1.18 to 3.36) mortality compared with high CRF. Further, each metabolic equivalent increment increase in CRF was associated with a 11.6%, 16.1%, and 14.0% reductions in all-cause, CVD, and cancer mortality, respectively.



**CONCLUSIONS** Given the prognostic ability of CPX-derived CRF for all-cause and disease-specific mortality outcomes, its use should be highly considered for apparently healthy populations as it may help to improve the efficacy of the individualized patient risk assessment and guide clinical decisions (45).

**Children Present a Window of Opportunity for Promoting Health: JACC Review Topic of the Week**

R. Fernandez-Jimenez, et al.

Cardiovascular disease is the leading cause of death and disability in the world, largely because of risk factors modifiable by changes in behavior. There is evolving evidence that our behavior as adults has its roots in the environment that we live in from early childhood. Early sustained multicomponent educational programs focused on health promotion in children may represent a window of opportunity to potentially prevent disease in adulthood. The integration of school-based, family-based, and community-based strategies, along with the support of public policies, are likely necessary for the success of these programs. In this review, the authors describe the future of promoting health. Specifically: 1) reasons why children should be a focus for health promotion (alarming trends of risk factors, association between unhealthy factors and subclinical disease, and cost-effectiveness); 2) strategies for health promotion in children (school-based, family-based, and community-based approaches) along with legislative efforts; and 3) research gaps are discussed (46).

**Promoting Physical Activity and Exercise: JACC Health Promotion Series**

G.F. Fletcher et al.

Physical inactivity is one of the leading modifiable risk factors for global mortality, with an estimated 20% to 30% increased risk of death compared with those who are physically active. The “behavior” of physical activity (PA) is multifactorial, including social, environmental, psychological, and genetic factors. Abundant scientific evidence has demonstrated that physically active people of all age groups and ethnicities have higher levels of cardiorespiratory fitness, health, and wellness, and a lower risk for developing several chronic medical illnesses, including cardiovascular disease, compared with those who are physically inactive. Although more

intense and longer durations of PA correlate directly with improved outcomes, even small amounts of PA provide protective health benefits. In this state-of-the-art review, the authors focus on “healthy PA” with the emphasis on the pathophysiological effects of physical inactivity and PA on the cardiovascular system, mechanistic/triggering factors, the role of preventive actions through personal, education/environment, and societal/authoritative factors, as well as factors to provide guidance for caregivers of health promotion regarding PA. Sustainable and comprehensive programs to increase PA among all individuals need to be developed and implemented at local, regional, national, and international levels to effect positive changes and improve global health, especially the reduction of cardiovascular disease (47).

**Blood Sugar Regulation for Cardiovascular Health Promotion and Disease Prevention: JACC Health Promotion Series**

P.E.H. Schwarz et al.

The primary objective of this study was to analyze the most up-to-date evidence regarding whether and how blood sugar regulation influences cardiovascular health promotion and disease prevention by carrying out an umbrella review. Three separate, systematic literature searches identified 2,343 papers in total. Overall, 44 studies were included for data extraction and analysis. The included systematic reviews and meta-analyses published between January 1, 2016, and December 31, 2017, were of good to very good quality (median Overview Quality Assessment Questionnaire score = 17). Identified evidence suggests that cardiovascular disease (CVD) prevention services should consider regulation of blood glucose as a key target for intervention. Furthermore, the recommendations for effective intervention and service development/training described here for prevention of CVD should be adopted into evidence-based practice guidelines. Multidisciplinary teams should be formed to deliver multicomponent interventions in community-based settings. There may be substantial opportunities for integrating CVD and diabetes prevention services (48).

**CV MEDICINE & SOCIETY**

**Psychopharmacology and Cardiovascular Disease**

I.L. Piña, et al.

This review discusses common mental health disorders and their associations with cardiovascular disease

risks. Commonly found mental health disorders include depression, anxiety, and personality types. The link between depression and cardiovascular disease mortality has been established. Depression is also common in patients with heart failure. In addition to discussing psychological disorders, a review of psychotropic drugs is also included. Drugs are described for therapy for depression and anxiety, as well as associations with cardiovascular drug-drug interactions. Drug-drug interactions are more common and potentially dangerous in elderly patients, in whom the conditions often coexist. The most common drug-drug interactions involve the P450 system of enzymes (49).

### **Critical Appraisal of the 2018 ACC Scientific Sessions Late-Breaking Trials From a Statistician's Perspective**

S.J. Pocock, et al.

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The late-breaking clinical trials presentations at the American College of Cardiology Scientific Sessions in March 2018 are an important contribution to the field of cardiology. This paper presents a constructive critical appraisal of 7 key studies: ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), VEST (Vest Prevention of Early Sudden Death Trial), SECURE-PCI (Statins Evaluation in Coronary Procedures and Revascularization), TREAT (Ticagrelor in Patients with ST-Elevation Myocardial Infarction treated with Pharmacological Thrombolysis), POISE (PeriOperative ISchemic Evaluation), SMART-DATE (Safety of 6-Month Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndrome), and CVD-REAL 2 (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors). For each study, our aim is to document and interpret the main findings, noting particularly when “positive spin” appears to occur, and to provide a balanced account of each study, paying attention to both constructive new findings and study limitations. These topical examples also provide useful general insights on what to look for when critiquing clinical trial presentations and publications (50).

### **Future of Personalized Cardiovascular Medicine: JACC State-of-the-Art Review**

R.M. Califf

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Previous decades have seen significant progress in the biological understanding of cardiovascular disease, as

well as major advances in computational and information technologies. However, anticipated improvements in outcomes, quality, and cost of cardiovascular medicine at the individual and population levels from these advances have lagged expectations. Further, trends showing widening gaps in the pace of technological development and its successful uptake and application in practice suggests that substantial systemic changes are needed. Recent declines in key U.S. health outcomes have added further urgency to seek scalable approaches that deliver the right treatment to the right patient and to develop information-driven policies that improve health. The clinical care and research enterprises are currently in the midst of assimilating changes entrained by a “fourth industrial revolution” marked by the convergence of biology, physical sciences, and information science. These changes, if managed appropriately, can simultaneously enable cost-effective personalized medical care as well as more effective and targeted population health interventions. In this paper derived from a lecture in honor of cardiologist Paul Dudley White, the author explores how White’s prescient insights into prevention and treatment continue to resonate today as we seek to assimilate ubiquitous computing, sophisticated sensor technologies, and bidirectional digital communication into the practice of cardiology. How the ongoing acceleration in basic science and information technologies can be wedded to the principles articulated by White as we pursue scalable approaches to personalized medicine is also examined (51).

## **HYPERTENSION**

### **2017 ACC/AHA Blood Pressure Treatment Guideline Recommendations and Cardiovascular Risk**

L.D. Colantonio, et al.

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**BACKGROUND** The 2017 American College of Cardiology/American Heart Association (ACC/AHA) blood pressure (BP) guideline provides updated recommendations for antihypertensive medication initiation and intensification.

**OBJECTIVES** Determine the risk for cardiovascular disease (CVD) events among adults recommended and not recommended antihypertensive medication initiation or intensification by the 2017 ACC/AHA BP guideline.

**METHODS** The authors analyzed data for black and white REGARDS (REasons for Geographic And Racial Differences in Stroke) study participants (age  $\geq 45$  years).

Systolic BP (SBP) and diastolic BP (DBP) were measured twice at baseline (2003 to 2007) and averaged. Participants not taking ( $n = 14,039$ ) and taking ( $n = 15,179$ ) antihypertensive medication were categorized according to their recommendations for antihypertensive medication initiation and intensification by the 2017 ACC/AHA guideline. Overall, 4,094 CVD events (stroke, coronary heart disease, and heart failure) occurred by December 31, 2014.

**RESULTS** Among participants not taking antihypertensive medication, 34.4% were recommended pharmacological antihypertensive treatment initiation. The CVD event rate per 1,000 person-years among participants recommended antihypertensive medication initiation with SBP/DBP  $\geq 140/90$  mm Hg was 22.7 (95% confidence interval [CI]: 20.3 to 25.0). Among participants with SBP/DBP 130 to 139/80 to 89 mm Hg, the CVD event rate was 20.5 (95% CI: 18.5 to 22.6) and 3.4 (95% CI: 2.4 to 4.4) for those recommended and not recommended antihypertensive medication initiation, respectively. Among participants taking antihypertensive medication, 62.8% were recommended treatment intensification. The CVD event rate per 1,000 person-years among participants recommended treatment intensification was 33.6 (95% CI: 31.5 to 35.6) and 22.4 (95% CI: 20.8 to 23.9) for those with SBP/DBP  $\geq 140/90$  mm Hg and 130 to 139/80 to 89 mm Hg, respectively.

**CONCLUSIONS** Implementing the 2017 ACC/AHA guideline would direct antihypertensive medication initiation and intensification to adults with high CVD risk (52).

## IMAGING

### PET/MR Imaging of Malondialdehyde-Acetaldehyde Epitopes With a Human Antibody Detects Clinically Relevant Atherothrombosis

M.L. Senders, et al.

**BACKGROUND** Oxidation-specific epitopes (OSEs) are proinflammatory, and elevated levels in plasma predict cardiovascular events.

**OBJECTIVES** The purpose of this study was to develop novel positron emission tomography (PET) probes to noninvasively image OSE-rich lesions.

**METHODS** An antigen-binding fragment (Fab) antibody library was constructed from human fetal cord blood. After multiple rounds of screening against malondialdehyde-acetaldehyde (MAA) epitopes, the Fab LA25 containing minimal nontemplated insertions in the CDR3 region was identified and characterized. In mice, pharmacokinetics, biodistribution, and plaque specificity studies were performed with Zirconium-89 ( $^{89}\text{Zr}$ )-labeled LA25. In

rabbits,  $^{89}\text{Zr}$ -LA25 was used in combination with an integrated clinical PET/magnetic resonance (MR) system.  $^{18}\text{F}$ -fluorodeoxyglucose PET and dynamic contrast-enhanced MR imaging were used to evaluate vessel wall inflammation and plaque neovascularization, respectively. Extensive ex vivo validation was carried out through a combination of gamma counting, near infrared fluorescence, autoradiography, immunohistochemistry, and immunofluorescence.

**RESULTS** LA25 bound specifically to MAA epitopes in advanced and ruptured human atherosclerotic plaques with accompanying thrombi and in debris from distal protection devices. PET/MR imaging 24 h after injection of  $^{89}\text{Zr}$ -LA25 showed increased uptake in the abdominal aorta of atherosclerotic rabbits compared with nonatherosclerotic control rabbits, confirmed by ex vivo gamma counting and autoradiography.  $^{18}\text{F}$ -fluorodeoxyglucose PET, dynamic contrast-enhanced MR imaging, and near-infrared fluorescence signals were also significantly higher in atherosclerotic rabbit aortas compared with control aortas. Enhanced liver uptake was also noted in atherosclerotic animals, confirmed by the presence of MAA epitopes by immunostaining.

**CONCLUSIONS**  $^{89}\text{Zr}$ -LA25 is a novel PET radiotracer that may allow noninvasive phenotyping of high-risk OSE-rich lesions (53).

### Coronary Adventitial and Perivascular Adipose Tissue Inflammation in Patients With Vasospastic Angina

K. Ohyama, et al.

**BACKGROUND** Recent studies suggested that perivascular components, such as perivascular adipose tissue (PVAT) and adventitial vasa vasorum (VV), play an important role as a source of various inflammatory mediators in cardiovascular disease.

**OBJECTIVES** The authors tested their hypothesis that coronary artery spasm is associated with perivascular inflammation in patients with vasospastic angina (VSA) using  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography/computed tomography (PET/CT).

**METHODS** This study prospectively examined 27 consecutive VSA patients with acetylcholine-induced diffuse spasm in the left anterior descending artery (LAD) and 13 subjects with suspected angina but without organic coronary lesions or coronary spasm. Using CT coronary angiography and electrocardiogram-gated  $^{18}\text{F}$ -FDG PET/CT, coronary PVAT volume and coronary perivascular FDG uptake

in the LAD were examined. In addition, adventitial VV formation in the LAD was examined with optical coherence tomography, and Rho-kinase activity was measured in circulating leukocytes.

**RESULTS** Patient characteristics were comparable between the 2 groups. CT coronary angiography and ECG-gated  $^{18}\text{F}$ -FDG PET/CT showed that coronary PVAT volume and coronary perivascular FDG uptake significantly increased in the VSA group compared with the non-VSA group. Furthermore, optical coherence tomography showed that adventitial VV formation significantly increased in the VSA group compared with the non-VSA group, as did Rho-kinase activity. Importantly, during the follow-up period with medical treatment, both coronary perivascular FDG uptake and Rho-kinase activity significantly decreased in the VSA group.

**CONCLUSIONS** These results provide the first evidence that coronary spasm is associated with inflammation of coronary adventitia and PVAT, where  $^{18}\text{F}$ -FDG PET/CT could be useful for disease activity assessment. (Morphological and Functional Change of Coronary Perivascular Adipose Tissue in Vasospastic Angina [ADIPO-VSA Trial]; [UMIN000016675](#)) (54).

### **$^{18}\text{F}$ -Sodium Fluoride Uptake in Abdominal Aortic Aneurysms: The SoFIA<sup>3</sup> Study**

R.O. Forsythe, et al.

**BACKGROUND** Fluorine-18-sodium fluoride ( $^{18}\text{F}$ -NaF) uptake is a marker of active vascular calcification associated with high-risk atherosclerotic plaque.

**OBJECTIVES** In patients with abdominal aortic aneurysm (AAA), the authors assessed whether  $^{18}\text{F}$ -NaF positron emission tomography (PET) and computed tomography (CT) predicts AAA growth and clinical outcomes.

**METHODS** In prospective case-control ( $n = 20$  per group) and longitudinal cohort ( $n = 72$ ) studies, patients with AAA (aortic diameter  $>40$  mm) and control subjects (aortic diameter  $<30$  mm) underwent abdominal ultrasound,  $^{18}\text{F}$ -NaF PET-CT, CT angiography, and calcium scoring. Clinical endpoints were aneurysm expansion and the composite of AAA repair or rupture.

**RESULTS** Fluorine-18-NaF uptake was increased in AAA compared with nonaneurysmal regions within the same aorta ( $p = 0.004$ ) and aortas of control subjects ( $p = 0.023$ ). Histology and micro-PET-CT demonstrated that  $^{18}\text{F}$ -NaF uptake localized to areas of aneurysm disease and active calcification. In 72

patients within the longitudinal cohort study (mean age  $73 \pm 7$  years, 85% men, baseline aneurysm diameter  $48.8 \pm 7.7$  mm), there were 19 aneurysm repairs (26.4%) and 3 ruptures (4.2%) after  $510 \pm 196$  days. Aneurysms in the highest tertile of  $^{18}\text{F}$ -NaF uptake expanded  $2.5\times$  more rapidly than those in the lowest tertile (3.10 [interquartile range (IQR): 2.34 to 5.92 mm/year] vs. 1.24 [IQR: 0.52 to 2.92 mm/year];  $p = 0.008$ ) and were nearly  $3\times$  as likely to experience AAA repair or rupture (15.3% vs. 5.6%; log-rank  $p = 0.043$ ).

**CONCLUSIONS** Fluorine-18-NaF PET-CT is a novel and promising approach to the identification of disease activity in patients with AAA and is an additive predictor of aneurysm growth and future clinical events. (Sodium Fluoride Imaging of Abdominal Aortic Aneurysms [SoFIA<sup>3</sup>]; [NCT02229006](#); Magnetic Resonance Imaging [MRI] for Abdominal Aortic Aneurysms to Predict Rupture or Surgery: The MA3RS Trial; [ISRCTN76413758](#)) (55).

### **Late Gadolinium Enhancement in Patients With Hypertrophic Cardiomyopathy and Preserved Systolic Function**

A. Mentias, et al.

**BACKGROUND** A high proportion of patients with hypertrophic cardiomyopathy (HCM) have evidence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR).

**OBJECTIVES** This study sought to assess the incremental prognostic utility of LGE in patients with HCM.

**METHODS** We studied 1,423 consecutive low-/intermediate-risk patients with HCM (age  $\geq 18$  years) with preserved left ventricular (LV) ejection fraction (mean age  $66 \pm 14$  years, 60% men) who underwent transthoracic echocardiography (TTE) (including dimensions and LV outflow tract gradients) and CMR (including LGE as a % of LV mass) at our center between January 2008 and December 2015. The primary composite endpoint was sudden cardiac death (SCD) and appropriate implantable cardioverter-defibrillator discharge. The percent 5-year SCD risk score was calculated.

**RESULTS** The mean 5-year SCD risk score was  $2.3 \pm 2.0$ . Mean maximal LV outflow tract gradient (TTE) was  $70 \pm 55$  mm Hg (median 74 mm Hg [interquartile range (IQR): 10 to 67 mm Hg]); indexed LV mass and LGE (both on CMR) were  $91 \pm 10$  g/m<sup>2</sup> and  $8.4 \pm 12\%$  (IQR: 0% to 19%); 50% had LGE on CMR. Of these, 458 were nonobstructive and 965 were obstructive (of which 686 were underwent myectomy). At  $4.7 \pm 2.0$  years of

follow-up, 60 (4%) met the composite endpoint. On quadratic spline analysis, LGE  $\geq 15\%$  was associated with increased risk of composite events. In the obstructive subgroup, on competing risk regression analysis,  $\geq 15\%$  LGE (subhazard ratio: 3.04 [95% confidence interval: 1.48 to 6.10]) was associated with a higher rate and myectomy (subhazard ratio: 0.44 [95% confidence interval: 0.20 to 0.76]) was associated with a lower rate of composite endpoints (both  $p < 0.01$ ). Similarly, sequential addition of LGE  $\geq 15\%$  and myectomy to % 5-year SCD risk score improved the log likelihood ratios from  $-227.85$  to  $-219.14$  (chi-square 17) and to  $-215.14$  (chi-square 8; both  $p < 0.01$ ). Association of %LGE with composite events was similar even in myectomy and nonobstructive subgroups.

**CONCLUSIONS** In low-/intermediate-risk adult patients with HCM (obstructive, myectomy, and non-obstructive subgroups) with preserved systolic function, %LGE was significantly associated with a higher rate of composite endpoint, providing incremental prognostic utility (56).

### Coronary CT Angiographic and Flow Reserve-Guided Management of Patients With Stable Ischemic Heart Disease

B.L. Nørgaard, et al.

**BACKGROUND** Clinical outcomes following coronary computed tomography-derived fractional flow reserve (FFR<sub>CT</sub>) testing in clinical practice are unknown.

**OBJECTIVES** This study sought to assess real-world clinical outcomes following a diagnostic strategy including first-line coronary computed tomography angiography (CTA) with selective FFR<sub>CT</sub> testing.

**METHODS** The study reviewed the results of 3,674 consecutive patients with stable chest pain evaluated with CTA and FFR<sub>CT</sub> testing to guide downstream management in patients with intermediate stenosis (30% to 70%). The composite endpoint (all-cause death, myocardial infarction, hospitalization for unstable angina, and unplanned revascularization) was determined in 4 patient groups: 1) CTA stenosis  $< 30\%$ , optimal medical treatment (OMT), and no additional testing; 2) FFR<sub>CT</sub>  $> 0.80$ , OMT, no additional testing; 3) FFR<sub>CT</sub>  $\leq 0.80$ , OMT, no additional testing; and 4) FFR<sub>CT</sub>  $\leq 0.80$ , OMT, and referral to invasive coronary angiography. Patients were followed for a median of 24 (range 8 to 41) months.

**RESULTS** FFR<sub>CT</sub> was available in 677 patients, and the test result was negative ( $> 0.80$ ) in 410 (61%) patients. In 75% of the patients with FFR<sub>CT</sub>  $> 0.80$ , maximum coronary stenosis was  $\geq 50\%$ . The cumulative incidence proportion (95% confidence interval [CI]) of the composite endpoint at the end of follow-up was comparable in groups 1 (2.8%; 95% CI: 1.4% to 4.9%) and 2 (3.9%; 95% CI: 2.0% to 6.9%) ( $p = 0.58$ ) but was higher (when compared with group 1) in groups 3 (9.4%;  $p = 0.04$ ) and 4 (6.6%;  $p = 0.08$ ). Risk of myocardial infarction was lower in group 4 (1.3%) than in group 3 (8%;  $p < 0.001$ ).

**CONCLUSIONS** In patients with intermediate-range coronary stenosis, FFR<sub>CT</sub> is effective in differentiating patients who do not require further diagnostic testing or intervention (FFR<sub>CT</sub>  $> 0.80$ ) from higher-risk patients (FFR<sub>CT</sub>  $\leq 0.80$ ) in whom further testing with invasive coronary angiography and possibly intervention may be needed. Further studies assessing the risk and optimal management strategy in patients undergoing first-line CTA with selective FFR<sub>CT</sub> testing are needed (57).

### Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review

V.R. Taqueti, et al.

Coronary microvascular disease (CMD) refers to the subset of disorders affecting the structure and function of the coronary microcirculation, is prevalent in patients across a broad spectrum of cardiovascular risk factors, and is associated with an increased risk of adverse events. Contemporary evidence supports that most patients with CMD also have macrovessel atherosclerosis, which has important implications for their prognosis and management. In this state-of-the-art review, the authors summarize the pathophysiology of CMD, provide an update of diagnostic testing strategies, and classify CMD into phenotypes according to severity and coexistence with atherosclerosis. They examine emerging data highlighting the significance of CMD in specific populations, including obesity and insulin resistance, myocardial injury and heart failure with preserved ejection fraction, and nonobstructive and obstructive coronary artery disease. Finally, they discuss the role of CMD as a potential target for novel interventions beyond conventional approaches, representing a new frontier in cardiovascular disease reduction (58).



### **Coronary Physiology Beyond Coronary Flow Reserve in Microvascular Angina: JACC State-of-the-Art Review**

K.L. Gould, et al.

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Angina with no angiographic stenosis, commonly called “microvascular angina,” encompasses a wide continuum of coronary pathophysiology in conflicting published reports. Comprehensive quantitative myocardial perfusion offers new insights beyond overly simplistic coronary flow reserve. Integrating regional absolute stress flow, relative stress flow, coronary flow reserve, and qualitative subendocardial perfusion gradient on tomograms of relative images, provides correct diagnosis, quantitative physiological classification, and potential treatment. Angina without angiographic stenosis is associated with abnormal quantitative perfusion with rare, but instructive, exceptions. However, microvascular dysfunction without angina is common, particularly associated with risk factors. Reduced subendocardial/epicardial relative activity is common with diffuse coronary artery disease without focal stenosis with or without angina depending on the severity of reduced subendocardial perfusion. Precision quantitative myocardial perfusion in 5,900 cases objectively classifies angina with no angiographic stenosis into 4 categories: subendocardial ischemia due to diffuse coronary artery disease (most common), overlooked stenosis, diffuse microvascular dysfunction due to risk factors or specific microvasculopathies, and nonischemic cardiac pain mechanisms (rare), or some mix of these prototypes, of which 95% associate with risk factors, or subclinical or clinically manifest coronary atherosclerosis needing vigorous risk factor treatment (59).

### **Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations**

V.M. Ferreira, et al.

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This JACC Scientific Expert Panel provides consensus recommendations for an update of the cardiovascular magnetic resonance (CMR) diagnostic criteria for myocardial inflammation in patients with suspected acute or active myocardial inflammation (Lake Louise Criteria) that include options to use parametric mapping techniques. While each parameter may indicate myocardial inflammation, the authors propose that CMR provides strong evidence for myocardial inflammation, with increasing specificity, if the CMR scan demonstrates the combination of

myocardial edema with other CMR markers of inflammatory myocardial injury. This is based on at least one T2-based criterion (global or regional increase of myocardial T2 relaxation time or an increased signal intensity in T2-weighted CMR images), with at least one T1-based criterion (increased myocardial T1, extracellular volume, or late gadolinium enhancement). While having both a positive T2-based marker and a T1-based marker will increase specificity for diagnosing acute myocardial inflammation, having only one (i.e., T2-based OR T1-based) marker may still support a diagnosis of acute myocardial inflammation in an appropriate clinical scenario, albeit with less specificity. The update is expected to improve the diagnostic accuracy of CMR further in detecting myocardial inflammation (60).

## **METABOLIC & LIPID DISORDERS**

### **Obesity: Pathophysiology and Management**

K.M. Gadde, et al.

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Obesity continues to be among the top health concerns across the globe. Despite our failure to contain the high prevalence of obesity, we now have a better understanding of its pathophysiology, and how excess adiposity leads to type 2 diabetes, hypertension, and cardiovascular disease. Lifestyle modification is recommended as the cornerstone of obesity management, but many patients do not achieve long-lasting benefits due to difficulty with adherence as well as physiological and neurohormonal adaptation of the body in response to weight loss. Fortunately, 5 drug therapies—orlistat, lorcaserin, liraglutide, phentermine/topiramate, and naltrexone/bupropion—are available for long-term weight management. Additionally, several medical devices are available for short-term and long-term use. Bariatric surgery yields substantial and sustained weight loss with resolution of type 2 diabetes, although due to the high cost and a small risk of serious complications, it is generally recommended for patients with severe obesity. Benefit-to-risk balance should guide treatment decisions (61).

### **Autosomal Recessive Hypercholesterolemia: Long-Term Cardiovascular Outcomes**

L. D’Erasmus, et al.

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**BACKGROUND** Autosomal recessive hypercholesterolemia (ARH) is a rare lipid disorder characterized by premature atherosclerotic cardiovascular disease (ASCVD). There are sparse data for clinical management and cardiovascular outcomes in ARH.

**OBJECTIVES** Evaluation of changes in lipid management, achievement of low-density lipoprotein cholesterol (LDL-C) goals and cardiovascular outcomes in ARH.

**METHODS** Published ARH cases were identified by electronic search. All corresponding authors and physicians known to treat these patients were asked to provide follow-up information, using a standardized protocol.

**RESULTS** We collected data for 52 patients (28 females, 24 males;  $31.1 \pm 17.1$  years of age; baseline LDL-C:  $571.9 \pm 171.7$  mg/dl). During a mean follow-up of  $14.1 \pm 7.3$  years, there was a significant increase in the use of high-intensity statin and ezetimibe in combination with lipoprotein apheresis; in 6 patients, lomitapide was also added. Mean LDL-C achieved at nadir was  $164.0 \pm 85.1$  mg/dl ( $-69.6\%$  from baseline), with a better response in patients taking lomitapide ( $-88.3\%$ ). Overall, 23.1% of ARH patients reached LDL-C of  $<100$  mg/dl. During follow-up, 26.9% of patients had incident ASCVD, and 11.5% had a new diagnosis of aortic valve stenosis (absolute risk per year of 1.9% and 0.8%, respectively). No incident stroke was observed. Age ( $\geq 30$  years) and the presence of coronary artery disease at diagnosis were the major predictors of incident ASCVD.

**CONCLUSIONS** Despite intensive treatment, LDL-C in ARH patients remains far from targets, and this translates into a poor long-term cardiovascular prognosis. Our data highlight the importance of an early diagnosis and treatment and confirm the fact that an effective treatment protocol for ARH is still lacking (62).

### Lipids, Lipoproteins, and Metabolites and Risk of Myocardial Infarction and Stroke

M.V. Holmes, et al.

**BACKGROUND** Blood lipids are established risk factors for myocardial infarction (MI), but uncertainty persists about the relevance of lipids, lipoprotein particles, and circulating metabolites for MI and stroke subtypes.

**OBJECTIVES** This study sought to investigate the associations of plasma metabolic markers with risks of incident MI, ischemic stroke (IS), and intracerebral hemorrhage (ICH).

**METHODS** In a nested case-control study (912 MI, 1,146 IS, and 1,138 ICH cases, and 1,466 common control subjects) 30 to 79 years of age in China Kadoorie Biobank, nuclear magnetic resonance spectroscopy measured 225 metabolic markers in

baseline plasma samples. Logistic regression was used to estimate adjusted odds ratios (ORs) for a 1-SD higher metabolic marker.

**RESULTS** Very low-, intermediate-, and low-density lipoprotein particles were positively associated with MI and IS. High-density lipoprotein (HDL) particles were inversely associated with MI apart from small HDL. In contrast, no lipoprotein particles were associated with ICH. Cholesterol in large HDL was inversely associated with MI and IS (OR: 0.79 and 0.88, respectively), whereas cholesterol in small HDL was not (OR: 0.99 and 1.06, respectively). Triglycerides within all lipoproteins, including most HDL particles, were positively associated with MI, with a similar pattern for IS. Glycoprotein acetyls, ketone bodies, glucose, and docosahexaenoic acid were associated with all 3 diseases. The 225 metabolic markers showed concordant associations between MI and IS, but not with ICH.

**CONCLUSIONS** Lipoproteins and lipids showed similar associations with MI and IS, but not with ICH. Within HDL particles, cholesterol concentrations were inversely associated, whereas triglyceride concentrations were positively associated with MI. Glycoprotein acetyls and several non-lipid-related metabolites associated with all 3 diseases (63).

### Metabolic Surgery: Weight Loss, Diabetes, and Beyond

M. Pareek, et al.

The alarming rise in the worldwide prevalence of obesity is paralleled by an increasing burden of type 2 diabetes mellitus. Metabolic surgery is the most effective means of obtaining substantial and durable weight loss in individuals with obesity. Randomized trials have recently shown the superiority of surgery over medical treatment alone in achieving improved glycemic control, as well as a reduction in cardiovascular risk factors. The mechanisms seem to extend beyond the magnitude of weight loss alone and include improvements in incretin profiles, insulin secretion, and insulin sensitivity. Moreover, observational data suggest that the reduction in cardiovascular risk factors translates to better patient outcomes. This review describes commonly used metabolic surgical procedures and their current indications and summarizes the evidence related to weight loss and glycemic outcomes. It further examines their potential effects on cardiovascular outcomes and mortality and discusses future perspectives (64).

## Metabolically Healthy Obesity, Transition to Metabolic Syndrome, and Cardiovascular Risk

M. Mongraw-Chaffin, et al.

**BACKGROUND** Debate over the cardiometabolic risk associated with metabolically healthy obesity (MHO) continues. Many studies have investigated this relationship by examining MHO at baseline with longitudinal follow-up, with inconsistent results.

**OBJECTIVES** The authors hypothesized that MHO at baseline is transient and that transition to metabolic syndrome (MetS) and duration of MetS explains heterogeneity in incident cardiovascular disease (CVD) and all-cause mortality.

**METHODS** Among 6,809 participants of the MESA (Multi-Ethnic Study of Atherosclerosis) the authors used Cox proportional hazards and logistic regression models to investigate the joint association of obesity ( $\geq 30$  kg/m<sup>2</sup>) and MetS (International Diabetes Federation consensus definition) with CVD and mortality across a median of 12.2 years. We tested for interaction and conducted sensitivity analyses for a number of conditions.

**RESULTS** Compared with metabolically healthy normal weight, baseline MHO was not significantly associated with incident CVD; however, almost one-half of those participants developed MetS during follow-up (unstable MHO). Those who had unstable MHO had increased odds of CVD (odds ratio [OR]: 1.60; 95% confidence interval [CI]: 1.14 to 2.25), compared with those with stable MHO or healthy normal weight. Dose response for duration of MetS was significantly and linearly associated with CVD (1 visit with MetS OR: 1.62; 95% CI: 1.27 to 2.07; 2 visits, OR: 1.92; 95% CI: 1.48 to 2.49; 3+ visits, OR: 2.33; 95% CI: 1.89 to 2.87; p value for trend <0.001) and MetS mediated approximately 62% (44% to 100%) of the relationship between obesity at any point during follow-up and CVD.

**CONCLUSIONS** Metabolically healthy obesity is not a stable or reliable indicator of future risk for CVD. Weight loss and lifestyle management for CVD risk factors should be recommended to all individuals with obesity (65).

## Genetic Variants in *SGLT1*, Glucose Tolerance, and Cardiometabolic Risk

S.B. Seidelmann, et al.

**BACKGROUND** Loss-of-function mutations in the *SGLT1* (sodium/glucose co-transporter-1) gene result in a rare glucose/galactose malabsorption disorder

and neonatal death if untreated. In the general population, variants related to intestinal glucose absorption remain uncharacterized.

**OBJECTIVES** The goal of this study was to identify functional *SGLT1* gene variants and characterize their clinical consequences.

**METHODS** Whole exome sequencing was performed in the ARIC (Atherosclerosis Risk in Communities) study participants enrolled from 4 U.S. communities. The association of functional, nonsynonymous substitutions in *SGLT1* with 2-h oral glucose tolerance test results was determined. Variants related to impaired glucose tolerance were studied, and Mendelian randomization analysis of cardiometabolic outcomes was performed.

**RESULTS** Among 5,687 European-American subjects (mean age  $54 \pm 6$  years; 47% male), those who carried a haplotype of 3 missense mutations (frequency of 6.7%)—Asn51Ser, Ala411Thr, and His615Gln—had lower 2-h glucose and odds of impaired glucose tolerance than noncarriers ( $\beta$ -coefficient:  $-8.0$ ; 95% confidence interval [CI]:  $-12.7$  to  $-3.3$ ; OR: 0.71; 95% CI: 0.59 to 0.86, respectively). The association of the haplotype with oral glucose tolerance test results was consistent in a replication sample of 2,791 African-American subjects ( $\beta = -16.3$ ; 95% CI:  $-36.6$  to 4.1; OR: 0.39; 95% CI: 0.17 to 0.91) and an external European-Finnish population sample of 6,784 subjects ( $\beta = -3.2$ ; 95% CI:  $-6.4$  to  $-0.02$ ; OR: 0.81; 95% CI: 0.68 to 0.98). Using a Mendelian randomization approach in the index cohort, the estimated 25-year effect of a reduction of 20 mg/dl in 2-h glucose via *SGLT1* inhibition would be reduced prevalent obesity (OR: 0.43; 95% CI: 0.23 to 0.63), incident diabetes (hazard ratio [HR]: 0.58; 95% CI: 0.35 to 0.81), heart failure (HR: 0.53; 95% CI: 0.24 to 0.83), and death (HR: 0.66; 95% CI: 0.42 to 0.90).

**CONCLUSIONS** Functionally damaging missense variants in *SGLT1* protect from diet-induced hyperglycemia in multiple populations. Reduced intestinal glucose uptake may protect from long-term cardiometabolic outcomes, providing support for therapies that target *SGLT1* function to prevent and treat metabolic conditions (66).

## Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes: JACC State-of-the-Art Review

T.A. Zelniker, et al.

Patients with type 2 diabetes mellitus have an increased risk for the development of cardiac and

other vascular events, heart failure (HF), and decline in renal function. After several large cardiovascular outcome trials with mostly neutral results, 2 studies of the sodium-glucose co-transporter 2 inhibitors (SGLT2is), empagliflozin and canagliflozin, reported favorable effects on the primary endpoint, a composite of myocardial infarction, stroke, and cardiovascular death. In addition, reductions of hospitalizations for HF were observed; in the case of empagliflozin, reductions in both cardiovascular mortality and total mortality occurred. These findings prompted several analyses to elucidate the mechanisms of action of SGLT2is and have initiated several large clinical trials in patients with HF without type 2 diabetes mellitus. This review summarizes known and possible mechanisms that contribute to these salutary effects of SGLT2is. Also discussed is the interplay between cardiac and renal function, as well as safety issues associated with this class of drugs (67).

### Associations of Body Mass and Fat Indexes With Cardiometabolic Traits

J.A. Bell, et al.

**BACKGROUND** Body mass index (BMI) is criticized for not distinguishing fat from lean mass and ignoring fat distribution, leaving its ability to detect health effects unclear.

**OBJECTIVES** The aim of this study was to compare BMI with total and regional fat indexes from dual-energy x-ray absorptiometry in their associations with cardiometabolic traits. Duration of exposure to and change in each index across adolescence were examined in relation to detailed traits in young adulthood.

**METHODS** BMI was examined alongside total, trunk, arm, and leg fat indexes (each in kilograms per square meter) from dual-energy x-ray absorptiometry at ages 10 and 18 years in relation to 230 traits from targeted metabolomics at age 18 years in 2,840 offspring from the Avon Longitudinal Study of Parents and Children.

**RESULTS** Higher total fat mass index and BMI at age 10 years were similarly associated with cardiometabolic traits at age 18 years, including higher systolic and diastolic blood pressure, higher very low-density lipoprotein and low-density lipoprotein cholesterol, lower high-density lipoprotein cholesterol, higher triglycerides, and higher insulin and glycoprotein acetyls. Associations were stronger for both indexes measured at age 18 years and for gains in each index from age 10 to 18 years (e.g.,

0.45 SDs [95% confidence interval: 0.38 to 0.53] in glycoprotein acetyls per SD unit gain in fat mass index vs. 0.38 SDs [95% confidence interval: 0.27 to 0.48] per SD unit gain in BMI). Associations resembled those for trunk fat index. Higher lean mass index was weakly associated with traits and was not protective against higher fat mass index.

**CONCLUSIONS** The results of this study support abdominal fatness as a primary driver of cardiometabolic dysfunction and BMI as a useful tool for detecting its effects (68).

### Association of Serum Cholesterol Efflux Capacity With Mortality in Patients With ST-Segment Elevation Myocardial Infarction

M. Guerin, et al.

**BACKGROUND** Serum cholesterol efflux capacity, a biomarker that integrates contributors and modulators of the initial step of the reverse cholesterol transport, has been associated with atherosclerosis independently of high-density lipoprotein (HDL) cholesterol level.

**OBJECTIVES** The authors evaluated the prognostic impact of serum cholesterol efflux capacity on mortality in a large cohort of patients hospitalized for an acute myocardial infarction (MI).

**METHODS** Serum cholesterol efflux capacity, cholesteryl ester transfer protein (CETP) activity, total cholesterol, low-density lipoprotein cholesterol, HDL cholesterol, and triglyceride levels were measured in 1,609 consecutive patients admitted with an acute MI. The primary endpoint was all-cause mortality evaluated at 6 years with a median follow-up of 1.9 years (interquartile range: 1.5 to 4.2 years). An analysis by quartile of serum cholesterol efflux capacity was also performed.

**RESULTS** In a fully adjusted model that included age, sex, traditional cardiovascular risk factors including lipid levels, and prognostic factors of MI, serum cholesterol efflux capacity was a strong predictor of survival (adjusted hazard ratio for mortality per 1-SD increase in serum cholesterol efflux capacity, 0.79; 95% confidence interval: 0.66 to 0.95;  $p = 0.0132$ ). Patients displaying an elevated serum cholesterol efflux capacity had a marked lower rate of mortality at 6 years (adjusted hazard ratio: 0.54 [0.32 to 0.89];  $p = 0.0165$ ) as compared with patients with reduced serum cholesterol efflux capacity.

**CONCLUSIONS** Serum cholesterol efflux capacity, an integrative marker of reverse cholesterol transport pathway and efficacy, was inversely associated with

all-cause mortality in MI patients independently of HDL cholesterol level and other risk factors (69).

### Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel

A.C. Sturm, et al.

Although awareness of familial hypercholesterolemia (FH) is increasing, this common, potentially fatal, treatable condition remains underdiagnosed. Despite FH being a genetic disorder, genetic testing is rarely used. The Familial Hypercholesterolemia Foundation convened an international expert panel to assess the utility of FH genetic testing. The rationale includes the following: 1) facilitation of definitive diagnosis; 2) pathogenic variants indicate higher cardiovascular risk, which indicates the potential need for more aggressive lipid lowering; 3) increase in initiation of and adherence to therapy; and 4) cascade testing of at-risk relatives. The Expert Consensus Panel recommends that FH genetic testing become the standard of care for patients with definite or probable FH, as well as for their at-risk relatives. Testing should include the genes encoding the low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*), and proprotein convertase subtilisin/kexin 9 (*PCSK9*); other genes may also need to be considered for analysis based on patient phenotype. Expected outcomes include greater diagnoses, more effective cascade testing, initiation of therapies at earlier ages, and more accurate risk stratification (70).

### Cardiovascular Risk and Statin Eligibility of Young Adults After an MI: Partners YOUNG-MI Registry

A. Singh, et al.

**BACKGROUND** Despite significant progress in primary prevention, the rate of MI has not declined in young adults.

**OBJECTIVES** The purpose of this study was to evaluate statin eligibility based on the 2013 American College of Cardiology/American Heart Association guidelines for treatment of blood cholesterol and 2016 U.S. Preventive Services Task Force recommendations for statin use in primary prevention in a cohort of adults who experienced a first-time myocardial infarction (MI) at a young age.

**METHODS** The YOUNG-MI registry is a retrospective cohort from 2 large academic centers, which includes patients who experienced an MI at age  $\leq 50$  years. Diagnosis of type 1 MI was adjudicated by study

physicians. Pooled cohort risk equations were used to estimate atherosclerotic cardiovascular disease risk score based on data available prior to MI or at the time of presentation.

**RESULTS** Of 1,685 patients meeting inclusion criteria, 210 (12.5%) were on statin therapy prior to MI and were excluded. Among the remaining 1,475 individuals, the median age was 45 years, there were 294 (20%) women, and 846 (57%) had ST-segment elevation MI. At least 1 cardiovascular risk factor was present in 1,225 (83%) patients. The median 10-year atherosclerotic cardiovascular disease risk score of the cohort was 4.8% (interquartile range: 2.8% to 8.0%). Only 724 (49%) and 430 (29%) would have met criteria for statin eligibility per the 2013 American College of Cardiology/American Heart Association guidelines and 2016 U.S. Preventive Services Task Force recommendations, respectively. This finding was even more pronounced in women, in whom 184 (63%) were not eligible for statins by either guideline, compared with 549 (46%) men ( $p < 0.001$ ).

**CONCLUSIONS** The vast majority of adults who present with an MI at a young age would not have met current guideline-based treatment thresholds for statin therapy prior to their MI. These findings highlight the need for better risk assessment tools among young adults (71).

### Impact of Statins on Cardiovascular Outcomes Following Coronary Artery Calcium Scoring

J.D. Mitchell, et al.

**BACKGROUND** Compared with traditional risk factors, coronary artery calcium (CAC) scores improve prognostic accuracy for atherosclerotic cardiovascular disease (ASCVD) outcomes. However, the relative impact of statins on ASCVD outcomes stratified by CAC scores is unknown.

**OBJECTIVES** The authors sought to determine whether CAC can identify patients most likely to benefit from statin treatment.

**METHODS** The authors identified consecutive subjects without pre-existing ASCVD or malignancy who underwent CAC scoring from 2002 to 2009 at Walter Reed Army Medical Center. The primary outcome was first major adverse cardiovascular event (MACE), a composite of acute myocardial infarction, stroke, and cardiovascular death. The effect of statin therapy on outcomes was analyzed stratified by CAC presence and severity, after adjusting for baseline comorbidities with inverse probability of treatment weights based on propensity scores.



**RESULTS** A total of 13,644 patients (mean age 50 years; 71% men) were followed for a median of 9.4 years. Comparing patients with and without statin exposure, statin therapy was associated with reduced risk of MACE in patients with CAC (adjusted subhazard ratio: 0.76; 95% confidence interval: 0.60 to 0.95;  $p = 0.015$ ), but not in patients without CAC (adjusted subhazard ratio: 1.00; 95% confidence interval: 0.79 to 1.27;  $p = 0.99$ ). The effect of statin use on MACE was significantly related to the severity of CAC ( $p < 0.0001$  for interaction), with the number needed to treat to prevent 1 initial MACE outcome over 10 years ranging from 100 (CAC 1 to 100) to 12 (CAC  $>100$ ).

**CONCLUSIONS** In a largescale cohort without baseline ASCVD, the presence and severity of CAC identified patients most likely to benefit from statins for the primary prevention of cardiovascular diseases (72).

## RHYTHM DISORDERS

### Role of Stress Kinase JNK in Binge Alcohol-Evoked Atrial Arrhythmia

J. Yan, et al.

**BACKGROUND** Excessive binge alcohol drinking has acute cardiac arrhythmogenic effects, including promotion of atrial fibrillation (AF), which underlies “Holiday Heart Syndrome.” The mechanism that couples binge alcohol abuse with AF susceptibility remains unclear. We previously reported stress-activated c-Jun N-terminal kinase (JNK) signaling contributes to AF development. This is interesting because JNK is implicated in alcohol-caused organ malfunction beyond the heart.

**OBJECTIVES** The purpose of this study was to detail how JNK promotes binge alcohol-evoked susceptibility to AF.

**METHODS** The authors found binge alcohol-exposure leads to activated JNK, specifically JNK2. Furthermore, binge alcohol induces AF, higher incidence of diastolic intracellular  $Ca^{2+}$  activity ( $Ca^{2+}$  waves, sarcoplasmic reticulum [SR]  $Ca^{2+}$  leakage), and membrane voltage ( $V_m$ ) and systolic  $Ca^{2+}$  release spatiotemporal heterogeneity ( $\Delta t_{V_m-Ca}$ ). These changes were completely eliminated by JNK inhibition both in vivo and in vitro. Calmodulin kinase II (CaMKII) is a proarrhythmic molecule known to drive SR  $Ca^{2+}$  mishandling.

**RESULTS** The authors report for the first time that binge alcohol activates JNK2, which subsequently phosphorylates the CaMKII protein, enhancing

CaMKII-driven SR  $Ca^{2+}$  mishandling. CaMKII inhibition eliminates binge alcohol-evoked arrhythmic activities.

**CONCLUSIONS** Our studies demonstrate that binge alcohol exposure activates JNK2 in atria, which then drives CaMKII activation, prompting aberrant  $Ca^{2+}$  waves and, thus, enhanced susceptibility to atrial arrhythmia. Our results reveal a previously unrecognized form of alcohol-driven kinase-on-kinase proarrhythmic crosstalk. Atrial JNK2 function represents a potential novel therapeutic target to treat and/or prevent AF (73).

### Interplay Between Genetic Substrate, QTc Duration, and Arrhythmia Risk in Patients With Long QT Syndrome

A. Mazzanti, et al.

**BACKGROUND** Long QT syndrome (LQTS) is a common inheritable arrhythmogenic disorder, often secondary to mutations in the *KCNQ1*, *KCNH2*, and *SCN5A* genes. The disease is characterized by a prolonged ventricular repolarization (QTc interval) that confers susceptibility to life-threatening arrhythmic events (LAEs).

**OBJECTIVES** This study sought to create an evidence-based risk stratification scheme to personalize the quantification of the arrhythmic risk in patients with LQTS.

**METHODS** Data from 1,710 patients with LQTS followed up for a median of 7.1 years (interquartile range [IQR]: 2.7 to 13.4 years) were analyzed to estimate the 5-year risk of LAEs based on QTc duration and genotype and to assess the antiarrhythmic efficacy of beta-blockers.

**RESULTS** The relationship between QTc duration and risk of events was investigated by comparison of linear and cubic spline models, and the linear model provided the best fit. The 5-year risk of LAEs while patients were off therapy was then calculated in a multivariable Cox model with QTc and genotype considered as independent factors. The estimated risk of LAEs increased by 15% for every 10-ms increment of QTc duration for all genotypes. Intergenotype comparison showed that the risk for patients with LQT2 and LQT3 increased by 130% and 157% at any QTc duration versus patients with LQT1. Analysis of response to beta-blockers showed that only nadolol reduced the arrhythmic risk in all genotypes significantly compared with no therapy (hazard ratio: 0.38; 95% confidence interval: 0.15 to 0.93;  $p = 0.03$ ).

**CONCLUSIONS** The study provides an estimator of risk of LAEs in LQTS that allows a granular estimate of

5-year arrhythmic risk and demonstrate the superiority of nadolol in reducing the risk of LAEs in LQTS (74).

### Propranolol Versus Metoprolol for Treatment of Electrical Storm in Patients With Implantable Cardioverter-Defibrillator

S. Chatzidou, et al.

**BACKGROUND** Electrical storm (ES), characterized by unrelenting recurrences of ventricular arrhythmias, is observed in approximately 30% of patients with implantable cardioverter-defibrillators (ICDs) and is associated with high mortality rates.

**OBJECTIVES** Sympathetic blockade with  $\beta$ -blockers, usually in combination with intravenous (IV) amiodarone, have proved highly effective in the suppression of ES. In this study, we compared the efficacy of a nonselective  $\beta$ -blocker (propranolol) versus a  $\beta_1$ -selective blocker (metoprolol) in the management of ES.

**METHODS** Between 2011 and 2016, 60 ICD patients (45 men, mean age  $65.0 \pm 8.5$  years) with ES developed within 24 h from admission were randomly assigned to therapy with either propranolol (160 mg/24 h, Group A) or metoprolol (200 mg/24 h, Group B), combined with IV amiodarone for 48 h.

**RESULTS** Patients under propranolol therapy in comparison with metoprolol-treated individuals presented a 2.67 times decreased incidence rate (incidence rate ratio: 0.375; 95% confidence interval: 0.207 to 0.678;  $p = 0.001$ ) of ventricular arrhythmic events (tachycardia or fibrillation) and a 2.34 times decreased rate of ICD discharges (incidence rate ratio: 0.428; 95% CI: 0.227 to 0.892;  $p = 0.004$ ) during the intensive care unit (ICU) stay, after adjusting for age, sex, ejection fraction, New York Heart Association functional class, heart failure type, arrhythmia type, and arrhythmic events before ICU admission. At the end of the first 24-h treatment period, 27 of 30 (90.0%) patients in group A, while only 16 of 30 (53.3%) patients in group B were free of arrhythmic events ( $p = 0.03$ ). The termination of arrhythmic events was 77.5% less likely in Group B compared with Group A (hazard ratio: 0.225; 95% CI: 0.112 to 0.453;  $p < 0.001$ ). Time to arrhythmia termination and length of hospital stay were significantly shorter in the propranolol group ( $p < 0.05$  for both).

**CONCLUSIONS** The combination of IV amiodarone and oral propranolol is safe, effective, and superior to the combination of IV amiodarone and oral metoprolol in the management of ES in ICD patients (75).

### Clinical Outcomes of His Bundle Pacing Compared to Right Ventricular Pacing

M. Abdelrahman, et al.

**BACKGROUND** Right ventricular pacing (RVP) is associated with heart failure and increased mortality. His bundle pacing (HBP) is a physiological alternative to RVP.

**OBJECTIVES** This study sought to evaluate clinical outcomes of HBP compared to RVP.

**METHODS** All patients requiring initial pacemaker implantation between October 1, 2013, and December 31, 2016, were included in the study. Permanent HBP was attempted in consecutive patients at 1 hospital and RVP at a sister hospital. Implant characteristics, all-cause mortality, heart failure hospitalization (HFH), and upgrades to biventricular pacing (BiVP) were tracked. Primary outcome was the combined endpoint of death, HFH, or upgrade to BiVP. Secondary endpoints were mortality and HFH.

**RESULTS** HBP was successful in 304 of 332 consecutive patients (92%), whereas 433 patients underwent RVP. The primary endpoint of death, HFH, or upgrade to BiVP was significantly reduced in the HBP group (83 of 332 patients [25%]) compared to RVP (137 of 433 patients [32%]; hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.534 to 0.944;  $p = 0.02$ ). This difference was observed primarily in patients with ventricular pacing  $>20\%$  (25% in HBP vs. 36% in RVP; HR: 0.65; 95% CI: 0.456 to 0.927;  $p = 0.02$ ). The incidence of HFH was significantly reduced in HBP (12.4% vs. 17.6%; HR: 0.63; 95% CI: 0.430 to 0.931;  $p = 0.02$ ). There was a trend toward reduced mortality in HBP (17.2% vs. 21.4%, respectively;  $p = 0.06$ ).

**CONCLUSIONS** Permanent HBP was feasible and safe in a large real-world population requiring permanent pacemakers. His bundle pacing was associated with reduction in the combined endpoint of death, HFH, or upgrade to BiVP compared to RVP in patients requiring permanent pacemakers (76).

### Present Status of Brugada Syndrome: JACC State-of-the-Art Review

J. Brugada, et al.

The Brugada syndrome is an inherited disorder associated with risk of ventricular fibrillation and sudden cardiac death in a structurally normal heart. Diagnosis is based on a characteristic electrocardiographic pattern (coved type ST-segment elevation  $\geq 2$  mm followed by a negative T-wave in  $\geq 1$  of the right precordial leads  $V_1$  to  $V_2$ ), observed

either spontaneously or during a sodium-channel blocker test. The prevalence varies among regions and ethnicities, affecting mostly males. The risk stratification and management of patients, principally asymptomatic, still remains challenging. The current main therapy is an implantable cardioverter-defibrillator, but radiofrequency catheter ablation has been recently reported as an effective new treatment. Since its first description in 1992, continuous achievements have expanded our understanding of the genetics basis and electrophysiological mechanisms underlying the disease. Currently, despite several genes identified, *SCN5A* has attracted most attention, and in approximately 30% of patients, a genetic variant may be implicated in causation after a comprehensive analysis (77).

### The Diagnostic Yield of Brugada Syndrome After Sudden Death With Normal Autopsy

M. Papadakis, et al.

**BACKGROUND** Familial evaluation after a sudden death with negative autopsy (sudden arrhythmic death syndrome; SADS) may identify relatives at risk of fatal arrhythmias.

**OBJECTIVES** This study aimed to assess the impact of systematic ajmaline provocation testing using high right precordial leads (RPLs) on the diagnostic yield of Brugada syndrome (BrS) in a large cohort of SADS families.

**METHODS** Three hundred three SADS families (911 relatives) underwent evaluation with resting electrocardiogram using conventional and high RPLs, echocardiography, exercise, and 24-h electrocardiogram monitor. An ajmaline test with conventional and high RPLs was undertaken in 670 (74%) relatives without a familial diagnosis after initial evaluation. Further investigations were guided by clinical suspicion.

**RESULTS** An inherited cardiac disease was diagnosed in 128 (42%) families and 201 (22%) relatives. BrS was the most prevalent diagnosis ( $n = 85$ , 28% of families;  $n = 140$ , 15% of relatives). Ajmaline testing was required to unmask the BrS in 97% of diagnosed individuals. The use of high RPLs showed a 16% incremental diagnostic yield of ajmaline testing by diagnosing BrS in an additional 49 families. There were no differences of the characteristics between individuals and families with a diagnostic pattern in the conventional and the high RPLs. On follow-up, a spontaneous type 1 Brugada pattern and/or clinically significant arrhythmic events developed in 17% ( $n = 25$ ) of the concealed BrS cohort.

**CONCLUSIONS** Systematic use of ajmaline testing with high RPLs increases substantially the yield of BrS in SADS families. Assessment should be performed in expert centers where patients are counseled appropriately for the potential implications of provocation testing (78).

### Electroanatomic and Pathologic Right Ventricular Outflow Tract Abnormalities in Patients With Brugada Syndrome

M. Pieroni, et al.

**BACKGROUND** The prevalence and significance of structural abnormalities in Brugada syndrome (BrS) are still largely debated.

**OBJECTIVES** The authors investigated the relationship between genetic background, electroanatomic abnormalities, and pathologic substrate in BrS.

**METHODS** They performed 3-dimensional electroanatomic unipolar and bipolar mapping in 30 patients with BrS. Twenty patients underwent 3-dimensional electroanatomic unipolar and bipolar mapping-guided right ventricular outflow tract (RVOT) endomyocardial biopsy. Programmed ventricular stimulation and genetic analysis were performed in all patients.

**RESULTS** Low-voltage areas (LVAs) were observed at unipolar map in 93% of patients and at bipolar map in 50% of cases. Unipolar LVAs were always larger than bipolar LVAs, were always colocalized, and in all cases included RVOT. Disease-causing mutations were detected in 10 (33%) patients. Programmed ventricular stimulation was positive in 16 cases (53%). In 75% of patients, RVOT histology showed pathologic findings with myocardial inflammation in 80% of them. Among patients with abnormal bipolar map submitted to endomyocardial biopsy, 9 (81%) showed evidence of myocardial inflammation. Conversely, bipolar map was abnormal in 83% of patients with myocardial inflammation. Myocardial inflammation was also more prevalent among inducible patients (83% vs. 25% in noninducible;  $p = 0.032$ ).

**CONCLUSIONS** BrS is characterized by electroanatomical and structural abnormalities localized to RVOT with a gradient of the pathologic substrate from epicardium to endocardium possibly driven by myocardial inflammation. These findings reclassify BrS as a combination of structural and electrical defects opening the way to new risk stratification and therapeutic strategies (79).

## VALVULAR HEART DISEASE

### Early Experience With New Transcatheter Mitral Valve Replacement

V. Bapat, et al.

**BACKGROUND** Transcatheter mitral valve replacement (TMVR) is a potential therapy for patients with symptomatic, severe mitral regurgitation (MR). The feasibility of this therapy remains to be defined.

**OBJECTIVES** The authors report their early experience with TMVR using a new valve system.

**METHODS** The valve is a self-expanding, nitinol valve with bovine pericardial leaflets that is placed using a transapical delivery system. Patients with symptomatic MR who were deemed high or extreme risk by the local heart teams were enrolled in a global pilot study at 14 sites (United States, Australia, and Europe).

**RESULTS** Fifty consecutively enrolled patients (mean age:  $73 \pm 9$  years; 58.0% men; 84% secondary MR) underwent TMVR with the valve. The mean Society for Thoracic Surgery score was  $6.4 \pm 5.5\%$ ; 86% of patients were New York Heart Association functional class III or IV, and the mean left ventricular ejection fraction was  $43 \pm 12\%$ . Device implant was successful in 48 patients with a median deployment time of 14 min (interquartile range: 12 to 17 min). The 30-day mortality was 14%, with no disabling strokes, or repeat interventions. Median follow-up was 173 days (interquartile range: 54 to 342 days). At latest follow-up, echocardiography confirmed mild or no residual MR in all patients who received implants. Improvements in symptom class (79% in New York Heart Association functional class I or II at follow-up;  $p < 0.0001$  vs. baseline) and Minnesota Heart Failure Questionnaire scores ( $56.2 \pm 26.8$  vs.  $31.7 \pm 22.1$ ;  $p = 0.011$ ) were observed.

**CONCLUSIONS** TMVR with the valve was feasible in a study group at high or extreme risk for conventional mitral valve replacement. These results inform trial design of TMVR in lower-risk patients with severe mitral valve regurgitation (Evaluation of the Safety and Performance of the Twelve Intrepid Transcatheter Mitral Valve Replacement System in High Risk Patients with Severe, Symptomatic Mitral Regurgitation - The Twelve Intrepid TMVR Pilot Study; [NCT02322840](#)) (80).

### Long-Term Outcomes Following Surgical Aortic Bioprosthesis Implantation

T. Rodriguez-Gabella, et al.

**BACKGROUND** Few data exist on long-term outcomes and structural valve degeneration (SVD) in

consecutive unselected patients undergoing surgical aortic valve replacement (SAVR).

**OBJECTIVES** The goal of this study was to determine the long-term outcomes of a contemporary cohort of consecutive unselected SAVR recipients with a focus on evaluating clinical outcomes and SVD based on echocardiographic criteria.

**METHODS** A total of 672 consecutive patients (mean age:  $72 \pm 8$  years; 61.5% male) undergoing SAVR with a bioprosthesis between 2002 and 2004 were included. Baseline and follow-up data were prospectively collected in a dedicated database. Baseline post-operative echocardiographic data were obtained in the 624 patients alive at hospital discharge and in 209 patients at 10 years (87% of the patients at risk). SVD was defined as subclinical (increase  $>10$  mm Hg in mean transvalvular gradient + decrease  $>0.3$  cm<sup>2</sup> in valve area and/or new-onset mild or moderate aortic regurgitation) and clinically relevant (increase  $>20$  mm Hg in mean transvalvular gradient + decrease  $>0.6$  cm<sup>2</sup> in valve area and/or new-onset moderate-to-severe aortic regurgitation).

**RESULTS** At a median follow-up of 10 years (interquartile range: 5 to 13 years), 432 patients (64.3%) had died. Older age, left ventricular dysfunction, atrial fibrillation, chronic obstructive pulmonary disease, greater body mass index, and diabetes mellitus were associated with an increased mortality risk ( $p < 0.05$  for all). Clinically relevant SVD occurred in 6.6% of patients; 30.1% of patients had subclinical SVD. A greater body mass index and the use of a specific aortic bioprosthesis were independently associated with clinically relevant SVD ( $p < 0.05$  for both), and 83% of these patients underwent aortic valve reintervention (valve-in-valve transcatheter aortic valve replacement in 44% of them).

**CONCLUSIONS** The 10-year mortality rate in elderly SAVR recipients of a bioprosthetic valve was considerable, chiefly determined by their older age and the presence of comorbidities. Clinically relevant SVD was infrequent, but close to one third of the population exhibited subclinical SVD. These results provide contemporary data on long-term clinical outcomes and SVD post-SAVR, and they should be taken into consideration when evaluating late clinical outcomes and valve durability after transcatheter aortic valve replacement (81).

### 1-Year Outcomes of Transcatheter Mitral Valve Replacement in Patients With Severe Mitral Annular Calcification

M. Guerrero, et al.

**BACKGROUND** The risk of surgical mitral valve replacement in patients with severe mitral annular

calcification (MAC) is high. Several patients worldwide with severe MAC have been treated successfully with transcatheter mitral valve replacement (TMVR) using balloon-expandable aortic transcatheter valves. The TMVR in MAC Global Registry is a multicenter registry that collects data on outcomes of these procedures.

**OBJECTIVES** The goal of this study was to evaluate 1-year outcomes in this registry.

**METHODS** This study was a multicenter retrospective review of clinical outcomes.

**RESULTS** A total of 116 extreme surgical risk patients with severe MAC underwent TMVR; 106 had a procedure date >1 year before data-lock and were included in the analysis. Their mean age was  $73 \pm 12$  years, and 68% were female. The mean Society of Thoracic Surgeons score was  $15.3 \pm 11.6\%$ , and 90% were in New York Heart Association functional class III or IV. Thirty-day and 1-year all-cause mortality was 25% and 53.7%, respectively. Most patients who survived 30 days were alive at 1 year (49 of 77 [63.6%]), and the majority (71.8%) were in New York Heart Association functional class I or II. Echocardiography data at 1 year were available in 34 patients. Mean left ventricular ejection fraction was  $58.6 \pm 11.2\%$ , mean mitral valve area was  $1.9 \pm 0.5$  cm<sup>2</sup>, mean mitral gradient was  $5.8 \pm 2.2$  mm Hg, and 75% had zero or trace mitral regurgitation.

**CONCLUSIONS** TMVR with balloon-expandable aortic valves in extreme surgical risk patients with severe MAC is feasible but associated with high 30-day and 1-year mortality. Most patients who survive the 30-day post-procedural period are alive at 1 year and have sustained improvement of symptoms and transcatheter valve performance. The role of TMVR in patients with MAC requires further evaluation in clinical trials (82).

### Transcatheter Tricuspid Valve Interventions: Landscape, Challenges, and Future Directions

L. Asmarats, et al.

Tricuspid regurgitation is a common finding in patients with left-sided valvular or myocardial disease, often being a marker for late-stage chronic heart failure with a grim prognosis. However, isolated tricuspid valve surgery remains infrequent and is associated with the highest mortality among all valve procedures. Hence, a largely unmet clinical need exists for less invasive therapeutic options in

these patients. In recent times, multiple percutaneous therapies have been developed for treating severe tricuspid regurgitation, including tricuspid valve repair and, more recently replacement, opening an entirely new venue for managing tricuspid regurgitation. The aim of this review is to provide an updated overview and a clinical perspective on novel transcatheter tricuspid valve therapies, highlighting potential challenges and future directions (83).

### Myocardial Fibrosis in Patients With Primary Mitral Regurgitation With and Without Prolapse

D. Kitkungvan, et al.

**BACKGROUND** Recent studies reported left ventricular (LV) fibrosis in patients with primary mitral regurgitation (MR) thought to be principally due to mitral valve prolapse (MVP).

**OBJECTIVES** This study sought to evaluate the prevalence, characteristics, and prognostic implications of LV fibrosis in a large cohort of primary MR patients with and without MVP using cardiovascular magnetic resonance (CMR).

**METHODS** Patients referred for contrast CMR assessment of chronic primary MR were enrolled and underwent comprehensive assessment of cardiac remodeling, severity of MR, and LV replacement fibrosis. Primary MR patients were stratified into: an MVP group if there was >2 mm mitral leaflet displacement on cine-CMR, or a non-MVP group. Patients were followed for arrhythmic events (sudden cardiac death, aborted sudden cardiac arrest, and sustained or inducible ventricular arrhythmia).

**RESULTS** A total of 356 primary MR patients (177 MVP and 179 non-MVP) were enrolled. LV fibrosis was more prevalent in the MVP group than the non-MVP group (36.7% vs. 6.7%;  $p < 0.001$ ). The presence of MVP had the strongest association (odds ratio: 6.82;  $p < 0.001$ ) with LV fibrosis even after adjustment for clinical variables, measures of cardiac remodeling, and MR severity. During follow-up (median 1,354 days), MVP patients with LV fibrosis had the highest event rate for arrhythmic events.

**CONCLUSIONS** In primary MR patients, LV fibrosis is more prevalent in MVP than non-MVP, suggesting a unique pathophysiology beyond volume overload in MVP. LV fibrosis in primary MR may represent a risk marker of arrhythmic events (84).



## Open Atrial Transcatheter Mitral Valve Replacement in Patients With Mitral Annular Calcification

H.M. Russell, et al.

**BACKGROUND** Mitral valve replacement in the setting of severe mitral annular calcification remains a surgical challenge. Transcatheter mitral valve replacement (TMVR) using an aortic balloon-expandable transcatheter heart valve is emerging as a potential treatment option for high surgical risk patients. Transseptal, transapical, or transatrial access is not always feasible, so an understanding of alternative implantation techniques is important.

**OBJECTIVES** The authors sought to present a step-by-step description of a contemporary transatrial TMVR technique using balloon-expandable aortic transcatheter heart valves. This procedure has evolved over time to address valve migration, left ventricular outflow tract obstruction, and paravalvular leak. The authors present a refined technique that has been associated with the most reproducible outcomes.

**METHODS** A step-by-step description of the TMVR technique and outcomes of 8 patients treated using this technique are described. Baseline patient clinical and echocardiographic characteristics and 30-day post-TMVR outcomes are presented.

**RESULTS** Eight patients underwent transatrial TMVR at a single institution. Five had previous cardiac surgery. Mean STS score was 8%. Technical success by MVARC (Mitral Valve Academic Research Consortium) criteria was 100%. There was zero in-hospital and 30-day mortality. Procedural success by MVARC criteria at 30 days was 100%. Paravalvular leak immediately post-implant was none or trace in 6 and mild in 1.

**CONCLUSIONS** The technique described is reproducible and was associated with favorable outcomes in this early experience. It represents a useful technique for the treatment of mitral valve disease in the setting of severe annular calcification. A structured and defined implantation technique is critical to investigators as this field evolves (85).

## Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic Severe Aortic Stenosis

R. Waksman, et al.

**BACKGROUND** Transcatheter aortic valve replacement (TAVR) is now the standard of care for patients with symptomatic severe aortic stenosis who are

extreme, high, or intermediate risk for surgical aortic valve replacement (SAVR).

**OBJECTIVES** The authors sought to evaluate TAVR in a prospective multicenter trial involving low-risk patients.

**METHODS** The Low Risk TAVR (Feasibility of Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic, Severe Aortic Stenosis) trial was the first U.S. Food and Drug Administration-approved Investigational Device Exemption trial to enroll in the United States. This investigator-led trial was a prospective, multicenter, unblinded, comparison to historical controls from the Society of Thoracic Surgeons (STS) database. The primary endpoint was all-cause mortality at 30 days.

**RESULTS** The authors enrolled 200 low-risk patients with symptomatic severe aortic stenosis at 11 centers to undergo TAVR. The authors compared outcomes with an inverse probability weighting-adjusted control cohort of 719 patients who underwent SAVR at the same institutions using the STS database. At 30 days, there was zero all-cause mortality in the TAVR group versus 1.7% mortality in the SAVR group. There was zero in-hospital stroke rate in the TAVR group versus 0.6% stroke in the SAVR group. Permanent pacemaker implantation rates were similar between TAVR and SAVR (5.0% vs. 4.5%). The rates of new-onset atrial fibrillation (3.0%) and length of stay ( $2.0 \pm 1.1$  days) were low in the TAVR group. One patient (0.5%) in the TAVR group had >mild paravalvular leak at 30 days. Fourteen percent of TAVR patients had evidence of subclinical leaflet thrombosis at 30 days.

**CONCLUSIONS** TAVR is safe in low-risk patients with symptomatic severe aortic stenosis, with low procedural complication rates, short hospital length of stay, zero mortality, and zero disabling stroke at 30 days. Subclinical leaflet thrombosis was observed in a minority of TAVR patients at 30 days. (Feasibility of Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic, Severe Aortic Stenosis [Low Risk TAVR; [NCT02628899](#)] (86).

## Primary Hemostatic Disorders and Late Major Bleeding After Transcatheter Aortic Valve Replacement

M. Kibler, et al.

**BACKGROUND** Periprocedural and late (>30 days) bleedings represent major complications after transcatheter aortic valve replacement and have been

identified as potential areas for improved patient care.

**OBJECTIVES** The authors sought to evaluate the impact of ongoing primary hemostasis disorders on late major/life-threatening bleeding complications (MLBCs).

**METHODS** Bleedings were assessed according to the VARC-2 (Valve Academic Research Consortium-2) criteria. Closure time of adenosine diphosphate (CT-ADP), a surrogate marker of high molecular weight von Willebrand multimers proteolysis was assessed 24 h after the procedure. Ongoing primary hemostasis disorder was defined by a CT-ADP >180 s.

**RESULTS** Among 372 patients who survived at 30 days, MLBCs occurred in 42 patients (11.3%) at a median follow-up of 383 days (interquartile range: 188 to 574 days). MLBCs were mainly of gastrointestinal origin (42.8%) and were associated with increased overall mortality (hazard ratio [HR]: 5.66; 95% confidence interval [CI]: 3.10 to 10.31;  $p < 0.001$ ) and cardiac mortality (HR: 11.62; 95% CI: 4.59 to 29.37;  $p < 0.001$ ). A 2.5-fold elevation of MLBCs could be evidenced in patients with a CT-ADP > 180 s (27.4% vs. 11.5%;  $p < 0.001$ ). Multivariate regression analysis identified paravalvular leak (PVL) (HR: 6.31; 95% CI: 3.43 to 11.60;  $p < 0.0001$ ) and CT-ADP > 180 s (HR: 3.08; 95% CI: 1.62 to 5.81;  $p = 0.0005$ ) as predictor of MLBCs.

**CONCLUSIONS** MLBCs after transcatheter aortic valve replacement are frequent and associated with an increased morbidity and mortality. PVL and CT-ADP >180 s were identified as strong predictors for MLBCs. These findings strongly suggest that persistent HMW defects contribute to enhanced bleeding risk in patients with residual PVL (87).

### Antibiotic Prophylaxis and Incidence of Endocarditis Before and After the 2007 AHA Recommendations

M.H. Thornhill, et al.

**BACKGROUND** The American Heart Association updated its recommendations for antibiotic prophylaxis (AP) to prevent infective endocarditis (IE) in 2007, advising that AP cease for those at moderate risk of IE, but continue for those at high risk.

**OBJECTIVES** The authors sought to quantify any change in AP prescribing and IE incidence.

**METHODS** High-risk, moderate-risk, and unknown/low-risk individuals with linked prescription and Medicare or commercial health care data were

identified in the Truven Health MarketScan databases from May 2003 through August 2015 (198,522,665 enrollee-years of data). AP prescribing and IE incidence were evaluated by Poisson model analysis.

**RESULTS** By August 2015, the 2007 recommendation change was associated with a significant 64% (95% confidence interval [CI]: 59% to 68%) estimated fall in AP prescribing for moderate-risk individuals and a 20% (95% CI: 4% to 32%) estimated fall for those at high risk. Over the same period, there was a barely significant 75% (95% CI: 3% to 200%) estimated increase in IE incidence among moderate-risk individuals and a significant 177% estimated increase (95% CI: 66% to 361%) among those at high risk. In unknown/low-risk individuals, there was a significant 52% (95% CI: 46% to 58%) estimated fall in AP prescribing, but no significant increase in IE incidence.

**CONCLUSIONS** AP prescribing fell among all IE risk groups, particularly those at moderate risk. Concurrently, there was a significant increase in IE incidence among high-risk individuals, a borderline significant increase in moderate-risk individuals, and no change for those at low/unknown risk. Although these data do not establish a cause-effect relationship between AP reduction and IE increase, the fall in AP prescribing in those at high risk is of concern and, coupled with the borderline increase in IE incidence among those at moderate risk, warrants further investigation (88).

### 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients

T.G. Gleason, et al.

**BACKGROUND** The CoreValve U.S. Pivotal High Risk Trial was the first randomized trial to show superior 1-year mortality of transcatheter aortic valve replacement (TAVR) compared with surgical aortic valve replacement (SAVR) among high operative mortality-risk patients.

**OBJECTIVES** The authors sought to compare TAVR to SAVR for mid-term 5-year outcomes of safety, performance, and durability.

**METHODS** Surgical high-risk patients were randomized (1:1) to TAVR with the self-expanding bioprosthesis or SAVR. VARC-1 (Valve Academic Research Consortium I) definitions were applied. Severe hemodynamic structural valve deterioration

was defined as a mean gradient  $\geq 40$  mm Hg or a change in gradient  $\geq 20$  mm Hg or new severe aortic regurgitation. Five-year follow-up was planned.

**RESULTS** A total of 797 patients were randomized at 45 U.S. centers, of whom 750 underwent an attempted implant (TAVR = 391, SAVR = 359). The overall mean age was 83 years, and the STS score was 7.4%. All-cause mortality rates at 5 years were 55.3% for TAVR and 55.4% for SAVR. Subgroup analysis showed no differences in mortality. Major stroke rates were 12.3% for TAVR and 13.2% for SAVR. Mean aortic valve gradients were  $7.1 \pm 3.6$  mm Hg for TAVR and  $10.9 \pm 5.7$  mm Hg for SAVR. No clinically significant valve thrombosis was observed. Freedom from severe SVD was 99.2% for TAVR and 98.3% for SAVR ( $p = 0.32$ ), and freedom from valve reintervention was 97.0% for TAVR and 98.9% for SAVR ( $p = 0.04$ ). A permanent pacemaker was implanted in 33.0% of TAVR and 19.8% of SAVR patients at 5 years.

**CONCLUSIONS** This study shows similar mid-term survival and stroke rates in high-risk patients following TAVR or SAVR. Severe structural valve deterioration and valve reinterventions were uncommon. (Safety and Efficacy Study of the Medtronic CoreValve<sup>®</sup> System in the Treatment of Symptomatic Severe Aortic Stenosis in High Risk and Very High Risk Subjects Who Need Aortic Valve Replacement; [NCT01240902](#)) (89).

### Prosthesis–Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry

H.C. Herrmann, et al.

**BACKGROUND** Prosthesis-patient mismatch (PPM) after surgical aortic valve replacement (AVR) for aortic stenosis is generally associated with worse outcomes. Transcatheter AVR (TAVR) can achieve a larger valve orifice and the effects of PPM after TAVR are less well studied.

**OBJECTIVES** The authors utilized the Society of Thoracic Surgeons/American College of Cardiology TVT (Transcatheter Valve Therapy) registry to examine the frequency, predictors, and association with outcomes of PPM after TAVR in 62,125 patients enrolled between 2014 and 2017.

**METHODS** On the basis of the discharge echocardiographic effective valve area indexed to body surface area, PPM was classified as severe ( $<0.65$  cm<sup>2</sup>/m<sup>2</sup>), moderate (0.65 to 0.85 cm<sup>2</sup>/m<sup>2</sup>), or none ( $>0.85$  cm<sup>2</sup>/m<sup>2</sup>). Multi-variable regression models were utilized to examine predictors of severe PPM as well as adjusted outcomes,

including mortality, heart failure (HF) rehospitalization, stroke, and quality of life, at 1 year in 37,470 Medicare patients with claims linkage.

**RESULTS** Severe and moderate PPM were present following TAVR in 12% and 25% of patients, respectively. Predictors of severe PPM included small ( $\leq 23$ -mm diameter) valve prosthesis, valve-in-valve procedure, larger body surface area, female sex, younger age, non-white/Hispanic race, lower ejection fraction, atrial fibrillation, and severe mitral or tricuspid regurgitation. At 1 year, mortality was 17.2%, 15.6%, and 15.9% in severe, moderate, and no PPM patients, respectively ( $p = 0.02$ ). HF rehospitalization had occurred in 14.7%, 12.8%, and 11.9% of patients with severe, moderate, and no PPM, respectively ( $p < 0.0001$ ). There was no association of severe PPM with stroke or quality-of-life score at 1 year.

**CONCLUSIONS** Severe PPM after TAVR was present in 12% of patients and was associated with higher mortality and HF rehospitalization at 1 year. Further investigation is warranted into the prevention of severe PPM in patients undergoing TAVR (90).

### The Mitral Annulus Disjunction Arrhythmic Syndrome

L.A. Dejgaard, et al.

**BACKGROUND** Mitral annulus disjunction (MAD) is an abnormal atrial displacement of the mitral valve leaflet hinge point. MAD has been associated with mitral valve prolapse (MVP) and sudden cardiac death.

**OBJECTIVES** The purpose of this study was to describe the clinical presentation, MAD morphology, association with MVP, and ventricular arrhythmias in patients with MAD.

**METHODS** The authors clinically examined patients with MAD. By echocardiography, the authors assessed the presence of MVP and measured MAD distance in parasternal long axis. Using cardiac magnetic resonance (CMR), the authors assessed circumferential MAD in the annular plane, longitudinal MAD distance, and myocardial fibrosis. Aborted cardiac arrest and sustained ventricular tachycardia were defined as severe arrhythmic events.

**RESULTS** The authors included 116 patients with MAD (age  $49 \pm 15$  years; 60% female). Palpitations were the most common symptom (71%). Severe arrhythmic events occurred in 14 (12%) patients. Longitudinal MAD distance measured by CMR was 3.0 mm (interquartile range [IQR]: 0 to 7.0 mm) and circumferential MAD was 150° (IQR: 90° to 210°). Patients with severe

arrhythmic events were younger (age  $37 \pm 13$  years vs.  $51 \pm 14$  years;  $p = 0.001$ ), had lower ejection fraction ( $51 \pm 5\%$  vs.  $57 \pm 7\%$ ;  $p = 0.002$ ) and had more frequently papillary muscle fibrosis (4 [36%] vs. 6 [9%];  $p = 0.03$ ). MVP was evident in 90 (78%) patients and was not associated with ventricular arrhythmia.

**CONCLUSIONS** Ventricular arrhythmias were frequent in patients with MAD. A total of 26 (22%) patients with MAD did not have MVP, and MVP was not associated with arrhythmic events, indicating MAD itself as an arrhythmogenic entity. MAD was detected around a large part of the mitral annulus circumference and was interspersed with normal tissue (91).

### Ross Procedure in Adults for Cardiologists and Cardiac Surgeons: JACC State-of-the-Art Review

A. Mazine, et al.

The ideal aortic valve substitute for young and middle-aged adults remains elusive. The Ross procedure (pulmonary autograft replacement) is the only operation that allows replacement of the diseased aortic valve with a living substitute. However, use of this procedure has declined significantly due to concerns over increased surgical risk and potential long-term failure of the operation. Several recent publications from expert centers have shown that in the current era, the Ross procedure can be performed safely and reproducibly in appropriately selected patients. Furthermore, an increasing body of evidence suggests that the Ross procedure is associated with better long-term outcomes compared with conventional aortic valve replacement in young and middle-aged adults. In this paper, the authors review the indications and technical considerations of the Ross procedure, describe its advantages and drawbacks, and discuss patient selection criteria. Finally, the authors provide a comprehensive synthesis of the current Ross procedure reports to enable cardiologists and surgeons to make appropriate decisions for their patients with aortic valve disease (92).

### Rheumatic Heart Disease Worldwide: JACC Scientific Expert Panel

D.A. Watkins, et al.

Rheumatic heart disease (RHD) is a preventable heart condition that remains endemic among vulnerable groups in many countries. After a period of relative neglect, there has been a resurging interest in RHD worldwide over the past decade. In this Scientific

Expert Panel, the authors summarize recent advances in the science of RHD and sketch out priorities for current action and future research. Key questions for laboratory research into disease pathogenesis and epidemiological research on the burden of disease are identified. The authors present a variety of pressing clinical research questions on optimal RHD prevention and advanced care. In addition, they propose a policy and implementation research agenda that can help translate current evidence into tangible action. The authors maintain that, despite knowledge gaps, there is sufficient evidence for national and global action on RHD, and they argue that RHD is a model for strengthening health systems to address other cardiovascular diseases in limited-resource countries (93).

### Beating-Heart Mitral Valve Repair Using a Novel ePTFE Cordal Implantation Device: A Prospective Trial

J.S. Gammie et al.

**BACKGROUND** Conventional mitral valve (MV) operations allow direct anatomic assessment and repair on an arrested heart, but require cardiopulmonary bypass, aortic cross-clamping, sternotomy or thoracotomy, and cardioplegic cardiac arrest, and are associated with significant perioperative disability, and risks of morbidity and mortality.

**OBJECTIVES** This study evaluated safety and performance of a transesophageal echocardiographic-guided device designed to implant artificial expanded polytetrafluoroethylene (ePTFE) cords on mitral leaflets in the beating heart.

**METHODS** In a prospective multicenter study, 30 consecutive patients with severe degenerative mitral regurgitation (MR) were treated with a mitral valve repair system (MVRS) via small left thoracotomy. The primary (30-day) endpoint was successful implantation of cords with MR reduction to moderate or less.

**RESULTS** The primary endpoint was met in 27 of 30 patients (90%). Three patients required conversion to open mitral surgery. There were no deaths, strokes, or permanent pacemaker implantations. At 1 month, MR was mild or less in 89% (24 of 27) and was moderate in 11% (3 of 27). At 6 months, MR was mild or less in 85% (22 of 26), moderate in 8% (2 of 26), and severe in 8% (2 of 26). Favorable cardiac remodeling at 6 months included decreases in end-diastolic ( $161 \pm 36$  ml to  $122 \pm 30$  ml;  $p < 0.001$ ) and left atrial volumes ( $106 \pm 36$  ml to  $69 \pm 24$  ml;  $p < 0.001$ ). The anterior-posterior mitral annular dimension decreased from  $34.7 \pm 5.8$  mm to

$28.2 \pm 5.1$  mm;  $p < 0.001$  as did the mitral annular area ( $10.0 \pm 2.7$  cm<sup>2</sup> vs.  $6.9 \pm 2.0$  cm<sup>2</sup>;  $p < 0.0001$ ).

**CONCLUSIONS** MVRS ePTFE cordal implantation can reduce the invasiveness and morbidity of conventional MV surgery. The device's safety profile is promising and prospective trials comparing the outcomes of the MVRS to conventional MV repair surgery are warranted. (CE Mark Study for the Harpoon Medical Device [TRACER]; [NCT02768870](#)) (94).

## VASCULAR MEDICINE

### Cryptogenic Stroke and Patent Foramen Ovale

M.K. Mojadidi, et al.

Nearly one-half of patients with cryptogenic stroke have a patent foramen ovale (PFO). The dilemma of whether to close these PFOs percutaneously, in an effort to reduce the risk of recurrent paradoxical embolism, has been a matter of ongoing debate for more than a decade. Early randomized clinical trials failed to demonstrate a significant benefit of percutaneous PFO closure for secondary prevention of cryptogenic stroke in an intention-to-treat analysis. The long-term follow-up data from the RESPECT trial and 2 new randomized trials (CLOSE and REDUCE) have clarified these findings. They showed that with good patient selection, transcatheter PFO closure significantly reduces the risk of recurrent stroke compared with medical therapy in patients with cryptogenic stroke, with no increased risk of serious adverse events or influence on major bleeding (95).

### Cryptogenic Stroke and High-Risk Patent Foramen Ovale: The DEFENSE-PFO Trial

P.H. Lee, et al.

**BACKGROUND** Recent reports showing the favorable role of patent foramen ovale (PFO) closure in patients with cryptogenic stroke have raised the issue of selecting optimal candidates.

**OBJECTIVES** This study, DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale), evaluated whether the benefits of PFO closure can be determined on the basis of the morphologic characteristics of the PFO, as evaluated by transesophageal echocardiography.

**METHODS** Patients with cryptogenic stroke and high-risk PFO were divided between a transcatheter PFO closure and a medication-only group. High-risk PFO included PFO with atrial septal aneurysm, hypermobility (phasic septal excursion into either

atrium  $\geq 10$  mm), or PFO size (maximum separation of the septum primum from the secundum)  $\geq 2$  mm. The primary endpoint was a composite of stroke, vascular death, or Thrombolysis In Myocardial Infarction-defined major bleeding during 2 years of follow-up.

**RESULTS** From September 2011 until October 2017, 120 patients (mean age: 51.8 years) underwent randomization. PFO size, frequency of septal aneurysm (13.3% vs. 8.3%;  $p = 0.56$ ), and hypermobility (45.0% vs. 46.7%;  $p > 0.99$ ) were similar between the groups. All PFO closures were successful. The primary endpoint occurred exclusively in the medication-only group (6 of 60 patients; 2-year event rate: 12.9% [log-rank  $p = 0.013$ ]; 2-year rate of ischemic stroke: 10.5% [ $p = 0.023$ ]). The events in the medication-only group included ischemic stroke ( $n = 5$ ), cerebral hemorrhage ( $n = 1$ ), Thrombolysis In Myocardial Infarction-defined major bleeding ( $n = 2$ ), and transient ischemic attack ( $n = 1$ ). Nonfatal procedural complications included development of atrial fibrillation ( $n = 2$ ), pericardial effusion ( $n = 1$ ), and pseudoaneurysm ( $n = 1$ ).

**CONCLUSIONS** PFO closure in patients with high-risk PFO characteristics resulted in a lower rate of the primary endpoint as well as stroke recurrence. (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale [DEFENSE-PFO]; [NCT01550588](#)) (96).

### External Aortic Root Support to Prevent Aortic Dilatation in Patients With Marfan Syndrome

C. Izgi, et al.

**BACKGROUND** Personalized external aortic root support (PEARS) was introduced in 2004 for prevention of aortic root dilatation in Marfan patients. The individual's aortic root is replicated by 3-dimensional printing. A polymer mesh sleeve is manufactured, which is implanted with the aim to support and stabilize the aortic wall.

**OBJECTIVES** The aim of this study was to assess effectiveness of PEARS for prevention of aortic root dilatation in Marfan patients.

**METHODS** A total of 24 consecutive Marfan patients operated 2004 to 2012 were prospectively monitored with magnetic resonance imaging. Following a pre-defined protocol, baseline and follow-up aorta measurements were made in a blinded random sequence.

**RESULTS** The mean age of the patients was  $33 \pm 13.3$  years (range: 16 to 58 years), and the mean aortic root diameter was  $45 \pm 2.8$  mm (range: 41 to 52 mm). Follow-



up was  $6.3 \pm 2.6$  years. There was no increase in the aortic root and ascending aorta diameters, but there was a tendency toward reduction: annulus diameter  $28.9 \pm 2.3$  mm to  $28.5 \pm 2.4$  mm (change  $-0.39$  mm, 95% confidence interval [CI]:  $-1.05$  to  $0.27$  mm), sinus of Valsalva diameter  $44.9 \pm 2.9$  mm to  $44.5 \pm 3.0$  mm (change  $-0.37$  mm, 95% CI:  $-1.23$  to  $0.51$  mm), and ascending aorta diameter  $32.4 \pm 3.6$  mm to  $32.3 \pm 3.7$  mm (change  $-0.10$  mm, 95% CI:  $-0.92$  to  $0.74$  mm). In the same period, the descending aorta diameter increased from  $22.9 \pm 2.4$  mm to  $24.2 \pm 3.0$  mm (change  $1.32$  mm, 95% CI:  $0.70$  to  $1.94$  mm;  $p < 0.001$ ) with a tendency toward increase in aortic arch diameter  $24.1 \pm 2.0$  mm to  $24.5 \pm 2.8$  mm (change  $0.41$  mm, 95% CI:  $-0.56$  to  $1.37$  mm).

**CONCLUSIONS** PEARS is effective in stabilizing the aortic root and preventing its dilatation. It is a viable alternative for prevention of aortic root dissection in Marfan patients (97).

### Oral Fluoroquinolone and the Risk of Aortic Dissection

C.-C. Lee, et al.

**BACKGROUND** Previous studies raised safety concerns on the association between fluoroquinolone treatment and serious collagen disorders, aortic aneurysm and dissection (AA/AD).

**OBJECTIVES** This study sought to evaluate this association via a case-crossover analysis in a large national administrative database.

**METHODS** A case-crossover design was used to compare the distributions of fluoroquinolone exposure for the same patient across a 60-day period before the AA/AD event (hazard period) and 1 randomly selected 60-day period (referent period) between 60 to 180 days before the AA/AD events. In the sensitivity analysis, the authors repeated the main analysis using a 1:5 ratio of hazard period to referent period, to adjust for the effect of time-variant confounders. A disease-risk score-matched time control analysis was performed to investigate the potential time-trend bias. The risks were calculated by a conditional logistic regression model.

**RESULTS** A total of 1,213 hospitalized AA/AD patients were identified between 2001 and 2011. In the main case-crossover analysis, exposure to fluoroquinolone was more frequent during the hazard periods than during the referent periods (1.6% vs. 0.6%; odds ratio [OR]: 2.71; 95% confidence interval [CI]: 1.14 to 6.46). In the sensitivity analysis, after adjustment for infections and co-medications, the risk remains

significant (OR: 2.05; 95% CI: 1.13 to 3.71). An increased risk of AA/AD was observed for prolonged exposure to fluoroquinolones (OR: 2.41 for 3- to 14-day exposure; OR: 2.83 for >14-day exposure). Susceptible period analysis revealed that the use of fluoroquinolone within 60 days was associated with the highest risk of AA/AD. In the case-time-control analysis, there was no evidence that the observed association is due to temporal changes in fluoroquinolone exposure.

**CONCLUSIONS** Exposure to fluoroquinolone was substantially associated with AA/AD. This risk was modified by the duration of fluoroquinolone use and the length of the hazard period (98).

### Losartan Versus Atenolol for Prevention of Aortic Dilation in Patients With Marfan Syndrome

G. Teixido-Tura, et al.

**BACKGROUND** Beta-blockers are the standard treatment in Marfan syndrome (MFS). Recent clinical trials with limited follow-up yielded conflicting results on losartan's effectiveness in MFS.

**OBJECTIVES** The present study aimed to evaluate the benefit of losartan compared with atenolol for the prevention of aortic dilation and complications in Marfan patients over a longer observation period (>5 years).

**METHODS** A total of 128 patients included in the previous LOAT (LOsartan vs ATenolol) clinical trial (64 in the atenolol and 64 in the losartan group) were followed up for an open-label extension of the study, with the initial treatment maintained.

**RESULTS** Mean clinical follow-up was  $6.7 \pm 1.5$  years. A total of 9 events (14.1%) occurred in the losartan group and 12 (18.8%) in the atenolol group. Survival analysis showed no differences in the combined endpoint of need for aortic surgery, aortic dissection, or death ( $p = 0.462$ ). Aortic root diameter increased with no differences between groups:  $0.4$  mm/year (95% confidence interval:  $0.2$  to  $0.5$ ) in the losartan and  $0.4$  mm/year (95% confidence interval:  $0.3$  to  $0.6$ ) in the atenolol group. In the subgroup analyses, no significant differences were observed considering age, baseline aortic root diameter, or type of dominant negative versus haploinsufficient FBN1 mutation.

**CONCLUSIONS** Long-term outcome of Marfan syndrome patients randomly assigned to losartan or atenolol showed no differences in aortic dilation rate or presence of clinical events between treatment

groups. Therefore, losartan might be a useful, low-risk alternative to beta-blockers in the long-term management of these patients (99).

### Pathology of Peripheral Artery Disease in Patients With Critical Limb Ischemia

N. Narula, et al.

**BACKGROUND** Critical limb ischemia (CLI) is the most serious complication of peripheral artery disease (PAD).

**OBJECTIVES** The purpose of this study was to characterize pathology of PAD in below- and above-knee amputation specimens in patients presenting with CLI.

**METHODS** Peripheral arteries from 95 patients (121 amputation specimens) were examined; 75 patients had presented with CLI, and the remaining 20 had amputations performed for other reasons. The pathological characteristics were separately recorded for femoral and popliteal arteries (FEM-POP), and infra-popliteal arteries (INFRA-POP).

**RESULTS** A total of 299 arteries were examined. In the 239 arteries from CLI patients, atherosclerotic plaques were more frequent in FEM-POP (23 of 34, 67.6%)

compared with INFRA-POP (79 of 205, 38.5%) arteries. Of these 239 arteries, 165 (69%) showed  $\geq 70\%$  stenosis, which was due to significant pathological intimal thickening, fibroatheroma, fibrocalcific lesions, or restenosis in 45 of 165 (27.3%), or was due to luminal thrombi with (39 of 165, 23.6%) or without (81 of 165, 49.1%) significant atherosclerotic lesions. Presence of chronic luminal thrombi was more frequently observed in arteries with insignificant atherosclerosis (OR: 16.7;  $p = 0.0002$ ), more so in INFRA-POP compared with FEM-POP (OR: 2.14;  $p = 0.0041$ ) arteries. Acute thrombotic occlusion was less frequently encountered in INFRA-POP than FEM-POP arteries (OR: 0.27;  $p = 0.0067$ ). Medial calcification was present in 170 of 239 (71.1%) large arteries.

**CONCLUSIONS** Thrombotic luminal occlusion associated with insignificant atherosclerosis is commonly observed in CLI and suggests the possibility of atherothromboembolic disease. The pathological characteristics of arteries in CLI suggest possible mechanisms of progression of PAD to CLI, especially in INFRA-POP arteries, and may support the preventive role of antithrombotic agents (100).

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