

HIGHLIGHTS OF THE YEAR

Editor-in-Chief's Top Picks From 2017



Valentin Fuster

Each week, I record audio summaries for every article in *JACC*, as well as an issue summary. While this process has been time-consuming, I have become quite familiar with every paper that we publish. Thus, I personally select papers (both original investigations and review articles) from 15 distinct specialties each year for your review. In addition to my personal choices, I have included manuscripts 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 manuscripts 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, Hypertension, Imaging, Metabolic & Lipid Disorders, Rhythm Disorders, Valvular Heart Disease, and Vascular Medicine (1-110).

BASIC & TRANSLATIONAL RESEARCH

The Aging Cardiovascular System: Understanding It at the Cellular and Clinical Levels

F. Paneni, et al.

Cardiovascular disease (CVD) presents a great burden for elderly patients, their caregivers, and health systems. Structural and functional alterations of vessels accumulate throughout life, culminating in increased risk of developing CVD. The growing elderly population worldwide highlights the need to understand how aging promotes CVD in order to develop new strategies to confront this challenge. This review provides examples of some major unresolved clinical problems encountered in daily cardiovascular practice as we care for elderly patients. Next, the authors summarize the current understanding of the mechanisms implicated in cardiovascular aging, and the potential for targeting novel pathways implicated in endothelial dysfunction, mitochondrial oxidative stress, chromatin remodeling, and genomic instability. Lastly, the authors consider critical aspects of vascular repair, including autologous transplantation of bone marrow-derived stem cells in elderly patients (1).

Basic Biology of Oxidative Stress and the Cardiovascular System: Part 1 of a 3-Part Series

M.N. Sack, et al.

The generation of reactive oxygen species (ROS) is a fundamental aspect of normal human biology.

However, when ROS generation exceeds endogenous antioxidant capacity, oxidative stress arises. If unchecked, ROS production and oxidative stress mediate tissue and cell damage that can spiral in a cycle of inflammation and more oxidative stress. This article is part 1 of a 3-part series covering the role of oxidative stress in cardiovascular disease. The broad theme of this first paper is the mechanisms and biology of oxidative stress. Specifically, the authors review the basic biology of oxidative stress, relevant aspects of mitochondrial function, and stress-related cell death pathways (apoptosis and necrosis) as they relate to the heart and cardiovascular system. They then explore telomere biology and cell senescence. As important regulators and sensors of oxidative stress, telomeres are segments of repetitive nucleotide sequence at each end of a chromosome that protect the chromosome ends from deterioration (2).

A Combination of Allogeneic Stem Cells Promotes Cardiac Regeneration

M. Natsumeda, et al.

BACKGROUND The combination of autologous mesenchymal stem cells (MSCs) and cardiac stem cells (CSCs) synergistically reduces scar size and improves cardiac function in ischemic cardiomyopathy. Whereas allogeneic (allo-)MSCs are immunoevasive, the capacity of CSCs to similarly elude the immune system remains controversial, potentially limiting the



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success of allogeneic cell combination therapy (ACCT).

OBJECTIVES This study sought to test the hypothesis that ACCT synergistically promotes cardiac regeneration without provoking immunologic reactions.

METHODS Göttingen swine with experimental ischemic cardiomyopathy were randomized to receive transendocardial injections of allo-MSCs + allo-CSCs (ACCT: 200 million MSCs/1 million CSCs, n = 7), 200 million allo-MSCs (n = 8), 1 million allo-CSCs (n = 4), or placebo (Plasma-Lyte A, n = 6). Swine were assessed by cardiac magnetic resonance imaging and pressure volume catheterization. Immune response was tested by histologic analyses.

RESULTS Both ACCT and allo-MSCs reduced scar size by $-11.1 \pm 4.8\%$ ($p = 0.012$) and $-9.5 \pm 4.8\%$ ($p = 0.047$), respectively. Only ACCT, but not MSCs or CSCs, prevented ongoing negative remodeling by offsetting increases in chamber volumes. Importantly, ACCT exerted the greatest effect on systolic function, improving the end-systolic pressure-volume relation ($+0.98 \pm 0.41$ mm Hg/ml; $p = 0.016$). The ACCT group had more phosphohistone H3+ (a marker of mitosis) cardiomyocytes ($p = 0.04$), and noncardiomyocytes ($p = 0.0002$) than did the placebo group in some regions of the heart. Inflammatory sites in ACCT and MSC-treated swine contained immunotolerant CD3⁺/CD25⁺/FoxP3⁺ regulatory T cells ($p < 0.0001$). Histologic analysis showed absent to low-grade inflammatory infiltrates without cardiomyocyte necrosis.

CONCLUSIONS ACCT demonstrates synergistic effects to enhance cardiac regeneration and left ventricular functional recovery in a swine model of chronic ischemic cardiomyopathy without adverse immunologic reaction. Clinical translation to humans is warranted (3).

Impact of Oxidative Stress on the Heart and Vasculature: Part 2 of a 3-Part Series

T. Münzel, et al.

Vascular disease and heart failure impart an enormous burden in terms of global morbidity and mortality. Although there are many different causes of cardiac and vascular disease, most causes share an important pathological mechanism: oxidative stress. In the failing heart, oxidative stress occurs in the myocardium and correlates with left ventricular dysfunction. Reactive oxygen species (ROS) negatively affect myocardial calcium handling, cause arrhythmia, and contribute to cardiac remodeling by

inducing hypertrophic signaling, apoptosis, and necrosis. Similarly, oxidative balance in the vasculature is tightly regulated by a wealth of pro- and antioxidant systems that orchestrate region-specific ROS production and removal. Reactive oxygen species also regulate multiple vascular cell functions, including endothelial and smooth muscle cell growth, proliferation, and migration; angiogenesis; apoptosis; vascular tone; host defenses; and genomic stability. However, excessive levels of ROS promote vascular disease through direct and irreversible oxidative damage to macromolecules, as well as disruption of redox-dependent vascular wall signaling processes (4).

Interleukin-1 Beta as a Target for Atherosclerosis Therapy: Biological Basis of CANTOS and Beyond

P. Libby

Inflammatory pathways drive atherogenesis and link conventional risk factors to atherosclerosis and its complications. One inflammatory mediator has come to the fore as a therapeutic target in cardiovascular disease. The experimental and clinical evidence reviewed here support interleukin-1 beta (IL-1 β) as both a local vascular and systemic contributor in this regard. Intrinsic vascular wall cells and lesional leukocytes alike can produce this cytokine. Local stimuli in the plaque favor the generation of active IL-1 β through the action of a molecular assembly known as the inflammasome. Clinically applicable interventions that interfere with IL-1 action can improve cardiovascular outcomes, ushering in a new era of anti-inflammatory therapies for atherosclerosis. The translational path described here illustrates how advances in basic vascular biology may transform therapy. Biomarker-directed application of anti-inflammatory interventions promises to help us achieve a more precise and personalized allocation of therapy for our cardiovascular patients (5).

LOX-1 in Atherosclerosis and Myocardial Ischemia: Biology, Genetics, and Modulation

N.V.K. Pothineni, et al.

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), one of the scavenger receptors for oxidized low-density lipoprotein cholesterol (ox-LDL), plays a crucial role in the uptake of ox-LDL by cells in the arterial wall. Mounting evidence suggests a role for LOX-1 in various steps of the atherosclerotic process, from initiation to plaque destabilization. Studies of

the genetic structure of LOX-1 have also uncovered various genetic polymorphisms that could modulate the risk of atherosclerotic cardiovascular events. As evidence supporting the vital role of LOX-1 in atherogenesis keeps accumulating, there is growing interest in LOX-1 as a potential therapeutic target. This review discusses the discovery and genetics of LOX-1; describes existing evidence supporting the role of LOX-1 in atherogenesis and its major complication, myocardial ischemia; and summarizes LOX-1 modulation by some naturally occurring compounds and efforts toward development of small molecules and biologics that could be of therapeutic use (6).

Oxidative Stress and Cardiovascular Risk: Obesity, Diabetes, Smoking, and Pollution: Part 3 of a 3-Part Series

B. Niemann, et al.

Oxidative stress occurs whenever the release of reactive oxygen species (ROS) exceeds endogenous antioxidant capacity. In this paper, we review the specific role of several cardiovascular risk factors in promoting oxidative stress: diabetes, obesity, smoking, and excessive pollution. Specifically, the risk of developing heart failure is higher in patients with diabetes or obesity, even with optimal medical treatment, and the increased release of ROS from cardiac mitochondria and other sources likely contributes to the development of cardiac dysfunction in this setting. Here, we explore the role of different ROS sources arising in obesity and diabetes, and the effect of excessive ROS production on the development of cardiac lipotoxicity. In parallel, contaminants in the air that we breathe pose a significant threat to human health. This paper provides an overview of cigarette smoke and urban air pollution, considering how their composition and biological effects have detrimental effects on cardiovascular health (7).

The Role of Nitroglycerin and Other Nitrogen Oxides in Cardiovascular Therapeutics

S. Divakaran, et al.

The use of nitroglycerin in the treatment of angina pectoris began not long after its original synthesis in 1847. Since then, the discovery of nitric oxide as a biological effector and better understanding of its roles in vasodilation, cell permeability, platelet function, inflammation, and other vascular processes have advanced our knowledge of the hemodynamic

(mostly mediated through vasodilation of capacitance and conductance arteries) and nonhemodynamic effects of organic nitrate therapy, via both nitric oxide-dependent and -independent mechanisms. Nitrates are rapidly absorbed from mucous membranes, the gastrointestinal tract, and the skin; thus, nitroglycerin is available in a number of preparations for delivery via several routes: oral tablets, sublingual tablets, buccal tablets, sublingual spray, transdermal ointment, and transdermal patch, as well as intravenous formulations. Organic nitrates are commonly used in the treatment of cardiovascular disease, but clinical data limit their use mostly to the treatment of angina. They are also used in the treatment of subsets of patients with heart failure and pulmonary hypertension. One major limitation of the use of nitrates is the development of tolerance. Although several agents have been studied for use in the prevention of nitrate tolerance, none are currently recommended owing to a paucity of supportive clinical data. Only 1 method of preventing nitrate tolerance remains widely accepted: the use of a dosing strategy that provides an interval of no or low nitrate exposure during each 24-h period. Nitric oxide's important role in several cardiovascular disease mechanisms continues to drive research toward finding novel ways to affect both endogenous and exogenous sources of this key molecular mediator (8).

Translational Perspective on Epigenetics in Cardiovascular Disease

P. van der Harst, et al.

A plethora of environmental and behavioral factors interact, resulting in changes in gene expression and providing a basis for the development and progression of cardiovascular diseases. Heterogeneity in gene expression responses among cells and individuals involves epigenetic mechanisms. Advancing technology allowing genome-scale interrogation of epigenetic marks provides a rapidly expanding view of the complexity and diversity of the epigenome. In this review, the authors discuss the expanding landscape of epigenetic modifications and highlight their importance for future understanding of disease. The epigenome provides a mechanistic link between environmental exposures and gene expression profiles ultimately leading to disease. The authors discuss the current evidence for transgenerational epigenetic inheritance and summarize the data linking epigenetics to cardiovascular disease. Furthermore, the potential

targets provided by the epigenome for the development of future diagnostics, preventive strategies, and therapy for cardiovascular disease are reviewed. Finally, the authors provide some suggestions for future directions (9).

CARDIAC FAILURE

Biological Phenotypes of Heart Failure With Preserved Ejection Fraction

G.A. Lewis, et al.

Heart failure with preserved ejection fraction (HFpEF) involves multiple pathophysiological mechanisms, which result in the heterogeneous phenotypes that are evident clinically, and which have potentially confounded previous HFpEF trials. A greater understanding of the *in vivo* human processes involved, and in particular, which are the causes and which are the downstream effects, may allow the syndrome of HFpEF to be distilled into distinct diagnoses based on the underlying biology. From this, specific interventions can follow, targeting individuals identified on the basis of their biological phenotype. This review describes the biological phenotypes of HFpEF and therapeutic interventions aimed at targeting these phenotypes (10).

Cardiopulmonary Exercise Testing: What Is its Value?

M. Guazzi, et al.

Compared with traditional exercise tests, cardiopulmonary exercise testing (CPET) provides a thorough assessment of exercise integrative physiology involving the pulmonary, cardiovascular, muscular, and cellular oxidative systems. Due to the prognostic ability of key variables, CPET applications in cardiology have grown impressively to include all forms of exercise intolerance, with a predominant focus on heart failure with reduced or with preserved ejection fraction. As impaired cardiac output and peripheral oxygen diffusion are the main determinants of the abnormal functional response in cardiac patients, invasive CPET has gained new popularity, especially for diagnosing early heart failure with preserved ejection fraction and exercise-induced pulmonary hypertension. The most impactful advance has recently come from the introduction of CPET combined with echocardiography or CPET imaging, which provides basic information regarding cardiac and valve morphology and function. This review highlights modern CPET use as a single or

combined test that allows the pathophysiological bases of exercise limitation to be translated, quite easily, into clinical practice (11).

Extracorporeal Ultrafiltration for Fluid Overload in Heart Failure: Current Status and Prospects for Further Research

M.R. Costanzo, et al.

More than 1 million heart failure hospitalizations occur annually, and congestion is the predominant cause. Rehospitalizations for recurrent congestion portend poor outcomes independently of age and renal function. Persistent congestion trumps serum creatinine increases in predicting adverse heart failure outcomes. No decongestive pharmacological therapy has reduced these harmful consequences. Simplified ultrafiltration devices permit fluid removal in lower-acuity hospital settings, but with conflicting results regarding safety and efficacy. Ultrafiltration performed at fixed rates after onset of therapy-induced increased serum creatinine was not superior to standard care and resulted in more complications. In contrast, compared with diuretic agents, some data suggest that adjustment of ultrafiltration rates to patients' vital signs and renal function may be associated with more effective decongestion and fewer heart failure events. Essential aspects of ultrafiltration remain poorly defined. Further research is urgently needed, given the burden of congestion and data suggesting sustained benefits of early and adjustable ultrafiltration (12).

Geometry as a Confounder When Assessing Ventricular Systolic Function: Comparison Between Ejection Fraction and Strain

T.M. Stokke, et al.

BACKGROUND Preserved left ventricular (LV) ejection fraction (EF) and reduced myocardial strain are reported in patients with hypertrophic cardiomyopathy, ischemic heart disease, diabetes mellitus, and more.

OBJECTIVES The authors performed a combined mathematical and echocardiographic study to understand the inconsistencies between EF and strains.

METHODS An analytical equation showing the relationship between EF and the 4 parameters, global longitudinal strain (GLS), global circumferential strain (GCS), wall thickness, and short-axis diameter, was derived from an elliptical LV model. The equation was validated by measuring the 4 parameters by echocardiography in 100 subjects with EF ranging from 16% to 72% and comparing model-predicted EF

with measured EF. The effect of the different parameters on EF was explored in the model and compared with findings in the patients.

RESULTS Calculated EF had very good agreement with measured EF ($r = 0.95$). The model showed that GCS contributes more than twice as much to EF than GLS. A significant reduction of GLS could be compensated by a small increase of GCS or wall thickness or reduced diameter. The model further demonstrated how EF can be maintained in ventricles with increased wall thickness or reduced diameter, despite reductions in both longitudinal and circumferential shortening. This was consistent with similar EF in 20 control subjects and 20 hypertrophic cardiomyopathy patients with increased wall thickness and reductions in both circumferential and longitudinal shortening (all $p < 0.01$).

CONCLUSIONS Reduced deformation despite preserved EF can be explained through geometric factors. Due to geometric confounders, strain better reflects systolic function in patients with preserved EF (13).

Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes

K.S. Shah, et al.

BACKGROUND Patients with heart failure (HF) have a poor prognosis and are categorized by ejection fraction (EF).

OBJECTIVES This study sought to characterize differences in outcomes in patients hospitalized with heart failure with preserved ejection fraction (HFpEF) (EF $\geq 50\%$), heart failure with borderline ejection fraction (HFbEF) (EF 41% to 49%), and heart failure with reduced ejection fraction (HFrEF) (EF $\leq 40\%$).

METHODS Data from GWTG-HF (Get With The Guidelines-Heart Failure) were linked to Medicare data for longitudinal follow-up. Multivariable models were constructed to examine 5-year outcomes and to compare survival to median survival of the U.S. population.

RESULTS A total of 39,982 patients from 254 hospitals who were admitted for HF between 2005 and 2009 were included: 18,299 (46%) had HFpEF, 3,285 (8.2%) had HFbEF, and 18,398 (46%) had HFrEF. Overall, median survival was 2.1 years. In risk-adjusted survival analysis, all 3 groups had similar 5-year mortality (HFrEF 75.3% vs. HFpEF 75.7%; hazard ratio: 0.99 [95% confidence interval: 0.958 to 1.022]; HFbEF 75.7% vs. HFpEF 75.7%; hazard ratio: 0.99 [95% confidence interval: 0.947 to 1.046]). In risk-adjusted analyses, the composite of mortality and

rehospitalization was similar for all subgroups. Cardiovascular and HF readmission rates were higher in those with HFrEF and HFbEF compared with those with HFpEF. When compared with the U.S. population, HF patients across all age and EF groups had markedly lower median survival.

CONCLUSIONS Among patients hospitalized with HF, patients across the EF spectrum have a similarly poor 5-year survival with an elevated risk for cardiovascular and HF admission. These findings underscore the need to improve treatment of patients with HF (14).

Hemodynamic Response to Nitroprusside in Patients With Low-Gradient Severe Aortic Stenosis and Preserved Ejection Fraction

J.W. Lloyd, et al.

BACKGROUND Low-gradient severe aortic stenosis (LGSAS) with preserved ejection fraction (EF) is incompletely understood. The influence of arterial afterload and diastolic dysfunction on the hemodynamic presentation of LGSAS remains unknown.

OBJECTIVES The authors sought to determine the acute hemodynamic response to sodium nitroprusside in LGSAS with preserved EF.

METHODS Symptomatic patients with LGSAS and preserved EF underwent cardiac catheterization with comparison of hemodynamic measurements before and after nitroprusside.

RESULTS Forty-one subjects (25 with low flow [LF], stroke volume index [SVI] ≤ 35 ml/m², 16 with normal flow [NF]) were included. At baseline, LF patients had lower total arterial compliance (0.36 ± 0.12 ml/m²/mm Hg vs. 0.48 ± 0.16 ml/m²/mm Hg; $p = 0.01$) and greater effective arterial elastance (2.77 ± 0.84 mm Hg · m²/ml vs. 1.89 ± 0.82 mm Hg · m²/ml; $p = 0.002$). In all patients, nitroprusside reduced elastance, left ventricular filling pressures, and pulmonary artery pressures and improved compliance ($p < 0.05$). Aortic valve area increased to ≥ 1.0 cm² in 6 LF (24%) and 4 NF (25%) subjects. Change in SVI with nitroprusside varied inversely to baseline SVI and demonstrated improvement in LF only (3 ± 6 ml/m²; $p = 0.02$).

CONCLUSIONS Nitroprusside reduces afterload and left ventricular filling pressures in patients with LGSAS and preserved EF, enabling reclassification to moderate stenosis in 25% of patients. An inverse relationship between baseline SVI and change in SVI with afterload reduction was observed, suggesting that heightened sensitivity to afterload is a significant

contributor to LF-LGSAS pathophysiology. These data highlight the utility of afterload reduction in the diagnostic assessment of LGSAS (15).

Implantable Hemodynamic Monitoring for Heart Failure Patients

W.T. Abraham, et al.

Rates of heart failure hospitalization remain unacceptably high. Such hospitalizations are associated with substantial patient, caregiver, and economic costs. Randomized controlled trials of noninvasive telemedical systems have failed to demonstrate reduced rates of hospitalization. The failure of these technologies may be due to the limitations of the signals measured. Intracardiac and pulmonary artery pressure-guided management has become a focus of hospitalization reduction in heart failure. Early studies using implantable hemodynamic monitors demonstrated the potential of pressure-based heart failure management, whereas subsequent studies confirmed the clinical utility of this approach. One large pivotal trial proved the safety and efficacy of pulmonary artery pressure-guided heart failure management, showing a marked reduction in heart failure hospitalizations in patients randomized to active pressure-guided management. “Next-generation” implantable hemodynamic monitors are in development, and novel approaches for the use of this data promise to expand the use of pressure-guided heart failure management (16).

Left Ventricular Assist Device as a Bridge to Recovery for Patients With Advanced Heart Failure

D.G. Jakovljevic, et al.

BACKGROUND Left ventricular assist devices (LVADs) have been used as an effective therapeutic option in patients with advanced heart failure, either as a bridge to transplantation, as destination therapy, or in some patients, as a bridge to recovery.

OBJECTIVES This study evaluated whether patients undergoing an LVAD bridge-to-recovery protocol can achieve cardiac and physical functional capacities equivalent to those of healthy controls.

METHODS Fifty-eight male patients—18 implanted with a continuous-flow LVAD, 16 patients with LVAD explanted (recovered patients), and 24 heart transplant candidates (HTx)—and 97 healthy controls performed a maximal graded cardiopulmonary

exercise test with continuous measurements of respiratory gas exchange and noninvasive (rebreathing) hemodynamic data. Cardiac function was represented by peak exercise cardiac power output (mean arterial blood pressure \times cardiac output) and functional capacity by peak exercise O_2 consumption.

RESULTS All patients demonstrated a significant exertional effort as demonstrated with the mean peak exercise respiratory exchange ratio >1.10 . Peak exercise cardiac power output was significantly higher in healthy controls and explanted LVAD patients compared with other patients (healthy 5.35 ± 0.95 W; explanted 3.45 ± 0.72 W; LVAD implanted 2.37 ± 0.68 W; and HTx 1.31 ± 0.31 W; $p < 0.05$), as was peak O_2 consumption (healthy 36.4 ± 10.3 ml/kg/min; explanted 29.8 ± 5.9 ml/kg/min; implanted 20.5 ± 4.3 ml/kg/min; and HTx 12.0 ± 2.2 ml/kg/min; $p < 0.05$). In the LVAD explanted group, 38% of the patients achieved peak cardiac power output and 69% achieved peak O_2 consumption within the ranges of healthy controls.

CONCLUSIONS The authors have shown that a substantial number of patients who recovered sufficiently to allow explantation of their LVAD can even achieve cardiac and physical functional capacities nearly equivalent to those of healthy controls (17).

Left Ventricular Assist Devices for Lifelong Support

S.P. Pinney, et al.

Continuous-flow left ventricular assist devices (LVADs) have revolutionized advanced heart failure care. These compact, fully implantable heart pumps are capable of providing meaningful increases in survival, functional capacity, and quality of life. Implantation volumes continue to grow, but several challenges remain to be overcome before LVADs will be considered as the therapy of choice for all patients with advanced heart failure. They must be able to consistently extend survival for the long term (7 to 10 years), rather than the midterm (3 to 5 years) more typical of contemporary devices; they must incorporate design elements that reduce shear stress and avoid stasis to reduce the frequent adverse events of bleeding, stroke, and pump thrombosis; and they must become more cost-effective. The advancements in engineering, implantation technique, and medical management detailed in this review will highlight the progress made toward achieving lifelong LVAD support and the challenges that remain (18).

Mode of Death in Heart Failure With Preserved Ejection Fraction

M. Vaduganathan, et al.

Little is known about specific modes of death in patients with heart failure with preserved ejection fraction (HFpEF). Herein, the authors critically appraise the current state of data and offer potential future directions. They conducted a systematic review of 1,608 published HFpEF papers from January 1, 1985, to December 31, 2015, which yielded 8 randomized clinical trials and 24 epidemiological studies with mode-of-death data. Noncardiovascular modes of death represent an important competing risk in HFpEF. Although sudden death accounted for ~25% to 30% of deaths in trials, its definition is nonspecific; it is unclear what proportion represents arrhythmic deaths. Moving forward, reporting and definitions of modes of death must be standardized and tailored to the HFpEF population. Broad-scale systematic autopsies and long-term rhythm monitoring may clarify the underlying pathology and mechanisms driving mortal events. There is an unmet need for a longitudinal multicenter, global registry of patients with HFpEF to map its natural history (19).

Pulmonary Artery Pressure-Guided Management of Patients With Heart Failure and Reduced Ejection Fraction

M.M. Givertz, et al.

BACKGROUND Despite increased use of guideline-directed medical therapy (GDMT), some patients with heart failure and reduced ejection fraction (HFrEF) remain at high risk for hospitalization and mortality. Remote monitoring of pulmonary artery (PA) pressures provides clinicians with actionable information to help further optimize medications and improve outcomes.

OBJECTIVES CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients trial) analyzed PA pressure-guided heart failure (HF) management in patients with HFrEF based on their ability to tolerate GDMT.

METHODS CHAMPION enrolled 550 patients with chronic HF regardless of left ventricular ejection fraction. A pre-specified sub-group analysis compared HF hospitalization and mortality rates between treatment and control groups in HFrEF patients (left ventricular ejection fraction \leq 40%). Post hoc analyses in patients who tolerated GDMT were also performed. Hospitalizations and mortality were

assessed using Andersen-Gill and Cox proportional hazards models.

RESULTS In 456 patients with HFrEF, HF hospitalization rates were 28% lower in the treatment group than in the control group (hazard ratio [HR]: 0.72; 95% confidence interval [CI]: 0.59 to 0.88; $p = 0.0013$), with a strong trend for 32% lower mortality (HR: 0.68; 95% CI: 0.45 to 1.02; $p = 0.06$). A 445-patient subset received at least 1 GDMT (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, or beta-blocker) at baseline; these patients had 33% lower HF hospitalization rates (HR: 0.67; 95% CI: 0.54 to 0.82; $p = 0.0002$) and 47% lower mortality (HR: 0.63; 95% CI: 0.41 to 0.96; $p = 0.0293$) than controls. Compared with controls, patients receiving both components of optimal GDMT ($n = 337$) had 43% lower HF hospitalizations (HR: 0.57; 95% CI: 0.45 to 0.74; $p < 0.0001$) and 57% lower mortality (HR: 0.43; 95% CI: 0.24 to 0.76; $p = 0.0026$).

CONCLUSIONS PA pressure-guided HF management reduces morbidity and mortality in patients with HFrEF on GDMT, underscoring the important synergy of addressing hemodynamic and neurohormonal targets of HF therapy. (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients [CHAMPION]; [NCT00531661](#)) (20).

A Test in Context: E/A and E/e' to Assess Diastolic Dysfunction and LV Filling Pressure

S.S. Mitter, et al.

Diastolic dysfunction represents a combination of impaired left ventricular (LV) relaxation, restoration forces, myocyte lengthening load, and atrial function, culminating in increased LV filling pressures. Current Doppler echocardiography guidelines recommend using early to late diastolic transmitral flow velocity (E/A) to assess diastolic function, and E to early diastolic mitral annular tissue velocity (E/e') to estimate LV filling pressures. Although both parameters have important diagnostic and prognostic implications, they should be interpreted in the context of a patient's age and the rest of the echocardiogram to describe diastolic function and guide patient management. This review discusses: 1) the physiological basis for the E/A and E/e' ratios; 2) their roles in diagnosing diastolic dysfunction; 3) prognostic implications of abnormalities in E/A and E/e'; 4) special scenarios of the E/A and E/e' ratios that are either useful or challenging when evaluating diastolic function clinically; and 5) their usefulness in guiding therapeutic decision making (21).

CARDIOMYOPATHIES/MYOCARDIAL & PERICARDIAL DISEASES

Catecholamine-Dependent β -Adrenergic Signaling in a Pluripotent Stem Cell Model of Takotsubo Cardiomyopathy

T. Borchert, et al.

BACKGROUND Takotsubo syndrome (TTS) is characterized by an acute left ventricular dysfunction and is associated with life-threatening complications in the acute phase. The underlying disease mechanism in TTS is still unknown. A genetic basis has been suggested to be involved in the pathogenesis.

OBJECTIVES The aims of the study were to establish an in vitro induced pluripotent stem cell (iPSC) model of TTS, to test the hypothesis of altered β -adrenergic signaling in TTS iPSC-cardiomyocytes (CMs), and to explore whether genetic susceptibility underlies the pathophysiology of TTS.

METHODS Somatic cells of patients with TTS and control subjects were reprogrammed to iPSCs and differentiated into CMs. Three-month-old CMs were subjected to catecholamine stimulation to simulate neurohumoral overstimulation. We investigated β -adrenergic signaling and TTS cardiomyocyte function.

RESULTS Enhanced β -adrenergic signaling in TTS-iPSC-CMs under catecholamine-induced stress increased expression of the cardiac stress marker *NR4A1*; cyclic adenosine monophosphate levels; and cyclic adenosine monophosphate-dependent protein kinase A-mediated hyperphosphorylation of RYR2-S2808, PLN-S16, TNI-S23/24, and Cav1.2-S1928, and leads to a reduced calcium time to transient 50% decay. These cellular catecholamine-dependent responses were mainly mediated by β_1 -adrenoceptor signaling in TTS. Engineered heart muscles from TTS-iPSC-CMs showed an impaired force of contraction and a higher sensitivity to isoprenaline-stimulated inotropy compared with control subjects. In addition, altered electrical activity and increased lipid accumulation were detected in catecholamine-treated TTS-iPSC-CMs, and were confirmed by differentially expressed lipid transporters *CD36* and *CPT1C*. Furthermore, we uncovered genetic variants in different key regulators of cardiac function.

CONCLUSIONS Enhanced β -adrenergic signaling and higher sensitivity to catecholamine-induced toxicity were identified as mechanisms associated with the TTS phenotype. (International Takotsubo Registry [InterTAK Registry] [InterTAK]; [NCT01947621](#)) (22).

Chronic Chagas Heart Disease Management: From Etiology to Cardiomyopathy Treatment

E.A. Bocchi, et al.

Trypanosoma cruzi (*T. cruzi*) infection is endemic in Latin America and is becoming a worldwide health burden. It may lead to heterogeneous phenotypes. Early diagnosis of *T. cruzi* infection is crucial. Several biomarkers have been reported in Chagas heart disease (ChHD), but most are nonspecific for *T. cruzi* infection. Prognosis of ChHD patients is worse compared with other etiologies, with sudden cardiac death as an important mode of death. Most ChHD patients display diffuse myocarditis with fibrosis and hypertrophy. The remodeling process seems to be associated with etiopathogenic mechanisms and neurohormonal activation. Pharmacological treatment and antiarrhythmic therapy for ChHD is mostly based on results for other etiologies. Heart transplantation is an established, valuable therapeutic option in refractory ChHD. Implantable cardioverter-defibrillators are indicated for prevention of secondary sudden cardiac death. Specific etiological treatments should be revisited and reserved for select patients. Understanding and management of ChHD need improvement, including development of randomized trials (23).

Histopathological and Immunological Characteristics of Tachycardia-Induced Cardiomyopathy

K.A.L. Mueller, et al.

BACKGROUND Tachycardiomyopathy or tachycardia-induced cardiomyopathy (TCM) has been known for decades as a reversible form of nonischemic cardiomyopathy. However, its mechanism and properties remain poorly understood.

OBJECTIVES The current study investigated endomyocardial biopsy samples from patients with TCM and compared them with samples from patients with dilated cardiomyopathy (DCM) and inflammatory cardiomyopathy (ICM).

METHODS The study included 189 patients with new-onset heart failure and severely reduced ejection fraction not caused by valvular or ischemic heart disease. Nineteen patients retrospectively fulfilled common criteria of TCM, 79 patients had a diagnosis of DCM, and 91 had a diagnosis of ICM.

RESULTS Patients with TCM, on the basis of clinical criteria, had stronger myocardial expression of major histocompatibility complex class II molecule and enhanced infiltration of CD68⁺ macrophages compared with patients with DCM. Furthermore,

when compared with patients with ICM, the presence of T cells and macrophages was significantly reduced in TCM. Myocardial fibrosis was detected to a significantly lower degree in patients with TCM compared with patients with DCM and ICM. Electron microscopic examination revealed severe structural changes in patients with TCM. A disturbed distribution pattern of mitochondria was predominantly present in TCM. Quantitative assessment of myocyte morphology revealed significantly enhanced myocyte size compared with patients with ICM. Ribonucleic acid expression analysis identified changes in metabolic pathways among the patient groups.

CONCLUSIONS TCM is characterized by changes in cardiomyocyte and mitochondrial morphology accompanied by a macrophage-dominated cardiac inflammation. Thus, further prospective studies are warranted to characterize patients with TCM by endomyocardial biopsy more clearly (24).

Hypertrophic Cardiomyopathy With Left Ventricular Apical Aneurysm: Implications for Risk Stratification and Management

E.J. Rowin, et al.

BACKGROUND A previously under-recognized subset of hypertrophic cardiomyopathy (HCM) patients with left ventricular (LV) apical aneurysms is being identified with increasing frequency. However, risks associated with this subgroup are unknown.

OBJECTIVES The authors aimed to clarify clinical course and prognosis of a large cohort of HCM patients with LV apical aneurysms over long-term follow-up.

METHODS The authors retrospectively analyzed 1,940 consecutive HCM patients at 2 centers, 93 of which (4.8%) were identified with LV apical aneurysms; mean age was 56 ± 13 years, and 69% were male.

RESULTS Over 4.4 ± 3.2 years, 3 of the 93 patients with LV apical aneurysms (3%) died suddenly or of heart failure, but 22 (24%) survived with contemporary treatment interventions: 18 experienced appropriate implantable cardioverter-defibrillator discharges, 2 underwent heart transplants, and 2 were resuscitated after cardiac arrest. The sudden death (SD) event rate was 4.7%/year, which includes sudden death, successful resuscitation from cardiac arrest or appropriate ICD interventions triggered by VF or rapid VT. Notably, recurrent monomorphic ventricular tachycardia requiring ≥ 2 implantable cardioverter-defibrillator shocks occurred in 13 patients, including 6 who underwent successful radiofrequency ablation of the arrhythmic focus

without ventricular tachycardia recurrence. Five non-anticoagulated patients experienced nonfatal thromboembolic events (1.1%/year), whereas 13 with apical clots and anticoagulation did not incur embolic events. There was no consistent relationship between aneurysm size and adverse HCM-related events. Rate of HCM-related deaths combined with life-saving aborted disease-related events was 6.4%/year, 3-fold greater than the 2.0%/year event rate in 1,847 HCM patients without aneurysms ($p < 0.001$).

CONCLUSIONS HCM patients with LV apical aneurysms are at high risk for arrhythmic sudden death and thromboembolic events. Identification of this phenotype expands risk stratification and can lead to effective treatment interventions for potentially life-threatening complications (25).

CARDIO-ONCOLOGY

Cardiovascular Complications of Cancer Therapy: Best Practices in Diagnosis, Prevention, and Management: Part 1

H.-M. Chang, et al.

Modern cancer therapy has successfully cured many cancers and converted a terminal illness into a chronic disease. Because cancer patients often have coexisting heart diseases, expert advice from cardiologists will improve clinical outcome. In addition, cancer therapy can also cause myocardial damage, induce endothelial dysfunction, and alter cardiac conduction. Thus, it is important for practicing cardiologists to be knowledgeable about the diagnosis, prevention, and management of the cardiovascular complications of cancer therapy. In this first part of a 2-part review, we will review cancer therapy-induced cardiomyopathy and ischemia. This review is based on a MEDLINE search of published data, published clinical guidelines, and best practices in major cancer centers. With the number of cancer survivors expanding quickly, the time has come for cardiologists to work closely with cancer specialists to prevent and treat cancer therapy-induced cardiovascular complications (26).

Cardiovascular Complications of Cancer Therapy: Best Practices in Diagnosis, Prevention, and Management: Part 2

H.-M. Chang, et al.

In this second part of a 2-part review, we will review cancer or cancer therapy-associated systemic and pulmonary hypertension, QT prolongation, arrhythmias, pericardial disease, and radiation-induced

cardiotoxicity. This review is based on a MEDLINE search of published data, published clinical guidelines, and best practices in major cancer centers. Newly developed targeted therapy can exert off-target effects causing hypertension, thromboembolism, QT prolongation, and atrial fibrillation. Radiation therapy often accelerates atherosclerosis. Furthermore, radiation can damage the heart valves, the conduction system, and pericardium, which may take years to manifest clinically. Management of pericardial disease in cancer patients also posed clinical challenges. This review highlights the unique opportunity of caring for cancer patients with heart problems caused by cancer or cancer therapy. It is an invitation to action for cardiologists to become familiar with this emerging subspecialty (27).

Diagnosing and Managing Carcinoid Heart Disease in Patients With Neuroendocrine Tumors: An Expert Statement

J. Davar, et al.

Carcinoid heart disease is a frequent occurrence in patients with carcinoid syndrome and is responsible for substantial morbidity and mortality. The pathophysiology of carcinoid heart disease is poorly understood; however, chronic exposure to excessive circulating serotonin is considered one of the most important contributing factors. Despite recognition, international consensus guidelines specifically addressing the diagnosis and management of carcinoid heart disease are lacking. Furthermore, there is considerable variation in multiple aspects of screening and management of the disease. The aim of these guidelines was to provide succinct, practical advice on the diagnosis and management of carcinoid heart disease as well as its surveillance. Recommendations and proposed algorithms for the investigation, screening, and management have been developed based on an evidence-based review of the published data and on the expert opinion of a multidisciplinary consensus panel consisting of neuroendocrine tumor experts, including oncologists, gastroenterologists, and endocrinologists, in conjunction with cardiologists and cardiothoracic surgeons (28).

CONGENITAL HEART DISEASE

Cardiovascular Risk Factors From Childhood and Midlife Cognitive Performance: The Young Finns Study

S.P. Rovio, et al.

BACKGROUND In adults, high blood pressure (BP), adverse serum lipids, and smoking associate with

cognitive deficits. The effects of these risk factors from childhood on midlife cognitive performance are unknown.

OBJECTIVES This study sought to investigate the associations between childhood/adolescence cardiovascular risk factors and midlife cognitive performance.

METHODS From 1980, a population-based cohort of 3,596 children (baseline age: 3 to 18 years) have been followed for 31 years in 3- to 9-year intervals. BP, serum lipids, body mass index, and smoking were assessed in all follow-ups. Cumulative exposure as the area under the curve for each risk factor was determined in childhood (6 to 12 years), adolescence (12 to 18 years), and young adulthood (18 to 24 years). In 2011, cognitive testing was performed in 2,026 participants aged 34 to 49 years.

RESULTS High systolic BP, elevated serum total-cholesterol, and smoking from childhood were independently associated with worse midlife cognitive performance, especially memory and learning. The number of early life risk factors, including high levels (extreme 75th percentile for cumulative risk exposure between ages 6 and 24 years) of systolic BP, total-cholesterol, and smoking associated inversely with midlife visual and episodic memory and visuospatial associative learning (-0.140 standard deviations per risk factor, $p < 0.0001$) and remained significant after adjustment for contemporaneous risk factors. Individuals with all risk factors within recommended levels between ages 6 and 24 years performed 0.29 standard deviations better ($p = 0.006$) on this cognitive domain than those exceeding all risk factor guidelines at least twice. This difference corresponds to the effect of 6 years aging on this cognitive domain.

CONCLUSIONS Cumulative burden of cardiovascular risk factors from childhood/adolescence associate with worse midlife cognitive performance independent of adulthood exposure (29).

Clinical Outcomes Following the Ross Procedure in Adults: A 25-Year Longitudinal Study

E. Martin, et al.

BACKGROUND Very few reports of long-term outcomes of patients who underwent the Ross procedure have been published.

OBJECTIVES The authors reviewed their 25-year experience with the Ross procedure with the aim of defining very-long-term survival and factors associated with Ross-related failure.

METHODS Between January 1990 and December 2014, the Ross procedure was performed in 310 adults (mean age 40.8 years) at a single institution. All patients were prospectively added to a dedicated cardiac surgery registry. Complete post-operative clinical examination and history were obtained, and transthoracic echocardiography was performed according to a standardized protocol. There was no loss to follow-up. Median follow-up was 15.1 years and up to 25 years.

RESULTS Bicuspid aortic valve was diagnosed in 227 patients (73.2%), and the most common indication for surgery was aortic stenosis (n = 225 [72.6%]). Freedom from any Ross-related reintervention was 92.9% and 70.1% at 10 and 20 years, respectively. Independent risk factors for pulmonary autograft degeneration were pre-operative large aortic annulus (hazard ratio: 1.1; p = 0.01), pre-operative aortic insufficiency (hazard ratio: 2.7; p = 0.002), and concomitant replacement of the ascending aorta (hazard ratio: 7.7; p = 0.0003). There were 4 hospital deaths (1.3%), and overall survival at 10 and 20 years was 94.1% and 83.6%, respectively. Long-term survival was not significantly different in patients who required Ross-related reintervention (log-rank p = 0.70). However, compared with the general population, survival was significantly lower in patients following the Ross procedure when matched on age and sex (p < 0.0001).

CONCLUSIONS The Ross procedure was associated with excellent long-term valvular outcomes and survival, regardless of the need for reintervention. Adults presenting with aortic insufficiency or a dilated aortic annulus or ascending aorta were at greater risk for reintervention. Unlike previous reports, long-term survival was lower in Ross patients compared with matched subjects (30).

Protein-Losing Enteropathy in Patients With Congenital Heart Disease

M. Itkin, et al.

BACKGROUND Protein-losing enteropathy (PLE), characterized by loss of proteins in the intestine, is a devastating complication in patients with congenital heart disease. The cause of PLE is unknown, but lymphatic involvement has been suspected.

OBJECTIVES The authors evaluated the use of lymphangiographic imaging and liver lymphatic embolization as a treatment for PLE.

METHODS This was a single-center, retrospective review of imaging and interventions used in 8 consecutive patients with liver lymphatic embolization and congenital heart disease with elevated central venous pressure complicated by PLE.

RESULTS Liver lymphangiography was performed in 8 patients (5 males, 3 females; median age, 21 years), 7 of whom demonstrated leakage of liver lymph into the duodenum through abnormal hepatoduodenal lymphatic communications. This was confirmed by duodenoscopy with simultaneous injection of isosulfan blue dye into the liver lymphatics in 6 of 7 patients. Liver lymphatic embolization with ethiodized oil in 2 patients resulted in a temporary increase in albumin blood level and symptom improvement in 1 patient, but was complicated by duodenal bleeding in both patients. Of the remaining 6 patients, liver lymphatic embolization with n-butyl cyanoacrylate glue resulted in sustained improvement of the serum albumin level and symptoms in 3 patients, temporary improvement in 2 patients, and no change in 1 patient with median follow-up of 135 days (range, 84 to 1,005 days).

CONCLUSIONS The authors demonstrated liver lymph leakage as a cause of PLE in patients with congenital heart disease and elevated central venous pressure. Lymphatic embolization led to improved albumin levels and relief of symptoms. Further experience with the technique is needed to determine long-term outcome of this procedure (31).

CORONARY DISEASE & INTERVENTIONS

Anomalous Aortic Origin of a Coronary Artery From the Inappropriate Sinus of Valsalva

M.K. Cheezum, et al.

Anomalous aortic origin of a coronary artery (AAOCA) from the inappropriate sinus of Valsalva is increasingly recognized by cardiac imaging. Although most AAOCA subtypes are benign, autopsy studies report an associated risk of sudden death with interarterial anomalous left coronary artery (ALCA) and anomalous right coronary artery (ARCA). Despite efforts to identify high-risk ALCA and ARCA patients who may benefit from surgical repair, debate remains regarding their classification, prevalence, risk stratification, and management. We comprehensively reviewed 77 studies reporting the prevalence of AAOCA among >1 million patients, and 20 studies examining outcomes of interarterial ALCA/ARCA patients. Observational data suggests that interarterial ALCA is rare (weighted prevalence = 0.03%; 95% confidence interval [CI]: 0.01% to 0.04%) compared with interarterial ARCA (weighted prevalence = 0.23%; 95% CI: 0.17% to 0.31%). Recognizing the challenges in managing these patients, we review cardiac tests used to examine AAOCA and knowledge gaps in management (32).

Bleeding-Related Deaths in Relation to the Duration of Dual-Antiplatelet Therapy After Coronary Stenting

T. Palmerini, et al.

BACKGROUND Although some randomized controlled trials (RCTs) and meta-analyses have suggested that prolonged dual-antiplatelet therapy (DAPT) may be associated with increased mortality, the mechanistic underpinnings of this association remain unclear.

OBJECTIVES The aim of this study was to analyze the associations among bleeding, mortality, and DAPT duration after drug-eluting stent implantation in a meta-analysis of RCTs.

METHODS RCTs comparing different DAPT durations after drug-eluting stent placement were sought through the MEDLINE, Embase, and Cochrane databases and the proceedings of international meetings. Deaths were considered possibly bleeding related if occurring within 1 year of the episodes of bleeding. Primary analysis was by intention-to-treat. Secondary analysis was performed in a modified intention-to-treat population in which events occurring when all patients were on DAPT were excluded.

RESULTS Individual patient data were obtained for 6 RCTs, and aggregate data were available for 12 RCTs. Patients with bleeding had significantly higher rates of mortality compared with those without, and in a time-adjusted multivariate analysis, bleeding was an independent predictor of mortality occurring within 1 year of the bleeding episode (hazard ratio: 6.93; 95% confidence interval: 4.53 to 10.60; $p < 0.0001$). Shorter DAPT was associated with lower rates of all-cause death compared with longer DAPT (hazard ratio: 0.85; 95% confidence interval: 0.73 to 1.00; $p = 0.05$), which was driven by lower rates of bleeding-related deaths with shorter DAPT compared with prolonged DAPT (hazard ratio: 0.65; 95% confidence interval: 0.43 to 0.99; $p = 0.04$). Mortality unrelated to bleeding was comparable between the 2 groups. Similar results were apparent in the modified intention-to-treat population.

CONCLUSIONS Bleeding was strongly associated with the occurrence of mortality within 1 year after the bleeding event. Shorter compared with longer DAPT was associated with lower risk for bleeding-related death, a finding that may underlie the lower all-cause mortality with shorter DAPT in the RCTs of different DAPT durations after DES (33).

Cardiovascular Risk Following Fertility Therapy: Systematic Review and Meta-Analysis

N. Dayan, et al.

BACKGROUND The longer term cardiovascular effects of fertility therapy are unknown.

OBJECTIVES The aim of this study was to summarize data linking fertility therapy with subsequent cardiovascular outcomes.

METHODS We systematically searched published reports for studies addressing the question “does fertility therapy increase the risk of longer term cardiovascular outcomes?” We included: 1) human studies; 2) case control, cohort, or randomized designs with 3) exposure to fertility therapy and 4) cardiovascular outcomes clearly reported; 5) presence of comparison group; 6) minimum 1-year follow-up; and 7) adjustment for age. Two independent reviewers screened abstracts, titles, and full texts, and assessed study quality. We used the DerSimonian and Laird random-effects models to pool hazard ratios (HRs) with 95% confidence intervals (CIs) of the following outcomes: acute cardiac event; stroke; venous thromboembolism; hypertension; and diabetes mellitus, comparing women who received fertility therapy with those who did not.

RESULTS Six observational studies met inclusion criteria including 41,910 women who received fertility therapy and 1,400,202 women who did not. There was no increased risk of a cardiac event (pooled HR: 0.91; 95% CI: 0.67 to 1.25; $I^2 = 36.6\%$), or diabetes mellitus (pooled HR: 0.93; 95% CI: 0.87 to 1.001; $I^2 = 0\%$). Results were not pooled for hypertension ($I^2 = 95.0\%$) and venous thromboembolism ($I^2 = 82.3\%$). There was a trend toward higher risk of stroke (pooled HR: 1.25; 95% CI: 0.96 to 1.63; $I^2 = 0\%$).

CONCLUSIONS The small number of studies and significant heterogeneity precludes definitive reassurance about the longer term cardiovascular safety of these treatments, particularly stroke. Future studies are needed to address ongoing knowledge gaps in this area (34).

Comparison of Different Diastolic Resting Indexes to iFR: Are They All Equal?

M. van't Veer, et al.

BACKGROUND Pressure measurement for the duration of the wave-free period (WFP) is considered essential for resting-state physiological assessment of coronary stenosis severity using the instantaneous wave-free ratio (iFR).

OBJECTIVES The aim of this study was to compare other diastolic resting indexes to iFR.

METHODS In the population of the VERIFY2 (Pd/Pa vs. iFR in an Unselected Population Referred for Invasive Angiography) study, iFR calculated by proprietary software (Volcano Harvest, Volcano Corporation, Rancho Cordova, California) was compared with the ratio of resting distal coronary pressure and aortic pressure during the complete duration of diastole (dPR), 25% to 75% of diastole (dPR₂₅₋₇₅), and midpoint of diastole (dPR_{mid}), along with Matlab calculated iFR (iFR_{matlab}) and iFR-like indexes shortening the length of the WFP by 50 and 100 ms (iFR_{-50ms} and iFR_{-100ms}), respectively. Mutual differences, Spearman correlations, area under the curve values from receiver-operating characteristic analyses, and diagnostic performance with respect to iFR and fractional flow reserve (FFR) were calculated for all indexes.

RESULTS Median iFR in 197 patients with 257 vessels was 0.91 with an interquartile range of 0.87 to 0.95. The mutual differences (\pm SD) with iFR were 0.006 ± 0.011 (dPR), 0.001 ± 0.007 (dPR₂₅₋₇₅), 0.001 ± 0.008 (dPR_{mid}), 0.005 ± 0.009 (iFR_{matlab}), 0.003 ± 0.008 (iFR_{-50ms}), and 0.001 ± 0.009 (iFR_{-100ms}). Correlations for all indexes with iFR were >0.99 ($p < 0.001$ for all). Area under the curve values for predicting iFR were >0.99 for all indexes as well. Diagnostic accuracy compared with FFR was 76% to 77% for all indexes including iFR.

CONCLUSIONS All diastolic resting indexes tested were identical to iFR, both numerically and with respect to their agreement with FFR. A numerically equal value to iFR can be determined without restriction to the WFP. Cutoff values, guidelines, and clinical recommendations for iFR can therefore be extended to these other indexes. (Pd/Pa vs iFR in an Unselected Population Referred for Invasive Angiography [VERIFY2]; [NCT02377310](#)) (35).

Coronary Artery Disease in Patients With Out-of-Hospital Refractory Ventricular Fibrillation Cardiac Arrest

D. Yannopoulos, et al.

BACKGROUND The prevalence of coronary artery disease (CAD) among patients with refractory out-of-hospital (OH) ventricular fibrillation (VF)/ventricular tachycardia (VT) cardiac arrest is unknown.

OBJECTIVES The goal of this study was to describe the prevalence and complexity of CAD and report survival to hospital discharge in patients experiencing

refractory VF/VT cardiac arrest treated with a novel protocol of early transport to a cardiac catheterization laboratory (CCL) for extracorporeal life support (ECLS) and revascularization.

METHODS Between December 1, 2015, and December 1, 2016, consecutive adult patients with refractory OH VF/VT cardiac arrest requiring ongoing cardiopulmonary resuscitation were transported by emergency medical services to the CCL. ECLS, coronary angiography, and percutaneous coronary intervention were performed, as appropriate. Functionally favorable survival to hospital discharge (Cerebral Performance Category 1 or 2) was determined. Outcomes in a historical comparison group were also evaluated.

RESULTS Sixty-two (86%) of 72 transported patients met emergency medical services transport criteria. Fifty-five (89%) of the 62 patients met criteria for continuing resuscitation on CCL arrival; 5 had return of spontaneous circulation, 50 received ECLS, and all 55 received coronary angiography. Forty-six (84%) of 55 patients had significant CAD, 35 (64%) of 55 had acute thrombotic lesions, and 46 (84%) of 55 had percutaneous coronary intervention with 2.7 ± 2.0 stents deployed per patient. The mean SYNTAX score was 29.4 ± 13.9 . Twenty-six (42%) of 62 patients were discharged alive with Cerebral Performance Category 1 or 2 versus 26 (15.3%) of 170 in the historical comparison group (odds ratio: 4.0; 95% confidence interval: 2.08 to 7.7; $p < 0.0001$).

CONCLUSIONS Complex but treatable CAD was prevalent in patients with refractory OH VF/VT cardiac arrest who also met criteria for continuing resuscitation in the CCL. A systems approach using ECLS and reperfusion seemed to improve functionally favorable survival (36).

Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis

B. Xu, et al.

BACKGROUND Quantitative flow ratio (QFR) is a novel angiography-based method for deriving fractional flow reserve (FFR) without pressure wire or induction of hyperemia. The accuracy of QFR when assessed online in the catheterization laboratory has not been adequately examined to date.

OBJECTIVES The goal of this study was to assess the diagnostic performance of QFR for the diagnosis of hemodynamically significant coronary stenosis defined by $FFR \leq 0.80$.

METHODS This prospective, multicenter trial enrolled patients who had at least 1 lesion with a diameter stenosis of 30% to 90% and a reference diameter ≥ 2 mm according to visual estimation. QFR, quantitative coronary angiography (QCA), and wire-based FFR were assessed online in blinded fashion during coronary angiography and re-analyzed offline at an independent core laboratory. The primary endpoint was that QFR would improve the diagnostic accuracy of coronary angiography such that the lower boundary of the 2-sided 95% confidence interval (CI) of this estimate exceeded 75%.

RESULTS Between June and July 2017, a total of 308 patients were consecutively enrolled at 5 centers. Online QFR and FFR results were both obtained in 328 of 332 interrogated vessels. Patient- and vessel-level diagnostic accuracy of QFR was 92.4% (95% CI: 88.9% to 95.1%) and 92.7% (95% CI: 89.3% to 95.3%), respectively, both of which were significantly higher than the pre-specified target value ($p < 0.001$). Sensitivity and specificity in identifying hemodynamically significant stenosis were significantly higher for QFR than for QCA (sensitivity: 94.6% vs. 62.5%; difference: 32.0% [$p < 0.001$]; specificity: 91.7% vs. 58.1%; difference: 36.1% [$p < 0.001$]). Positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for QFR were 85.5%, 97.1%, 11.4, and 0.06. Offline analysis also revealed that vessel-level QFR had a high diagnostic accuracy of 93.3% (95% CI: 90.0% to 95.7%).

CONCLUSIONS The study met its prespecified primary performance goal for the level of diagnostic accuracy of QFR in identifying hemodynamically significant coronary stenosis. (The FAVOR [Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis] II China study); [NCT03191708](#) (37).

Double Kissing Crush Versus Provisional Stenting for Left Main Distal Bifurcation Lesions: DKCRUSH-V Randomized Trial

S.-L. Chen, et al.

BACKGROUND Provisional stenting (PS) is the most common technique used to treat distal left main (LM) bifurcation lesions in patients with unprotected LM coronary artery disease undergoing percutaneous coronary intervention. The double kissing (DK) crush planned 2-stent technique has been shown to improve clinical outcomes in non-LM bifurcations compared with PS, and in LM bifurcations compared with

culotte stenting, but has never been compared with PS in LM bifurcation lesions.

OBJECTIVES The authors sought to determine whether a planned DK crush 2-stent technique is superior to PS for patients with true distal LM bifurcation lesions.

METHODS The authors randomized 482 patients from 26 centers in 5 countries with true distal LM bifurcation lesions (Medina 1,1,1 or 0,1,1) to PS ($n = 242$) or DK crush stenting ($n = 240$). The primary endpoint was the 1-year composite rate of target lesion failure (TLF): cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization. Routine 13-month angiographic follow-up was scheduled after ascertainment of the primary endpoint.

RESULTS TLF within 1 year occurred in 26 patients (10.7%) assigned to PS, and in 12 patients (5.0%) assigned to DK crush (hazard ratio: 0.42; 95% confidence interval: 0.21 to 0.85; $p = 0.02$). Compared with PS, DK crush also resulted in lower rates of target vessel myocardial infarction I (2.9% vs. 0.4%; $p = 0.03$) and definite or probable stent thrombosis (3.3% vs. 0.4%; $p = 0.02$). Clinically driven target lesion revascularization (7.9% vs. 3.8%; $p = 0.06$) and angiographic restenosis within the LM complex (14.6% vs. 7.1%; $p = 0.10$) also tended to be less frequent with DK crush compared with PS. There was no significant difference in cardiac death between the groups.

CONCLUSIONS In the present multicenter randomized trial, percutaneous coronary intervention of true distal LM bifurcation lesions using a planned DK crush 2-stent strategy resulted in a lower rate of TLF at 1 year than a PS strategy. (Double Kissing and Double Crush Versus Provisional T Stenting Technique for the Treatment of Unprotected Distal Left Main True Bifurcation Lesions: A Randomized, International, Multi-Center Clinical Trial [DKCRUSH-V]; [ChiCTR-TRC-11001213](#)) (38).

Effect of Technique on Outcomes Following Bioresorbable Vascular Scaffold Implantation: Analysis From the ABSORB Trials

G.W. Stone, et al.

BACKGROUND Procedural technique may affect clinical outcomes after bioresorbable vascular scaffold (BVS) implantation. Prior studies suggesting such a relationship have not adjusted for baseline patient and lesion characteristics that may have influenced operator choice of technique and outcomes.

OBJECTIVES This study sought to determine whether target lesion failure (TLF) (cardiac death, target-vessel myocardial infarction, or ischemia-driven target lesion revascularization) and scaffold thrombosis (ScT) rates within 3 years of BVS implantation are affected by operator technique (vessel size selection and pre- and post-dilation parameters).

METHODS TLF and ScT rates were determined in 2,973 patients with 3,149 BVS-treated coronary artery lesions from 5 prospective studies (ABSORB II, ABSORB China, ABSORB Japan, ABSORB III, and ABSORB Extend). Outcomes through 3 years (and between 0 to 1 and 1 to 3 years) were assessed according to pre-specified definitions of optimal technique (pre-dilation, vessel sizing, and post-dilation). Multivariable analysis was used to adjust for differences in up to 18 patient and lesion characteristics.

RESULTS Optimal pre-dilation (balloon to core laboratory-derived reference vessel diameter ratio $\geq 1:1$), vessel size selection (reference vessel diameter ≥ 2.25 mm and ≤ 3.75 mm), and post-dilation (with a noncompliant balloon at ≥ 18 atm and larger than the nominal scaffold diameter, but not by >0.5 mm larger) in all BVS-treated lesions were performed in 59.2%, 81.6%, and 12.4% of patients, respectively. BVS implantation in properly sized vessels was an independent predictor of freedom from TLF through 1 year (hazard ratio [HR]: 0.67; $p = 0.01$) and through 3 years (HR: 0.72; $p = 0.01$), and of freedom from ScT through 1 year (HR: 0.36; $p = 0.004$). Aggressive pre-dilation was an independent predictor of freedom from ScT between 1 and 3 years (HR: 0.44; $p = 0.03$), and optimal post-dilation was an independent predictor of freedom from TLF between 1 and 3 years (HR: 0.55; $p = 0.05$).

CONCLUSIONS In the present large-scale analysis from the major ABSORB studies, after multivariable adjustment for baseline patient and lesion characteristics, vessel sizing and operator technique were strongly associated with BVS-related outcomes during 3-year follow-up. (ABSORB II Randomized Controlled Trial [ABSORB II]; [NCT01425281](#); ABSORB III Randomized Controlled Trial [RCT] [ABSORB-III]; [NCT01751906](#); A Clinical Evaluation of Absorb Bioresorbable Vascular Scaffold [Absorb BVS] System in Chinese Population—ABSORB CHINA Randomized Controlled Trial [RCT] [ABSORB CHINA]; [NCT01923740](#); ABSORB EXTEND Clinical Investigation [ABSORB EXTEND]; [NCT01023789](#); AVJ-301 Clinical Trial: A Clinical Evaluation of AVJ-301 [Absorb BVS] in Japanese Population [ABSORB JAPAN]; [NCT01844284](#)) (39).

The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve

M. Götberg, et al.

In this review, the authors reflect upon the role of coronary physiology in the modern management of coronary artery disease. They critically appraise the scientific background of the instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR), from early experimental studies to validation studies against indexes of ischemia, to clinical trials assessing outcome. At this important juncture for the field, the authors make predictions for the future of physiological stenosis assessment, outlining developments for both iFR and FFR in new clinical domains beyond the confines of stable angina. With a focus on the evolving future of iFR and FFR, the authors describe how physiological assessment with iFR may advance its application from simply justifying to guiding revascularization (40).

High-Sensitivity Cardiac Troponin Concentration and Risk of First-Ever Cardiovascular Outcomes in 154,052 Participants

P. Willeit, et al.

BACKGROUND High-sensitivity assays can quantify cardiac troponins I and T (hs-cTnI, hs-cTnT) in individuals with no clinically manifest myocardial injury.

OBJECTIVES The goal of this study was to assess associations of cardiac troponin concentration with cardiovascular disease (CVD) outcomes in primary prevention studies.

METHODS A search was conducted of PubMed, Web of Science, and EMBASE for prospective studies published up to September 2016, reporting on associations of cardiac troponin concentration with first-ever CVD outcomes (i.e., coronary heart disease [CHD], stroke, or the combination of both). Study-specific estimates, adjusted for conventional risk factors, were extracted by 2 independent reviewers, supplemented with de novo data from PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease Study), then pooled by using random effects meta-analysis.

RESULTS A total of 28 relevant studies were identified involving 154,052 participants. Cardiac troponin was detectable in 80.0% (hs-cTnI: 82.6%; hs-cTnT: 69.7%). In PROSPER, positive associations of log-linear shape were observed between hs-cTnT and CVD outcomes.

In the meta-analysis, the relative risks comparing the top versus the bottom troponin third were 1.43 (95% confidence interval [CI]: 1.31 to 1.56) for CVD (11,763 events), 1.67 (95% CI: 1.50 to 1.86) for fatal CVD (7,775 events), 1.59 (95% CI: 1.38 to 1.83) for CHD (7,061 events), and 1.35 (95% CI: 1.23 to 1.48) for stroke (2,526 events). For fatal CVD, associations were stronger in North American studies ($p = 0.010$) and those measuring hs-cTnT rather than hs-cTnI ($p = 0.027$).

CONCLUSIONS In the general population, high cardiac troponin concentration within the normal range is associated with increased CVD risk. This association is independent of conventional risk factors, strongest for fatal CVD, and applies to both CHD and stroke (41).

Mechanisms of Very Late Bioresorbable Scaffold Thrombosis: The INVEST Registry

K. Yamaji, et al.

BACKGROUND Very late scaffold thrombosis (VLScT) occurs more frequently after bioresorbable scaffold (Absorb BVS 1.1, Abbott Vascular, Santa Clara, California) implantation than with metallic everolimus-eluting stents.

OBJECTIVES The purpose of this study was to elucidate mechanisms underlying VLScT as assessed by optical coherence tomography (OCT).

METHODS The INVEST (Independent OCT Registry on Very Late Bioresorbable Scaffold Thrombosis) registry is an international consortium of investigators who used OCT to examine patients with VLScT.

RESULTS Between June 2013 and May 2017, 36 patients with 38 lesions who had VLScT underwent OCT at 19 centers. VLScT occurred at a median of 20 months (interquartile range: 16 to 27 months) after implantation. At the time of VLScT, 83% of patients received aspirin monotherapy and 17% received dual-antiplatelet therapy. The mechanisms underlying VLScT were (in descending order) scaffold discontinuity (42.1%), malapposition (18.4%), neoatherosclerosis (18.4%), underexpansion or scaffold recoil (10.5%), uncovered struts (5.3%), and edge-related disease progression (2.6%). Discontinuity (odds ratio [OR]: 110; 95% confidence interval [CI]: 73.5 to 173; $p < 0.001$), malapposed struts (OR: 17.0; 95% CI: 14.8 to 19.7; $p < 0.001$), and uncovered struts (OR: 7.3; 95% CI: 6.2 to 8.8; $p < 0.001$) were more frequent in the thrombosed than the nonthrombosed scaffold regions. In 2

of 16 patients with scaffold discontinuity, intercurrent OCT before VLScT provided evidence of circularly apposed scaffold struts with minimal tissue coverage.

CONCLUSIONS The leading mechanism underlying VLScT was scaffold discontinuity, which suggests an unfavorable resorption-related process, followed by malapposition and neoatherosclerosis. It remains to be determined whether modifications in scaffold design and optimized implantation can mitigate the risk of VLScT. (Independent OCT Registry on Very Late Bioresorbable Scaffold Thrombosis [INVEST]; NCT03180931) (42).

Risk Stratification for Patients in Cardiogenic Shock After Acute Myocardial Infarction

J. Pöss, et al.

BACKGROUND Mortality in cardiogenic shock (CS) remains high. Early risk stratification is crucial to make adequate treatment decisions.

OBJECTIVES This study sought to develop an easy-to-use, readily available risk prediction score for short-term mortality in patients with CS, derived from the IABP-SHOCK II (Intraaortic Balloon Pump in Cardiogenic Shock) trial.

METHODS The score was developed using a stepwise multivariable regression analysis.

RESULTS Six variables emerged as independent predictors for 30-day mortality and were used as score parameters: age >73 years, prior stroke, glucose at admission >10.6 mmol/l (191 mg/dl), creatinine at admission >132.6 μ mol/l (1.5 mg/dl), Thrombolysis In Myocardial Infarction flow grade <3 after percutaneous coronary intervention, and arterial blood lactate at admission >5 mmol/l. Either 1 or 2 points were attributed to each variable, leading to a score in 3 risk categories: low (0 to 2), intermediate (3 or 4), and high (5 to 9). The observed 30-day mortality rates were 23.8%, 49.2%, and 76.6%, respectively ($p < 0.0001$). Validation in the IABP-SHOCK II registry population showed good discrimination with an area under the curve of 0.79. External validation in the CardShock trial population ($n = 137$) showed short-term mortality rates of 28.0% (score 0 to 2), 42.9% (score 3 to 4), and 77.3% (score 5 to 9; $p < 0.001$) and an area under the curve of 0.73. Kaplan-Meier analysis revealed a stepwise increase in mortality between the different score categories (0 to 2 vs. 3 to 4: $p = 0.04$; 0 to 2 vs. 5 to 9: $p = 0.008$).

CONCLUSIONS The IABP-SHOCK II risk score can be easily calculated in daily clinical practice and strongly correlated with mortality in patients with infarct-related CS. It may help stratify patient risk for short-term mortality and might, thus, facilitate clinical decision making. (Intraaortic Balloon Pump in Cardiogenic Shock II [IABP-SHOCK II]; NCT00491036) (43).

Stable High-Sensitivity Cardiac Troponin T Levels and Outcomes in Patients With Chest Pain

A. Roos, et al.

BACKGROUND There is a paucity of data on the association between high-sensitivity cardiac troponin (hs-cTn) levels and outcomes in patients with chest pain but no myocardial infarction (MI), or any other condition that may lead to acutely elevated troponin levels.

OBJECTIVES The authors hypothesized that any detectable high-sensitivity cardiac troponin T (hs-cTnT) level is associated with adverse outcomes.

METHODS All patients (N = 22,589) >25 years of age with chest pain and hs-cTnT analyzed concurrently in the emergency department of Karolinska University Hospital, Stockholm, Sweden from 2011 to 2014 were eligible for inclusion. After excluding all patients with acute conditions that may have affected hs-cTnT, or MI associated with the visit, or insufficient information to determine whether troponin levels were stable, Cox regression was used to estimate risks for all-cause, cardiovascular, and noncardiovascular mortality, MI, and heart failure at different levels of troponins.

RESULTS A total of 19,460 patients with a mean age of 54 ± 17 years were included. During a mean follow-up of 3.3 ± 1.2 years, 1,349 (6.9%) patients died. Adjusted hazard ratios (with 95% confidence intervals) for all-cause mortality were 2.00 (1.66 to 2.42), 2.92 (2.38 to 3.59), 4.07 (3.28 to 5.05), 6.77 (5.22 to 8.78), and 9.68 (7.18 to 13.00) in patients with hs-cTnT levels of 5 to 9, 10 to 14, 15 to 29, 30 to 49, and ≥ 50 ng/l, respectively, compared with patients with hs-cTnT levels <5 ng/l. There was a strong and graded association between all detectable levels of hs-cTnT and risk for MI, heart failure, and cardiovascular and noncardiovascular mortality.

CONCLUSIONS Among patients with chest pain and stable troponin levels, any detectable level of hs-cTnT is associated with an increased risk of death and

cardiovascular outcomes and should merit further attention (44).

CVD PREVENTION & HEALTH PROMOTION

Adherence Tradeoff to Multiple Preventive Therapies and All-Cause Mortality After Acute Myocardial Infarction

M.J. Korhonen, et al.

BACKGROUND Angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARB), beta-blockers and statins are recommended after acute myocardial infarction (AMI). Patients may adhere to some, but not all, therapies.

OBJECTIVES The authors investigated the effect of tradeoffs in adherence to ACE inhibitors/ARBs, beta-blockers, and statins on survival among older people after AMI.

METHODS The authors identified 90,869 Medicare beneficiaries ≥ 65 years of age who had prescriptions for ACE inhibitors/ARBs, beta-blockers, and statins, and survived ≥ 180 days after AMI hospitalization in 2008 to 2010. Adherence was measured by proportion of days covered (PDC) during 180 days following hospital discharge. Mortality follow-up extended up to 18 months after this period. The authors used Cox proportional hazards models to estimate hazard ratios of mortality for groups adherent to 2, 1, or none of the therapies versus group adherent to all 3 therapies.

RESULTS Only 49% of the patients adhered (PDC $\geq 80\%$) to all 3 therapies. Compared with being adherent to all 3 therapies, multivariable-adjusted hazard ratios (95% confidence intervals [CIs]) for mortality were 1.12 (95% CI: 1.04 to 1.21) for being adherent to ACE inhibitors/ARBs and beta-blockers only, 0.98 (95% CI: 0.91 to 1.07) for ACEI/ARBs and statins only, 1.17 (95% CI: 1.10 to 1.25) beta-blockers and statins only, 1.19 (95% CI: 1.07 to 1.32) for ACE inhibitors/ARBs only, 1.32 (95% CI: 1.21 to 1.44) for beta-blockers only, 1.26 (95% CI: 1.15 to 1.38) statins only, and 1.65 (95% CI: 1.54 to 1.76) for being nonadherent (PDC <80%) to all 3 therapies.

CONCLUSIONS Patients adherent to ACE inhibitors/ARBs and statins only had similar mortality rates as those adherent to all 3 therapies, suggesting limited additional benefit for beta-blockers in patients who were adherent to statins and ACE inhibitors/ARBs. Nonadherence to ACE inhibitors/ARBs and/or statins was associated with higher mortality (45).

Effect of Current Dietary Recommendations on Weight Loss and Cardiovascular Risk Factors

D.J.A. Jenkins, et al.

BACKGROUND Dietary recommendations emphasize increased consumption of fruit, vegetables, and whole grain cereals for prevention of chronic disease.

OBJECTIVES This study assessed the effect of dietary advice and/or food provision on body weight and cardiovascular disease risk factors.

METHODS Healthy overweight men (n = 209) and women (n = 710), mean age 44.7 years, body mass index (BMI) 32.4 kg/m², were randomized between November 2005 and August 2009 to receive Health Canada's food guide (control, n = 486) or 1 of 3 interventions: dietary advice consistent with both Dietary Approaches to Stop Hypertension (DASH) and dietary portfolio principles (n = 145); weekly food provision reflecting this advice (n = 148); or food delivery plus advice (n = 140). Interventions lasted 6 months with 12-month follow-up. Semiquantitative food frequency questionnaires and fasting blood, anthropometric and blood pressure measurements were obtained at baseline, 6 months, and 18 months.

RESULTS Participant retention at 6 and 18 months was 91% and 81%, respectively, after food provision compared to 67% and 57% when no food was provided (p < 0.0001). Test and control treatments showed small reductions in body weight (-0.8 to -1.2 kg), waist circumference (-1.1 to -1.9 cm), and mean arterial pressure (0.0 to -1.1 mm Hg) at 6 months and Framingham coronary heart disease risk score at 18 months (-0.19 to -0.42%), which were significant overall. Outcomes did not differ among test and control groups.

CONCLUSIONS Provision of foods increased retention but only modestly increased intake of recommended foods. Current dietary recommendations showed small overall benefits in coronary heart disease risk factors. Additional dietary strategies to maximize these benefits are required. (Fruits, Vegetables, and Whole Grains: A Community-based Intervention; [NCT00516620](#)) (46).

The Future Role of the United States in Global Health: Emphasis on Cardiovascular Disease

V. Fuster, et al.

U.S. global health investment has focused on detection, treatment, and eradication of infectious diseases such as tuberculosis, malaria, and human immunodeficiency virus/acquired immunodeficiency

syndrome, with significant results. Although efforts should be maintained and expanded to provide ongoing therapy for chronic infectious disease, there is a pressing need to meet the challenge of noncommunicable diseases, which constitute the highest burden of diseases globally. A Committee of the National Academies of Sciences, Engineering, and Medicine has made 14 recommendations that require ongoing commitments to eradication of infectious disease and increase the emphasis on chronic diseases such as cardiovascular disease. These include improving early detection and treatment, mitigating disease risk factors, shifting global health infrastructure to include management of cardiovascular disease, developing global partners and private-public ventures to meet infrastructure and funding challenges, streamlining medical product development and supply, increasing research and development capacity, and addressing gaps in global political and institutional leadership to meet the shifting challenge (47).

Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015

G.A. Roth, et al.

BACKGROUND The burden of cardiovascular diseases (CVDs) remains unclear in many regions of the world.

OBJECTIVES The GBD (Global Burden of Disease) 2015 study integrated data on disease incidence, prevalence, and mortality to produce consistent, up-to-date estimates for cardiovascular burden.

METHODS CVD mortality was estimated from vital registration and verbal autopsy data. CVD prevalence was estimated using modeling software and data from health surveys, prospective cohorts, health system administrative data, and registries. Years lived with disability (YLD) were estimated by multiplying prevalence by disability weights. Years of life lost (YLL) were estimated by multiplying age-specific CVD deaths by a reference life expectancy. A sociodemographic index (SDI) was created for each location based on income per capita, educational attainment, and fertility.

RESULTS In 2015, there were an estimated 422.7 million cases of CVD (95% uncertainty interval: 415.53 to 427.87 million cases) and 17.92 million CVD deaths (95% uncertainty interval: 17.59 to 18.28 million CVD deaths). Declines in the age-standardized CVD death rate occurred between 1990 and 2015 in all high-income and some middle-income countries. Ischemic heart disease was the leading cause of CVD health lost globally, as well as in each world region,

followed by stroke. As SDI increased beyond 0.25, the highest CVD mortality shifted from women to men. CVD mortality decreased sharply for both sexes in countries with an SDI >0.75.

CONCLUSIONS CVDs remain a major cause of health loss for all regions of the world. Sociodemographic change over the past 25 years has been associated with dramatic declines in CVD in regions with very high SDI, but only a gradual decrease or no change in most regions. Future updates of the GBD study can be used to guide policymakers who are focused on reducing the overall burden of noncommunicable disease and achieving specific global health targets for CVD (48).

Healthful and Unhealthful Plant-Based Diets and the Risk of Coronary Heart Disease in U.S. Adults

A. Satija, et al.

BACKGROUND Plant-based diets are recommended for coronary heart disease (CHD) prevention. However, not all plant foods are necessarily beneficial for health.

OBJECTIVES This study sought to examine associations between plant-based diet indices and CHD incidence.

METHODS We included 73,710 women in NHS (Nurses' Health Study) (1984 to 2012), 92,329 women in NHS2 (1991 to 2013), and 43,259 men in Health Professionals Follow-up Study (1986 to 2012), free of chronic diseases at baseline. We created an overall plant-based diet index (PDI) from repeated semiquantitative food-frequency questionnaire data, by assigning positive scores to plant foods and reverse scores to animal foods. We also created a healthful plant-based diet index (hPDI) where healthy plant foods (whole grains, fruits/vegetables, nuts/legumes, oils, tea/coffee) received positive scores, whereas less-healthy plant foods (juices/sweetened beverages, refined grains, potatoes/fries, sweets) and animal foods received reverse scores. To create an unhealthful PDI (uPDI), we gave positive scores to less-healthy plant foods and reverse scores to animal and healthy plant foods.

RESULTS Over 4,833,042 person-years of follow-up, we documented 8,631 incident CHD cases. In pooled multivariable analysis, higher adherence to PDI was independently inversely associated with CHD (hazard ratio [HR] comparing extreme deciles: 0.92; 95% confidence interval [CI]: 0.83 to 1.01; *p* trend = 0.003). This inverse association was stronger for hPDI (HR: 0.75; 95% CI: 0.68 to 0.83; *p* trend <0.001).

Conversely, uPDI was positively associated with CHD (HR: 1.32; 95% CI: 1.20 to 1.46; *p* trend <0.001).

CONCLUSIONS Higher intake of a plant-based diet rich in healthier plant foods is associated with substantially lower CHD risk, whereas a plant-based diet index that emphasizes less-healthy plant foods is associated with higher CHD risk (49).

Herbal Medications in Cardiovascular Medicine

R. Liperoti, et al.

Herbal medications are commonly used for clinical purposes, including the treatment of cardiovascular conditions. Compared with conventional medications, herbal medications do not require clinical studies before their marketing or formal approval from regulatory agencies, and for this reason their efficacy and safety are rarely proven. In this review, we summarize available evidence on herbal medications mostly used in cardiovascular medicine. We show that the use of these medications for the treatment of cardiovascular diseases is often not supported by scientific evidence. Despite most of these herbs showing an effect on biological mechanisms related to the cardiovascular system, data on their clinical effects are lacking. Potential relevant side effects, including increased risk of drug interactions, are described, and the possibility of contamination or substitution with other medications represents a concern. Physicians should always assess the use of herbal medications with patients and discuss the possible benefits and side effects with them (50).

How Low to Go With Glucose, Cholesterol, and Blood Pressure in Primary Prevention of CVD

K.N. Hong, et al.

Diabetes, hyperlipidemia, and hypertension are modifiable risk factors that predict cardiovascular disease events. The effect of these risk factors on incident cardiovascular disease increases with progressively higher levels of glucose, low-density lipoprotein cholesterol, and blood pressure. The thresholds for initiating treatment of these modifiable risk factors and the optimal goals of risk factor modification are a focus of primary prevention research. Although an aggressive approach is appealing, adverse events may occur, and potential physiological barriers may exist. This paper discusses primary prevention of coronary heart disease that may be achieved through modification of diabetes, hyperlipidemia, and hypertension by summarizing

current guidelines and pertinent clinical trial data from intervention trials that included a primary prevention cohort (51).

Ideal Cardiovascular Health, Mortality, and Vascular Events in Elderly Subjects: The Three-City Study

B. Gaye, et al.

BACKGROUND The benefit of ideal cardiovascular health (CVH) on health-related outcomes in middle-aged patients is firmly established. In the growing elderly population, the high prevalence of comorbidities and medications for chronic diseases may offset such benefit.

OBJECTIVES This study analyzed the association of ideal CVH with mortality, incident coronary heart disease, and stroke events in elderly individuals from the community.

METHODS Between 1999 and 2001, 9,294 men and women, noninstitutionalized and aged 65 years and over were examined, and thereafter followed up for the occurrence of vascular events and mortality within the Three-City Study. Hazard ratios (HRs) were estimated by Cox proportional hazard model and compared subjects with 3 to 4 and subjects with 5 to 7 ideal metrics with those with 0 to 2 ideal metrics, respectively.

RESULTS The mean age was 73.8 ± 5.3 years, and 36.7% were men. Only 5% of the participants had ≥ 5 metrics at the ideal level. After a median follow-up of 10.9 years and 8.6 years, respectively 1,987 deaths and 680 adjudicated coronary heart disease or stroke events had occurred. In multivariate analysis, the risk of mortality and of vascular events decreased across the categories of ideal metrics. In particular, in subjects with ≥ 5 metrics at the ideal level (compared with those with ≤ 2), there was a 29% (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.55 to 0.90) decreased risk of all-cause mortality and 67% (HR: 0.33; 95% CI: 0.19 to 0.57) for coronary heart disease and stroke combined (p for trend < 0.001).

CONCLUSIONS Even in the elderly, higher CVH status is highly beneficial regarding mortality and vascular event risks (52).

Predicting Subclinical Atherosclerosis in Low-Risk Individuals: Ideal Cardiovascular Health Score and Fuster-BEWAT Score

J.M. Fernández-Alvira, et al.

BACKGROUND The ideal cardiovascular health score (ICHS) is recommended for use in primary prevention.

Simpler tools not requiring laboratory tests, such as the Fuster-BEWAT (blood pressure [B], exercise [E], weight [W], alimentation [A], and tobacco [T]) score (FBS), are also available.

OBJECTIVES The purpose of this study was to compare the effectiveness of ICHS and FBS in predicting the presence and extent of subclinical atherosclerosis.

METHODS A total of 3,983 participants 40 to 54 years of age were enrolled in the PESA (Progression of Early Subclinical Atherosclerosis) cohort. Subclinical atherosclerosis was measured in right and left carotids, abdominal aorta, right and left iliofemoral arteries, and coronary arteries. Subjects were classified as having poor, intermediate, or ideal cardiovascular health based on the number of favorable ICHS or FBS.

RESULTS With poor ICHS and FBS as references, individuals with ideal ICHS and FBS showed lower adjusted odds of having atherosclerotic plaques (ICHS odds ratio [OR]: 0.41; 95% confidence interval [CI]: 0.31 to 0.55 vs. FBS OR: 0.49; 95% CI: 0.36 to 0.66), coronary artery calcium (CACs) ≥ 1 (CACs OR: 0.41; 95% CI: 0.28 to 0.60 vs. CACS OR: 0.53; 95% CI: 0.38 to 0.74), higher number of affected territories (OR: 0.32; 95% CI: 0.26 to 0.41 vs. OR: 0.39; 95% CI: 0.31 to 0.50), and higher CACS level (OR: 0.40; 95% CI: 0.28 to 0.58 vs. OR: 0.52; 95% CI: 0.38 to 0.72). Similar levels of significantly discriminating accuracy were found for ICHS and FBS with respect to the presence of plaques (C-statistic: 0.694; 95% CI: 0.678 to 0.711 vs. 0.692; 95% CI: 0.676 to 0.709, respectively) and for CACS ≥ 1 (C-statistic: 0.782; 95% CI: 0.765 to 0.800 vs. 0.780; 95% CI: 0.762 to 0.798, respectively).

CONCLUSIONS Both scores predict the presence and extent of subclinical atherosclerosis with similar accuracy, highlighting the value of the FBS as a simpler and more affordable score for evaluating the risk of subclinical disease (53).

Relationship of Alcohol Consumption to All-Cause, Cardiovascular, and Cancer-Related Mortality in U.S. Adults

B. Xi, et al.

BACKGROUND Previous studies have revealed inconsistent findings regarding the association of light to moderate alcohol consumption with cardiovascular disease (CVD) and cancer mortality.

OBJECTIVES The aim of this study was to examine the association between alcohol consumption and risk of mortality from all causes, cancer, and CVD in U.S. adults.

METHODS Data were obtained by linking 13 waves of the National Health Interview Surveys (1997 to 2009) to the National Death Index records through December 31, 2011. A total of 333,247 participants ≥ 18 years of age were included. Self-reported alcohol consumption patterns were categorized into 6 groups: lifetime abstainers; lifetime infrequent drinkers; former drinkers; and current light, moderate, or heavy drinkers. Secondary exposure included participants' binge-drinking status. The main outcome was all-cause, cancer, or CVD mortality.

RESULTS After a median follow-up of 8.2 years (2.7 million person-years), 34,754 participants died of all causes (including 8,947 CVD deaths and 8,427 cancer deaths). Compared with lifetime abstainers, those who were light or moderate alcohol consumers were at a reduced risk of mortality for all causes (light-hazard ratio [HR]: 0.79; 95% confidence interval [CI]: 0.76 to 0.82; moderate-HR: 0.78; 95% CI: 0.74 to 0.82) and CVD (light-HR: 0.74; 95% CI: 0.69 to 0.80; moderate-HR: 0.71; 95% CI: 0.64 to 0.78), respectively. In contrast, there was a significantly increased risk of mortality for all causes (HR: 1.11; 95% CI: 1.04 to 1.19) and cancer (HR: 1.27; 95% CI: 1.13 to 1.42) in adults with heavy alcohol consumption. Binge drinking ≥ 1 d/week was also associated with an increased risk of mortality for all causes (HR: 1.13; 95% CI: 1.04 to 1.23) and cancer (HR: 1.22; 95% CI: 1.05 to 1.41).

CONCLUSIONS Light and moderate alcohol intake might have a protective effect on all-cause and CVD-specific mortality in U.S. adults. Heavy or binge drinking was associated with increased risk of all-cause and cancer-specific mortality (54).

Sports Cardiology: Core Curriculum for Providing Cardiovascular Care to Competitive Athletes and Highly Active People

A.L. Baggish, et al.

The last few decades have seen substantial growth in the populations of competitive athletes and highly active people (CAHAP). Although vigorous physical exercise is an effective way to reduce the risk of cardiovascular (CV) disease, CAHAP remain susceptible to inherited and acquired CV disease, and may be most at risk for adverse CV outcomes during intense physical activity. Traditionally, multidisciplinary teams comprising athletic trainers, physical therapists, primary care sports medicine physicians, and orthopedic surgeons have provided clinical care for CAHAP. However, there is increasing recognition that a care team including

qualified CV specialists optimizes care delivery for CAHAP. In recognition of the increasing demand for CV specialists competent in the care of CAHAP, the American College of Cardiology has recently established a Sports and Exercise Council. An important primary objective of this council is to define the essential skills necessary to practice effective sports cardiology (55).

Trending Cardiovascular Nutrition Controversies

A.M. Freeman, et al.

The potential cardiovascular benefits of several trending foods and dietary patterns are still incompletely understood, and nutritional science continues to evolve. However, in the meantime, a number of controversial dietary patterns, foods, and nutrients have received significant media exposure and are mired by hype. This review addresses some of the more popular foods and dietary patterns that are promoted for cardiovascular health to provide clinicians with accurate information for patient discussions in the clinical setting (56).

Vitamin D and Cardiovascular Disease: Controversy Unresolved

I. Al Mheid, et al.

Vitamin D deficiency is typically caused by inadequate cutaneous synthesis secondary to decreased exposure to sunlight. Serum levels of 25-hydroxyvitamin D $1 < 20$ ng/ml are diagnostic of vitamin D deficiency. Vitamin D has various cardiovascular pleiotropic effects by activating its nuclear receptor in cardiomyocytes and vascular endothelial cells and by regulating the renin-angiotensin-aldosterone system, adiposity, energy expenditure, and pancreatic cell activity. In humans, vitamin D deficiency is associated with the following: vascular dysfunction; arterial stiffening; left ventricular hypertrophy; and worsened metrics of diabetes, hypertension, and hyperlipidemia. It is also linked with worse cardiovascular morbidity and mortality. However, meta-analyses of vitamin D supplementation trials have failed to show clear improvements in blood pressure, insulin sensitivity, or lipid parameters, thus suggesting that the link between vitamin D deficiency and cardiovascular disease may be an epiphenomenon. Ongoing larger randomized trials will clarify whether monitoring and supplementation of vitamin D play roles in cardiovascular protection (57).

HYPERTENSION

Prevalence and Clinical Manifestations of Primary Aldosteronism Encountered in Primary Care Practice

S. Monticone, et al.

BACKGROUND Despite being widely recognized as the most common form of secondary hypertension, among the general hypertensive population the true prevalence of primary aldosteronism (PA) and its main subtypes, aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH), remains a matter of debate.

OBJECTIVES This study sought to determine the prevalence and clinical phenotype of PA in a large cohort of unselected patients with hypertension, consecutively referred to our hypertension unit, by 19 general practitioners from Torino, Italy.

METHODS Following withdrawal from all interfering medications, patients were screened for PA using the ratio of serum aldosterone to plasma renin activity. PA was diagnosed according to Endocrine Society guidelines. The diagnosis was confirmed or excluded by an intravenous saline infusion test or captopril challenge test and subtype differentiation was performed by adrenal computed tomography scanning and adrenal vein sampling, using strict criteria to define successful cannulation and lateralization of aldosterone production.

RESULTS A total of 1,672 primary care patients with hypertension (569 newly diagnosed and 1,103 patients already diagnosed with arterial hypertension) were included in the study. A total of 99 patients (5.9%) were diagnosed with PA and conclusive subtype differentiation by adrenal vein sampling was made in 91 patients (27 patients with an APA and 64 patients with BAH). The overall prevalence of PA increased with the severity of hypertension, from 3.9% in stage 1 hypertension to 11.8% in stage 3 hypertension. Patients with PA more frequently displayed target organ damage and cardiovascular events compared with those without PA, independent of confounding variables.

CONCLUSIONS Our results demonstrated that PA is a frequent cause of secondary hypertension, even in the general population of patients with hypertension, and indicates that most of these patients should be screened for PA (58).

Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences

S. Javaheri, et al.

Sleep apnea is highly prevalent in patients with cardiovascular disease. These disordered breathing

events are associated with a profile of perturbations that include intermittent hypoxia, oxidative stress, sympathetic activation, and endothelial dysfunction, all of which are critical mediators of cardiovascular disease. Evidence supports a causal association of sleep apnea with the incidence and morbidity of hypertension, coronary heart disease, arrhythmia, heart failure, and stroke. Several discoveries in the pathogenesis, along with developments in the treatment of sleep apnea, have accumulated in recent years. In this review, we discuss the mechanisms of sleep apnea, the evidence that addresses the links between sleep apnea and cardiovascular disease, and research that has addressed the effect of sleep apnea treatment on cardiovascular disease and clinical endpoints. Finally, we review the recent development in sleep apnea treatment options, with special consideration of treating patients with heart disease. Future directions for selective areas are suggested (59).

IMAGING

Cardiac MR With Late Gadolinium Enhancement in Acute Myocarditis With Preserved Systolic Function: ITAMY Study

G.D. Aquaro, et al.

BACKGROUND The prognostic role of cardiac magnetic resonance (CMR) and late gadolinium enhancement (LGE) has not been clarified in acute myocarditis (AM) with preserved left ventricular (LV) ejection fraction (EF).

OBJECTIVES This study sought to evaluate the role of CMR and LGE in the prognosis of AM with preserved LVEF.

METHODS This study analyzed data from ITAMY (ITalian multicenter study on Acute MYocarditis) and evaluated CMR results from 386 patients (299 male; mean age 35 ± 15 years) with AM and preserved LVEF. Clinical follow-up was performed for a median of 1,572 days. A clinical combined endpoint of cardiac death, appropriate implantable cardioverter-defibrillator firing, resuscitated cardiac arrest, and hospitalization for heart failure was used.

RESULTS Among the 374 patients with suitable images, LGE involved the subepicardial layer inferior and lateral wall in 154 patients (41%; IL group), the mid-wall layer of the anteroseptal wall in 135 patients (36%; AS [anteroseptal] group), and other segments in 59 patients (16%; other-LGE group), and it was absent in 26 patients (no-LGE group). The AS group had a greater extent of LGE and a higher LV end-diastolic

volume index than other groups, but levels of inflammatory markers were lower than in the other groups. Kaplan-Meier curve analysis indicated that the AS group had a worse prognosis than the other groups ($p < 0.0001$). Finally, in multivariable analysis, AS LGE was the best independent CMR predictor of the combined endpoint (odds ratio: 2.73; 95% confidence interval: 1.2 to 5.9; $p = 0.01$).

CONCLUSIONS In patients with AM and preserved LVEF, LGE in the midwall layer of the AS myocardial segment is associated with a worse prognosis than other patterns of presentation (60).

Clinical Significance of Lipid-Rich Plaque Detected by Optical Coherence Tomography: A 4-Year Follow-Up Study

L. Xing, et al.

BACKGROUND Lipid-rich plaque (LRP) is thought to be a precursor to cardiac events. However, its clinical significance in coronary arteries has never been systematically investigated.

OBJECTIVES This study investigated the prevalence and clinical significance of LRP in the nonculprit region of the target vessel in patients undergoing percutaneous coronary intervention (PCI).

METHODS The study included 1,474 patients from 20 sites across 6 countries undergoing PCI, who had optical coherence tomography (OCT) imaging of the target vessel. Major adverse cardiac events (MACE) were defined as a composite of cardiac death, acute myocardial infarction, and ischemia-driven revascularization. Patients were followed for up to 4 years (median of 2 years).

RESULTS Lipid-rich plaque was detected in nonculprit regions of the target vessel in 33.6% of patients. The cumulative rate of nonculprit lesion-related MACE (NC-MACE) over 48 months in patients with LRP was higher than in those without LRP (7.2% vs. 2.6%, respectively; $p = 0.033$). Acute coronary syndrome at index presentation (risk ratio: 2.538; 95% confidence interval [CI]: 1.246 to 5.173; $p = 0.010$), interruption of statin use ≥ 1 year (risk ratio: 4.517; 95% CI: 1.923 to 10.610; $p = 0.001$), and LRP in nonculprit regions (risk ratio: 2.061; 95% CI: 1.050 to 4.044; $p = 0.036$) were independently associated with increased NC-MACE. Optical coherence tomography findings revealed that LRP in patients with NC-MACE had longer lipid lengths ($p < 0.001$), wider maximal lipid arcs ($p = 0.023$), and smaller minimal lumen areas ($p = 0.003$) than LRPs in patients without MACE.

CONCLUSIONS Presence of LRP in the nonculprit regions of the target vessel by OCT predicts increased risk for future NC-MACE, which is primarily driven by revascularization for recurrent ischemia. Lipid-rich plaque with longer lipid length, wider lipid arc, and higher degree of stenosis identified patients at higher risk of future cardiac events. (The Massachusetts General Hospital Optical Coherence Tomography Registry; [NCT01110538](#)) (61).

Detection of Atherosclerotic Inflammation by ^{68}Ga -DOTATATE PET Compared to ^{18}F FDG PET Imaging

J.M. Tarkin, et al.

BACKGROUND Inflammation drives atherosclerotic plaque rupture. Although inflammation can be measured using fluorine-18-labeled fluorodeoxyglucose positron emission tomography (^{18}F FDG PET), ^{18}F FDG lacks cell specificity, and coronary imaging is unreliable because of myocardial spillover.

OBJECTIVES This study tested the efficacy of gallium-68-labeled DOTATATE (^{68}Ga -DOTATATE), a somatostatin receptor subtype-2 (SST_2)-binding PET tracer, for imaging atherosclerotic inflammation.

METHODS We confirmed ^{68}Ga -DOTATATE binding in macrophages and excised carotid plaques. ^{68}Ga -DOTATATE PET imaging was compared to ^{18}F FDG PET imaging in 42 patients with atherosclerosis.

RESULTS Target *SSTR2* gene expression occurred exclusively in “proinflammatory” M1 macrophages, specific ^{68}Ga -DOTATATE ligand binding to SST_2 receptors occurred in CD68-positive macrophage-rich carotid plaque regions, and carotid *SSTR2* mRNA was highly correlated with in vivo ^{68}Ga -DOTATATE PET signals ($r = 0.89$; 95% confidence interval [CI]: 0.28 to 0.99; $p = 0.02$). ^{68}Ga -DOTATATE mean of maximum tissue-to-blood ratios (mTBR_{max}) correctly identified culprit versus nonculprit arteries in patients with acute coronary syndrome (median difference: 0.69; interquartile range [IQR]: 0.22 to 1.15; $p = 0.008$) and transient ischemic attack/stroke (median difference: 0.13; IQR: 0.07 to 0.32; $p = 0.003$). ^{68}Ga -DOTATATE mTBR_{max} predicted high-risk coronary computed tomography features (receiver operating characteristics area under the curve [ROC AUC]: 0.86; 95% CI: 0.80 to 0.92; $p < 0.0001$), and correlated with Framingham risk score ($r = 0.53$; 95% CI: 0.32 to 0.69; $p < 0.0001$) and ^{18}F FDG uptake ($r = 0.73$; 95% CI: 0.64 to 0.81; $p < 0.0001$). ^{18}F FDG mTBR_{max}

differentiated culprit from nonculprit carotid lesions (median difference: 0.12; IQR: 0.0 to 0.23; $p = 0.008$) and high-risk from lower-risk coronary arteries (ROC AUC: 0.76; 95% CI: 0.62 to 0.91; $p = 0.002$); however, myocardial [^{18}F]FDG spillover rendered coronary [^{18}F]FDG scans uninterpretable in 27 patients (64%). Coronary ^{68}Ga -DOTATATE PET scans were readable in all patients.

CONCLUSIONS We validated ^{68}Ga -DOTATATE PET as a novel marker of atherosclerotic inflammation and confirmed that ^{68}Ga -DOTATATE offers superior coronary imaging, excellent macrophage specificity, and better power to discriminate high-risk versus low-risk coronary lesions than [^{18}F]FDG. (Vascular Inflammation Imaging Using Somatostatin Receptor Positron Emission Tomography [VISION]; [NCT02021188](#)) (62).

Intracoronary Imaging, Cholesterol Efflux, and Transcriptomes After Intensive Statin Treatment: The YELLOW II Study

A.S. Kini, et al.

BACKGROUND Despite extensive evidence demonstrating the beneficial effects of statins on clinical outcomes, the mechanisms underlying these effects remain elusive.

OBJECTIVES This study assessed changes in plaque morphology using intravascular imaging, with a comprehensive evaluation of cholesterol efflux capacity (CEC) and peripheral blood mononuclear cell (PBMC) transcriptomics in patients receiving high-dose statin therapy.

METHODS In a prospective study, 85 patients with stable coronary artery disease underwent percutaneous coronary intervention for a culprit lesion, followed by intracoronary multimodality imaging, including optical coherence tomography (OCT) of an obstructive nonculprit lesion. All subjects received 40 mg of rosuvastatin daily for 8 to 12 weeks, when the nonculprit lesion was reimaged and intervention performed. Blood samples were drawn at both times to assess CEC and transcriptomic profile in PBMC.

RESULTS Baseline OCT minimal fibrous cap thickness (FCT) was $100.9 \pm 41.7 \mu\text{m}$, which increased to $108.6 \pm 39.6 \mu\text{m}$ at follow-up, and baseline CEC was 0.81 ± 0.14 , which increased at follow-up to 0.84 ± 0.14 ($p = 0.003$). Thin-cap fibroatheroma prevalence decreased from 20.0% to 7.1% ($p = 0.003$). Changes in FCT were independently associated with CEC increase by multivariate analysis (β : 0.30; $p = 0.01$). PBMC microarray analysis detected 117 genes that

were differentially expressed at follow-up compared to baseline, including genes playing key roles in cholesterol synthesis (*SQLE*), regulation of fatty acids unsaturation (*FADS1*), cellular cholesterol uptake (*LDLR*), efflux (*ABCA1* and *ABCG1*), and inflammation (*DHCR24*). Weighted coexpression network analysis revealed unique clusters of genes associated with favorable FCT and CEC changes.

CONCLUSIONS The study demonstrated an independent association between fibrous cap thickening and improved CEC that may contribute to morphological changes suggesting plaque stabilization among patients taking intensive statin therapy. Furthermore, the significant perturbations in PBMC transcriptome may help determine the beneficial effects of statin on plaque stabilization. (Reduction in Coronary Yellow Plaque, Lipids and Vascular Inflammation by Aggressive Lipid Lowering [YELLOW II]; [NCT01837823](#)) (63).

Prognostic Value of Cardiac Magnetic Resonance Tissue Characterization in Risk Stratifying Patients With Suspected Myocarditis

C. Gräni, et al.

BACKGROUND Diagnosing myocarditis is challenged by nonspecific clinical signs and symptoms and low accuracy of endomyocardial biopsy. Cardiac magnetic resonance imaging (CMR) provides both cardiac anatomy and tissue characterization in this setting, but the prognostic value of this method as a primary assessment tool in patients with suspected myocarditis remains limited.

OBJECTIVES This study sought to determine cardiac event-free survival of a consecutive cohort with suspected myocarditis with regard to CMR findings.

METHODS Six hundred seventy patients with suspected myocarditis underwent CMR including late gadolinium enhancement (LGE) parameters between 2002 and 2015 and were included and followed. We performed multivariable model for major adverse cardiovascular events (MACE) and determined the continuous net reclassification improvement by LGE markers.

RESULTS At a median follow-up of 4.7 years (interquartile range [IQR]: 2.3 to 7.3 years), 98 patients experienced a MACE. Two hundred ninety-four (44%) patients showed LGE presence, which was associated with a more than doubling risk of MACE (hazard ratio [HR]: 2.22; 95% confidence interval [CI]: 1.47 to 3.35; $p < 0.001$). Annualized MACE rates were 4.8% and 2.1% corresponding to

LGE presence and absence, respectively ($p < 0.001$). In the multivariable model, LGE presence maintained significant association with MACE (HR: 1.72; 95% CI: 1.08 to 2.76; $p = 0.023$). The computed continuous net reclassification improvement was 0.39 (95% CI: 0.10 to 0.67) when LGE presence was added to the multivariable model for MACE. Regarding location and pattern, septal and midwall LGE showed strongest associations with MACE (HR: 2.55; 95% CI: 1.77 to 3.83 and HR: 2.39; 95% CI: 1.54 to 3.69, respectively; both $p < 0.001$). A patchy distribution portended to a near 3-fold increased hazard to MACE (HR: 2.93; 95% CI: 1.79 to 4.80; $p < 0.001$). LGE extent (per 10% increase) corresponded to a 79% increase in risk of MACE (HR: 1.79; 95% CI: 1.25 to 2.57; $p = 0.002$). A normal CMR study corresponded to low annual MACE and death rates of 0.8% and 0.3%, respectively.

CONCLUSIONS CMR tissue characterization provides effective risk stratification in patients with suspected myocarditis (64).

Radiation Exposure and Vascular Access in Acute Coronary Syndromes: The RAD-Matrix Trial

A. Sciahbasi, et al.

BACKGROUND It remains unclear whether radial access increases the risk of operator or patient radiation exposure compared to transfemoral access when performed by expert operators.

OBJECTIVES This study sought to determine whether radial access increases radiation exposure.

METHODS A total of 8,404 patients, with or without ST-segment elevation acute coronary syndrome, were randomly assigned to radial or femoral access for coronary angiography and percutaneous intervention, and collected fluoroscopy time and dose-area product (DAP). RAD-MATRIX is a radiation sub-study of the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX) trial. We anticipated that 13 or more operators, each wearing a thorax (primary endpoint), wrist, and head (secondary endpoints) lithium fluoride thermoluminescent dosimeter, and randomizing at least 13 patients per access site, were needed to establish noninferiority of radial versus femoral access.

RESULTS Among 18 operators, performing 777 procedures in 767 patients, the noninferiority primary endpoint was not achieved (p value for noninferiority = 0.843). Operator equivalent dose at the thorax (77 μ Sv) was significantly higher with radial

than femoral access (41 μ Sv; $p = 0.02$). After normalization of operator radiation dose by fluoroscopy time or DAP, the difference remained significant. Radiation dose at wrist or head did not differ between radial and femoral access. Thorax operator dose did not differ for right radial (84 μ Sv) compared to left radial access (52 μ Sv; $p = 0.15$). In the overall MATRIX population, fluoroscopy time and DAP were higher with radial compared to femoral access: 10 min versus 9 min ($p < 0.0001$) and 65 Gy·cm² versus 59 Gy·cm² ($p = 0.0001$), respectively.

CONCLUSIONS Compared to femoral access, radial access is associated with greater operator and patient radiation exposure when performed by expert operators in current practice. Radial operators and institutions should be sensitized towards radiation risks and adopt adjunctive radioprotective measures. (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX; NCT101433627) (65).

Subclinical Atherosclerosis Burden by 3D Ultrasound in Mid-Life: The PESA Study

B. López-Melgar, et al.

BACKGROUND Detection of subclinical atherosclerosis improves risk prediction beyond cardiovascular risk factors (CVRFs) and risk scores, but quantification of plaque burden may improve it further. Novel 3-dimensional vascular ultrasound (3DVUS) provides accurate volumetric quantification of plaque burden.

OBJECTIVES The authors evaluated associations between 3DVUS-based plaque burden and CVRFs and explored potential added value over simple plaque detection.

METHODS The authors included 3,860 (92.2%) PESA (Progression of Early Subclinical Atherosclerosis) study participants (age 45.8 \pm 4.3 years; 63% men). Bilateral carotid and femoral territories were explored by 3DVUS to determine the number of plaques and territories affected, and to quantify global plaque burden defined as the sum of all plaque volumes. Linear regression and proportional odds models were used to evaluate associations of plaque burden with CVRFs and estimated 10-year cardiovascular risk.

RESULTS Plaque burden was higher in men (63.4 mm³ [interquartile range (IQR): 23.8 to 144.8 mm³] vs. 25.7 mm³ [IQR: 11.5 to 61.6 mm³] in women; $p < 0.001$), in the femoral territory (64 mm³ [IQR: 27.6 to 140.5 mm³] vs. 23.1 mm³ [IQR: 9.9 to 48.7 mm³] in the carotid territory; $p < 0.001$), and with increasing age ($p < 0.001$). Age, sex, smoking, and dyslipidemia were

more strongly associated with femoral than with carotid disease burden, whereas hypertension and diabetes showed no territorial differences. Plaque burden was directly associated with estimated cardiovascular risk independently of the number of plaques or territories affected ($p < 0.01$).

CONCLUSIONS 3DVUS quantifies higher plaque burden in men, in the femoral territory, and with increasing age during midlife. Plaque burden correlates strongly with CVRFs, especially at the femoral level, and reflects estimated cardiovascular risk more closely than plaque detection alone. (Progression of Early Subclinical Atherosclerosis [PESA] Study; [NCT01410318](#)) (66).

A Test in Context: Myocardial Strain Measured by Speckle-Tracking Echocardiography

P. Collier, et al.

Strain-based imaging techniques (and specifically speckle-tracking echocardiography) have been shown to have clinical utility in a variety of settings. This technique is being embraced and increasingly adopted in many echocardiography laboratories worldwide. This review appraised speckle-tracking echocardiography in a clinical context by providing a critical evaluation of the prognostic and diagnostic insights that this technology can provide. In particular, we discuss the use of speckle-tracking strain in selected areas, such as undifferentiated left ventricular hypertrophy, cardio-oncology, aortic stenosis, and ischemic heart disease. The potential utility of regional and chamber strains (namely segmental left ventricular strain, left atrial strain, and right ventricular strain) are also discussed. Future directions for this technology are explored. Before its clinical application, it is particularly important that physicians be cognizant of the technical challenges and inherent limitations of strain data, which are also addressed here (67).

METABOLIC & LIPID DISORDERS

Diabetes Mellitus–Induced Microvascular Destabilization in the Myocardium

R. Hinkel, et al.

BACKGROUND Diabetes mellitus causes microcirculatory rarefaction and may impair the responsiveness of ischemic myocardium to proangiogenic factors.

OBJECTIVES This study sought to determine whether microvascular destabilization affects organ function and therapeutic neovascularization in diabetes mellitus.

METHODS The authors obtained myocardial samples from patients with end-stage heart failure at time of transplant, with or without diabetes mellitus. Diabetic (db) and wild-type (wt) pigs were used to analyze myocardial vascularization and function. Chronic ischemia was induced percutaneously (day 0) in the circumflex artery. At day 28, recombinant adeno-associated virus (rAAV) (5×10^{12} viral particles encoding vascular endothelial growth factor-A [VEGF-A] or thymosin beta 4 [T β 4]) was applied regionally. CD31+ capillaries per high power field (c/hpf) and NG2+ pericyte coverage were analyzed. Global myocardial function (ejection fraction [EF] and left ventricular end-diastolic pressure) was assessed at days 28 and 56.

RESULTS Diabetic human myocardial explants revealed capillary rarefaction and pericyte loss compared to nondiabetic explants. Hyperglycemia in db pigs, even without ischemia, induced capillary rarefaction in the myocardium (163 ± 14 c/hpf in db vs. 234 ± 8 c/hpf in wt hearts; $p < 0.005$), concomitant with a distinct loss of EF (44.9% vs. 53.4% in nondiabetic controls; $p < 0.05$). Capillary density further decreased in chronic ischemic hearts, as did EF (both $p < 0.05$). Treatment with rAAV.T β 4 enhanced capillary density and maturation in db hearts less efficiently than in wt hearts, similar to collateral growth. rAAV.VEGF-A, though stimulating angiogenesis, induced neither pericyte recruitment nor collateral growth. As a result, rAAV.T β 4 but not rAAV.VEGF-A improved EF in db hearts ($34.5 \pm 1.4\%$), but less so than in wt hearts ($44.8 \pm 1.5\%$).

CONCLUSIONS Diabetes mellitus destabilized microvascular vessels of the heart, affecting the amplitude of therapeutic neovascularization via rAAV.T β 4 in a translational large animal model of hibernating myocardium (68).

Enteric Coating and Aspirin Nonresponsiveness in Patients With Type 2 Diabetes Mellitus

D.L. Bhatt, et al.

BACKGROUND A limitation of aspirin is that some patients, particularly those with diabetes, may not have an optimal antiplatelet effect.

OBJECTIVES The goal of this study was to determine if oral bioavailability mediates nonresponsiveness.

METHODS The rate and extent of serum thromboxane generation and aspirin pharmacokinetics were measured in 40 patients with diabetes in a randomized, single-blind, triple-crossover study. Patients were exposed to three 325-mg aspirin formulations: plain aspirin, PL2200 (a modified-release lipid-based

aspirin), and a delayed-release enteric-coated (EC) aspirin. Onset of antiplatelet activity was determined by the rate and extent of inhibition of serum thromboxane B₂ (TXB₂) generation. Aspirin nonresponsiveness was defined as a level of residual serum TXB₂ associated with elevated thrombotic risk (<99.0% inhibition or TXB₂ >3.1 ng/ml) within 72 h after 3 daily aspirin doses.

RESULTS The rate of aspirin nonresponsiveness was 15.8%, 8.1%, and 52.8% for plain aspirin, PL2200, and EC aspirin, respectively ($p < 0.001$ for both comparisons vs. EC aspirin; $p = 0.30$ for comparison between plain aspirin and PL2200). Similarly, 56% of EC aspirin-treated subjects had serum TXB₂ levels >3.1 ng/ml, compared with 18% and 11% of subjects after administration of plain aspirin and PL2200 ($p < 0.0001$). Compared with findings for plain aspirin and PL2200, this high rate of nonresponsiveness with EC aspirin was associated with lower exposure to acetylsalicylic acid (63% and 70% lower geometric mean maximum plasma concentration [C_{max}] and 77% and 82% lower AUC_{0-t} [area under the curve from time 0 to the last time measured]) and 66% and 72% lower maximum decrease of TXB₂, with marked interindividual variability.

CONCLUSIONS A high proportion of patients treated with EC aspirin failed to achieve complete inhibition of TXB₂ generation due to incomplete absorption. Reduced bioavailability may contribute to “aspirin resistance” in patients with diabetes. (Pharmacodynamic Evaluation of PL2200 Versus Enteric-Coated and Immediate Release Aspirin in Diabetic Patients; [NCT01515657](#)) (69).

Normal LDL-Cholesterol Levels Are Associated With Subclinical Atherosclerosis in the Absence of Risk Factors

L. Fernández-Friera, et al.

BACKGROUND Absence of cardiovascular risk factors (CVRFs) is traditionally considered low risk for atherosclerosis; however, individuals without CVRFs, as currently defined, still have events.

OBJECTIVES This study sought to identify predictors of subclinical atherosclerosis in CVRF-free individuals.

METHODS Participants from the PESA (Progression of Early Subclinical Atherosclerosis) study ($n = 4,184$) without conventional CVRFs were evaluated ($n = 1,779$; 45.0 ± 4.1 years, 50.3% women). CVRF freedom was defined as no current smoking and untreated blood pressure <140/90 mm Hg, fasting

glucose <126 mg/dl, total cholesterol <240 mg/dl, low-density lipoprotein cholesterol (LDL-C) <160 mg/dl, and high-density lipoprotein cholesterol ≥ 40 mg/dl. A subgroup with optimal CVRFs ($n = 740$) was also defined as having blood pressure <120/80 mm Hg, fasting glucose <100 mg/dl, glycosylated hemoglobin <5.7%, and total cholesterol <200 mg/dl. We evaluated ultrasound-detected carotid, iliofemoral, and abdominal aortic plaques; coronary artery calcification; serum biomarkers; and lifestyle. Adjusted odds ratios (with 95% confidence interval) and ordinal logistic regression models were used.

RESULTS Subclinical atherosclerosis (plaque or coronary artery calcification) was present in 49.7% of CVRF-free participants. Together with male sex and age, LDL-C was independently associated with atherosclerosis presence and extent, in both the CVRF-free and CVRF-optimal groups (odds ratio [$\times 10$ mg/dl]: 1.14 to 1.18; $p < 0.01$ for all). Atherosclerosis presence and extent was also associated in the CVRF-free group with glycosylated hemoglobin levels.

CONCLUSIONS Many CVRF-free middle-aged individuals have atherosclerosis. LDL-C, even at levels currently considered normal, is independently associated with the presence and extent of early systemic atherosclerosis in the absence of major CVRFs. These findings support more effective LDL-C lowering for primordial prevention, even in individuals conventionally considered at optimal risk. (Progression of Early Subclinical Atherosclerosis [PESA] Study; [NCT01410318](#)) (70).

Novel Diabetes Drugs and the Cardiovascular Specialist

N. Sattar, et al.

Recently, treatment with 2 newer classes of type 2 diabetes drugs were found to reduce events in patients with diabetes and cardiovascular (CV) disease, a group common in cardiology clinics. The sodium-glucose cotransporter 2 inhibitor, empagliflozin, markedly and rapidly reduced CV death and heart failure hospitalization, likely with hemodynamic/metabolic-driven mechanisms of action. More recently, the glucagon-like peptide-1 receptor agonists liraglutide and semaglutide also reduced CV death and/or major adverse CV events, but did so more slowly and did not influence heart failure risks, suggesting alternative mechanisms of benefit. We will discuss drug therapy for diabetes relative to CV risk, briefly summarize key findings of CV benefit from recent trials, discuss potential

mechanisms for benefits of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 agonists, and suggest how such drugs might be embraced by CV specialists to reduce CV events and mortality in their patients (71).

PCSK9 Inhibitors: Economics and Policy

M.A. Hlatky, et al.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors substantially reduce low-density lipoprotein cholesterol, but it is presently unclear whether they also reduce mortality. The list prices of PCSK9 inhibitors in the United States (>\$14,500 per year) are >100× higher than generic statins, and only a small fraction of their higher cost is likely to be recovered by prevention of cardiovascular events. The projected cost effectiveness of PCSK9 inhibitors does not meet generally accepted benchmarks for good value in the United States, but their value would be improved by substantial price reductions. For individual patients, the high out-of-pocket costs of PCSK9 inhibitors may impede access and reduce long-term adherence. The budgetary impact of PCSK9 inhibitors would be very large if all potentially eligible patients were treated, which poses dilemmas for policymakers, payers, and society (72).

RHYTHM DISORDERS

5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials

V.Y. Reddy, et al.

BACKGROUND The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial demonstrated that left atrial appendage closure (LAAC) with the Watchman device (Boston Scientific, St. Paul, Minnesota) was equivalent to warfarin for preventing stroke in atrial fibrillation, but had a high rate of complications. In a second randomized trial, PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), the complication rate was low. The warfarin cohort experienced an unexpectedly low ischemic stroke rate, rendering the efficacy endpoints inconclusive. However, these outcomes were based on relatively few patients followed for a relatively short time.

OBJECTIVES The final results of the PREVAIL trial, both alone and as part of a patient-level meta-analysis

with the PROTECT AF trial, are reported with patients in both trials followed for 5 years.

METHODS PREVAIL and PROTECT AF are prospective randomized clinical trials with patients randomized 2:1 to LAAC or warfarin; together, they enrolled 1,114 patients for 4,343 patient-years. Analyses are by intention-to-treat, and rates are events per 100 patient-years.

RESULTS For the PREVAIL trial, the first composite coprimary endpoint of stroke, systemic embolism (SE), or cardiovascular/unexplained death did not achieve noninferiority (posterior probability for noninferiority = 88.4%), whereas the second coprimary endpoint of post-procedure ischemic stroke/SE did achieve noninferiority (posterior probability for noninferiority = 97.5%); the warfarin arm maintained an unusually low ischemic stroke rate (0.73%). In the meta-analysis, the composite endpoint was similar between groups (hazard ratio [HR]: 0.820; $p = 0.27$), as were all-stroke/SE (HR: 0.961; $p = 0.87$). The ischemic stroke/SE rate was numerically higher with LAAC, but this difference did not reach statistical significance (HR: 1.71; $p = 0.080$). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding favored LAAC (HR: 0.20; $p = 0.0022$; HR: 0.45; $p = 0.03$; HR: 0.59; $p = 0.027$; HR: 0.73; $p = 0.035$; HR: 0.48; $p = 0.0003$, respectively).

CONCLUSIONS These 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial, demonstrate that LAAC with Watchman provides stroke prevention in nonvalvular atrial fibrillation comparable to warfarin, with additional reductions in major bleeding, particularly hemorrhagic stroke, and mortality. (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; [NCT00129545](#); and Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; [NCT01182441](#)) (73).

Cardiac Pacemakers: Function, Troubleshooting, and Management: Part 1 of a 2-Part Series

S.K. Mulpuru, et al.

Advances in cardiac surgery toward the mid-20th century created a need for an artificial means of stimulating the heart muscle. Initially developed as large external devices, technological advances resulted in miniaturization of electronic circuitry and eventually the development of totally implantable devices. These advances continue to date, with the

recent introduction of leadless pacemakers. In this first part of a 2-part review, we describe indications, implant-related complications, basic function/programming, common pacemaker-related issues, and remote monitoring, which are relevant to the practicing cardiologist. We provide an overview of magnetic resonance imaging and perioperative management among patients with cardiac pacemakers (74).

Advances and Future Directions in Cardiac Pacemakers: Part 2 of a 2-Part Series

M. Madhavan, et al.

In the second part of this 2-part series on pacemakers, we present recent advances in pacemakers and preview future developments. Cardiac resynchronization therapy (CRT) is a potent treatment for heart failure in the setting of ventricular dyssynchrony. Successful CRT using coronary venous pacing depends on appropriate patient selection, lead implantation, and device programming. Despite optimization of these factors, nonresponse to CRT may occur in one-third of patients, which has led to a search for alternative techniques such as multisite pacing, His bundle pacing, and endocardial left ventricular pacing. A paradigm shift in pacemaker technology has been the development of leadless pacemaker devices, and on the horizon is the development of batteryless devices. Remote monitoring has ushered in an era of greater safety and the ability to respond to device malfunction in a timely fashion, improving outcomes (75).

Anterior T-Wave Inversion in Young White Athletes and Nonathletes: Prevalence and Significance

A. Malhotra, et al.

BACKGROUND Anterior T-wave inversion (ATWI) on electrocardiography (ECG) in young white adults raises the possibility of cardiomyopathy, specifically arrhythmogenic right ventricular cardiomyopathy (ARVC). Whereas the 2010 European consensus recommendations for ECG interpretation in young athletes state that ATWI beyond lead V₁ warrants further investigation, the prevalence and significance of ATWI have never been reported in a large population of asymptomatic whites.

OBJECTIVES This study investigated the prevalence and significance of ATWI in a large cohort of young, white adults including athletes.

METHODS Individuals 16 to 35 years of age (n = 14,646), including 4,720 females (32%) and 2,958 athletes (20%), were evaluated by using a health questionnaire, physical examination, and 12-lead ECG. ATWI was defined as T-wave inversion in ≥ 2 contiguous anterior leads (V₁ to V₄).

RESULTS ATWI was detected in 338 individuals (2.3%) and was more common in women than in men (4.3% vs. 1.4%, respectively; p < 0.0001) and more common among athletes than in nonathletes (3.5% vs. 2.0%, respectively; p < 0.0001). T-wave inversion was predominantly confined to leads V₁ to V₂ (77%). Only 1.2% of women and 0.2% of men exhibited ATWI beyond V₂. No one with ATWI fulfilled diagnostic criteria for ARVC after further evaluation. During a mean follow-up of 23.1 ± 12.2 months none of the individuals with ATWI experienced an adverse event.

CONCLUSIONS ATWI confined to leads V₁ to V₂ is a normal variant or physiological phenomenon in asymptomatic white individuals without a relevant family history. ATWI beyond V₂ is rare, particularly in men, and may warrant investigation (76).

Catheter Ablation of Ventricular Tachycardia in Structurally Normal Hearts: Indications, Strategies, and Outcomes—Part I

S.R. Dukkipati, et al.

Catheter ablation of ventricular tachycardia (VT) is being increasingly performed; yet, there is often confusion regarding indications, outcomes, and how to identify those patient populations most likely to benefit. The management strategy differs between those with structural heart disease and those without. For the former, an implantable cardioverter-defibrillator (ICD) is typically required due to an elevated risk for sudden cardiac death, and catheter ablation can be used as adjunctive therapy to treat or prevent repetitive ICD therapies. In contrast, VT or premature ventricular contractions in the setting of a structurally normal heart carries a low risk for sudden cardiac death; accordingly, there is typically no indication for an ICD. In these patients, catheter ablation is considered for symptom management or to treat tachycardiomyopathy and is potentially curative. Here, the authors discuss the pathophysiology, mechanism, and management of VT that occurs in the setting of a structurally normal heart and the role of catheter ablation (77).

Catheter Ablation of Ventricular Tachycardia in Structural Heart Disease: Indications, Strategies, and Outcomes—Part II

S.R. Dukkupati, et al.

In contrast to ventricular tachycardia (VT) that occurs in the setting of a structurally normal heart, VT that occurs in patients with structural heart disease carries an elevated risk for sudden cardiac death (SCD), and implantable cardioverter-defibrillators (ICDs) are the mainstay of therapy. In these individuals, catheter ablation may be used as adjunctive therapy to treat or prevent repetitive ICD therapies when antiarrhythmic drugs are ineffective or not desired. However, certain patients with frequent premature ventricular contractions (PVCs) or VT and tachycardiomyopathy should be considered for ablation before ICD implantation because left ventricular function may improve, consequently decreasing the risk of SCD and obviating the need for an ICD. The goal of this paper is to review the pathophysiology, mechanism, and management of VT in the setting of structural heart disease and discuss the evolving role of catheter ablation in decreasing ventricular arrhythmia recurrence (78).

Cerebral Amyloid Angiopathy: Diagnosis, Clinical Implications, and Management Strategies in Atrial Fibrillation

C.V. DeSimone, et al.

With an aging population, clinicians are more frequently encountering patients with atrial fibrillation who are also at risk of intracerebral hemorrhage due to cerebral amyloid angiopathy, the result of β -amyloid deposition in cerebral vessels. Cerebral amyloid angiopathy is common among elderly patients, and is associated with an increased risk of intracerebral bleeding, especially with the use of anticoagulation. Despite this association, this entity is absent in current risk-benefit analysis models, which may result in underestimation of the chance of bleeding in the subset of patients with this disease. Determining the presence and burden of cerebral amyloid angiopathy is particularly important when planning to start or restart anticoagulation after an intracerebral hemorrhage. Given the lack of randomized trial data to guide management strategies, we discuss a heart-brain team approach that includes clinician-patient shared decision making for the use of pharmacologic and nonpharmacologic approaches to diminish stroke risk (79).

Clinical Benefit of Ablating Localized Sources for Human Atrial Fibrillation: The Indiana University FIRM Registry

J.M. Miller, et al.

BACKGROUND Mounting evidence shows that localized sources maintain atrial fibrillation (AF). However, it is unclear in unselected “real-world” patients if sources drive persistent atrial fibrillation (PeAF), long-standing persistent atrial fibrillation (LPeAF), or paroxysmal atrial fibrillation (PAF); if right atrial sites are important; and what the long-term success of source ablation is.

OBJECTIVES The aim of this study was to analyze the role of rotors and focal sources in a large academic registry of consecutive patients undergoing source mapping for AF.

METHODS One hundred seventy consecutive patients (mean age 59 ± 12 years, 79% men) with PAF (37%), PeAF (31%), or LPeAF (32%). Of these, 73 (43%) had undergone at least 1 prior ablation attempt (mean 1.9 ± 0.8 ; range: 1 to 4). Focal impulse and rotor modulation (FIRM) with an endocardial basket catheter was used in all cases.

RESULTS FIRM analysis revealed sources in the right atrium in 85% of patients (1.8 ± 1.3) and in the left atrium in 90% of patients (2.0 ± 1.3). FIRM ablation terminated AF to sinus rhythm or atrial flutter or tachycardia in 59% (PAF), 37% (PeAF), and 19% (LPeAF) of patients, with 15 of 67 terminations due to right atrial ablation. On follow-up, freedom from AF after a single FIRM procedure for the entire series was 95% (PAF), 83% (PeAF), and 82% (LPeAF) at 1 year and freedom from all atrial arrhythmias was 77% (PAF), 75% (PeAF), and 57% (LPeAF).

CONCLUSIONS In the Indiana University FIRM registry, FIRM-guided ablation produced high single-procedure success, mostly in patients with nonparoxysmal AF. Data from mapping, acute terminations, and outcomes strongly support the mechanistic role of biatrial rotors and focal sources in maintaining AF in diverse populations. Randomized trials of FIRM-guided ablation and mechanistic studies to determine how rotors form, progress, and regress are needed (80).

Complexity and Distribution of Drivers in Relation to Duration of Persistent Atrial Fibrillation

H.S. Lim, et al.

BACKGROUND The underlying mechanisms sustaining human persistent atrial fibrillation (PsAF) is poorly understood.

OBJECTIVES This study sought to investigate the complexity and distribution of AF drivers in PsAF of varying durations.

METHODS Of 135 consecutive patients with PsAF, 105 patients referred for de novo ablation of PsAF were prospectively recruited. Patients were divided into 3 groups according to AF duration: PsAF presenting in sinus rhythm (AF induced), PsAF <12 months, and PsAF >12 months. Patients wore a 252-electrode vest for body surface mapping. Localized drivers (re-entrant or focal) were identified using phase-mapping algorithms.

RESULTS In this patient cohort, the most prominent re-entrant driver regions included the pulmonary vein (PV) regions and inferoposterior left atrial wall. Focal drivers were observed in 1 or both PV regions in 75% of patients. Comparing between the 3 groups, with longer AF duration AF complexity increased, reflected by increased number of re-entrant rotations ($p < 0.05$), number of re-entrant rotations and focal events ($p < 0.05$), and number of regions harboring re-entrant ($p < 0.01$) and focal ($p < 0.05$) drivers. With increased AF duration, a higher proportion of patients had multiple extra-PV driver regions, specifically in the inferoposterior left atrium ($p < 0.01$), superior right atrium ($p < 0.05$), and inferior right atrium ($p < 0.05$). Procedural AF termination was achieved in 70% of patients, but decreased with longer AF duration.

CONCLUSIONS The complexity of AF drivers increases with prolonged AF duration. Re-entrant and focal drivers are predominantly located in the PV antral and adjacent regions. However, with longer AF duration, multiple drivers are distributed at extra-PV sites. AF termination rate declines as patients progress to longstanding PsAF, underscoring the importance of early intervention (81).

Contemporary Outcomes in Patients With Long QT Syndrome

R.K. Rohatgi, et al.

BACKGROUND Long QT syndrome (LQTS) is a potentially lethal cardiac channelopathy with a 1% to 5% annual risk of LQTS-triggered syncope, aborted cardiac arrest, or sudden cardiac death.

OBJECTIVES This study sought to evaluate LQTS outcomes from a single center in the contemporary era.

METHODS The authors conducted a retrospective study comprising the 606 patients with LQTS (LQT1 in 47%, LQT2 in 34%, and LQT3 in 9%) who were evaluated in Mayo Clinic's Genetic Heart Rhythm Clinic

from January 1999 to December 2015. Breakthrough cardiac events (BCEs) were defined as LQTS-attributable syncope or seizures, aborted cardiac arrest, appropriate ventricular fibrillation-terminating implantable cardioverter-defibrillator shocks, and sudden cardiac death.

RESULTS There were 166 (27%) patients who were symptomatic prior to their first Mayo Clinic evaluation. Median age at first symptom was 12 years. Treatment strategies included no active therapy in 47 (8%) patients, beta-blockers alone in 350 (58%) patients, implantable cardioverter-defibrillators alone in 25 (4%) patients, left cardiac sympathetic denervation alone in 18 (3%) patients, and combination therapy in 166 (27%) patients. Over a median follow-up of 6.7 (IQR: 3.9 to 9.8) years, 556 (92%) patients have not experienced an LQTS-triggered BCE. Only 8 of 440 (2%) previously asymptomatic patients have experienced a single BCE. In contrast, 42 of 166 (25%) previously symptomatic patients have experienced ≥ 1 BCE. Among the 30 patients with ≥ 2 BCEs, 2 patients have died and 3 LQT3 patients underwent cardiac transplantation.

CONCLUSIONS Although outcomes have improved markedly, further optimization of treatment strategies is still needed given that 1 in 4 previously symptomatic patients experienced at least 1 subsequent, albeit nonlethal, LQTS-triggered cardiac event (82).

The Continued Search for Physiological Pacing: Where Are We Now?

P. Vijayaraman, et al.

Cardiac pacing is an effective treatment for patients with bradycardia due to sinus node dysfunction or atrioventricular block. Despite decades of technological advances, the optimal ventricular pacing site to mimic normal human ventricular physiology and best hemodynamic response remains elusive. Beginning with atrial synchronous right ventricular (RV) apical pacing, the search has continued through alternate RV pacing sites, minimizing RV pacing, biventricular pacing, left ventricular (LV) pacing, and His-bundle pacing. Understanding the deleterious effects of long-term RV apical pacing in vulnerable populations has created tremendous interest in alternate pacing options. This paper reviews the current status of available pacing options, with particular focus on His-bundle pacing. Permanent His-bundle pacing has emerged as the leading candidate for physiological pacing because it provides nearly normal electrical activation of both

ventricles and thereby avoids ventricular dyssynchrony. Synchronized LV pacing, multisite LV pacing, and LV endocardial pacing offer promise as novel pacing options in select patients (83).

Dual-Chamber Pacing With Closed Loop Stimulation in Recurrent Reflex Vasovagal Syncope: The SPAIN Study

G. Baron-Esquivias, et al.

BACKGROUND Pacing in vasovagal syncope remains controversial.

OBJECTIVES The authors evaluated dual-chamber pacing with closed loop stimulation (DDD-CLS) in patients with cardioinhibitory vasovagal syncope.

METHODS This randomized, double-blind, controlled study included Canadian and Spanish patients age ≥ 40 years, with high burden syncope (≥ 5 episodes, ≥ 2 episodes in the past year), and a cardioinhibitory head-up tilt test (bradycardia < 40 beats/min for 10 s or asystole > 3 s). Patients were randomized to either DDD-CLS pacing for 12 months followed by sham DDI mode pacing at 30 pulses/min for 12 months (group A), or sham DDI mode for 12 months followed by DDD-CLS pacing for 12 months (group B). Patients in both arms crossed-over after 12 months of follow-up or when a maximum of 3 syncopal episodes occurred within 1 month.

RESULTS A total of 46 patients completed the protocol; 22 were men (47.8%), and mean age was 56.30 ± 10.63 years. The mean number of previous syncopal episodes was 12 (range 9 to 20). The proportion of patients with $\geq 50\%$ reduction in the number of syncopal episodes was 72% (95% confidence interval [CI]: 47% to 90%) with DDD-CLS compared with 28% (95% CI: 9.7% to 53.5%) with sham DDI mode ($p = 0.017$). A total of 4 patients (8.7%) had events during DDD-CLS and 21 (45.7%) during sham DDI (hazard ratio: 6.7; 95% CI: 2.3 to 19.8). Kaplan-Meier curve was significantly different between groups in time to first syncope: 29.2 months (95% CI: 15.3 to 29.2 months) versus 9.3 months (95% CI: 6.21 months, NA; $p < 0.016$); odds ratio: 0.11 (95% CI: 0.03 to 0.37; $p < 0.0001$).

CONCLUSIONS DDD-CLS pacing significantly reduced syncope burden and time to first recurrence by 7-fold, prolonging time to first syncope recurrence in patients age ≥ 40 years with head-up tilt test-induced vasovagal syncope compared with sham pacing. (Closed Loop Stimulation for Neuromediated Syncope [SPAIN Study]; [NCT01621464](#)) (84).

Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: The EFFORTLESS Study

L. Boersma, et al.

BACKGROUND The subcutaneous implantable cardioverter-defibrillator (S-ICD) was developed to defibrillate ventricular arrhythmias, avoiding drawbacks of transvenous leads. The global EFFORTLESS S-ICD (Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD) registry is collecting outcomes in 985 patients during a 5-year follow-up.

OBJECTIVES The primary goal of the EFFORTLESS registry is to determine the safety of the S-ICD by evaluating complications and inappropriate shock rate.

METHODS This is the first report on the full patient cohort and study endpoints with follow-up ≥ 1 year. The predefined endpoints are 30- and 360-day complications, and shocks for atrial fibrillation or supraventricular tachycardia.

RESULTS Patients were followed for 3.1 ± 1.5 years and 82 completed the study protocol 5-year visit. Average age was 48 years, 28% were women, ejection fraction was $43 \pm 18\%$, and 65% had a primary prevention indication. The S-ICD system and procedure complication rate was 4.1% at 30 days and 8.4% at 360 days. The 1-year complication rate trended toward improvement from the first to last quartile of enrollment (11.3% [quartile 1] to 7.8% [quartile 2], 6.6% [quartile 3], and 7.4% [quartile 4]; quartile 1 vs. quartiles 2 to 4; $p = 0.06$). Few device extractions occurred due to need for antitachycardia ($n = 5$), or biventricular ($n = 4$) or bradycardia pacing ($n = 1$). Inappropriate shocks occurred in 8.1% at 1 year and 11.7% after 3.1 years. At implant, 99.5% of patients had a successful conversion of induced ventricular tachycardia or ventricular fibrillation. The 1- and 5-year rates of appropriate shock were 5.8% and 13.5%, respectively. Conversion success for discrete spontaneous episodes was 97.4% overall.

CONCLUSIONS This registry demonstrates that the S-ICD fulfills predefined endpoints for safety and efficacy. Midterm performance rates on complications, inappropriate shocks, and conversion efficacy were comparable to rates observed in transvenous implantable cardioverter-defibrillator studies. (Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD [The EFFORTLESS S-ICD Registry]; [NCT01085435](#)) (85).

Implantable Cardioverter-Defibrillators With Versus Without Resynchronization Therapy in Patients With a QRS Duration >180 ms

V. Sundaram, et al.

BACKGROUND More than 20% of Medicare beneficiaries receiving cardiac resynchronization therapy defibrillators (CRT-D) have a very wide (≥ 180 ms) QRS complex duration (QRSD). Outcomes of CRT-D in these patients are not well-established because they have been underrepresented in clinical trials.

OBJECTIVES This study examined outcomes in patients with CRT-D in a very wide QRSD with left bundle branch block (LBBB) versus those without LBBB.

METHODS Medicare patients from the Implantable Cardioverter Defibrillator Registry (January 1, 2005, through April 30, 2006) with a CRT-D and confirmed Class I or IIa indications for CRT-D were matched to implantable cardioverter-defibrillator (ICD) patients without CRT despite having Class I or IIa indications for CRT. Mortality and heart failure hospitalizations over 4 years with CRT-D versus standard ICDs based on QRSD and morphology were analyzed.

RESULTS We analyzed 24,960 patients. Among those with LBBB, patients with a QRSD ≥ 180 ms had a greater adjusted survival benefit with CRT-D versus standard ICD (hazard ratio [HR] for death: 0.65; 95% confidence interval [CI]: 0.59 to 0.72) compared with those having a QRSD 120 to 149 ms (HR: 0.85; 95% CI: 0.80 to 0.92) and 150 to 179 ms (HR: 0.87; 95% CI: 0.81 to 0.93). CRT-D versus ICD was associated with an improvement in survival in those with non-LBBB and a QRSD ≥ 180 ms (adjusted HR for death: 0.78; 95% CI: 0.68 to 0.91), but not in those with non-LBBB and a QRSD 150 to 179 ms (adjusted HR for death: 1.06; 95% CI: 0.95 to 1.19).

CONCLUSIONS Improvements in both survival and heart failure hospitalizations with CRT-D were greatest in patients with a QRSD ≥ 180 ms with or without LBBB, whereas patients with a QRSD 150 to 179 ms without LBBB had no improvement in survival with CRT-D, and those with a QRSD 150 to 179 ms and LBBB had only a modest improvement (86).

Insulin-Requiring Versus Noninsulin-Requiring Diabetes and Thromboembolic Risk in AF Patients With Atrial Fibrillation: PREFER in AF

G. Patti, et al.

BACKGROUND Diabetes is a known risk predictor for thromboembolic events in patients with atrial

fibrillation (AF), but no study has explored the prognostic weight of insulin in this setting.

OBJECTIVES This study evaluated the differential role of insulin versus no insulin therapy on thromboembolic risk in patients with diabetes and AF.

METHODS We accessed individual patient data from the prospective, real-world, multicenter, PREFER in AF (European Prevention of thromboembolic events-European Registry in Atrial Fibrillation). We compared the rates of stroke/systemic embolism at 1 year according to diabetes status (no diabetes, diabetes without insulin therapy, diabetes on insulin therapy).

RESULTS In an overall population of 5,717 patients, 1,288 had diabetes, 22.4% of whom were on insulin. For patients with diabetes who were on insulin, there was a significantly increased risk of stroke/systemic embolism at 1 year versus either no diabetes (5.2% vs. 1.9%; hazard ratio: 2.89; 95% confidence interval: 1.67 to 5.02; $p = 0.0002$) or diabetes without insulin treatment (5.2% vs. 1.8%; hazard ratio: 2.96; 95% confidence interval: 1.49 to 5.87; $p = 0.0019$). Notably, rates of stroke/embolism were similar in patients with diabetes not receiving insulin versus patients without diabetes (hazard ratio: 0.97; 95% confidence interval: 0.58 to 1.61; $p = 0.90$). The selective predictive role of insulin-requiring diabetes was independent of potential confounders, including diabetes duration, and was maintained in various subpopulations, including the subgroup receiving anticoagulant therapy.

CONCLUSIONS In this cohort of anticoagulated patients with AF, the sole presence of diabetes not requiring insulin did not imply an increased thromboembolic risk. Conversely, insulin-requiring diabetes contributed most, if not exclusively, to the overall increase of thromboembolic risk in AF (87).

Lean Body Mass Is the Predominant Anthropometric Risk Factor for Atrial Fibrillation

M. Fenger-Grøn, et al.

BACKGROUND Obesity is repeatedly emphasized as a risk factor for atrial fibrillation or flutter (AF). However, the underlying evidence may be questioned, as the obvious correlations between various anthropometric measures hamper identification of the characteristics that are biologically driving AF risk, and recent studies suggest that fat carries limited or no independent risk of AF.

OBJECTIVES This study sought to assess mutually adjusted associations among AF risk and height, weight, body mass index, hip and waist circumference, waist-to-hip ratio, and bioelectrical impedance-derived measures of fat mass, lean body mass, and fat percentage.

METHODS Anthropometric measures and self-reported life-style information were collected from 1993 to 1997 in a population-based cohort including 55,273 persons age 50 to 64 years who were followed in Danish registers until June 2013.

RESULTS During a median of 17 years of follow-up, 3,868 persons developed AF. Adjusted hazard ratios per population SD difference (HRs) showed highly statistically significant, positive associations for all 9 anthropometric measures (HRs ranging from 1.08 [95% confidence interval (CI): 1.05 to 1.12] for waist-to-hip ratio to 1.37 [95% CI: 1.33 to 1.42] for lean body mass). Pairwise mutual adjustment of the 9 measures left the association for lean body mass virtually unchanged (lowest HR: 1.33 [95% CI: 1.28 to 1.39] when adjusting for height), whereas no other association remained substantial when adjusted for lean body mass (highest HR: 1.05 [95% CI: 1.01 to 1.10] for height).

CONCLUSIONS Lean body mass was the predominant anthropometric risk factor for AF, whereas no association was observed for either of the obesity-related anthropometric measures after adjustment for lean body mass (88).

Obesity and Atrial Fibrillation Prevalence, Pathogenesis, and Prognosis: Effects of Weight Loss and Exercise

C.J. Lavie, et al.

Both obesity and atrial fibrillation (AF) are increasing in epidemic proportions, and both increase the prevalence of cardiovascular disease events. Obesity has adverse effects on cardiovascular hemodynamics and cardiac structure and function, and increases the prevalence of AF, partly related to electroanatomic remodeling in obese patients. However, numerous studies, including in AF, have demonstrated an obesity paradox, where overweight and obese patients with these disorders have a better prognosis than do leaner patients with the same degree of severity of cardiovascular disease/AF. In this paper, the authors discuss special issues regarding AF in obesity, as well as the evidence that despite the presence of an obesity paradox, there are benefits of weight loss, physical activity/exercise training, and

increases in cardiorespiratory fitness on the prognosis of obese patients with AF (89).

Structure and Function of the Left Atrium and Left Atrial Appendage: AF and Stroke Implications

V. Delgado, et al.

Atrial fibrillation (AF) and stroke are important major health problems that share common risk factors and frequently coexist. Left atrial (LA) remodeling is an important underlying substrate for AF and stroke. LA dilation and dysfunction form a prothrombotic milieu characterized by blood stasis and endothelial dysfunction. In addition, alterations of the atrial cardiomyocytes, increase of noncollagen deposits in the interstitial space and fibrosis, favor the occurrence of re-entry that predisposes to AF. Eventually, AF further impairs LA function and promotes LA remodeling, closing a self-perpetuating vicious circle. Multimodality imaging provides a comprehensive evaluation of several aspects of LA remodeling and offers several parameters to identify patients at risk of AF and stroke. How multimodality imaging can be integrated in clinical management of patients at risk of AF and stroke is the focus of the present review paper (90).

VALVULAR HEART DISEASE

Atrial Infarction and Ischemic Mitral Regurgitation Contribute to Post-MI Remodeling of the Left Atrium

J. Aguero, et al.

BACKGROUND Left atrial (LA) remodeling after an acute myocardial infarction (MI) is poorly characterized regarding its determinants or its effect on ischemic mitral regurgitation (MR) development.

OBJECTIVES The purpose of this study was: 1) to compare LA structural remodeling in experimental MI swine models recapitulating the effects of left ventricular (LV) dysfunction, ischemic MR, and left atrial infarction (LAI); and 2) to analyze how LA remodeling influences ischemic MR development.

METHODS Three models of MI were generated: 1) proximal left circumflex (LCx) coronary artery occlusion involving the LA branch (LAI group); 2) proximal LCx occlusion not involving the LA branch (LCx group); and 3) left anterior descending (LAD) occlusion (LAD group). Serial cardiac magnetic resonance scans were performed to define LA and LV

remodeling and ischemic MR, and were correlated with histology.

RESULTS Occlusion of the LA branch (LAI group) induced a greater degree of LA dilation at 1 and 8 weeks post-MI than the LCx and LAD groups, along with early and severe impairment of LA function. In the LCx and LAD groups, LA dysfunction was less pronounced and not consistent. Development of ischemic MR was more pronounced in the LAI group than in the LCx group. Histology confirmed atrial infarction with extensive fibrosis in the LAI group and interstitial fibrosis in the LCx group. In the LAD group, LA remodeling was not observed by cardiac magnetic resonance or histology.

CONCLUSIONS We provide the first experimental evidence of the deleterious effect of acute LAI on atrial structural remodeling, characterized by early LA dilation, dysfunction, and fibrosis, and early occurrence of ischemic MR (91).

Challenges in Infective Endocarditis

T.J. Cahill, et al.

Infective endocarditis is defined by a focus of infection within the heart and is a feared disease across the field of cardiology. It is frequently acquired in the health care setting, and more than one-half of cases now occur in patients without known heart disease. Despite optimal care, mortality approaches 30% at 1 year. The challenges posed by infective endocarditis are significant. It is heterogeneous in etiology, clinical manifestations, and course. *Staphylococcus aureus*, which has become the predominant causative organism in the developed world, leads to an aggressive form of the disease, often in vulnerable or elderly patient populations. There is a lack of research infrastructure and funding, with few randomized controlled trials to guide practice. Longstanding controversies such as the timing of surgery or the role of antibiotic prophylaxis have not been resolved. The present article reviews the challenges posed by infective endocarditis and outlines current and future strategies to limit its impact (92).

Early Feasibility Study of a Transcatheter Tricuspid Valve Annuloplasty: SCOUT Trial 30-Day Results

R.T. Hahn, et al.

BACKGROUND The SCOUT (Percutaneous Tricuspid Valve Annuloplasty System for Symptomatic Chronic Functional Tricuspid Regurgitation) trial is a

prospective, single-arm, multicenter, early feasibility study of a novel transcatheter device to plicate the tricuspid annulus (TA) and reduce tricuspid regurgitation (TR).

OBJECTIVES This study tested the feasibility and safety of a novel transcatheter device and assessed its early performance and functional outcomes.

METHODS Between November 2015 and June 2016, 15 patients with New York Heart Association (NYHA) functional class \geq II and moderate or greater functional TR were enrolled. Primary performance and safety endpoint outcomes were technically successful at 30 days with no reintervention. Echocardiographic measurements (TA diameter, effective regurgitant orifice area [EROA], left ventricular stroke volume [LVSV]) and quality-of-life (QoL) measurements (NYHA functional class, Minnesota Living with Heart Failure Questionnaire [MLHFQ], and 6-min walk test [6MWT]) were performed at baseline and 30 days.

RESULTS All patients (mean 73.2 ± 6.9 years of age, 87% female) underwent successful device implantation with no deaths, strokes, bleeding, tamponade, or valve reintervention. Technical success rate at 30 days was 80%, with 3 single-pledget annular detachments without reintervention. In the remaining 12 patients, there were significant reductions in TA (12.3 ± 3.1 cm² to 11.3 ± 2.7 cm², respectively; $p = 0.019$) and EROA (0.51 ± 0.18 cm² vs. 0.32 ± 0.18 cm², respectively; $p = 0.020$), with significant increase in LVSV (63.6 ± 17.9 ml vs. 71.5 ± 25.7 ml, respectively; $p = 0.021$). In the intention-to-treat cohort, there were significant improvements in NYHA functional class (\geq 1 class, $p = 0.001$), MLHFQ (47.4 ± 17.6 to 20.9 ± 14.8 ; $p < 0.001$), and 6MWT (245.2 ± 110.1 to 298.0 m ± 107.6 m; $p = 0.008$).

CONCLUSIONS The 30-day results of the SCOUT trial confirmed the safety of the novel transcatheter device, which reduced TA and EROA, increased LVSV, and improved QoL. (Early Feasibility of the Mitralign Percutaneous Tricuspid Valve Annuloplasty System (PTVAS) Also Known as TriAlign [SCOUT]; [NCT02574650](https://clinicaltrials.gov/ct2/show/study/NCT02574650).) (93).

The Evolving Nature of Infective Endocarditis in Spain: A Population-Based Study (2003 to 2014)

C. Olmos, et al.

BACKGROUND Little information exists regarding population-based epidemiological changes in infective endocarditis (IE) in Europe.

OBJECTIVES This study sought to analyze temporal trends in IE in Spain from 2003 to 2014.

METHODS This retrospective, population-based, temporal trend study analyzed the incidence, epidemiological and clinical characteristics, and outcome of all patients discharged from hospitals included in the Spanish National Health System with a diagnosis of IE, from January 2003 to December 2014.

RESULTS Overall, 16,867 episodes of IE were identified during the study period, 66.3% in men. The rate of IE significantly increased, from 2.72 in 2003 to 3.49 per 100,000 person-years in 2014, and this rise was higher among older adults. The most frequent microorganisms were staphylococci (28.7%), followed by streptococci (20.4%) and enterococci (13.1%). Twenty-three percent of patients underwent cardiac surgery. The in-hospital mortality rate was 20.4%. Throughout the study period, the proportion of patients with previously known heart valve disease and diabetes mellitus significantly increased, whereas the prevalence of intravenous drug use decreased. Regarding microorganisms, *Staphylococcus aureus* and streptococci slightly declined, whereas coagulase-negative staphylococci and enterococci consistently increased over the years. In-hospital complications and cardiac surgery rates significantly increased across the years. The risk-adjusted in-hospital mortality rate diminished (0.2% per year) during the study period.

CONCLUSIONS The incidence of IE episodes significantly increased over the decade of the study period, particularly among older adults. Relevant changes in clinical and microbiological profile included older patients with more comorbidity and a rise in enterococci and coagulase-negative staphylococcal infections. Adjusted mortality rates slightly declined over the study period (94).

Maternal and Fetal Outcomes of Anticoagulation in Pregnant Women With Mechanical Heart Valves

Z.L. Steinberg, et al.

BACKGROUND Anticoagulation for mechanical heart valves during pregnancy is essential to prevent thromboembolic events. Each regimen has drawbacks with regard to maternal or fetal risk.

OBJECTIVES This meta-analysis sought to estimate and compare the risk of adverse maternal and fetal outcomes in pregnant women with mechanical heart valves who received different methods of anticoagulation.

METHODS Studies were identified using a Medline search including all publications up to June 5, 2016.

Study inclusion required reporting of maternal death, thromboembolism, and valve failure, and/or fetal spontaneous abortion, death, and congenital defects in pregnant women treated with any of the following: 1) a vitamin K antagonist (VKA) throughout pregnancy; 2) low-molecular-weight heparin (LMWH) throughout pregnancy; 3) LMWH for the first trimester, followed by a VKA (LMWH and VKA); or 4) unfractionated heparin for the first trimester, followed by a VKA (UFH and VKA).

RESULTS A total of 800 pregnancies from 18 publications were included. Composite maternal risk was lowest with VKA (5%), compared with LMWH (16%; ratio of averaged risk [RAR]: 3.2; 95% confidence interval [CI]: 1.5 to 7.5), LMWH and VKA (16%; RAR: 3.1; 95% CI: 1.2 to 7.5), or UFH and VKA (16%; RAR: 3.1; 95% CI: 1.5 to 7.1). Composite fetal risk was lowest with LMWH (13%; RAR: 0.3; 95% CI: 0.1 to 0.8), compared with VKA (39%), LMWH and VKA (23%), or UFH and VKA (34%). No significant difference in fetal risk was observed between women taking ≤ 5 mg daily warfarin and those with an LMWH regimen (RAR: 0.9; 95% CI: 0.3 to 2.4).

CONCLUSIONS VKA treatment was associated with the lowest risk of adverse maternal outcomes, whereas the use of LMWH throughout pregnancy was associated with the lowest risk of adverse fetal outcomes. Fetal risk was similar between women taking ≤ 5 mg warfarin daily and women treated with LMWH (95).

Outcomes in Transcatheter Aortic Valve Replacement for Bicuspid Versus Tricuspid Aortic Valve Stenosis

S.-H. Yoon, et al.

BACKGROUND Transcatheter aortic valve replacement (TAVR) is being increasingly performed in patients with bicuspid aortic valve stenosis (AS).

OBJECTIVES This study sought to compare the procedural and clinical outcomes in patients with bicuspid versus tricuspid AS from the Bicuspid AS TAVR multicenter registry.

METHODS Outcomes of 561 patients with bicuspid AS and 4,546 patients with tricuspid AS were compared after propensity score matching, assembling 546 pairs of patients with similar baseline characteristics. Procedural and clinical outcomes were recorded according to Valve Academic Research Consortium-2 criteria.

RESULTS Compared with patients with tricuspid AS, patients with bicuspid AS had more frequent conversion to surgery (2.0% vs. 0.2%; $p = 0.006$) and a significantly lower device success rate (85.3% vs. 91.4%; $p = 0.002$). Early-generation devices were

implanted in 320 patients with bicuspid and 321 patients with tricuspid AS, whereas new-generation devices were implanted in 226 and 225 patients with bicuspid and tricuspid AS, respectively. Within the group receiving early-generation devices, bicuspid AS had more frequent aortic root injury (4.5% vs. 0.0%; $p = 0.015$) when receiving the balloon-expanding device, and moderate-to-severe paravalvular leak (19.4% vs. 10.5%; $p = 0.02$) when receiving the self-expanding device. Among patients with new-generation devices, however, procedural results were comparable across different prostheses. The cumulative all-cause mortality rates at 2 years were comparable between bicuspid and tricuspid AS (17.2% vs. 19.4%; $p = 0.28$).

CONCLUSIONS Compared with tricuspid AS, TAVR in bicuspid AS was associated with a similar prognosis, but lower device success rate. Procedural differences were observed in patients treated with the early-generation devices, whereas no differences were observed with the new-generation devices (96).

Outcomes With Transcatheter Mitral Valve Repair in the United States: An STS/ACC TVT Registry Report

P. Sorajja, et al.

BACKGROUND Post-market surveillance is needed to evaluate the real-world clinical effectiveness and safety of U.S. Food and Drug Administration-approved devices.

OBJECTIVES The authors examined the commercial experience with transcatheter mitral valve repair for the treatment of mitral regurgitation.

METHODS Data from the Society of Thoracic Surgery/American College of Cardiology Transcatheter Valve Therapy Registry on patients commercially treated with transcatheter mitral valve repair were analyzed. The study population consisted of 2,952 patients treated at 145 hospitals between November 2013 and September 2015. In 1,867 patients, data were linked to patient-specific Centers for Medicare and Medicaid Services administrative claims for analyses.

RESULTS The median age was 82 years (55.8% men), with a median Society of Thoracic Surgery predicted risk of mortality of 6.1% (interquartile range: 3.7% to 9.9%) and 9.2% (interquartile range: 6.0% to 14.1%) for mitral repair and replacement, respectively. Overall, in-hospital mortality was 2.7%. Acute procedure success occurred in 91.8%. Among the patients with Centers for Medicare and Medicaid Services linkage data, the mortality at 30 days and at 1 year was 5.2%

and 25.8%, respectively, and repeat hospitalization for heart failure at 1 year occurred in 20.2%. Variables associated with mortality or rehospitalization for heart failure after multivariate adjustment were increasing age, lower baseline left ventricular ejection fraction, worse post-procedural mitral regurgitation, moderate or severe lung disease, dialysis, and severe tricuspid regurgitation.

CONCLUSIONS Our findings demonstrate that commercial transcatheter mitral valve repair is being performed in the United States with acute effectiveness and safety. Our findings may help determine which patients have favorable long-term outcomes with this therapy (97).

Relation of Mitral Valve Surgery Volume to Repair Rate, Durability, and Survival

J. Chikwe, et al.

BACKGROUND Degenerative mitral valve repair rates remain highly variable, despite established benefits of repair over replacement. The contribution of surgeon-specific factors is poorly defined.

OBJECTIVES This study evaluated the influence of surgeon case volume on degenerative mitral valve repair rates and outcomes.

METHODS A mandatory New York State database was queried and 5,475 patients were identified with degenerative mitral disease who underwent mitral valve operations between 2002 and 2013. Mitral repair rates, mitral reoperations within 12 months of repair, and survival were analyzed using multivariable Cox modeling and restricted cubic spline function.

RESULTS Median annual surgeon volume of any mitral operations was 10 (range 1 to 230), with a mean repair rate of 55% ($n = 20,797$ of 38,128). In the subgroup of patients with degenerative disease, the mean repair rate was 67% ($n = 3,660$ of 5,475), with a range of 0% to 100%. Mean repair rates ranged from 48% ($n = 179$ of 370) for surgeons with total annual volumes of ≤ 10 mitral operations to 77% ($n = 1,710$ of 2,216) for surgeons with total annual volumes of > 50 mitral operations ($p < 0.001$). Higher total annual surgeon volume was associated with increased repair rates of degenerative mitral valve disease (adjusted odds ratio [OR]: 1.13 for every additional 10 mitral operations; 95% confidence interval [CI]: 1.10 to 1.17; $p < 0.001$); a steady decrease in reoperation risk until 25 total mitral operations annually; and improved 1-year survival (adjusted hazard ratio: 0.95 for every additional 10 operations; 95% CI: 0.92 to 0.98; $p = 0.001$). For surgeons with a total annual volume of ≤ 25 mitral operations, repair rates were higher

(63.8%; n = 180 of 282) if they operated in the same institution as a surgeon with total annual mitral volumes of >50 and degenerative mitral valve repair rates of >70%, compared with surgeons operating in the other institutions (51.3%; n = 580 of 1,130) (adjusted OR: 1.79; 95% CI: 1.24 to 2.60; p < 0.001).

CONCLUSIONS This study suggests that individual surgeon volume is a determinant of not only mitral repair rates, but also freedom from reoperation, and survival. The data from this study support the guideline's concept of reference referral to experienced mitral surgeons to improve outcomes in patients with degenerative mitral valve disease (98).

Transcatheter Aortic Valve Implantation Within Degenerated Aortic Surgical Bioprostheses: PARTNER 2 Valve-in-Valve Registry

J.G. Webb, et al.

BACKGROUND Early experience with transcatheter aortic valve replacement (TAVR) within failed bioprosthetic surgical aortic valves has shown that valve-in-valve (VIV) TAVR is a feasible therapeutic option with acceptable acute procedural results.

OBJECTIVES The authors examined 30-day and 1-year outcomes in a large cohort of high-risk patients undergoing VIV TAVR.

METHODS Patients with symptomatic degeneration of surgical aortic bioprostheses at high risk ($\geq 50\%$ major morbidity or mortality) for reoperative surgery were prospectively enrolled in the multicenter PARTNER (Placement of Aortic Transcatheter Valves) 2 VIV trial and continued access registries.

RESULTS Valve-in-valve procedures were performed in 365 patients (96 initial registry, 269 continued access patients). Mean age was 78.9 ± 10.2 years, and mean Society of Thoracic Surgeons score was $9.1 \pm 4.7\%$. At 30 days, all-cause mortality was 2.7%, stroke was 2.7%, major vascular complication was 4.1%, conversion to surgery was 0.6%, coronary occlusion was 0.8%, and new pacemaker insertion was 1.9%. One-year all-cause mortality was 12.4%. Mortality fell from the initial registry to the subsequent continued access registry, both at 30 days (8.2% vs. 0.7%, respectively; p = 0.0001) and at 1 year (19.7% vs. 9.8%, respectively; p = 0.006). At 1 year, mean gradient was 17.6 mm Hg, and effective orifice area was 1.16 cm², with greater than mild paravalvular regurgitation of 1.9%. Left ventricular ejection fraction increased (50.6% to 54.2%), and mass index decreased (135.7 to 117.6 g/m²), with reductions in both mitral (34.9% vs. 12.7%) and tricuspid (31.8%

vs. 21.2%) moderate or severe regurgitation (all p < 0.0001). Kansas City Cardiomyopathy Questionnaire score increased (mean: 43.1 to 77.0) and 6-min walk test distance results increased (mean: 163.6 to 252.3 m; both p < 0.0001).

CONCLUSIONS In high-risk patients, TAVR for bioprosthetic aortic valve failure is associated with relatively low mortality and complication rates, improved hemodynamics, and excellent functional and quality-of-life outcomes at 1 year. (The PARTNER II Trial: Placement of AoRTic TraNscathetER Valves [PARTNER II]; [NCT01314313](#)) (99).

Transcatheter Aortic Valve Replacement in Pure Native Aortic Valve Regurgitation

S.-H. Yoon, et al.

BACKGROUND Limited data exist about safety and efficacy of transcatheter aortic valve replacement (TAVR) in patients with pure native aortic regurgitation (AR).

OBJECTIVES This study sought to compare the outcomes of TAVR with early- and new-generation devices in symptomatic patients with pure native AR.

METHODS From the pure native AR TAVR multicenter registry, procedural and clinical outcomes were assessed according to VARC-2 criteria and compared between early- and new-generation devices.

RESULTS A total of 331 patients with a mean STS score of 6.7 ± 6.7 underwent TAVR. The early- and new-generation devices were used in 119 patients (36.0%) and 212 patients (64.0%), respectively. STS score tended to be lower in the new-generation device group (6.2 ± 6.7 vs. 7.6 ± 6.7 ; p = 0.08), but transfemoral access was more frequently used in the early-generation device group (87.4% vs. 60.8%; p < 0.001). Compared with the early-generation devices, the new-generation devices were associated with a significantly higher device success rate (81.1% vs. 61.3%; p < 0.001) due to lower rates of second valve implantation (12.7% vs. 24.4%; p = 0.007) and post-procedural AR \geq moderate (4.2% vs. 18.8%; p < 0.001). There were no significant differences in major 30-day endpoints between the 2 groups. The cumulative rates of all-cause and cardiovascular death at 1-year follow-up were 24.1% and 15.6%, respectively. The 1-year all-cause mortality rate was significantly higher in the patients with post-procedural AR \geq moderate compared with those with post-procedural AR \leq mild (46.1% vs. 21.8%; log-rank p = 0.001). On multivariable analysis, post-procedural

AR \geq moderate was independently associated with 1-year all-cause mortality (hazard ratio: 2.85; 95% confidence interval: 1.52 to 5.35; $p = 0.001$).

CONCLUSIONS Compared with the early-generation devices, TAVR using the new-generation devices was associated with improved procedural outcomes in treating patients with pure native AR. In patients with pure native AR, significant post-procedural AR was independently associated with increased mortality (100).

Transcatheter Mitral Valve Replacement for Degenerated Bioprosthetic Valves and Failed Annuloplasty Rings

S.-H. Yoon, et al.

BACKGROUND Limited data exist regarding transcatheter mitral valve replacement (TMVR) for patients with failed mitral valve replacement and repair.

OBJECTIVES This study sought to evaluate the outcomes of TMVR in patients with failed mitral bioprosthetic valves (valve-in-valve [ViV]) and annuloplasty rings (valve-in-ring [ViR]).

METHODS From the TMVR multicenter registry, procedural and clinical outcomes of mitral ViV and ViR were compared according to Mitral Valve Academic Research Consortium criteria.

RESULTS A total of 248 patients with mean Society of Thoracic Surgeons score of $8.9 \pm 6.8\%$ underwent TMVR. Transseptal access and the balloon-expandable valve were used in 33.1% and 89.9%, respectively. Compared with 176 patients undergoing ViV, 72 patients undergoing ViR had lower left ventricular ejection fraction ($45.6 \pm 17.4\%$ vs. $55.3 \pm 11.1\%$; $p < 0.001$). Overall technical and device success rates were acceptable, at 92.3% and 85.5%, respectively. However, compared with the ViV group, the ViR group had lower technical success (83.3% vs. 96.0%; $p = 0.001$) due to more frequent second valve implantation (11.1% vs. 2.8%; $p = 0.008$), and lower device success (76.4% vs. 89.2%; $p = 0.009$) due to more frequent reintervention (16.7% vs. 7.4%; $p = 0.03$). Mean mitral valve gradients were similar between groups (6.4 ± 2.3 mm Hg vs. 5.8 ± 2.7 mm Hg; $p = 0.17$), whereas the ViR group had more frequent post-procedural mitral regurgitation moderate or higher (19.4% vs. 6.8%; $p = 0.003$). Furthermore, the ViR group had more frequent life-threatening bleeding (8.3% vs. 2.3%; $p = 0.03$), acute kidney injury (11.1% vs. 4.0%; $p = 0.03$), and subsequent lower procedural success (58.3% vs. 79.5%; $p = 0.001$). The 1-year all-cause mortality rate

was significantly higher in the ViR group compared with the ViV group (28.7% vs. 12.6%; log-rank test, $p = 0.01$). On multivariable analysis, failed annuloplasty ring was independently associated with all-cause mortality (hazard ratio: 2.70; 95% confidence interval: 1.34 to 5.43; $p = 0.005$).

CONCLUSIONS The TMVR procedure provided acceptable outcomes in high-risk patients with degenerated bioprostheses or failed annuloplasty rings, but mitral ViR was associated with higher rates of procedural complications and mid-term mortality compared with mitral ViV (101).

Tricuspid Valve Dysfunction Following Pacemaker or Cardioverter-Defibrillator Implantation

J.D. Chang, et al.

The potential for cardiac implantable electronic device leads to interfere with tricuspid valve (TV) function has gained increasing recognition as having hemodynamic and clinical consequences associated with incremental morbidity and death. The diagnosis and treatment of lead-related (as distinct from functional) tricuspid regurgitation pose unique challenges. Because of pitfalls in routine diagnostic imaging, a high level of clinical suspicion must be maintained to avoid overlooking the possibility that worsening heart failure is a consequence of mechanical interference with TV leaflet mobility or coaptation and is amenable to lead extraction or valve repair or replacement. The future of cardiac implantable electronic devices includes pacing and perhaps defibrillation without a lead traversing the TV (102).

Valvular Heart Disease Patients on Edoxaban or Warfarin in the ENGAGE AF-TIMI 48 Trial

R. De Caterina, et al.

BACKGROUND The use of non-vitamin K antagonist oral anticoagulants (NOACs) instead of vitamin K antagonists (VKAs) in patients with atrial fibrillation (AF) and coexisting valvular heart disease (VHD) is of substantial interest.

OBJECTIVES This study explored outcomes in patients with AF with and without VHD in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial, comparing edoxaban with warfarin.

METHODS Valvular heart disease was defined as history or baseline echocardiography evidence of at least moderate aortic/mitral regurgitation, aortic stenosis, or prior valve surgery (bioprosthesis replacement, valve repair, valvuloplasty). Patients with moderate to severe mitral stenosis or mechanical heart valves were excluded from the trial. Comparisons were made of rates of stroke/systemic embolic event (SSEE), major bleeding, additional efficacy and safety outcomes, as well as net clinical outcomes, in patients with or without VHD treated with edoxaban or warfarin, using adjusted Cox proportional hazards.

RESULTS After adjustment for multiple baseline characteristics, compared with no-VHD patients (n = 18,222), VHD patients (n = 2,824) had a similar rate of SSEE but higher rates of death (hazard ratio [HR]: 1.40; 95% confidence interval [CI]: 1.26 to 1.56; p < 0.001), major adverse cardiovascular events (HR: 1.29; 95% CI: 1.16 to 1.43; p < 0.001), and major bleeding (HR: 1.21; 95% CI: 1.03 to 1.42; p = 0.02). Higher-dose edoxaban regimen had efficacy similar to warfarin in the presence of VHD (for SSEE, HR: 0.69; 95% CI: 0.44 to 1.07, in patients with VHD, and HR: 0.91; 95% CI: 0.77 to 1.07, in patients without VHD; p interaction [p_{int}] = 0.26; and for less major bleeding, HR: 0.74; 95% CI: 0.53 to 1.02 in patients with VHD, and HR: 0.82; 95% CI: 0.71 to 0.94, in patients with no VHD; p_{int} = 0.57).

CONCLUSIONS The presence of VHD increased the risk of death, major adverse cardiovascular events, and major bleeding but did not affect the relative efficacy or safety of higher-dose edoxaban versus warfarin in AF. (Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs. Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation [ENGAGE AF-TIMI 48]; [NCT00781391](#)) (103).

VASCULAR MEDICINE

Carotid Artery Stenting Versus Endarterectomy for Stroke Prevention: A Meta-Analysis of Clinical Trials

P. Sardar, et al.

BACKGROUND Data conflict regarding the relative effectiveness of carotid artery stenting (CAS) and carotid artery endarterectomy (CEA) for the prevention of stroke due to carotid artery stenosis.

OBJECTIVES The authors performed an updated meta-analysis evaluating the efficacy and safety of CAS versus CEA, given recently published clinical trial data.

METHODS Databases were searched through April 30, 2016. Randomized trials with ≥50 patients, that had exclusive use of embolic-protection devices, and that compared CAS against CEA for the treatment of carotid artery stenosis were selected. We calculated summary odds ratios (ORs) and 95% confidence intervals (CIs) using a random-effects model.

RESULTS We analyzed 6,526 patients from 5 trials with a mean follow-up of 5.3 years. The composite outcome of periprocedural death, stroke, myocardial infarction (MI), or nonperiprocedural ipsilateral stroke was not significantly different between therapies (OR: 1.22; 95% CI: 0.94 to 1.59). The risk of any periprocedural stroke plus nonperiprocedural ipsilateral stroke was higher with CAS (OR: 1.50; 95% CI: 1.22 to 1.84). The risk of higher stroke with CAS was mostly attributed to periprocedural minor stroke (OR: 2.43; 95% CI: 1.71 to 3.46). CAS was associated with significantly lower risk of periprocedural MI (OR: 0.45; 95% CI: 0.27 to 0.75); cranial nerve palsy (OR: 0.07; 95% CI: 0.04 to 0.14); and the composite outcome of death, stroke, MI, or cranial nerve palsy during the periprocedural period (OR: 0.75; 95% CI: 0.60 to 0.93).

CONCLUSIONS CAS and CEA were associated with similar rates of a composite of periprocedural death, stroke, MI, or nonperiprocedural ipsilateral stroke. The risk of long-term overall stroke was significantly higher with CAS, and was mostly attributed to periprocedural minor stroke. CAS was associated with lower rates of periprocedural MI and cranial nerve palsy than CEA (104).

Inferior Vena Cava Filters to Prevent Pulmonary Embolism: Systematic Review and Meta-Analysis

B. Bikdeli, et al.

BACKGROUND Inferior vena cava (IVC) filters are widely used for prevention of pulmonary embolism (PE). However, uncertainty persists about their efficacy and safety.

OBJECTIVES The authors conducted a systematic review and meta-analysis of the published reports on the efficacy and safety of IVC filters.

METHODS The authors searched PubMed, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov through October 3, 2016, for randomized controlled trials (RCTs) or prospective controlled observational studies of IVC filters versus none in patients at risk of PE. Inverse variance fixed-effects models with odds ratio (OR) as the effect

measure were used for primary analyses. Main outcomes included subsequent PE, PE-related mortality, all-cause mortality, and subsequent deep vein thrombosis (DVT).

RESULTS The authors' search retrieved 1,986 studies, of which 11 met criteria for inclusion (6 RCTs and 5 prospective observational studies). Quality of evidence for RCTs was low to moderate. Overall, patients receiving IVC filters had lower risk for subsequent PE (OR: 0.50; 95% confidence interval [CI]: 0.33 to 0.75); increased risk for DVT (OR: 1.70; 95% CI: 1.17 to 2.48); nonsignificantly lower PE-related mortality (OR: 0.51; 95% CI: 0.25 to 1.05); and no change in all-cause mortality (OR: 0.91; 95% CI: 0.70 to 1.19). Limiting the results to RCTs showed similar results. Findings were substantively similar across a wide range of sensitivity analyses.

CONCLUSIONS Very few prospective controlled studies, with limited quality of evidence, exist regarding the efficacy and safety of IVC filters. Overall, filters appear to reduce the risk of subsequent PE, increase the risk for DVT, and have no significant effect on overall mortality (105).

Left Main Coronary Artery Compression in Patients With Pulmonary Arterial Hypertension and Angina

N. Galiè, et al.

BACKGROUND Left main coronary artery (LMCA) compression is increasingly recognized as a cause of angina in pulmonary arterial hypertension (PAH).

OBJECTIVES This study aimed to evaluate the prevalence of LMCA extrinsic compression from a dilated pulmonary artery (PA) in patients with PAH and angina or angina-like symptoms, determine the usefulness of screening with computed tomography coronary angiography (CTCA), and assess the safety and efficacy of percutaneous coronary interventions (PCIs).

METHODS All patients with PAH and angina or angina-like symptoms attending the center between May 1, 2008, and December 31, 2013, underwent CTCA. Patients with confirmed LMCA stenosis on selective coronary angiography had PCI.

RESULTS Of 765 patients with PAH, 121 had angina or angina-like symptoms. Ninety-four patients had abnormal CTCA based on the relationship between the PA and the LMCA and underwent selective coronary angiography. LMCA stenosis $\geq 50\%$ was detected in 48 of the 94 patients. Forty-five patients underwent PCI with stenting, of whom 41 had sustained angina symptom relief. The 3 other

patients had surgical PA reduction plasty. Nine months after PCI, 5 patients had LMCA restenosis and PCI was successfully repeated. The best predictor of LMCA stenosis $\geq 50\%$ was a PA diameter ≥ 40 mm. Rates for death or double-lung transplant and the composite rates for death, double-lung transplant, or restenosis at 36 months were 5% and 30%, respectively.

CONCLUSIONS The prevalence of LMCA compression in patients with PAH and angina is high. These results suggest that CTCA is indicated in patients with PAH and angina or angina-like symptoms. PCI was well tolerated, improved symptoms, and resulted in favorable long-term outcomes (106).

Percutaneous Closure of Patent Foramen Ovale in Patients With Migraine: The PREMIUM Trial

J.M. Tobis, et al.

BACKGROUND Migraine is a prevalent and disabling disorder. Patent foramen ovale (PFO) has been associated with migraine, but its role in the disorder remains poorly understood.

OBJECTIVES This study examined the efficacy of percutaneous PFO closure as a therapy for migraine with or without aura.

METHODS The PREMIUM (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management) was a double-blind study investigating migraine characteristics over 1 year in subjects randomized to medical therapy with a sham procedure (right heart catheterization) versus medical therapy and PFO closure with the Amplatzer PFO Occluder device (St. Jude Medical, St. Paul, Minnesota). Subjects had 6 to 14 days of migraine per month, had failed at least 3 migraine preventive medications, and had significant right-to-left shunt defined by transcranial Doppler. Primary endpoints were responder rate defined as 50% reduction in migraine attacks and adverse events. Secondary endpoints included reduction in migraine days and efficacy in patients with versus without aura.

RESULTS Of 1,653 subjects consented, 230 were enrolled. There was no difference in responder rate in the PFO closure (45 of 117) versus control (33 of 103) groups. One serious adverse event (transient atrial fibrillation) occurred in 205 subjects who underwent PFO closure. Subjects in the PFO closure group had a significantly greater reduction in headache days (-3.4 vs. -2.0 days/month, $p = 0.025$). Complete migraine remission for 1 year occurred in 10 patients (8.5%) in

the treatment group versus 1 (1%) in the control group ($p = 0.01$).

CONCLUSIONS PFO closure did not meet the primary endpoint of reduction in responder rate in patients with frequent migraine. (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management [PREMIUM]; [NCT00355056](#)) (107).

Spontaneous Coronary Artery Dissection: Clinical Outcomes and Risk of Recurrence

J. Saw, et al.

BACKGROUND Spontaneous coronary artery dissection (SCAD) is underdiagnosed and an important cause of myocardial infarction (MI), especially in young women. Long-term cardiovascular outcomes, including recurrent SCAD, are inadequately reported.

OBJECTIVES This study sought to describe the acute and long-term cardiovascular outcomes and assess the predictors of recurrent SCAD.

METHODS Nonatherosclerotic SCAD patients were prospectively followed at Vancouver General Hospital systematically to ascertain baseline, predisposing and precipitating stressors, angiographic features, revascularization, use of medication, and in-hospital and long-term cardiovascular events. Clinical predictors for recurrent de novo SCAD were tested using univariate and multivariate Cox regression models.

RESULTS The authors prospectively followed 327 SCAD patients. Average age was 52.5 ± 9.6 years, and 90.5% were women (56.9% postmenopausal). All presented with MI; 25.7% had ST-segment elevation MI, 74.3% had non-ST-segment elevation MI, and 8.9% had ventricular tachycardia/ventricular fibrillation. Precipitating emotional stressors were reported in 48.3% and physical stressors in 28.1%. Fibromuscular dysplasia was present in 62.7%, connective tissue disorder in 4.9%, and systemic inflammatory disease in 11.9%. The majority (83.1%) were initially treated medically, with only 16.5% or 2.2% undergoing in-hospital percutaneous coronary intervention or coronary artery bypass graft surgery, respectively. The majority of SCAD patients were taking aspirin and beta-blocker therapy at discharge and at follow-up. Median hospital stay was 3.0 days, and the overall major adverse event rate was 7.3%. Median long-term follow-up was 3.1 years, and overall major adverse cardiac event rate was 19.9% (death rate: 1.2%; recurrent MI: 16.8%; stroke/transient ischemic attack: 1.2%; revascularization:

5.8%). Recurrent SCAD occurred in 10.4% of patients. In multivariate modeling, only hypertension increased (hazard ratio: 2.46; $p = 0.011$) and beta-blocker use diminished (hazard ratio: 0.36; $p = 0.004$) recurrent SCAD.

CONCLUSIONS In our large prospectively followed SCAD cohort, long-term cardiovascular events were common. Hypertension increased the risk of recurrent SCAD, whereas beta-blocker therapy appeared to be protective (108).

A Test in Context: D-Dimer

J.I. Weitz, et al.

D-dimer is a soluble fibrin degradation product that results from ordered breakdown of thrombi by the fibrinolytic system. Numerous studies have shown that D-dimer serves as a valuable marker of activation of coagulation and fibrinolysis. Consequently, D-dimer has been extensively investigated for the diagnosis of venous thromboembolism (VTE) and is used routinely for this indication. In addition, D-dimer has been evaluated for determining the optimal duration of anticoagulation in VTE patients, for diagnosing and monitoring disseminated intravascular coagulation, and as an aid in the identification of medical patients at high risk for VTE. Thus, quantification of D-dimer levels serves an important role in guiding therapy. This review: 1) describes how D-dimer is generated; 2) reviews the assays used for its detection; and 3) discusses the role of D-dimer determination in these various conditions (109).

A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies

S. Tsimikas

Evidence that elevated lipoprotein(a) (Lp[a]) levels contribute to cardiovascular disease (CVD) and calcific aortic valve stenosis (CAVS) is substantial. Development of isoform-independent assays, in concert with genetic, epidemiological, translational, and pathophysiological insights, have established Lp(a) as an independent, genetic, and likely causal risk factor for CVD and CAVS. These observations are consistent across a broad spectrum of patients, risk factors, and concomitant therapies, including patients with low-density lipoprotein cholesterol <70 mg/dl. Statins tend to increase Lp(a) levels, possibly contributing to the “residual risk” noted in outcomes

trials and at the bedside. Recently approved proprotein convertase subtilisin/kexin-type 9 inhibitors and mipomersen lower Lp(a) 20% to 30%, and emerging RNA-targeted therapies lower Lp(a) >80%. These approaches will allow testing of the “Lp(a) hypothesis” in clinical trials. This review summarizes the current landscape of Lp(a), discusses controversies, and reviews emerging therapies to reduce plasma Lp(a) levels to decrease risk of CVD and CAVS (110).

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