Atrial fibrillation (AF) is the most common heart rhythm disorder around the world. We report results of the first global assessment of AF, conducted within the framework of the recently published Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2010 Study). The estimated global prevalence of AF in 2010 was 33.5 million (20.9 million men and 12.6 million women). Between 1990 and 2010, there were significant increases in the estimated age-adjusted prevalence and incidence of AF. These increases were accompanied by increases in AF disease burden measured as disability-adjusted life-years and mortality associated with AF. Our findings indicate progressive increases in the worldwide prevalence and incidence of AF, as well as associated morbidity and mortality. Systematic, global surveillance of AF is required to better direct prevention and treatment strategies. As the first assessment of the global burden of AF, these findings have important implications for public health policy and healthcare costs. See p 837.

Left ventricular ejection fraction (LVEF) ≤30% or ≤35% in the presence of New York Heart Association class II/III heart failure is the recommended criterion to select a patient for a primary prevention implantable cardioverter-defibrillator after myocardial infarction (MI). However, impaired LVEF used alone as a risk-stratification tool is limited by poor specificity for arrhythmic versus nonarrhythmic cardiac death, with a survival benefit seen only in the chronic phase after MI. Although sudden cardiac death incidence has declined in the era of early revascularization for MI, it remains significantly elevated in the first 40 days. This study assessed the utility of an electrophysiology study (EPS) to guide implantation of an implantable cardioverter-defibrillator early after MI. Consecutive patients treated with primary percutaneous coronary intervention for ST-segment-elevation MI underwent early LVEF assessment with EPS performed if LVEF ≤40%. Patients were prospectively followed up with a primary end point of death or arrhythmia (sudden cardiac death, resuscitated cardiac arrest, or ventricular tachycardia/ventricular fibrillation). Patients with LVEF ≤30% or ≤35% and heart failure who were EPS negative (n=80) were compared with control patients (LVEF >40%, n=1286). We found that EPS-negative patients with severe left ventricular dysfunction had a similar long-term survival free of death or arrhythmia as patients with preserved LVEF. Although the use of EPS early after MI remains controversial, this study has important implications for future trials assessing EPS as a risk-stratification tool for prevention of sudden cardiac death. A negative EPS may delineate a subgroup of patients early after MI with impaired LVEF who can be managed safely long-term without a defibrillator. See p 848.

Pulmonary arterial hypertension is characterized by remodeling of the small muscular pulmonary arteries, which leads to increased right ventricular afterload, right-sided heart failure, and death. Enhanced proliferation, impaired apoptosis, and a metabolic shift to glycolysis of pulmonary arterial vascular smooth muscle cells (PA VSMCs) are important pathophysiological components of pulmonary vascular remodeling, the understanding of which is critical for identification of novel molecular targets. mTOR (mammalian target of rapamycin) is a key regulator of cell growth and metabolism that acts through 2 distinct complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Here, we show that both mTORC1 and mTORC2 pathways are upregulated in small remodeled pulmonary arteries and primary distal PA VSMCs from subjects with idiopathic pulmonary arterial hypertension (IPAH) and contribute to increased proliferation. Only mTORC2 regulates ATP levels and IPAH PA VSMC survival. Using molecular and pharmacology-based analyses, we demonstrate a novel mechanistic link from NADPH oxidase Nox4-dependent activation of mTORC2 via energy sensor AMP-activated protein kinase (AMPK) to the activation of mTORC1 and increased proliferation, as well as deficiency of proapoptotic Bim and IPAH PA VSMC survival. We also provide evidence that in contrast to the mTORC1 inhibitor rapamycin, the dual mTORC1/mTORC2 inhibitor PP242 not only inhibits proliferation but also induces apoptosis in PA VSMCs from IPAH patients without a significant effect on control cells. Treatment with PP242 induces apoptosis in small pulmonary arteries and reverses existing pulmonary vascular
remodeling in the rat chronic hypoxia model of pulmonary hypertension. These data suggest a novel role for mTORC2 in pulmonary vascular remodeling and provide a new potential target pathway for therapeutic interventions for this incurable disease. See p 864.

**Dantrolene Improves Survival After Ventricular Fibrillation by Mitigating Impaired Calcium Handling in Animal Models**

Despite decades of research in resuscitation, survival from sudden cardiac arrest due to ventricular fibrillation (VF) is still very low. The use of various antiarrhythmic agents has not resulted in the improvement in survival to discharge. Studying the molecular pathways and ion channels contributing to the maintenance of VF has become an area of interest in resuscitation research. In this study, we have demonstrated that targeting the VF-induced impairment of cardiac calcium cycling due to ryanodine receptor-2 dysfunction, by administration of dantrolene, significantly enhances defibrillation and facilitates the return of spontaneous circulation. The strategy also improved cardiac contractility postdefibrillation and reduced refibrillations. Modeling and computer simulations demonstrated that these effects of dantrolene are mostly mediated through its effects on Purkinje fibers. These findings suggest a novel therapeutic strategy in the management of sudden cardiac arrest due to VF. Dantrolene has been shown to be a safe drug and has been used in emergency settings such as malignant hyperthermia. Given its ease of delivery and rapid effect, dantrolene might prove to be an adjunctive treatment to cardiopulmonary resuscitation and defibrillation in sudden cardiac arrest due to VF. See p 875.

**The Echo Score Revisited: Impact of Incorporating Commissural Morphology and Leaflet Displacement to the Prediction of Outcome for Patients Undergoing Percutaneous Mitral Valvuloplasty**

The management of symptomatic mitral stenosis is based on the echocardiographic assessment of valve morphology to determine appropriate therapy. Percutaneous mitral valvuloplasty is currently considered to be the procedure of choice in patients with suitable valve anatomy. In the past 2 decades, the indications of the procedure have been expanded to include patients with unfavorable valve anatomy as a consequence of changes in epidemiology and advances in invasive techniques. Current echocardiographic scoring systems for percutaneous mitral valvuloplasty have inherent limitations that raise the need of an alternate approach to assess valve morphology. Technical refinements in echocardiographic examinations enable a detailed analysis of global mitral valve anatomy affected by the rheumatic process, taking into account the fundamental mechanistic derangement of rheumatic mitral valve stenosis, to assist physicians in selecting the best management strategies for the patients. See p 886.

**Nanoparticle-Mediated Delivery of Pitavastatin Inhibits Atherosclerotic Plaque Destabilization/Rupture in Mice by Regulating the Recruitment of Inflammatory Monocytes**

Acute myocardial infarction is the most severe type of coronary heart disease. Recent advances in therapeutic intervention for acute myocardial infarction have been associated with an increased prevalence of heart failure with high long-term mortality, which remains a serious concern worldwide. The pathophysiological process of acute myocardial infarction includes atherosclerotic coronary plaque destabilization and rupture. In clinical settings, the use of HMG-CoA reductase inhibitors (statins) reduces cardiovascular risks; however, even a high-dose strong statin is insufficient to suppress acute myocardial infarction. In the present study, we identified circulating CCR2\(^{+}\)Ly-6Chigh inflammatory monocytes/macrophages as a culprit and a therapeutic target for plaque destabilization and rupture. We engineered poly(lactic-co-glycolic acid) (PLGA) nanoparticles containing pitavastatin, which was taken up mainly by circulating monocytes. PLGA nanoparticle–mediated delivery of pitavastatin inhibited aortic atherosclerosis and the plaque destabilization and rupture associated with decreased monocyte chemokine and monocyte CCR2 signaling–mediated monocyte infiltration and gelatinase activity in the plaque. A nanoparticle-mediated drug-delivery system potentiates the therapeutic efficacy of pitavastatin at least 20-fold compared with daily oral administration of pitavastatin. We are now performing a phase I/IIa clinical trial of nanoparticles encapsulated with pitavastatin in patients with critical limb ischemia (UMIN [University Hospital Medical Information Network] clinical trial registry No. UMIN000008011). Given the safety profile of GMP (good manufacturing practices)-compliant pitavastatin-encapsulated nanoparticles, future clinical trials will examine their clinical value in patients with unstable coronary plaques. Finally, nanoparticle-mediated drug delivery is a novel modality that may advance current statin treatment for unstable plaques and achieve an optimal therapeutic strategy for the prevention of acute myocardial infarction in the future. See p 896.
Circulation: Clinical Summaries: Original Research Put Into Perspective for the Practicing Clinician

Circulation. 2014;129:827-828
doi: 10.1161/CIR.0000000000000021
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/129/8/827

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/