Frequency and Determinants of Implantable Cardioverter-Defibrillator Deployment Among Primary Prevention Candidates With Subsequent Sudden Cardiac Arrest in the Community

The implantable cardioverter defibrillator (ICD) represents a significant advance for the prevention of sudden cardiac death (SCD). Although clinical guidelines recommend the use of an ICD for primary prevention of SCD among specific patients with low ejection fraction, the extent of its use among those who experience SCD in the community has not been investigated. Using a prospective population-based approach in a large US community, we identified SCD case subjects who would have been eligible for a primary ICD based on echocardiograms performed before the SCD event and using relevant, time-dependent guideline criteria. We found that among cases with assessment of ejection fraction before the occurrence of SCD, 20% would have been eligible for a primary prevention ICD; however, among this eligible subgroup of subjects, only 13% received a primary prevention ICD. The ICD nonrecipients were older than the recipients, and approximately one fourth of them had associated comorbidities such as dementia or advanced renal disease. Further detailed investigations are needed to understand the role of additional factors that affect the decision-making process for primary prevention ICD implantation, such as socioeconomic factors, health insurance, patient preference, and clinical practice patterns. See p 1733.

Outcome After Implantation of a Cardiovertor-Defibrillator in Patients With Brugada Syndrome: A Multicenter Study-Part 2

Although the risk of appropriate implantable cardioverter-defibrillator therapy is important in patients with Brugada syndrome implanted for resuscitated sudden cardiac arrest (48% at 10 years) and syncope (19% at 10 years), risk stratification remains a challenge in asymptomatic patients with Brugada syndrome. Although low, the event rate is not nil (1%/y). The successful prevention of sudden cardiac death by device implantation is often paramount in the cardiologist’s mind, but our study shows that the decision to offer implantable cardioverter-defibrillators to these patients is not straightforward because of a 36% risk of complication. The main issue remains lead failure (29% at 10 years). As a consequence, the risk of inappropriate shock is important (37% at 10 years), as is the risk inherent to lead extraction. However, paying particular attention at implantation (R wave >5 mV), programming (long interval to detection duration, high ventricular fibrillation zone [>210-220 bpm]), and follow-up (implantable cardioverter-defibrillator with remote monitoring capabilities) reduces the risk of inappropriate shock. See p 1739.

Oxidized Ca2+/Calmodulin-Dependent Protein Kinase II Triggers Atrial Fibrillation

Atrial fibrillation is associated with hyperactivity of renin-angiotensin II signaling, enhanced oxidant stress, and increased activity of the multifunctional Ca2+ and calmodulin-dependent protein kinase II (CaMKII). Excessive CaMKII activity promotes arrhythmia initiation by enhancing Ca2+ leak from intracellular stores. We recently identified a mechanism whereby CaMKII is activated by oxidation of regulatory domain methionines in response to angiotensin II stimulation and, motivated by these findings, developed new mouse models to test the potential role of oxidation-activated CaMKII in atrial fibrillation. We identified increased oxidized CaMKII in atria from patients with atrial fibrillation compared with nonfibrillating control subjects and determined that atrial fibrillation patients treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers did not have increased atrial oxidized CaMKII. These findings suggest that CaMKII is oxidized by the renin-angiotensin II pathway and is associated with atrial fibrillation in the subgroup of patients not treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Angiotensin II-infused mice also showed increased atrial oxidized CaMKII and high rates of atrial fibrillation after rapid right atrial pacing. In contrast, genetically engineered mice with oxidation-resistant CaMKII and mice with atrial overexpression of a methionine-reducing enzyme, methionine sulfoxide reductase A, were resistant to atrial fibrillation compared with nonfibrillating control subjects who would have been eligible for primary prevention ICD implantation. Using a prospective population-based approach in a large US community, we identified SCD case subjects who would have been eligible for a primary ICD based on echocardiograms performed before the SCD event and using relevant, time-dependent guideline criteria. We found that among cases with assessment of ejection fraction before the occurrence of SCD, 20% would have been eligible for a primary prevention ICD; however, among this eligible subgroup of subjects, only 13% received a primary prevention ICD. The ICD nonrecipients were older than the recipients, and approximately one fourth of them had associated comorbidities such as dementia or advanced renal disease. Further detailed investigations are needed to understand the role of additional factors that affect the decision-making process for primary prevention ICD implantation, such as socioeconomic factors, health insurance, patient preference, and clinical practice patterns. See p 1733.

Impaired Cholesterol Metabolism and Enhanced Atherosclerosis in Clock Mutant Mice

Heart attacks happen mainly in the early hours of the day, suggesting that their occurrence might be related to circadian rhythms seen in various behavioral, physiological, and biochemical activities. Here, we show that disruption of circadian Clock activity as a result of a dominant-negative mutation (ClockΔ19Δ19) increases susceptibility to atherosclerosis in various mouse models. ClockΔ19Δ19 mice fed an atherogenic diet had increased plasma cholesterol, triglycerides, and atherosclerotic lesions compared with their wild-type siblings. Similarly, ClockΔ19Δ19 protein increased cholesterololemia and atherosclerosis in Ldlr<sup>−/−</sup> and Apoe<sup>−/−</sup> mice fed a chow or Western diets. Physiological studies revealed that high plasma cholesterol in ClockΔ19Δ19Apoe<sup>−/−</sup> mice was due in part to increased cholesterol uptake by enterocytes. In addition, macrophages in ClockΔ19Δ19Apoe<sup>−/−</sup> mice displayed higher lipid uptake and reduced cholesterol efflux compared with Apoe<sup>−/−</sup> siblings. Molecular studies demonstrated that...
knockdown of Clock gene expression in wild-type macrophages reduces ABCA1 expression and cholesterol efflux. Furthermore, Clock overexpression increases ABCA1 transcription. Evidence is presented to suggest that USF2 could participate in the modulatory effect of Clock on ABCA1 expression. These studies provide significant evidence for the importance of Clock in the proper physiological functioning of enterocytes and macrophages. Hence, disruptions in Clock function as a result of either mutations or other environmental factors such as a high-fat diet, transcontinental flights, and night shift work might deregulate enterocyte and macrophage function, increasing the risk for atherosclerosis. See p 1758.

**Loss of Collectrin, an Angiotensin-Converting Enzyme 2 Homolog, Uncouples Endothelial Nitric Oxide Synthase and Causes Hypertension and Vascular Dysfunction**

Hypertension is a major risk factor for stroke, heart disease, and kidney disease. Although the causes of hypertension in most cases are not known, a defect in the balance of nitric oxide and superoxide, important regulators of vascular tone, may be a key initiating event. Our studies have unveiled a novel gene, collectrin, as a determining factor in the development of hypertension in conditions in which the balance of nitric oxide and superoxide may be altered. Collectrin may regulate blood pressure homeostasis through its role in regulating the transport of l-arginine, a substrate for nitric oxide generation, in endothelial cells. Through the identification of pathways regulated by collectrin to control blood pressure, novel insights and potential new opportunities for improving treatments of hypertension and its complications may be possible. See p 1770.

**Flow-Gradient Patterns in Severe Aortic Stenosis With Preserved Ejection Fraction: Clinical Characteristics and Predictors of Survival**

Among patients with severe aortic stenosis (AS) and preserved ejection fraction, those with low gradient (LG) and reduced stroke volume may have an adverse prognosis. Whether stroke volume is predictive of outcome in large populations of patients with severe AS, including those with symptoms, has been an area of uncertainty. In the present investigation, we studied the long-term outcome of patients with severe AS and preserved ejection fraction according to stroke volume and aortic valve gradient. We examined 1704 consecutive patients with severe AS (aortic valve area <1.0 cm²) and preserved ejection fraction (≥50%) using 2-dimensional and Doppler echocardiography. Patients were stratified by stroke volume index (<35 mL/m² [low flow, LF] versus ≥35 mL/m² [normal flow, NF]) and aortic gradient (<40 mm Hg [LG] versus ≥40 mm Hg [high gradient, HG]) into 4 groups: NF/HG, NF/LG, LF/HG, and LF/LG. NF/LG (n=352, 21%), was associated with better survival with medical management (2-year estimate, 82% versus 67% in NF/HG; P<0.0001). LF/LG severe AS (n=53, 3%) was characterized by lower ejection fraction, higher prevalence of atrial fibrillation and heart failure, reduced arterial compliance, and reduced survival (2-year estimate, 60% versus 82% in NF/HG; P<0.001). In adjusted multivariable analysis, the LF/LG pattern was the strongest predictor of mortality (hazard ratio, 3.26; 95% confidence interval, 1.71-6.22; P<0.001 versus NF/LG). Aortic valve replacement was associated with a 69% mortality reduction (hazard ratio, 0.31; 95% confidence interval, 0.25-0.39; P<0.0001) in LF/LG and NF/HG; there was no survival benefit associated with aortic valve replacement in NF/LG and LF/HG. These findings have implications for the evaluation and subsequent management of AS severity. See p 1781.