Apolipoprotein B Synthesis Inhibition With Mipomersen in Heterozygous Familial Hypercholesterolemia: Results of a Randomized, Double-Blind, Placebo-Controlled Trial to Assess Efficacy and Safety as Add-On Therapy in Patients With Coronary Artery Disease

Heterozygous familial hypercholesterolemia is a common genetic disorder that leads to premature coronary artery disease. Despite aggressive lipid-lowering therapy, many patients with heterozygous familial hypercholesterolemia fail to achieve optimal low-density lipoprotein cholesterol (LDL-C) goals. We evaluated mipomersen, an apolipoprotein B synthesis inhibitor, to further lower LDL-C in patients with heterozygous familial hypercholesterolemia with coronary artery disease who were already on maximally tolerated lipid-lowering therapy and had LDL-C >2.6 mmol/L (100 mg/dL). The phase 2, double-blind, placebo-controlled trial randomized 124 patients (41 placebo, 83 mipomersen) to weekly subcutaneous mipomersen 200 mg or placebo (2:1) for 26 weeks. The primary end point was percent change in LDL-C from baseline at week 28. Safety assessments included adverse events, laboratory tests, and magnetic resonance imaging assessment of hepatic fat. Mean LDL-C decreased 28.0% with mipomersen compared with a 5.2% increase with placebo (P<0.001), and 45.1% compared with 4.9% achieved LDL-C <2.6 mmol/L (100 mg/dL), respectively. Mipomersen significantly (P<0.001) reduced apolipoprotein B (~26.3%) and lipoprotein(a) (~21.1%) compared with placebo. More frequent and severe injection site reactions occurred with mipomersen, and 5 mipomersen-treated patients (6%) had 2 consecutive alanine aminotransferase levels ≥3 times the upper limit of normal at least 7 days apart; none were associated with significant bilirubin increases. Hepatic fat content increased a median of 4.9% with mipomersen versus 0.4% with placebo (P<0.001). The clinical implications of such increases in hepatic fat and transaminase elevations are unclear and must be elucidated in longer-term studies. We conclude that mipomersen is effective to further reduce apolipoprotein B–containing lipoproteins, including LDL and lipoprotein(a), in patients with heterozygous familial hypercholesterolemia with coronary artery disease on statins and other lipid-lowering therapy. See p 2283.

Premature Atrial Contractions in the General Population: Frequency and Risk Factors

Although premature atrial contractions (PACs) have been associated with an increased risk of death, stroke, and atrial fibrillation, they are usually considered a benign phenomenon. Accordingly, little is known about the prevalence of and risk factors for PAC occurrence in the general population. In this study of individuals aged ≥50 years, we found that only 18 (1.0%) participants did not have at least 1 PAC during Holter monitoring. The number of PACs was strongly increasing with increasing age. In multivariable regression models, PAC occurrence was significantly associated with age, height, cardiovascular disease, exercise, and plasma levels of N-terminal pro B-type natriuretic peptides and high-density lipoprotein cholesterol. The underlying mechanisms of these relationships are currently unknown. Although obesity and hypertension are 2 of the most important risk factors for the occurrence of atrial fibrillation, they were not significantly associated with PAC burden in this study. These data could suggest that obesity and hypertension are major determinants of structural left atrial remodeling but do not influence the electric activity of the atria. Given the high prevalence of PACs in the population and its negative prognostic impact, more studies are needed to better understand this phenomenon. See p 2302.

Variation in Warfarin Dose Adjustment Practice Is Responsible for Differences in the Quality of Anticoagulation Control Between Centers and Countries: An Analysis of Patients Receiving Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial

The outcome of atrial fibrillation patients on warfarin partially depends on maintaining adequate time in therapeutic International Normalized Ratio (INR) range (TTR). Large differences in TTR have been reported between centers and countries, but the reasons are unclear. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, a warfarin dosing algorithm provided to participating centers recommended no change for in-range and 10% to 15% weekly dose changes for out-of-range INR values. We determined whether algorithm-consistent warfarin dosing could predict patient TTR and the composite outcome of stroke, systemic embolism, or major hemorrhage. Among 6022 nonvalvular atrial fibrillation patients from 44 countries, we found a strong association between the proportion of algorithm-consistent warfarin doses and mean country TTR (R²=0.65). The degree of algorithm-consistent warfarin dosing accounted for a majority of the TTR variation between centers and countries. Each 10% increase in center algorithm-consistent dosing independently predicted a 6.12% increase in TTR (95% confidence interval, 5.65–6.59), and an 8% decrease in rate of the composite clinical outcome (hazard ratio, 0.92; 95% confidence interval, 0.85–1.00). In summary, warfarin dosing practice that does not change the dose when the INR is in range, and that makes relatively small (10%–15%) weekly dose adjustments when the INR is out of range, is associated with improved TTR and clinical
Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms: Analysis of Repeat Hospitalizations

The standard method of analysis of deaths and hospital admissions in clinical trials that only considers first events may no longer be the most appropriate approach as cardiovascular diseases become more chronic conditions, increasingly characterized by recurrent nonfatal episodes. We examined alternative approaches, taking account of repeat heart failure hospitalizations (HFHs) in the The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure trial (EMPHASIS-HF). During the median 25 months extended double-blind follow-up, 186 of 1364 (14%) of eplerenone-treated and 277 of 1373 (20%) of placebo-treated patients experienced at least 1 HFH, ie, a relative risk reduction of 32% (95% confidence interval, 20–43); P<0.0001, or 6 fewer HFHs per 100 patients treated. There were a total of 312 HFH (10.7 per 100 person-years) in the eplerenone group in comparison with 481 (17.0) in the placebo group, giving a rate ratio of 0.63 (95% confidence interval, 0.55–0.73); P<0.0001, or 12 fewer HFHs per 100 patients treated. Of the 481 total HFHs in the placebo group, 204 (42%) did not count in the time-to-first-event analysis. In the eplerenone and placebo groups, there were 186 (6.4 per 100 person-years) and 277 (9.7) first HFH, respectively, giving a Poisson rate ratio of 0.65 (95% confidence interval, 0.54–0.73); P<0.0001. A negative binomial regression model used to analyze repeat HFH (excluding the first), gave a rate ratio of 0.52 (95% confidence interval, 0.33–0.82); P=0.004. Analyses of repeat events may give a better assessment of the effect of treatment on the burden of chronic diseases such as heart failure. See p 2317.

Secretory Products From Epicardial Adipose Tissue of Patients With Type 2 Diabetes Mellitus Induce Cardiomyocyte Dysfunction

Cardiac contractile dysfunction and myocardial insulin resistance frequently occur in patients with type 2 diabetes mellitus. Recent studies link adipose tissue–derived factors, termed adipokines, to the pathogenesis of these cardiac alterations. Epicardial adipose tissue is a visceral thoracic fat depot, surrounding the aortic arch, the large coronary arteries, the ventricles, and the apex of the human heart. Because no fascial boundaries separate the epicardial adipose tissue from the myocardium, factors released from this fat depot may directly affect the underlying tissues. In patients with type 2 diabetes mellitus, the adipose tissue is characterized by a chronic state of inflammation, which results in alterations in adipokine secretion. The present studies investigated whether alterations in the secretory profile of epicardial adipose tissue in patients with type 2 diabetes mellitus occur, and whether these alterations affect contractile function and insulin sensitivity in rat cardiomyocytes. Epicardial biopsies of patients with type 2 diabetes mellitus were characterized by clusters of CD14-positive monocytes and CD68-positive macrophages, which are both indicative of inflammation. Exposing cardiomyocytes to conditioned media prepared from epicardial adipose tissue from patients with type 2 diabetes mellitus induced reductions in contractile function and insulin resistance. These effects could be ascribed to a selective accumulation of activin A and angiopoietin-2 in the conditioned media. Collectively, these data show that inflammation of epicardial adipose tissue in patients with type 2 diabetes mellitus is associated with alterations in adipokine secretion, which may contribute to the pathogenesis of type 2 diabetes mellitus–related heart disease. See p 2324.

Transcatheter Aortic Valve Replacement for Degenerative Bioprosthetic Surgical Valves: Results From the Global Valve-in-Valve Registry

In the last decade, bioprosthetic valves have been used more commonly during surgical valve replacements; it is estimated that in subsequent years, many patients will suffer from failed surgical bioprostheses. The Global Valve-in-Valve Registry, which includes in the present analysis 202 patients from 38 centers, is the first large, comprehensive evaluation of transcatheter aortic valve replacement with the use of either Edwards SAPIEN (Edwards Lifesciences, Irvine, CA) or CoreValve (Medtronic, Minneapolis, MN) devices for failed surgically inserted aortic bioprostheses, including 1-year clinical and echocardiographic analyses. According to the registry, the valve-in-valve approach is effective and relatively safe. Improvement in patient functional capacity was clear: 84.1% of treated patients were classified as New York Heart Association class I/I early after the procedure. Clinical and hemodynamic results are maintained in 1-year follow-up. Thirty-day mortality and stroke rates (8.4% and 2%, respectively) are comparable to those in other transcatheter aortic valve replacement cohorts. An efficacy concern involved moderately elevated postprocedural gradients, with predictors in multivariate analysis that include the degree of bioprosthesis stenosis and treatment with an Edwards SAPIEN inside a small bioprosthesis. Safety concerns included ostial coronary obstruction (3.5%) and device malposition (15.3%) resulting in relatively high rates of a need for implantation of another transcatheter aortic valve replacement device (8.4%) and retrieval of a CoreValve (8.9%). Operators of valve-in-valve procedures should be skilled in handling device malposition and related technical maneuvers, if needed. The possible impact on cardiac surgery practice includes referral of patients with failed bioprostheses who are at very high surgical risk to valve-in-valve and selection of valve class during surgery (mechanical versus biological), in favor of the use of bioprostheses. See p 2335.
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