Aortic Root Dilatation in Adults with Surgically Repaired Tetralogy of Fallot: A Multicenter Cross-Sectional Study

The number of adults with repaired tetralogy of Fallot is increasing. Aortic root dilatation has been observed on longitudinal follow-up of patients with tetralogy of Fallot. Histological studies of aortas in patients with tetralogy of Fallot have reported striking similarities to the aortas of patients with Marfan syndrome. Despite the concern that patients with tetralogy of Fallot may harbor an aortopathy that can lead to aortic regurgitation, aortic aneurysms, and, potentially, aortic dissection, the scope of the problem remains uncertain. This multicenter study is the largest to assess the prevalence and predictors of aortic root dilatation in patients with tetralogy of Fallot. When an absolute threshold of 40 mm was used to define a dilated aortic root, a prevalence of 28.9% was observed. In multivariate analyses, the only independently associated factor was male sex. In contrast, an observed-to-expected aortic root diameter ratio cutoff value >1.5 yielded a prevalence estimate of 6.6%. No independent predictor was identified. Our results demonstrate that predictors of aortic root dilatation depend on the definition used to describe aortic root dilatation. Specifically, duration of systemic-to-pulmonary shunt, pulmonary atresia, right aortic arch, aortic regurgitation, and ventricular dimensions are not associated with aortic root dilatation. Aortopathy in tetralogy of Fallot, with aortic dilatation and moderate or severe aortic regurgitation, appears to be a less common issue than previous estimates derived from smaller studies would suggest. The paucity of documented adverse events and the results of this study should provide some reassurance regarding aortic root outcomes in tetralogy of Fallot. See p 172.

The Effect of Excess Weight Gain With Intensive Diabetes Mellitus Treatment on Cardiovascular Disease Risk Factors and Atherosclerosis in Type 1 Diabetes Mellitus: Results From the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) Study

Unlike other observational studies of patients with type 1 diabetes mellitus, the Diabetes Control and Complications Trial (DCCT) was a randomized, controlled trial. Patients assigned to the intensive treatment arm had better diabetes mellitus–related microvascular and initial macrovascular outcomes compared with the conventionally treated group, but roughly a quarter of the patients became obese. The rationale for this study was to determine whether this excess weight gain and accompanying worsening of cardiovascular risk factors in this subset would persist and be associated with subclinical atherosclerotic disease during long-term follow-up. We found during 8 to 9 years of follow-up that central obesity, increased lipid levels, and increased blood pressures in this group persisted and were associated with more subclinical atherosclerotic disease. We also found evidence for familial influences on atherosclerotic disease in the intensively treated subjects, but not those treated conventionally. The significance of this study is the recognition that obesity-related deterioration of cardiometabolic risk factors can occur in patients with type 1 diabetes mellitus treated with intensive diabetes mellitus management, even those who have experienced improvements in their glycemic control to near normal levels, and that this excessive weight gain can worsen atherosclerotic disease. It highlights the need to develop effective weight control strategies for obesity prevention to maximize the benefits of intensive diabetes mellitus therapy in type 1 diabetes mellitus. See p 180.

High Anthocyanin Intake Is Associated With a Reduced Risk of Myocardial Infarction in Young and Middle-Aged Women

To date, attention has focused on risk factors for coronary heart disease in older age groups, and risk factors may vary with age, particularly in women. Knowledge of modifiable risk factors to prevent myocardial infarction (MI) in young women is limited, particularly in relation to diet. Dietary flavonoids, bioactive compounds present in plant-based foods and drinks, exert potential beneficial effects on endothelial function and blood pressure in short-term trials, but the effects of habitual intakes on MI risk in younger women are unknown. The mechanisms underlying coronary heart disease in younger women may also differ, and coronary vasospasm, a consequence of endothelial dysfunction, may be important. We prospectively studied 93,600 young women from the Nurses’ Health Study II for up to 18 years and examined the relationship between intakes of flavonoid subclasses and risk of MI. Individuals with a higher intake of 1 subclass, anthocyanins (responsible for the red/blue color of plants and present in strawberries, blueberries, and red wine), had a significantly lower risk of MI than women consuming low intakes. This 32% reduction in risk was independent of established dietary/lifestyle CVD risk factors, including smoking, body mass index, and fruit and vegetable intake. To relate these findings to public health, we showed that the combined intake of the main anthocyanin sources (strawberries and blueberries) was also associated with a reduction in MI risk. This study suggests that high anthocyanin intakes may reduce MI risk in young women. Intervention trials are needed to assess clinically relevant end points, and prevention efforts should focus on increasing intakes of commonly consumed anthocyanin-rich foods. See p 188.

Preterm Heart in Adult Life: Cardiovascular Magnetic Resonance Reveals Distinct Differences in Left Ventricular Mass, Geometry, and Function

Recent improved survival of infants born prematurely has led to a growing cohort of very preterm infants now entering adulthood. Before birth, these individuals were exposed to a suboptimal intrauterine environment, and after delivery, key developmental stages that would normally occur in utero during the third trimester took place under ex utero physiological conditions. Cardiac development may be particularly affected. Experimental models have demonstrated that after preterm delivery cardiomyocytes undergo accelerated hypertrophy with an increase in interstitial myocardial collagen deposition and that the induced changes are sufficient to remodel the left ventricle. In this study, we used cardiovascular magnetic resonance and a computational atlas to reveal for the first time the impact of preterm birth on left ventricular structure and function in humans. We found that preterm birth is associated with increased left ventricular mass independently of variation in blood pressure and
that preterm-born young adults have shorter ventricles, smaller cavity diameters, and a displaced apex compared with term-born control subjects. Furthermore, we have identified distinct changes in left ventricular function related to premature birth, which is significantly worse in those whose mother also had preeclampsia. Because 10% of births are preterm, any adverse health impact of this unusual development pattern is relevant to a large population of adults. Whether interventions to modify these variations in left ventricular structure and function prevent the development of cardiac disease in a growing subgroup of the population will be of future interest. See p 197.

**Renal Dysfunction as a Predictor of Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation: Validation of the R,CHADS₂ Index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial Fibrillation) Study Cohorts**

A key step in the prevention of atrial fibrillation (AF)–related stroke is effective risk stratification. Although several schemes have been developed, currently available models account for little more than half the attributable risk, which indicates that other important predictive factors remain undefined. We identified factors associated with the occurrence of stroke and systemic embolism in ROCKET-AF, a large, international AF trial. In patients with nonvalvular AF, reduced creatinine clearance was a strong, independent predictor of stroke and systemic embolism, second only to prior stroke or transient ischemic attack. A model that included creatinine clearance (R,CHADS₂) improved net reclassification index by 6.2% compared with CHA₂DS₂-VASc (C statistic=0.578) and by 8.2% compared with CHADS₂ (C statistic=0.575). Validation of R,CHADS₂ in an external, separate population improved net reclassification index by 17.4% (95% confidence interval 12.1%–22.5%) relative to CHADS₂. These findings indicate that impaired renal function, like prior stroke, is a powerful predictor of incident stroke and systemic embolism in patients with nonvalvular AF receiving and not receiving therapeutic anticoagulation. Stroke risk stratification in patients with AF should include renal function. See p 224.

**Cell Selective Cardiovascular Biology of Microsomal Prostaglandin E Synthase-1**

Nonsteroidal anti-inflammatory drugs selective for inhibition of cyclooxygenase 2 (COX-2) were developed to conserve the analgesic and anti-inflammatory efficacy of older nonsteroidal anti-inflammatory drugs like diclofenac, also caused thrombotic events, hypertension, and cardiac failure attributable to suppression of COX-2–derived PGI₂. The microsomal prostaglandin E synthase-1 (mPGES-1) enzyme is downstream of COX-2 and accounts for most of the prostaglandin E₂ that is formed in humans. Some, but not all studies in mice lacking mPGES-1 suggest analgesic and anti-inflammatory efficacy similar to nonsteroidal anti-inflammatory drugs. Most, but not all studies suggest that unlike COX-2 disruption or inhibition, global mPGES-1 deletion does not predispose to hypertension or thrombogenesis in mice. Here, we show that this reassuring cardiovascular phenotype extends to mice lacking endothelial or vascular smooth muscle cell mPGES-1, consistent with augmented prostacyclin because of the rediversion of the mPGES-1 substrate to prostacyclin synthase. However, although global mPGES-1 deletion attenuates the response to vascular injury, again reflective of increased prostacyclin, selective enzyme deletion in vascular versus myeloid cells has contrasting effects on this phenotype. This appears in both cases to reflect suppression of prostaglandin E₂, rather than substrate rediversion and implicates macrophage prostaglandin E₂ in an exaggerated response to vascular injury. Contrasting cellular roles of mPGES-1 may complicate systemic enzyme inhibitors, whereas locally delivered inhibitors targeted at the macrophage merit consideration as an adjunct to treat pathological vascular remodeling, such as restenosis after angioplasty. See p 233.

**Long-Term Mortality Data From the Balloon Pump–Assisted Coronary Intervention Study (BCIS-1): A Randomized, Controlled Trial of Elective Balloon Counterpulsation During High-Risk Percutaneous Coronary Intervention**

The intra-aortic balloon pump improves myocardial perfusion and decreases myocardial oxygen demand and hence is a valuable adjunct when treating cardiogenic shock. It is also frequently used to treat complications during high-risk percutaneous coronary intervention (PCI); the only randomized trial to date that addresses this indication is the Balloon Pump–Assisted Coronary Intervention Study (BCIS-1). In BCIS-1, 301 patients with severe ischemic cardiomyopathy were randomly assigned to have elective intra-aortic balloon pump insertion before PCI or to have PCI without planned intra-aortic balloon pump support. The trial failed to show a difference in the occurrence of major cardiovascular events at hospital discharge. The present report documents the long-term survival in patients enrolled in this trial. All-cause mortality at a median of 51 months was 33% in the entire cohort, demonstrating that severe ischemic cardiomyopathy is associated with relatively poor long-term survival. The results also showed that elective intra-aortic balloon pump use is associated with a 34% relative reduction in all-cause mortality compared with PCI without planned balloon pump support. Although the trial was not initially designed to assess long-term mortality and the putative mechanism of benefit is unclear, these data suggest that there may be a role for elective intra-aortic balloon pump therapy during PCI in selected patients with poor left ventricular function and extensive coronary disease. See p 207.

**Enhanced Effect of Combining Human Cardiac Stem Cells and Bone Marrow Mesenchymal Stem Cells to Reduce Infarct Size and to Restore Cardiac Function After Myocardial Infarction**

Stem cell–based therapy represents a potentially transformative new therapy for left ventricular dysfunction and other cardiovascular diseases. Bone marrow mesenchymal stem cells (MSCs) and cardiac stem cells (CSCs) are two of the leading candidates for cellular cardiomyoplasty. On the basis of earlier observations that MSCs interact with and promote survival and lineage commitment of CSCs, we tested whether combining MSCs with CSCs would augment a therapeutic response relative to either cell alone. Using xenotransplantation of human MSCs and c-kit+ CSCs delivered intramyocardially to swine after myocardial infarction, we show that combining MSCs and CSCs greatly enhances the reduction in infarct size and the improvement in left ventricular diastolic and systolic function achieved with either cell alone. These data support the idea that cell combination therapy is a practical and effective strategy to improve responses to cell therapy and support the conduct of clinical trials testing coinjection of MSCs and CSCs in humans with cardiac injury resulting from myocardial infarction and possibly other sources of left ventricular dysfunction. See p 213.