Original Research Put Into Perspective for the Practicing Clinician

Volume 129  ■  Number 3  ■  January 21, 2014

Circulation: Clinical Summaries

Prenatal Diagnosis, Birth Location, Surgical Center, and Neonatal Mortality in Infants With Hypoplastic Left Heart Syndrome

There has been significant controversy about the effect of prenatal diagnosis of critical congenital heart disease on mortality, and many large studies have demonstrated no benefit. The authors take a novel approach to this question in neonates with hypoplastic left heart syndrome in 2 ways: (1) they use the Texas Birth Defects Registry, which allows for capture of death prior to transfer to a cardiac surgical center (CSC) and before surgery after transfer, and (2) distance between the birth hospital and a CSC (measured in calculated driving time) is investigated instead of prenatal diagnosis. The results demonstrated that birth >90 minutes from a CSC was associated with increased neonatal mortality compared with <10 minutes away, even when controlling for known risk factors. When timing of death was investigated, the majority of mortality associated with increased distance was pre-transfer and pre-surgical after transfer. Specifically, birth >90 minutes from a CSC was associated with >6-fold higher mortality before transfer than in patients born closer, with a similar effect seen even in those prenatally diagnosed. Birth 10 to 90 minutes from a CSC was associated with higher presurgical mortality after transfer, compared with those born <10 minutes away. The study also confirmed the association between low case volume and higher surgical mortality, and suggested that low case volume may also be associated with higher presurgical mortality. Efforts to improve prenatal diagnosis of hypoplastic left heart syndrome and subsequent delivery near a large volume CSC may therefore significantly improve neonatal survival in infants with hypoplastic left heart syndrome. See p 285.

Biomarkers in Relation to the Effects of Ticagrelor in Comparison With Clopidogrel in Non–ST-Elevation Acute Coronary Syndrome Patients Managed With or Without In-Hospital Revascularization: A Substudy From the Prospective Randomized Platelet Inhibition and Patient Outcomes (PLATO) Trial

Risk stratification and the use of specific biomarkers have been proposed for tailoring treatment in patients with non-ST-elevation acute coronary syndrome. We investigated the prognostic importance of high-sensitivity troponin T (hs-TnT), N-terminal pro-brain natriuretic peptide, and growth differentiation factor-15 in relation to randomized treatment (ticagrelor versus clopidogrel) and management strategy (with or without revascularization) in 9946 patients with non-ST-elevation acute coronary syndrome in the PLATelet inhibition and patient Outcomes (PLATO) trial. During index hospitalization, 5357 were revascularized, and 4589 were managed without revascularization. Increasing levels of hs-TnT were associated with increasing risk of cardiovascular death, myocardial infarction, and stroke in medically managed patients, but not in those managed invasively. N-terminal pro-brain natriuretic peptide and growth differentiation factor-15 levels were associated with the same events independent of management strategy. Ticagrelor versus clopidogrel reduced the rate of cardiovascular death, myocardial infarction, and stroke in patients with non-ST-elevation acute coronary syndrome and hs-TnT ≥14.0 ng/L in both invasively and noninvasively managed patients. In patients with hs-TnT <14.0 ng/L there was no difference between ticagrelor and clopidogrel in the noninvasive group. Thus, elevation of N-terminal pro-brain natriuretic peptide and growth differentiation factor-15 may be used as general indicators of raised relative risk, which remain even if the risk associated with the acute coronary artery disease is reduced by specific treatment with revascularization and ticagrelor. Determination of hs-TnT is useful because elevated levels identify patients with an increased risk for adverse outcomes specifically related to acute coronary artery disease, which can be reduced by revascularization and intense platelet inhibition with ticagrelor. Identification of patients with normal hs-TnT is also useful, because these patients seem to have no important benefits from either of these specific treatments. See p 293.

Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation: A Randomized, Controlled Trial

Drug-eluting stents have been shown to be superior to bare metal stents in terms of patient outcome. However, there is concern about the risk of late stent thrombosis after drug-eluting stent implantation. At present, the guidelines recommend that dual antiplatelet therapy should be given either for 6 to 12 months or for at least 12 months after drug-eluting stent implantation unless patients are at high risk for bleeding. These recommendations are based largely on registry data, and the optimal duration of dual antiplatelet therapy remains poorly defined. In the Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event (DES LATE) trial, we compared the effect of 12 versus >12 months of dual antiplatelet therapy in 5045 patients who received drug-eluting stents and were free of major adverse cardiovascular events and major bleeding for at least 12 months after stent placement. The 2 treatment strategies did not differ significantly in terms of the primary end point (a composite of death resulting from cardiac causes, myocardial infarction, or stroke 24 months after randomization) with a potential risk of major bleeding. These findings support the notion that the benefits of dual antiplatelet therapy after implantation of drug-eluting stents may not extend beyond 12 months. See p 304.

Derivation and Validation of a Risk Standardization Model for Benchmarking Hospital Performance for Health-Related Quality of Life Outcomes After Acute Myocardial Infarction

To use patients’ outcomes to assess, compare, and improve the quality of care of patients with acute myocardial infarction (AMI), these outcomes must be risk-standardized to account for differences in patient characteristics. This is a critical step in comparing outcomes between hospitals, because it ensures
that hospitals are judged on the care they deliver and not on the type of patients they treat. Given the importance of health-related quality of life (HRQL) outcomes among AMI patients, we developed a risk-standardization model for patients’ long-term HRQL after AMI. The model was able to explain 20% of the variation in HRQL outcomes, indicating that much of the variation is not explained by patient factors. This may indicate that the remaining variation in HRQL could be explained by the hospitals’ processes of care—such as early revascularization, smoking cessation, and cardiac rehabilitation. Importantly, we validated the model in an independent sample of AMI patients from a separate multicenter registry. This model fills an important gap in the use of patient-reported outcomes as markers of healthcare quality by providing a risk-standardization model that can account for patient characteristics. As such, it can facilitate a means for identifying hospitals that use processes of care that maximize patients’ HRQL, and in so doing, their strategies can then be disseminated to other hospitals. See p 313.

**Effects of Promoting Longer-Term and Exclusive Breastfeeding on Cardiometabolic Risk Factors at Age 11.5 Years: A Cluster-Randomized, Controlled Trial**

Several observational studies, and meta-analyses of these, have been published, showing protective effects of increased breastfeeding duration and exclusivity on cardiometabolic risk factors in later life. However, observational associations may be confounded by common causes of infant feeding choices and cardiometabolic outcomes. The unbiased effects of breastfeeding can probably only be convincingly demonstrated in a randomized, controlled trial. Although it is not feasible to randomly assign healthy term infants to be breast or bottle fed, it is possible to randomly assign mother-infant pairs to a breastfeeding promotion intervention. Our article is based on the 11.5-year follow-up of 17046 children enrolled when newly born into the Promotion of Breastfeeding Intervention Trial (PROBIT, ISRCTN37687716), a cluster-randomized trial of a breastfeeding promotion intervention based on the World Health Organization/United Nations Children’s Fund Baby-Friendly Hospital Initiative. The intervention resulted in 2 groups with substantially different exposures to exclusive and prolonged breastfeeding, providing a unique opportunity to test, in an intention-to-treat analysis, the extent to which breastfeeding causally influences cardiometabolic risk factors in childhood. Our results, based on the largest randomized trial of breastfeeding ever conducted, provide no evidence that an intervention to promote longer duration of exclusive breastfeeding lowered levels of several cardiometabolic risk factors in childhood. Blood pressure; fasting insulin, adiponectin, glucose, and apolipoprotein A1; and the presence of metabolic syndrome, in comparison with a shorter duration. Although we saw no evidence of an effect on cardiometabolic risk factors in our trial, there are several other important beneficial effects of breastfeeding that amply justify clinical and public health efforts to promote, protect, and support it. See p 321.

**Prepregnancy Obesity and Associations With Stroke and Myocardial Infarction in Women in the Years After Childbirth: A Nationwide Cohort Study**

As a consequence of the observed disturbingly low rate of temporal decline in coronary heart disease mortality in young women aged <45 years, and their adverse prognosis after myocardial infarction and ischemic stroke compared with men and older women, leading healthcare organizations including the American Heart Association have requested further insight into cardiovascular risk factors and the prognosis of cardiovascular disease in young women. In the current study, we used nationwide registers to explore the associations between prepregnancy body mass index and the risks of myocardial infarction, stroke, and a composite of myocardial infarction, ischemic stroke, and cardiovascular death, in a comprehensive population of all Danish women with no previous history of cardiovascular disease, giving birth 2004–2009 (median age 30.4 years). We found obesity to be significantly associated with increased risk of ischemic stroke and myocardial infarction over a median follow-up of 4.5 years, even after adjustment for several cardiovascular risk factors and pregnancy-associated risk factors. Additionally, being overweight or obese was associated with increased risk of the composite of myocardial infarction, stroke, and cardiovascular death. Thus, despite low absolute risks, the obesity-associated health risk becomes apparent even in these young women within a short follow-up. See p 330.

**Prevalence and Risk Factors for Pulmonary Arterial Hypertension in a Large Group of β-Thalassemia Patients Using Right Heart Catheterization: A Webthal Study**

The pathophysiology β-thalassemia, an inherited disorder of hemoglobin synthesis, involves chronic anemia and hemolysis, iron overload, hypercoagulability, and vascular abnormalities, all placing patients at higher risk of vascular morbidity including pulmonary arterial hypertension (PAH). The prevalence of PAH confirmed by right heart catheterization in patients with β-thalassemia has remained so far unknown. Such information remains essential as it carries screening and diagnostic reflections which may impact health care utilization measures, especially considering that PAH is associated with adverse clinical sequelae. In this large study of >1000 patients, the prevalence of confirmed PAH in β-thalassemia was considerably lower (2.1%) than what has been previously reported in echocardiographic studies, indicating that although serious, this morbidity is not as common as has been previously perceived. However, it should be noted that the tricuspid-valve regurgitant jet velocity threshold used to identify patients eligible for diagnostic intervention in this study was more conservative and reflective of the chronic anemia associated with the disease ≥3.2 m/s). Moreover, this study identified the β-thalassemia intermedia phenotype, splenectomy, and advanced age as factors that should highlight which patient subgroups may be at higher risk for PAH and may thus be considered for preventive strategies. See p 338.

**Activation of Histone Deacetylase-6 Induces Contractile Dysfunction Through Derailment of α-Tubulin Proteostasis in Experimental and Human Atrial Fibrillation**

Drugs currently used in atrial fibrillation (AF) have limited efficacy in preventing remodeling of cardiac tissue. Thus, pharmacological approaches preventing or limiting such remodeling, which is considered a prime substrate for the promotion of AF, are warranted (upstream therapy). There are strong indications that a loss of normal protein homeostasis in cardiomyocytes contributes significantly to the substrate for the development
and progression of AF. Our present study identifies histone deacetylase-6 (HDAC6)–induced deacetylation of α-tubulin and subsequent microtubule disruption as a critical step in the development of a substrate for AF. Consequently, inhibitors of HDAC6 represent promising drug candidates for upstream therapy. Because the HDAC6 inhibitor we used in model systems, tubacin, is not suitable for in vivo studies, alternative inhibitors such as tubastatin A and ACY-1215 have recently been developed. These inhibitors show beneficial effects in mice models of neurodegenerative diseases and cancer. In the present study, we provide the first evidence for the in vivo efficacy of such HDAC6 inhibitors in AF by demonstrating that tubastatin A protects against atrial remodeling in tachypaced dogs. Specific inhibition of HDAC6 has not been associated with any serious toxicity so far, and clinical trials are currently recruiting for phase 1/2 studies. Thus, should these trials substantiate the lack of toxicity of HDAC6 inhibitors in humans, our present study suggests that these drugs represent interesting candidates to be tested for upstream therapy in human AF. See p 346.

Vascular Progenitors From Cord Blood–Derived Induced Pluripotent Stem Cells Possess Augmented Capacity for Regenerating Ischemic Retinal Vasculature

The regeneration of retinal capillaries with cellular therapies could reverse the ischemic death of retinal neurons, and potentially ameliorate or prevent end-stage blindness in disorders such as diabetic retinopathy and branched vein occlusion. For example, unlimited supplies of transplantable vascular progenitors (VPs) along with retinal photoreceptors could be differentiated synchronously from patient-specific human induced pluripotent stem cells for comprehensive regeneration of the damaged retina. Additionally, cord blood cells offer an especially attractive universal donor source for generating human induced pluripotent stem cells, because they carry few somatic mutations, and they can more efficiently generate nonviral, clinically relevant pluripotent stem cell lines that could theoretically be assembled to create an human leukocyte antigen–defined stem cell bank via worldwide networks of existing repositories. In these studies, we identify an embryonic VP population differentiated from human induced pluripotent stem cells that can functionally integrate long-term into ischemia-damaged mouse retinal vasculature. We demonstrate for the first time that, in contrast to VPs differentiated from human induced pluripotent stem cells derived via standard methods, embryonic VPs from high-fidelity reprogrammed nonviral cord blood-induced pluripotent stem cells demonstrated lower culture senescence, expanded more robustly in culture, demonstrated more resistance to DNA damage, and were more akin molecularly to those generated from human embryonic stem cells. More importantly, VPs generated from cord blood-induced pluripotent stem cell lines possessed an inherent advantage for long-term in vivo survival, migration, homing, and specific engraftment to ischemia/reperfusion–injured retinal tissues. This humanized vascular regenerative model establishes an important tool for evaluating the further development of clinically relevant pluripotent stem cell–based therapies for treating blinding ischemic retinopathies. See p 359.
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/129/3/275

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/