52 000 participants (32 000 with prior cardiovascular disease in unfortified populations, 14 000 with prior cardiovascular disease in fortified populations, and 6000 with renal disease in fortified populations); thus, the meta-analysis should be sufficiently powered to detect a 10% reduction in rates of major vascular events, major coronary events, and stroke.

In the meantime, based on existing data, including the findings of the HOST trial by Jamison et al, there is insufficient evidence to justify routine use of homocysteine-lowering vitamin supplements for the prevention of vascular events among individuals at high risk for vascular disease.

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The Importance of Randomized Controlled Trials in Pediatric Cardiology

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Experience with randomized controlled clinical trials in pediatric cardiology is limited. Perhaps the most cited article in the field had a sample size of 1, a baby with transposition of the great arteries who successfully underwent balloon dilation of a patent foramen ovale.[1] When this procedure was found to improve survival from a median of less than a week to several years, the immediate challenge to clinicians was not to replicate the finding by a randomized trial but to determine how best to manage a living child with an oxygen saturation of 60% to 70% and persistent complex anatomical defects.

Within 25 years and incorporating many technical innovations into diagnosis and management, more than 95% of children born with this defect survived an arterial switch procedure with little morbidity until adulthood.[2,3] Along the path to these results, many treatment centers simply converted from performing the conventional "venous switch" procedure to an arterial switch procedure because of the high prevalence of right ventricular dysfunction and atrial dysrhythmias associated with the older procedure.[2,3] This achievement best exemplifies the "craft" era, when individual skill combined with rapidly improving technology substantially improved long-term survival for most congenital heart defects.

An important question is why, when a successful surgical procedure, the "venous switch," was widely accepted, did cardiologists and surgeons completely convert to a technically more difficult, completely different procedure, the arterial switch? How could such a radical change in therapy be advocated and accepted without the type of "gold standard" evidence provided by a randomized trial? Arguably, there were 2 reasons. One is that the success of the intervention relied on the skills of a complex multidisciplinary team repeatedly performing the same task; randomization either within or by treatment center seemed both inappropriate, impractical, and perhaps even unethical[3] A second, and perhaps more compelling reason relates to a fundamen-

See also p 1171.

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tal difference between pediatric and adult medicine. A palliated infant living with substantial morbidity as an adolescent and young adult is an unsatisfactory result. Just as the "venous switch" performed at younger ages eliminated the morbidity of chronic hypoxemia in infants, the arterial switch held out the hope that an affected infant's future would not include right ventricular failure and chronic untreatable dysrhythmias. Return to near normal life expectancy after treatment measured in decades rather than months or years as in adult trials was the goal.

There are several other possible reasons for the limited use of randomized clinical trials in pediatric cardiology: the relative rarity of individual diseases, the heterogeneity of presentation, rapid changes in technology making older diagnostic and therapeutic techniques obsolete, the importance of individual physician skill to outcome, difficulties in subject recruitment, etc. Nevertheless, when clinical trials have been performed, their effect has been substantial. Major trials performed in the 1980s and early 1990s initiated the pharmacological treatment for patent ductus arteriosus,[4] defined optimal treatment for Kawasaki disease,[5] and made rigorous the search for optimal cerebral protection during cardiopulmonary bypass in infants.[6]

During the last decade, because of US Food and Drug Administration requirements for licensing of devices and the mandate to collect data in pediatric patients to obtain indications for use of new pharmaceutical agents in children, many randomized trials in children have been financed by industry. In cardiology, important information has been acquired about the safety and efficacy of different catheter-based interventions as have medications for hypertension and dyslipidemia. These studies have been mutually beneficial for drug companies and pediatric research even though results have not been sufficiently published.[7-9] For example, a table providing doses of antihypertensive medications validated from clinical trials has been published as part of an evidence-based clinical guideline.[10] A critical outcome of such studies is the recognition that results in children and adults are not necessarily the same.

In this issue of *JAMA*, Shaddy and colleagues[11] report somewhat disappointing results from a randomized trial of carvedilol use for children with heart failure; study participants surprisingly did not seem to benefit from treatment. These findings stand in stark contrast to results from randomized trials involving adults and also anecdotal reports of successful experience in small uncontrolled studies.

Despite the findings, the study by Shaddy et al is not the final word in pediatric heart failure research but, rather, is a first and important step in a new era for the field. The lessons learned in the conduct of this trial were considerable. First, within the context of randomized trials, the outcomes of children with heart failure are different from adults, particularly in young children. This finding suggests that the study was significantly underpowered. Second, in attempting to recruit a sufficient sample size, the investigators combined patients with single ventricle physiology and those with conventional left ventricular systolic dysfunction into 1 group. The outcomes were significantly poorer for those with systemic right ventricle. Third, carvedilol is metabolized more rapidly in children than in adults, and, therefore, dosing may need to be different. Fourth, there is greater etiologic heterogeneity of disorders causing dilated cardiomyopathy in childhood, another possible factor leading to the negative result.[12] Fifth, in the absence of consensus criteria for the diagnosis of congestive heart failure in infants and children, Shaddy et al were forced to rely on a composite subjective end point related to assessment of clinical improvement by parents and clinicians.[11] And sixth, an important reassuring finding is that carvedilol did not appear to cause harm, paving the way for more ambitious future trials.

Recruitment has been a significant problem for conducting randomized trials in pediatric cardiology. The study by Shaddy et al has a sample size an order of magnitude (160 rather than >1000) less than comparable adult studies .[11,13] The same sense of urgency that inspired efforts to convert from the "venous switch" to the arterial switch for transposition of great arteries must inform current relationships with patients to improve recruitment into clinical trials. Much more needs to be learned about pediatric heart failure and the long-term care of congenital heart disease survivors. For example, a survey of those who care for patients with a single ventricle revealed that the most important factor predicting prescribing practice of digoxin, diuretics, angiotensin-converting enzyme inhibitors, and anticoagulation was not by clinical profile but by medical center submitting data to the registry.[14] These data provide the ethical rationale for a new effort at defining optimal cardiovascular therapy by recruiting patients into trials rather than continuing to treat patients using agents without proven efficacy. The National Heart, Lung, and Blood Institute–funded Pediatric Heart Network and registries devoted to specific pediatric cardiac problems have initiated multicenter randomized studies with these objectives in mind.[15]

A subtle but important difference between pediatric and adult research relates to goals. Adult cardiac trials, whether related to heart failure or prevention of recurrent myocardial infarction, are considered successful when the inevitable is delayed. For most adults, the inevitable still occurs. For children with heart disease, the goals are different: to treat pediatric patients effectively so that they can experience decades of as normal a quality of life as possible. This difference provides the ethical rationale for independent pediatric clinical research and rigorous clinical trials in pediatric patients as opposed to a reliance on adult outcomes, which often are not generalizable to children. After all, and especially in pediatric cardiology research and treatment, children are not simply little adults.

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Cardiovascular Risk and the Thiazolidinediones

Déjà Vu All Over Again?

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In 2005, the US Food and Drug Administration (FDA) held an advisory committee meeting to help determine the safety of selective cyclooxygenase 2 (COX-2) inhibitors, a popular group of drugs with a novel mechanism of action but with incompletely understood effects on the cardiovascular system. Although these drugs have some potential benefits with respect to gastrointestinal toxic effects, their benefit-risk ratio was and is still unclear. Fast forward 2 years to 2007, and the FDA held a similar advisory committee meeting about the safety of rosiglitazone, a widely used thiazolidinedione (TZD) with known benefits on glycemic control but potential cardiovascular toxic effects. What have clinicians, patients, and the public learned through these recent events?

The TZDs sensitize end organs to insulin through their effect on the peroxisome proliferation–activated receptor γ (PPAR-γ). The PPAR system is a group of nuclear receptors (α, γ, and δ) that serve as transcription factors for genes important in glucose, lipid, and bone metabolism.[1] The varied actions of the PPAR system fueled enthusiasm for the potential benefits of TZDs, even beyond their effects on hyperglycemia. However, early toxic effects observed with these agents, such as hepatic and heart failure,[2] should have fueled equal levels of caution. The heart failure observed with rosiglitazone and pioglitazone prompted changes in the warning section of the package inserts but no "black box" warning until very recently.[3]

Approval of the TZDs was based on their ability to reduce blood glucose levels and glycated hemoglobin levels. Little information was available on their effects on the macrovascular complications of diabetes before these agents were approved. Since their marketing, few adequately powered randomized controlled trials have been conducted in moderate- or high-risk patients to definitively determine the true benefits of these agents on macrovascular complications. The only completed trial that was specifically designed and powered to evaluate the efficacy of a TZD in reducing hard cardiovascular outcomes was the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), a placebo-controlled randomized trial in patients with evidence of existing macrovascular disease who otherwise received usual diabetes care.[4] The study failed to show a significant benefit of pioglitazone treatment on the primary composite end point of cardiovascular, cerebrovascular, and peripheral vascular outcomes. However, pioglitazone reduced by 16% a secondary composite end point including death from any

See also pp 1180 and 1189.

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