1. Prior studies have concluded that fewer than 50% of drugs approved for use in the United States have sufficient data to support labeling for dosing, safety, and efficacy in children.

2. Other studies estimated that 40%-100% of hospitalized children were prescribed at least one medication prescribed “off-label”. An analysis of 30,000 records from children hospitalized with cardiovascular disease concluded that 78% of these children received at least 1 off-label medication and 31% received more than 3.

3. There are many challenges to the development and approval of medications for children and the lack of approved medications for children limits the evaluation and dissemination of safety and efficacy data.

4. Where randomized clinical trials have shaped the care of adults with cardiovascular disease, reliance on data from randomized clinical trials may not adequately address the unique needs of children because the target pediatric population is small and heterogeneous for many conditions.

5. The STARTS-1 and STARTS-2 trials were designed to study the use of sildenafil in pulmonary hypertension in children. The authors outlined many factors that complicated these trials and noted that the findings of these trials resulted in a contraindication and medication warning on the label.

6. Additionally, the authors noted that randomized clinical trials in pediatric populations are also limited by lack of control for patient-specific variables and the retrospective nature of many trials which complicates data replication. Compared to studies in adults, pediatric cardiology clinical drug trials may have inconsistent results and conclusions.

7. Other factors that can complicate pediatric cardiology clinical trials of drugs include:
   - The possibility that a drug works in an adult patient population but not in children.
   - Endpoints for children and adults may vary and the long-life expectancy of children (relative to adults) can complicate defining appropriate endpoints in children.
   - Pediatric diseases may be rare, heterogeneous, and follow an ill-defined natural history of disease. The small population of children affected by cardiovascular disease makes it difficult to design well-powered randomized clinical trials to test the effectiveness and safety of new therapeutics.
   - Lack of established research infrastructure to study a pediatric population.
   - Ethical issues specific to pediatric research.
   - The need for formulations suited for infants and children (e.g., oral liquids and chewable tablets).
   - The need for pharmacokinetic dosing data. Infants and children go through stages of rapid growth and development which can affect the pharmacokinetics and pharmacodynamics of some drugs.
   - Poorly designed dose-response assessments.
   - The lack of clinical equipoise.
   - The lack of appropriate endpoints to evaluate impact of disease from the neonate through adolescents and the use of surrogate or composite endpoints.

8. Steps are being taken nationally and internationally to close the gap between data on adults and data on children. This effort will help to meet the demand for pediatric clinical trials including the establishment of networks designed to narrow the knowledge gap in pediatric cardiovascular diseases. The authors outline several differences in U.S. and E.U. laws in this area.

9. Endpoints for clinical trials typically measure improvements in how a patient feels, functions, or survives. Validated surrogate measures are needed to predict long-term outcomes or benefit in children.

10. The ultimate goal of pediatric drug studies is to approve drugs that are safe and effective in children, ultimately improving care for the pediatric population to which they apply. The STARTS-1 and STARTS-2 Trials for pulmonary hypertension in children highlight several of the challenges that we face in establishing safety, efficacy, and labeling for pediatric cardiovascular drugs but have provided valuable lessons applicable to future pediatric study design. Thoughtful, alternative study designs should be considered to optimize pharmacological treatment of cardiovascular diseases in children.