The Study of Antiarrhythmic Medications in Infancy (SAMIS)
A Multicenter, Randomized Controlled Trial Comparing the Efficacy and Safety of Digoxin Versus Propranolol for Prophylaxis of Supraventricular Tachycardia in Infants

Shubhayan Sanatani, MD; James E. Potts, PhD; John H. Reed, MD, MPH; J. Philip Saul, MD; Elizabeth A. Stephenson, MD; Karen A. Gibbs, RN, CCRP; Charles C. Anderson, MD; Andrew S. Mackie, MD; Pamela S. Ro, MD; Svjetlana Tisma-Dupanovic, MD; Ronald J. Kanter, MD; Anjan S. Batra, MD; Anne Fournier, MD; Andrew D. Blaufox, MD; Harinder R. Singh, MBBS, MD, DCH; Bertrand A. Ross, MD; Kenny K. Wong, MD; Yaniv Bar-Cohen, MD; Brian W. McCrindle, MD, MPH; Susan P. Etheridge, MD

Background—Supraventricular tachycardia (SVT) is one of the most common conditions requiring emergent cardiac care in children, yet its management has never been subjected to a randomized controlled clinical trial. The purpose of this study was to compare the efficacy and safety of the 2 most commonly used medications for antiarrhythmic prophylaxis of SVT in infants: digoxin and propranolol.

Methods and Results—This was a randomized, double-blind, multicenter study of infants <4 months with SVT (atrioventricular reciprocating tachycardia or atrioventricular nodal reentrant tachycardia), excluding Wolff-Parkinson-White, comparing digoxin with propranolol. The primary end point was recurrence of SVT requiring medical intervention. Time to recurrence and adverse events were secondary outcomes. Sixty-one patients completed the study, 27 randomized to digoxin and 34 to propranolol. SVT recurred in 19% of patients on digoxin and 31% of patients on propranolol (P=0.25). No first recurrence occurred after 110 days of treatment. The 6-month recurrence-free status was 79% for patients on digoxin and 67% for patients on propranolol (P=0.34), and there were no first recurrences in either group between 6 and 12 months. There were no deaths and no serious adverse events related to study medication.

Conclusions—There was no difference in SVT recurrence in infants treated with digoxin versus propranolol. The current standard practice may be treating infants longer than required and indicates the need for a placebo-controlled trial.

Clinical Trial Registration Information—http://clinicaltrials.gov; NCT-00390546.

(Circ Arrhythm Electrophysiol. 2012;5:984-991.)

Key Words: clinical trials ■ drugs ■ patients ■ pediatrics ■ supraventricular tachycardia

With an incidence of 1 in 250, supraventricular tachycardia (SVT) is one of the most common conditions requiring emergent cardiac care in children and is a significant global health burden.1-5 Atrioventricular reciprocating tachycardia (AVRT) is the most common tachycardia mechanism in infants and children, with an increasing proportion having atrioventricular nodal reentrant tachycardia approaching adulthood.6,7 The peak occurrence of AVRT is in utero and...
during infancy. As many as 50% of infants presenting with SVT have severe cardiomyopathy and heart failure because of unrecognized tachycardia. Heart failure may progress to cardiovascular collapse and is the genesis of the associated 1% to 4% mortality. Due to concerns for morbidity and mortality and the challenges in detecting SVT in infants, the general consensus among pediatric cardiologists who manage these patients has been to use medication to prevent recurrent SVT. In the context of this study, the term prophylaxis refers to the prevention of recurrent episodes of SVT. In a recent survey of pediatric cardiologists and electrophysiologists, Wong et al reported that 98% of respondents recommend prophylactic medication when presented with a hypothetical case of an infant with SVT.

There are no randomized controlled trials addressing the most effective medicine for preventing recurrent SVT. The 2 most common therapies referenced in the literature and corroborated in the survey by Wong et al were digoxin and propranolol. Despite the common recommendation of digoxin as first-line therapy, there is some question regarding its efficacy as an antiarrhythmic agent. Propranolol is reported to be effective in preventing recurrences, and its use continues to be recommended although not based on data from controlled trials. A larger percentage of electrophysiology-trained pediatric cardiologists chose propranolol over digoxin for initial therapy, compared with non-electrophysiologists who chose digoxin more often in the survey.

Once antiarrhythmic medication has been initiated, there are few data to guide the duration of therapy, because the frequency and timing of recurrences are not readily predictable. There is a wide range, from 0% to 78%, of reported recurrences of SVT, even with medical treatment. Based on uncontrolled, retrospective data, the recommendation has been to treat infants with SVT for the first year of life even in the absence of recurrences. Although it is recognized that as many as 30% of infants will have resolution of their SVT by their first birthday, some infants may not require medical therapy beyond the first few months after presentation. It is unclear when definitive resolution of the SVT substrate occurs. Studies to determine SVT resolution are often performed 12 months after initiating therapy, recognizing that resolution may occur earlier.

The purpose of this study was to compare the efficacy and safety of the 2 most commonly used first-line therapies for SVT prophylaxis in infants, digoxin and propranolol.

Methods
This was a randomized, double-blind, multicenter study undertaken in Canada and the United States. Centers were invited to participate through the Pediatric and Congenital Electrophysiology Society (see online-only Data Supplement for participating centers). Local institutional ethics approval was obtained at the 19 participating centers and a contract entered with the coordinating site (Vancouver). An Investigational New Drug Application for both medications was filed with the US Food and Drug Administration (IND No. 74,330), as per their requirement. The trial was also registered with the US National Institutes of Health (NCT00390546) and with Health Canada (CTA 9427-C2266-24C). Randomization was done centrally and distributed to the participating sites at the time of enrollment. Subjects were randomized in blocks of 4 within each study center. The treatment assigned to each subject was maintained by both the core and site pharmacists so that the information was available if unblinding was required. Individual patient management was by the pediatric cardiologist(s) at each participating center.

Patients
Families of infants with SVT presenting from birth to 4 months of age were approached to participate, including those with fetal tachycardia who had a postnatal recurrence. Patients with AVRT without preexcitation or atrioventricular nodal reentrant tachycardia were included. A diagnosis of SVT was made based on ECG evidence of a tachycardia with rates of >220 beats per minute, with an abrupt onset and termination and with a constant tachycardia cycle length. Other supportive diagnostic features included tachycardia termination with vagal maneuvers or adenosine. The presence of a 1:1 atrioventricular relationship during SVT with a P wave clearly visible after the QRS termination was supportive evidence of AVRT. Site investigators were responsible for assigning arrhythmia mechanisms; ECGs were reviewed by the coordinating site (S.S.).

Exclusion Criteria
Patients were excluded if they had significant persistent functional (shortening fraction <28%) or structural heart disease (excluding patent foramen ovale and patent ductus arteriosus). Patients with ventricular preexcitation (Wolff-Parkinson-White syndrome) were excluded due to concerns about the effect of digoxin on the antegrade accessory pathway conduction properties. Patients with other significant comorbidities that could affect medication compliance or tolerance or result in death were also excluded. Patients were excluded if they received >40 mcg of digoxin in the preceding 7 days or a total of >50 mg/kg of amiodarone within the prior month. Infants with SVT in utero, treated with maternal antiarrhythmic medications, who developed SVT after birth were included if at least 5 half-lives of the medication had elapsed before day 5 of study enrollment, thus ensuring that the prior antiarrhythmic agent had no influence on the recurrence end point. Patients with atrial ectopic tachycardia or the persistent form of junctional reciprocating tachycardia were excluded, because these arrhythmias are more difficult to treat and often do not respond to conventional antiarrhythmic agents.

Follow-Up and Testing
Pre-enrollment evaluation included a medical history, physical examination, ECG and echocardiogram and, with the exception of the echocardiogram repeated at 2-, 4-, 6-, and 12-month postenrollment follow-up visits. If an end point was met, the next follow-up was at 12 months. Follow-up within the study ended at the 12-month visit, conducted primarily to determine whether the patient was still having episodes of SVT. Assessments after 12 months were based on the common practice at the treating institutions.

Study Medication Doses and Administration
Subjects were randomized to either digoxin or propranolol, and the study drug was given for 6 months or until one of the study end points was reached (see below). To account for differences in pharmacokinetics, the first 2 doses of digoxin were administered orally at 0.010 mg/kg per dose TID, then 0.0035 mg/kg per dose TID for the third and subsequent doses. Three times a day digoxin was used to remain consistent with the propranolol dosing, which was administered orally at 0.5 mg/kg per dose as a single dose and increased to 1.0 mg/kg per dose TID for the second and subsequent doses. This is a typical starting dose for propranolol, recognizing that there may

Clinical Perspective on p 991
Editorial see p 882
be a need to increase the dose to improve its efficacy.18,31 The study drug was dispensed by the site pharmacist who adjusted the dose at the 2- and 4-month visits to keep the dose within the expected therapeutic range based on the infant’s weight. The site investigator and coordinator were not involved in the randomization of subjects or dispensation of study drug to remain blinded. Suspensions of digoxin and propranolol were dispensed in identical opaque vials but had different volumes and color, making it possible that the parents were not completely blinded to the study drug. However, they were asked not to discuss the medication with the study investigators or coordinators. No additional measures were used to ensure double-blinding was maintained.

**Study End Points and Outcomes**

The primary study end point was the recurrence of SVT after 5 days of study medication that required medical intervention to terminate. Medical intervention included vagal maneuvers (typically ice to the face), adenosine, or other antiarrhythmic medications. Because inadequate study drug had been administered, an SVT recurrence within 5 days of initiation was not considered an end point, unless it resulted in discontinuation of study medication. Self-limited episodes of SVT were also recorded and included episodes that the parents observed that did not require an intervention. These were not considered an end point because of the inability to confirm the underlying rhythm and significant variability in terms of what leads families to present for medical attention and the factors influencing spontaneous termination. In the absence of recurrent SVT, the other study end points were completion of 6 months of study medication, discontinuation of study medication, withdrawal of consent, loss to follow-up, or death.

The primary study outcome was the incidence of recurrent SVT after 5 days of initiating therapy that required medical intervention to terminate. The time from the start of study medication to the documented recurrence of SVT requiring medical intervention to terminate was a secondary outcome. All observed adverse events (AEs), regardless of suspected causal relationship to the study drug, were recorded. Serious AEs were reported as any AE that was life-threatening, requiring hospitalization or prolongation of hospitalization, or resulted in significant disability or incapacity.

**Compliance**

Medication compliance was defined as having taken >80% and <120% of the study drug and was assessed at each clinic visit by the site pharmacist inspecting the medication remaining since it was last dispensed. Participants who were noncompliant were counseled on the importance of complying with study requirements. Crossovers and cointerventions were considered as a change or escalation in medical therapy and resulted in a study end point having been met. The use of concomitant antiarrhythmic medication(s) was recorded.

**Information to Families**

At hospital discharge, families were given a standard information sheet concerning SVT recognition and vagal maneuvers for termination, as well as a diary for record keeping. Families were instructed on how to measure heart rate and to monitor the child’s heart rate 3 times daily at the time the study drug was administered.

A Data Safety Monitoring Board, Health Canada, and the Food and Drug Administration monitored the study.

**Statistical Analysis**

Calculation of the sample size was based on the recurrence of SVT after 5 days of study medication requiring medical intervention to terminate. The planned enrollment of 220 patients was estimated to provide 80% power, with the use of a χ² test and a 2-sided α level of 0.05, to detect a difference between groups, assuming an event rate of 50% in the digoxin group and an event rate of 30% in the propranolol group (absolute risk reduction, 20%) and a drop-out rate of 10%. These event rates were estimated based on the wide range of recurrence rates reported in the literature.5,12,22,32,33

The primary analysis was performed using the intention-to-treat principle for all enrolled subjects who received any amount of study medication. Baseline characteristics of the subjects were summarized using descriptive statistics. For continuous variables, the median values (range) are reported. Contingency tables were generated for all categorical variables. If clinically important differences were observed in any of the baseline variables, an adjusted analysis of the primary outcome was made using these variables as covariates. The difference between the incidences of recurrent SVT in the 2 treatment arms of the study was tested using a χ² test. A Kaplan-Meier analysis was used to compare the time (days) from the initiation of medical therapy to the study end point. A log-rank test was used to test for differences. A Cox proportional hazards model was used to calculate the hazard ratio estimates. Drug safety was evaluated by determining the incidence of AEs and serious AEs in each treatment arm of the study. Contingency tables were generated to describe the types and frequency of AEs and serious AEs.

All statistical tests were 2-sided, and α was set at 0.05. Statistics were performed using SAS Statistical Software Version 9.1.3 (SAS Institute, Cary, NC).

**Results**

**Patient Population**

Patients were enrolled between December 1, 2006 and August 31, 2010. Nineteen centers completed the Institutional Review Board process with 14 centers enrolling patients. Screening information was available for 221 infants from 10 of the 19 centers. The most common reasons for exclusion were preexcitation and failure to obtain consent. All patients had normal function on echocardiography while in sinus rhythm. Patients with structural heart disease other than a patent foramen ovale or patent ductus arteriosus were excluded from the study, except for 2 patients who were provided with exemption waivers, both with small muscular ventricular septal defects. Eight patients were excluded by the local site investigator for coexisting illnesses, including meningitis (n=1), lung infection (n=4), extreme prematurity (<28 weeks) (n=2), and gastrointestinal disease (n=1). Even after study enrollment had been extended for 1 year beyond that anticipated, only 72 of the desired 220 subjects had been enrolled. Consequently, after independent, unblinded verification of the results determined that a much larger sample size than that originally estimated would be necessary to demonstrate the primary outcome if one existed, the study was closed to new enrollment, whereas follow-up continued for those already enrolled.

Of the 72 subjects enrolled and randomized, 33 were randomized to digoxin and 39 to propranolol (Figure 1). There were 47 males who received study medication compared with 24 females. One subject was withdrawn after being randomized to digoxin because of renal impairment; however, this patient did not receive any study medication, and his results were not included in any statistical analyses. Another 10 patients were withdrawn after randomization, leaving a cohort of 61 patients. Reasons for discontinuing the study after randomization are shown in Figure 1. No patients were found to be in heart failure at the time of enrollment.
Approximately 70% of patients received adenosine acutely; 7% received another antiarrhythmic medication before enrollment. One patient had atrioventricular nodal reentrant tachycardia, which was confirmed by an esophageal study. The remainder were presumed to have AVRT, although the mechanism of the reentrant SVT could not be determined in a minority of patients. The baseline characteristics for patients randomized to each treatment arm of the study are presented in Table 1.

**SVT Recurrence**

There was no difference in the incidence of SVT recurrence while on study medication (Table 2). Four patients randomized to digoxin and 7 patients randomized to propranolol met the primary study end point of recurrent SVT requiring medical therapy beyond 5 days of initiating therapy (12 versus 18%; \( P=0.53 \)). Another 10 patients had their first episode of recurrent SVT within 5 days of initiating therapy. Only 3 of these patients continued on study drug (2 on digoxin and 1 on propranolol), with none having any further episodes of SVT. When these patients are considered as part of our intention-to-treat analysis, 6 patients randomized to digoxin and 12 patients randomized to propranolol met a study end point of recurrent SVT within 5 days of initiating therapy.

**Table 1. Patient Demographics**

<table>
<thead>
<tr>
<th></th>
<th>Digoxin (n=32)*</th>
<th>Propranolol (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment, d</td>
<td>16.5 (0–67)</td>
<td>7 (0–126)</td>
</tr>
<tr>
<td>Weight at presentation, kg</td>
<td>3.7 (2.2–6.0)</td>
<td>3.7 (1.6–7.6)</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>23:9</td>
<td>24:15</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>25/32 (78%)</td>
<td>34/39 (87%)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>2/32 (6%)</td>
<td>2/39 (5%)</td>
</tr>
<tr>
<td>Black</td>
<td>3/32 (10%)</td>
<td>1/39 (3%)</td>
</tr>
<tr>
<td>Native American</td>
<td>2/32 (6%)</td>
<td>0/39 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>0/32 (0%)</td>
<td>2/39 (5%)</td>
</tr>
<tr>
<td>Presumed mechanism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVRT</td>
<td>25/32 (78%)</td>
<td>33/39 (84%)</td>
</tr>
<tr>
<td>AVNRT</td>
<td>0/32 (0%)</td>
<td>1/39 (3%)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>7/32 (22%)</td>
<td>5/39 (13%)</td>
</tr>
<tr>
<td>SVT rate, bpm</td>
<td>260 (219–305)</td>
<td>270 (230–320)</td>
</tr>
<tr>
<td>RP interval, ms</td>
<td>80 (30–120)</td>
<td>80 (50–140)</td>
</tr>
<tr>
<td>Fetal SVT</td>
<td>3/25 (12%)</td>
<td>6/32 (19%)</td>
</tr>
</tbody>
</table>

AVRT indicates atrioventricular reciprocating tachycardia; AVNRT, atrioventricular nodal reciprocating tachycardia; bpm, beats per minute; SVT, supraventricular tachycardia.

The median (range) or the number (percentage) is reported.

*The number of subjects reflects the exclusion of one patient from the intention-to-treat analysis who was randomized but never received study drug because of impaired kidney function.

**Table 2. Recurrent SVT**

<table>
<thead>
<tr>
<th></th>
<th>Digoxin (n=32)</th>
<th>Propranolol (n=39)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent SVT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5 d, discontinued study drug</td>
<td>2 (6)</td>
<td>5 (13)</td>
<td>0.14</td>
</tr>
<tr>
<td>On study drug &gt;5 d, requiring medical therapy</td>
<td>4 (12)</td>
<td>7 (18)</td>
<td>0.53</td>
</tr>
<tr>
<td>On study drug &gt;5 d, self-limited</td>
<td>5 (16)</td>
<td>1 (3)</td>
<td>0.02</td>
</tr>
<tr>
<td>SVT reported at 12 mo*</td>
<td>4 (13)</td>
<td>4 (10)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

SVT indicates supraventricular tachycardia.

The median (range) or the number (percentage) is reported.

*SVT reported at the 12-mo follow-up visit by patients who previously met a study end point.
recurrent SVT, requiring a change in or escalation of medical therapy (19 versus 31%; \( P=0.25 \)).

The 6-month event-free status was 79% for patients on digoxin and 67% for patients on propranolol (\( P=0.34 \)) (Figure 2). No first recurrence occurred after 110 days of treatment, and there were no first recurrences between 6 and 12 months of follow-up. For our study cohort, treatment with propranolol was associated with a hazard ratio of 1.60 (95% CI, 0.60–4.26; \( P=0.35 \)) compared with digoxin.

Forty-three (82%) patients completed 6 months of study medication, 21 of 27 (78%) on digoxin and 22 of 34 (65%) on propranolol. There were more self-limited episodes of SVT, which did not require medical intervention in the patients randomized to digoxin (5 versus 1). Even if these self-limited episodes were considered as recurrences, there would not have been a difference in the overall recurrence rate between the patient groups.

Enrollment occurred with the sentinel episode of SVT in 37 of 61 (61%) patients. In the remaining 24 infants, including 8 with fetal tachycardia, enrollment occurred with a subsequent episode. There was no difference in recurrent SVT between patients with or without >1 episode of SVT before enrollment, irrespective of the study medication (digoxin, \( P=0.64 \); propranolol, \( P=0.61 \), respectively). Before reaching a study end point, no patient received concomitant antiarrhythmic medications while on study medication.

12-Month Follow-Up
Fifty-one of 61 (84%) patients attended the 12-month follow-up visit. Eight patients continued to have SVT, 4 of 27 had been randomized to digoxin and 4 of 34 to propranolol. Six patients were on antiarrhythmic therapy (β-blockers \( n=3 \), flecainide \( n=1 \), sotalol and digoxin \( n=1 \), propranolol and flecainide \( n=1 \)). Two other patients had self-limited SVT and received no medical therapy. In addition, 2 patients continued to receive medical therapy despite no recent episodes of SVT, one being treated with propranolol and the other with propafenone. All 10 of these patients experienced their first documented recurrence of SVT before 6 months of age. No patient had a documented first recurrence of SVT in the 6- to 12-month follow-up period.

Safety End Points
There were no deaths reported in the study cohort. Four patients were unblinded because of SVT or, in 1 case, for noncardiac reasons. None of the unblinded patients stayed on study drug; however, 3 of 4 patients completed 12-month follow-up visits. There were 6 hospital admissions related to recurrent SVT. There were 7 serious AEs reported, none was related to an arrhythmia or the treatment thereof (Table 3). In 1 patient, the study medication (propranolol) was stopped for 1 week as a result of an intercurrent illness. There were numerous reports (>30 total) of AEs in both groups, the vast majority of which were intercurrent viral illnesses. None of the AEs was considered to be related to the study medication.

Discussion
This study represents the first randomized controlled trial of medical prophylaxis for SVT in a pediatric population. There

<table>
<thead>
<tr>
<th>Table 3. A List of SAEs That Were Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalocele repair</td>
</tr>
<tr>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>Hernia repair</td>
</tr>
<tr>
<td>RSV bronchiolitis</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Wheezing, coughing, vomiting</td>
</tr>
</tbody>
</table>

SAEs indicates serious adverse events; RSV, respiratory syncytial virus.
are 3 important findings of this study. First, we detected no differences in SVT recurrence between digoxin and propranolol, the 2 most common clinical choices for SVT prophylaxis in infants. This may be because no difference exists or it may be that the study was underpowered to detect the difference. The clinical course of our patient cohort calls into question the 2-fold difference in medication choice between electrophysiologists and nonelectrophysiology-trained pediatric cardiologists.

The choice of antiarrhythmic medication for prevention of recurrent SVT is based on personal preference and institutional practice as opposed to data from controlled clinical trials. Digoxin efficacy as an antiarrhythmic is controversial, ineffective in some studies but highly effective in others. One might speculate that electrophysiology-trained physicians are less likely to use digoxin based on experience and treatment failures; however, this is not borne out in the literature nor in our study. This study set out to determine whether there is an identifiable difference in medication efficacy to account for the apparent differences in practice, but certainly no large clinically important difference exists. This justifies continuation of the current practice in which digoxin or propranolol is an acceptable first-line agent for the prevention of further episodes of SVT in infants. This is an important finding of this study for physicians treating infants with SVT. It is important to note that the study’s findings can only be generalized to infants with SVT without preexcitation and a structurally normal heart, recognizing that preexcitation can be subtle or intermittent in infants.

Second, both therapies were associated with a high initial success rate and no recurrences after 4 months of therapy. Although it is possible that participation in a trial resulted in improved parental compliance with medication administration, the natural history of SVT in this patient group is likely more benign than previously viewed. Recurrences were uncommon in both treatment groups. This likely reflects several maturational factors. Premature atrial beats are frequently the initiating events for infant SVT and occur with some frequency in 15% to 25% of newborns but rarely between the neonatal period and age 5 to 15 years. The arrhythmia substrate in infants may resolve spontaneously in up to 40% of infants, resulting in a low risk of SVT recurrence in infants without Wolff-Parkinson-White syndrome. Despite persistence of the substrate, a significant proportion of infants will not have episodes of SVT, likely related to autonomic influences and maturational changes, although some will present beyond infancy.

In this study, all recurrences occurred in the first few weeks of life, and the majority of patients were arrhythmia-free at 4 months of age. This finding suggests that the duration of prophylactic medication may be shortened, although ongoing vigilance for recurrence is warranted and placebo-controlled data are needed to define the optimal time for medication withdrawal. The only natural history study of SVT was a retrospective report from 1963 in which 35% of 47 infants had a documented recurrence within 1 year, but only 7% had a recurrence between 1 year and a median follow-up of almost 4 years. There are several descriptive studies in the literature reporting recurrence rates over lengthy observation periods. However, these studies include older patients at presentation with mixed substrates (eg, Wolff-Parkinson-White syndrome, congenital heart disease). The higher mortality rate and different medication choices make applicability to a contemporary cohort of infants <4 months without structural heart disease limited. Without a natural history study of untreated infants, it is difficult to assess the true efficacy of any pharmacological therapy.

Third, despite having multiple sites actively recruiting subjects, the numbers needed to demonstrate the difference that may exist between these therapies are not easily attained. The study is limited in that a smaller number of infants were recruited than estimated to power the study (72 versus 220). Reassuringly, this study suggests that any difference found would have no clinical relevance. Because of the lower risk of SVT recurrence than expected, a larger number of patients may have uncovered a statistically significant difference; as many as 300 subjects per group would be necessary to detect a significant difference between these drugs. This issue is encountered frequently in pediatric cardiology trials.

Neither digoxin nor propranolol had been evaluated for pediatric use in a controlled trial, and therefore, this study was required to be conducted with an Investigational New Drug Application because neither drug is indicated by the Food and Drug Administration for SVT in pediatric patients.

Despite this, these medications are used over newer antiarrhythmic agents whose side effect profiles have been the subject of greater scrutiny, perhaps because of their relative newness. Liver and thyroid changes, growth-related issues, and proarrhythmia described with the use of these medications are uncommon but could be viewed as requiring greater vigilance with ECG monitoring and laboratory testing at initiation and throughout use. In our study, both digoxin and propranolol proved safe. Although AEs were common, as one would expect in this population, serious AEs were uncommon, resolved satisfactorily, and none was related to the study drug.

**Limitations**

Apart from the issues of recruitment, potential limitations of this study include the selected dosing for propranolol, as a higher dosage is sometimes used, and the lack of dose titration before the 2-month visit, both of which could potentially influence drug efficacy. However, because recurrences occurred early, the issue of dose titration is likely not a discriminating factor. The administration of digoxin using a 3 times a day schedule is not the standard administration schedule and may have influenced the outcome of the study. Nonetheless, we felt this administration schedule was needed to preserve blinding of the drug.

**Conclusions**

We present the first randomized, blinded clinical trial in infants with SVT. This study did not demonstrate a difference in the recurrence rate of SVT in infants treated with...
digoxin versus propranolol. A low SVT recurrence rate was seen in both groups. Currently, it is standard practice to use prophylactic medication for 6 to 12 months, but this duration of therapy may not be necessary. The need for a placebo trial in infant SVT is supported by this study. However, although this study did demonstrate the feasibility of such studies in a vulnerable pediatric population, issues of adequate enrollment continue to be paramount to pediatric cardiology trials.

Acknowledgments
We thank the members of the Pediatric and Congenital Electrophysiology Society for their interest and effort in supporting this study. We also thank the Data Safety Monitoring Board for their conscientious review of our study protocol, methodology and results, Maureen Brinkman for her expertise in study design, and the regulatory support of Health Canada and the Food and Drug Administration.

Sources of Funding
This study was supported by a Grant-in-Aid from the Heart and Stroke Foundation of British Columbia and Yukon (grant number G-06-SA-2572).

Disclosures
None.

References


CLINICAL PERSPECTIVE

The Study of Antiarrhythmic Medications in Infancy (SAMIS) trial compared digoxin with propranolol in infants <4 months of age presenting with supraventricular tachycardia (SVT) in the absence of congenital heart disease and preexcitation. SVT most commonly presents during infancy and is a problem encountered by pediatricians globally. There is clinical equipoise about which medications to initiate to prevent future recurrences and no prior controlled trials to guide clinicians. Like many trials in pediatric cardiology, enrollment affected the conclusions, and the study did not find statistically significant differences. However, there is not likely to be an important clinical difference between the 2 medications studied. Both medications were safe and well tolerated. The most important findings, however, were about the clinical course of the patients. Recurrences were uncommon in both groups: only 33% of patients on propranolol and 21% on digoxin experienced recurrent SVT during the study period. Although the current standard practice is to treat infants for at least 6 to 12 months after presentation, no patient experienced a first SVT recurrence beyond 4 months after enrollment, suggesting that the substrate resolves in a significant proportion of infants. The study was conceived to understand some of the dogma around the treatment choices made in infant SVT. The study has challenged the current tendency to avoid digoxin in infant SVT and the arbitrarily chosen duration of treatment. The study suggests that a placebo-controlled trial might be more informative but likely to be hampered by enrollment issues. Therefore, clinicians should consider shortening the duration of therapy in this population and should reassure families about short-term recurrences. We will need further studies to determine predictors of long-term recurrence.
The Study of Antiarrhythmic Medications in Infancy (SAMIS): A Multicenter, Randomized Controlled Trial Comparing the Efficacy and Safety of Digoxin Versus Propranolol for Prophylaxis of Supraventricular Tachycardia in Infants


*Circ Arrhythm Electrophysiol*. 2012;5:984-991; originally published online September 8, 2012; doi: 10.1161/CIRCEP.112.972620

*Circulation: Arrhythmia and Electrophysiology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2012 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circep.ahajournals.org/content/5/5/984

Data Supplement (unedited) at:

http://circep.ahajournals.org/content/suppl/2012/09/08/CIRCEP.112.972620.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Arrhythmia and Electrophysiology* 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: Arrhythmia and Electrophysiology* is online at:

http://circep.ahajournals.org/subscriptions/
SUPPLEMENTAL MATERIAL

Steering Committee: Shubhayan Sanatani, MD, Division of Pediatric Cardiology, British Columbia Children's Hospital and The Department of Pediatrics, University of British Columbia, Vancouver, BC; Karen A. Gibbs, RN, CCRP, The Heart Centre, British Columbia Children's Hospital; Karen Leung, BSc Phm, Pharmacy, British Columbia Children's Hospital, Vancouver, BC; Alison M. MacDonald, BSc Pharm, Pharmacy, British Columbia Children's Hospital, Vancouver, BC; Ruth A. Milner, PhD, Department of Pediatrics, The University of British Columbia and The Clinical Research Support Unit, The Child and Family Research Institute, Vancouver, BC; James E. Potts, PhD, Division of Cardiology, Department of Pediatrics, The University of British Columbia and British Columbia Children's Hospital, Vancouver, BC.

Data and Safety Monitoring Board: Robert M. Gow, MBBS (Chair), Division of Cardiology, Children's Hospital of Eastern Ontario and The Department of Pediatrics, University of Ottawa, Ottawa, ON; Rollin Brant, PhD, The Centre for Community Child Health Research, Child and Family Research Institute and The Department of Statistics, University of British Columbia, Vancouver, BC; Bruce Carleton, PhD, The Pharmaceutical Outcomes Programme, Child and Family Research Institute and Pharmaceutical Sciences, University of British Columbia, Vancouver, BC; Rebecca Sherlock, MD, Division of Neonatology, Children's and Women's Health Centre of British Columbia and The Department of Pediatrics, University of British Columbia, Vancouver, BC; Alfonso Solimano, MD, Division of Neonatology, Children's and Women's Health Centre of British Columbia and The Department of Pediatrics, University of British Columbia, Vancouver, BC.
Women's Health Centre of British Columbia and The Department of Pediatrics, University of British Columbia, Vancouver, BC.