Title: Determining the Natural and “Unnatural” History of Anomalous Aortic Origin of a Coronary Artery with Interarterial or Intraconal or Intramural course (AAOCA): Establishing a Multi-Institutional Registry

Protocol No: 4

Protocol Date: 22 Sep 2015

Study Principal Investigator (Coordinating Investigator)

Julie A. Brothers, MD
The Children’s Hospital of Philadelphia
Division of Cardiology, 8NW75
Philadelphia, PA, 19104
Phone 267-426-7517
Fax 215-590-4978
Email: brothersj@email.chop.edu

Coordinating Site

Congenital Heart Surgeons’ Society Data Center
The Hospital for Sick Children
555 University Avenue
Room 4433 Black Wing
Toronto, ON, M5G 1X8
Phone 1-866-477-2477
Fax 416-813-8776
Email: chss.dc@sickkids.ca
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of Contents</td>
<td>ii</td>
</tr>
<tr>
<td>Abbreviations and Definitions of Terms</td>
<td>iv</td>
</tr>
<tr>
<td>Abstract</td>
<td>v</td>
</tr>
<tr>
<td><strong>1 Background Information and Rationale</strong></td>
<td>1</td>
</tr>
<tr>
<td>1.1 Introduction</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Compliance Statement</td>
<td>1</td>
</tr>
<tr>
<td>1.3 Relevant Literature and Data</td>
<td>2</td>
</tr>
<tr>
<td><strong>2 Study Objectives</strong></td>
<td>2</td>
</tr>
<tr>
<td>2.1 Clinical Objectives</td>
<td>3</td>
</tr>
<tr>
<td>2.2 Quantitative Objectives</td>
<td>3</td>
</tr>
<tr>
<td><strong>3 Registry Design</strong></td>
<td>3</td>
</tr>
<tr>
<td>3.1 General Schema of Study Design</td>
<td>3</td>
</tr>
<tr>
<td>3.2 Study Duration, Enrollment and Number of Sites</td>
<td>4</td>
</tr>
<tr>
<td>3.2.1 Duration of Study for Subject</td>
<td>4</td>
</tr>
<tr>
<td>3.2.2 Total Number of Study Sites/Total Number of Subjects Projected</td>
<td>4</td>
</tr>
<tr>
<td>3.3 Study Population</td>
<td>4</td>
</tr>
<tr>
<td>3.3.1 Inclusion Criteria</td>
<td>4</td>
</tr>
<tr>
<td>3.3.2 Exclusion Criteria</td>
<td>4</td>
</tr>
<tr>
<td>3.3.3 Case ascertainment</td>
<td>4</td>
</tr>
<tr>
<td>3.3.4 Data sources (for existing records)</td>
<td>5</td>
</tr>
<tr>
<td>3.4 Bias and Blinding</td>
<td>5</td>
</tr>
<tr>
<td><strong>4 Study Procedures</strong></td>
<td>5</td>
</tr>
<tr>
<td>4.1 Subject Identification and Data Collection</td>
<td>5</td>
</tr>
<tr>
<td>4.2 Follow-up</td>
<td>6</td>
</tr>
<tr>
<td>4.3 Unscheduled Visits</td>
<td>7</td>
</tr>
<tr>
<td>4.4 Subject Completion/Withdrawal</td>
<td>7</td>
</tr>
<tr>
<td><strong>5 Study Endpoints and Evaluations</strong></td>
<td>7</td>
</tr>
<tr>
<td>5.1 Primary Endpoints</td>
<td>7</td>
</tr>
<tr>
<td>5.2 Secondary Endpoints</td>
<td>7</td>
</tr>
<tr>
<td><strong>6 Measurements and Evaluations</strong></td>
<td>8</td>
</tr>
<tr>
<td>6.1 Subject Identification and Data Collection</td>
<td>7</td>
</tr>
<tr>
<td>6.2 Efficacy Evaluations</td>
<td>8</td>
</tr>
<tr>
<td>6.3 Pharmacokinetic Evaluation</td>
<td>8</td>
</tr>
<tr>
<td>6.4 Safety Evaluation</td>
<td>8</td>
</tr>
<tr>
<td><strong>7 Statistical Considerations</strong></td>
<td>8</td>
</tr>
<tr>
<td>7.1 Primary and Secondary Endpoints</td>
<td>8</td>
</tr>
<tr>
<td>7.2 Statistical Methods</td>
<td>8</td>
</tr>
<tr>
<td>7.3 Sample Size and Power</td>
<td>9</td>
</tr>
<tr>
<td><strong>8 Safety Management</strong></td>
<td>9</td>
</tr>
<tr>
<td><strong>9 Study Administration</strong></td>
<td>9</td>
</tr>
<tr>
<td>9.1 Data Collection and Management</td>
<td>9</td>
</tr>
<tr>
<td>9.2 Confidentiality</td>
<td>10</td>
</tr>
<tr>
<td>Protocol</td>
<td>AAOCA Study</td>
</tr>
</tbody>
</table>
9.3 REGULATORY AND ETHICAL CONSIDERATIONS ................................................................. 10
  9.3.1 Data and Safety Monitoring Plan .................................................................................. 10
  9.3.2 Risk Assessment ........................................................................................................... 10
  9.3.3 Potential Benefits of Study Participation .................................................................... 11
  9.3.4 Risk-Benefit Assessment ............................................................................................. 11
9.4 RECRUITMENT STRATEGY (OR CASE ASCERTAINMENT) .................................................... 11
9.5 INFORMED CONSENT/ASSENT ......................................................................................... 11
  9.5.1 Waiver/Alteration of Consent ......................................................................................... 12
9.6 PAYMENT TO SUBJECTS/FAMILIES ................................................................................ 12

10 PUBLICATIONS ................................................................................................................ 12

11 REFERENCES ...................................................................................................................... 13
### ABBREVIATIONS AND DEFINITIONS OF TERMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAOCA</td>
<td>Anomalous aortic origin of a coronary artery with interarterial or intracoronary or intramural course</td>
</tr>
<tr>
<td>ALCA</td>
<td>Anomalous left coronary artery</td>
</tr>
<tr>
<td>ARCA</td>
<td>Anomalous right coronary artery</td>
</tr>
<tr>
<td>CHSS</td>
<td>Congenital Heart Surgeons’ Society</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>REB</td>
<td>Research Ethics Board</td>
</tr>
<tr>
<td>SCD</td>
<td>Sudden cardiac death</td>
</tr>
</tbody>
</table>
ABSTRACT

Context: Anomalous aortic origin of a coronary artery with interarterial or intraconal or intramural course (AAOCA) is a rare heart anomaly associated with a high risk of sudden death in children. There is debate among cardiologists and cardiac surgeons regarding how to treat a child with AAOCA, especially those who do not have symptoms.

Objectives: The purpose of the study is to determine the outcome of surgical intervention versus observation in children and young adults with AAOCA. To do this we will create a registry of AAOCA subjects that will enable us to develop a risk stratification model utilizing a large multi-institutional registry under the auspices of the Congenital Heart Surgeons’ Society (CHSS). We will then test the hypothesis that subsets of subjects with AAOCA can be identified in whom the risk of intervention is less than the risk of observation.

Study Design/Setting/Participants: This is a retrospective and prospective study. Subjects will be enrolled either when identified retrospectively from medical records or prospectively when diagnosed with AAOCA. Baseline demographics, diagnoses, and test results will be obtained through retrospective chart review. Follow-up health-related information will be obtained through the annual follow-up form and questionnaires and subsequent clinical and surgical cardiac-related reports/records. The project will be carried out at several participating CHSS member institutions, with the data stored securely and typically analyzed at the CHSS Data Center.

Study Measures: Data will be analyzed for different risk factors at diagnosis, different treatment strategies and the impact of both on subject outcome.
1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Anomalous aortic origin of a coronary artery with interarterial or intraconal or intramural course (AAOCA) is a rare congenital anomaly that consists of either the left main coronary arising from the right sinus of Valsalva (ALCA) or the right coronary arising from the left (ARCA). Both carry an increased risk of myocardial ischemia and sudden death in children and young adults, especially during or just after exercise.

The treatment and management of asymptomatic children is controversial because the true risk of sudden death is unknown. We are currently unable to risk-stratify which children are at increased risk from those who are not. While most physicians would agree that surgical intervention is indicated if a subject presents with signs or symptoms of myocardial ischemia, what remains unclear is the treatment of asymptomatic subjects, especially those with ARCA, which may carry a lower risk of sudden death. This dilemma is even greater in young (<30 years) subjects who have a higher risk of sudden death than those asymptomatic individuals identified in later adulthood.

Our lack of established evidence-based treatment and management guidelines is largely because this is a rare anomaly with inadequate subject numbers in any one institution to power studies aimed at assessing risk of myocardial ischemia and sudden death over the long-term. Because these lesions are associated with a risk of sudden death, the clinician faces pressure to “do something” although there are no evidence-based guidelines on which to base a therapeutic plan. The center of the critical knowledge gap is the lack of risk stratification data on which to balance the risk and preventive efficacy of intervention against the risk of observation.

The Congenital Heart Surgeons Society (CHSS) Data Center

The CHSS is a consortium of approximately 170 surgeons from approximately 70 university-based hospitals/institutions in the United States, Canada, and South America. They all share an interest in the management and outcomes of surgery for congenital heart lesions. The CHSS Data Center was established in 1985 and has several studies ongoing, with over 6,000 neonates, children and adults being followed. The CHSS Data Center extracts subject information and contacts parents/guardians and subjects for follow-up information on a regular basis. The analyses from these data have enabled pediatric cardiovascular surgeons and cardiologists to utilize the best treatment options for a variety of congenital heart defects. They have also allowed for better counseling of patients and their families regarding prognostic outcomes. The collaboration of these institutions has led to improved treatment and management strategies in this population. Further, the CHSS has published many studies in several peer-reviewed journals.

1.2 Compliance Statement

This study will be conducted in full compliance with each CHSS member institutions’ research policies and procedures and all applicable laws and regulations. Any episode of noncompliance will be documented.

The participating sites will perform the study in accordance with this protocol, will obtain consent (and authorization, as applicable) and assent (as appropriate), and will report unexpected problems in accordance with CHSS member institutions’ Institutional Review Board (IRB)/Research Ethics Board (REB) policies and procedures and applicable laws and regulations. Collection, recording, and
reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

1.3 Relevant Literature and Data

Anomalous aortic origin of a coronary artery with interarterial or intraconal or intramural course (AAOCA) is a rare congenital anomaly in which the left main coronary artery arises from the right sinus of Valsalva (ALCA) or the right arises from the left sinus (ARCA). Both ALCA and ARCA are associated with sudden cardiac death (SCD) but the former appears to carry a higher risk (1-9). This risk is greatest during or just after exercise, notably among young, otherwise healthy children and young adults (3,7-9). The true prevalence of AAOCA is unknown; however, studies have reported anywhere from 0.1-0.3% of subjects (10-14).

The clinical challenge for physicians is diagnosing AAOCA prior to SCD, because these individuals often are asymptomatic (10,15). When symptomatic, the most common cardiovascular presenting complaints are those that occur during or just after exertion, including: chest pain, dizziness, or syncope (3,16-18). The initial diagnosis is usually made by transthoracic echocardiography but confirmatory tests often include CT scan, cardiac magnetic resonance imaging, or cardiac catheterization with coronary angiography.

Once the diagnosis is made, treatment and management remains controversial, with some cardiologists recommending exercise restrictions and others advocating surgical repair (19). While most cardiologists and cardiac surgeons would agree that surgical intervention is indicated if a subject of any age with AAOCA presents with signs or symptoms of myocardial ischemia, what remains unclear is the treatment of asymptomatic subjects who are identified with this anomaly by chance. This dilemma is even greater in the young (< 30 years) subjects who have a higher risk of SCD than those asymptomatic individuals identified in later adulthood (1,9). There are certainly many subjects who remain asymptomatic, survive childhood, and are diagnosed in late adulthood when they undergo routine angiography to evaluate for coronary artery disease (13,14).

The critical knowledge gap is mainly due to the lack of risk stratification data on which to balance the risk and preventive efficacy of intervention against the risk of observation. This knowledge gap persists because the lesion is relatively uncommon and no single institution has the capability to accomplish the necessary steps to develop a risk stratification model because there are inadequate subject numbers in any one institution. This proposal will address the steps required to create a risk stratification model using the infrastructure of the CHSS to rapidly develop the only registry of children and young adults with AAOCA ever assembled and thereby accomplish our study objectives as outlined below.

2 STUDY OBJECTIVES

Our overall purpose is to develop and maintain an ongoing comprehensive multi-institutional registry comprised of clinical information about subjects who have been evaluated and/or followed at any of the participating CHSS institutions. The database will provide:

1) clinical data warehousing,
2) interfacing with data analysis for critical program review, and
3) future access to clinical data for investigational purposes (with IRB/REB approval).
2.1 Clinical Objectives

A. To determine the natural history of AAOCA through examination of a large multi-center registry.
   1. Relate the natural history of AAOCA to initial diagnostic and prospectively acquired diagnostic and anatomic data.

B. To determine the “unnatural” history of AAOCA (e.g., after surgical or catheter-based intervention) through examination of a large multi-center registry.
   1. Relate the “unnatural” history to anatomic risk factors and surgical/interventional techniques

C. To develop clinically applicable predictive models of these natural and “unnatural” histories

D. Obtain follow-up data to assess long-term clinical outcome over time

2.2 Quantitative Objectives

A. To obtain information on demographic data, diagnoses, and tests and procedures performed

B. To obtain trends in relative frequency of AAOCA

3 REGISTRY DESIGN

3.1 General Schema of Study Design

All subjects evaluated and/or followed at CHSS member institutions for AAOCA will qualify to be included in the database. The database will be ongoing. Deceased subjects followed by CHSS member institutions prior to their death will be included in the retrospective aspect of the database. Data collection will be ongoing for a patient’s lifetime to assess for long-term outcomes of AAOCA. We will establish the registry by initially retrospectively identifying subjects with AAOCA who have been cared for by physicians in the CHSS participating institutions.

We will simultaneously prospectively enroll newly identified subjects into the registry upon diagnosis from January 21, 2009 forward. Following receipt of informed consent (and authorization, as applicable), the study Patient Enrollment Form will be completed at each participating site for enrollment into the study. This form, the signed consent form (and authorization, as applicable) and information from existing data and records, diagnostic tests, and surgical and/or catheter interventions will be securely sent to the CHSS Data Center. The CHSS Data Center Registration Form will be completed and a Study Number will be assigned at the CHSS Data Center. The study data will be extracted from the information obtained and entered into the study database in a de-identified manner. Specially trained personnel from the CHSS Data Center will contact the subject or parent/guardian (as appropriate) once every year, to obtain information on the subject’s clinical progress. Subsequent clinical and surgical cardiac-related reports/records will be obtained as well.
3.2 Study Duration, Enrollment and Number of Sites

3.2.1 Duration of Study for Subject

Study duration will be for a patient’s lifetime from study initiation or subject enrollment and registration, or until the subject withdraws or is withdrawn or discontinued from the study.

3.2.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at potentially 65 investigative sites in the United States, 5 sites in Canada and 2 sites in South America.

It is expected that approximately 1,000 to 1,500 subjects will be enrolled in this study. Enrollment will be at a rate of approximately 75 patients per year.

3.3 Study Population

3.3.1 Inclusion Criteria

1) Diagnosis and/or management of AAOCA at a CHSS member institution from January 1, 1998 forward

2) Male or female age 0-30 years at time of diagnosis

3) If surgical repair:
   a) Performed from January 1, 1998 to study initiation (January 20, 2009) for retrospective subjects
   b) Performed from January 21, 2009 forward for prospectively identified subjects
   c) Completed operative note

4) Structurally normal heart or with small, hemodynamically insignificant lesion, including: patent ductus arteriosus, atrial septal defect, ventricular septal defect, mild pulmonic valvar stenosis, or bicuspid aortic valve without aortic stenosis.

5) Parental/guardian permission (informed consent, and authorization as applicable), subject consent, and authorization as applicable if ≥ 18 years of age and if appropriate, child assent for the observational/questionnaire portion of the study.

3.3.2 Exclusion Criteria

1) Anomalous coronary from the pulmonary artery, coronary artery atresia, or other coronary artery anomalies (e.g., coronary-cameral fistula, coronary aneurysms, myocardial bridging)

2) Hemodynamically significant structural heart disease, except as outlined above.

3.3.3 Case ascertainment

Potential retrospective subjects will be identified by a query of all subjects identified with AAOCA from January 1, 1998 until January 20, 2009 through each participating hospital’s cardiology and cardiothoracic surgery databases and medical records. Subjects will also be identified from surgeons or cardiologists caring for these subjects at the individual institutions and upon new diagnosis from January 21, 2009 forward at the member institutions. The Patient Enrollment Form
will be used by the participating sites to enroll new subjects once diagnosed. The CHSS Data Center Registration Form will be used to register new subjects at the CHSS Data Center.

### 3.3.4 Data sources (for existing records)

To identify all subjects with AAOCA who meet the criteria as detailed above, the contact person at each hospital (or their designee) will query their hospital’s cardiology and cardiothoracic surgery databases as described above from January 1, 1998 until January 20, 2009. Subjects will also be identified from surgeons or cardiologists caring for these subjects at the individual institutions and upon new diagnosis.

### 3.4 Bias and Blinding

To avoid an over-represented sample in those children who have moved and/or have been seen at multiple institutions (i.e., surgery at one place but followed clinically at another), when all the information is input at the CHSS Data Center, the extractor will note children with the same date of birth and diagnosis and ensure they are entered into the registry only once.

### 4 STUDY PROCEDURES

#### 4.1 Subject Identification and Data Collection

The first phase will be to retrospectively identify subjects with AAOCA who have been cared for by physicians in the CHSS participating institutions. We will collect baseline demographic, tests/evaluation, and perioperative data. We will compile these data into a single AAOCA registry. To identify all subjects with AAOCA who meet the criteria as detailed above, the contact person at each hospital (or their designee) will query their hospital’s cardiology and cardiothoracic surgery databases and medical records (e.g., catheterization, echocardiography, exercise laboratory, surgical, and autopsy) from January 1, 1998 until January 20, 2009. Subjects will also be identified from surgeons or cardiologists caring for these subjects at the individual institutions and upon new diagnosis from January 21, 2009 forward at the member institutions.

Once the subject population is identified, families and/or patients will be contacted by phone by the Principal Investigator (PI) or the study coordinator at each participating institution. A verbal consent and authorization for telephone questionnaire and chart review will be obtained during this telephone contact. It is during this telephone conversation that permission will be asked to mail a written consent (and authorization, as applicable) to allow data to be sent to the CHSS Data Center for post-enrollment registration in the registry. For those subjects who are identified prospectively after the study has begun, written consent (and authorization, as applicable) will be obtained at the time of the cardiology or cardiac surgery related clinic visit at the individual CHSS member institutions. Once the subjects or parents/guardians, as applicable, have sent back the written informed consent (and authorization, as applicable) to participate in CHSS data registry, then the CHSS Data Center can proceed with ongoing annual follow-up and medical record data can be securely sent to the CHSS Data Center.

Waiver/alteration of consent and authorization for retrospective chart review will be maintained for decedents and subjects who cannot be located. These subjects will be completely de-identified in the database with their personal details like names, contact details and date of birth removed. They will be given a study number. Their data will be stored with the study number and not with any personal identifiers. These patients will not be followed up by the CHSS Data Center and they/their family members will not be contacted to obtain research information. Their data
will be included in the statistical analysis and no personally identifiable information will be published by the CHSS Data Center.

After consent (and authorization, as applicable) is obtained, each subject’s record will be retrospectively reviewed for baseline (i.e., at time of diagnosis and/or initial evaluation by the participating institution) and surgical (if applicable) data. This information will be collected and securely sent to the CHSS Data Center that is located at The Hospital for Sick Children in Toronto, Ontario, Canada. Appropriate patient identity protection safeguards will be observed by the CHSS member institutions as well as the CHSS Data Center while transmitting the patient information (e.g., patient care charts or CD or Echo tapes). Only de-identified data will be given to the investigators for future analysis. Data will be abstracted from these confidential medical records submitted to the Data Center. For those subjects identified after study initiation (i.e., on or after January 21, 2009), compact discs of any echocardiograms, MRIs, CT scans, and cardiac catheterizations will also be sent, when possible, to the CHSS Data Center.

Trained dedicated personnel at the CHSS Data Center will perform all data extraction and entry into a secure computerized database. Records will be kept in a locked, secure location with restricted access. Each study participant will be assigned a corresponding study number that is used for all further analysis, and specific variables will be entered into a secure, password protected computer at the Data Center. These data files will be restricted to the study investigators and the Data Center staff. Each member institution utilizes a Data Transfer Agreement with the CHSS Data Center to maintain the highest level of confidentiality for all participants.

4.2 Follow-Up

Upon consent (and authorization, as applicable) at the submitting institution and registration at the CHSS Data Center, Data Center staff will contact the subject or the parent/guardian of the subject (as applicable) to welcome them into the study and remind them of the annual contacts throughout their study participation. Similarly, when the subject is eligible to and provides consent (and authorization, as applicable) to participate in the study him/herself, and the CHSS Data Center is provided with this information, the CHSS Data Center staff will contact the subject to welcome him/her into the study (study continuation) and remind him/her of the annual contacts throughout his/her study participation.

This second phase will be a unique opportunity to obtain follow-up data on subjects from multiple institutions. This phase is very important in understanding the progression of the patients being treated with different approaches. This is an essential component of establishing the cohort and is unique to this type of Observational study. Using this cohort of surviving subjects, we will utilize a Follow-up Form and Questionnaires to collect information on the health status and quality of life of the subject. The CHSS Data Center non-standardized questionnaires and the PedsQL™ standardized questionnaires (20-27) cover several aspects of quality of life issues for patients, such as health status, activity level, and medical care. Demographics/contact information and medical/surgical updates are collected on the CHSS Data Center Follow-up Form. At yearly intervals, specially trained personnel from the CHSS Data Center will contact the subject or the parent/guardian of the subject, as appropriate (e.g., by telephone, mail, fax or electronically, as appropriate) for completion of the annual cross-sectional follow-up and questionnaires. If subjects or parents/guardians (as applicable) cannot be contacted after 3 attempts (without any communication back in any given year), then the subject may be considered “lost to follow-up.”
Throughout the course of the study the subject’s clinical and surgical cardiac-related reports will be obtained as well. Typically this information will be sent to the Data Center from the participating sites. In cases where the subject is followed at a non-CHSS institution or a non-participating CHSS institution, with the permission of the subject (parents/guardians, as applicable), the CHSS Data Center may send the subject (parents/guardians, as applicable) a Consent for Release of Medical Information form, which the subject (parents/guardians, as applicable) can then sign and take to their health care provider requesting that the specified information be released to the CHSS Data Center. Alternatively, the subject (parents/guardians, as applicable) may themselves request through the institution that holds the information, that the information be forwarded to the CHSS Data Center.

4.3 Unscheduled Visits

N/A

4.4 Subject Completion/Withdrawal

Subjects may withdraw (or be withdrawn by their parents/guardians, as applicable) from the study at any time without prejudice to their care. Subjects may also be discontinued from the study at the discretion of the Principal Investigator at the participating CHSS institution if there is an inability to re-contact the subject/subject’s parents/guardians and verify outcome, in which case the subject would be considered as “lost to follow-up.” The Investigator may also withdraw subjects to protect the subject for reasons of safety or for administrative reasons. If a subject withdraws or is withdrawn or discontinued from the study at any stage, no further information about him/her will be collected for use in the analysis. However information already collected will continue to be used as needed to maintain the integrity of the research.

5 STUDY ENDPOINTS AND EVALUATIONS

5.1 Primary Endpoints

After we have collected the data for our registry, we will utilize statistical analyses to ascertain the following. Our primary study endpoints will be: signs of myocardial ischemia, subject symptoms of myocardial ischemia, or sudden death between date of surgical repair or diagnosis (if observation alone) and any time in the follow-up period.

5.2 Secondary Endpoints

Secondary endpoints will include the following:

a. The relationship between anatomic risk factors and surgical/interventional techniques to evidence of myocardial ischemia or sudden death after surgery.

b. The relationship between initial and follow-up diagnostic tests and anatomic data to evidence of myocardial ischemia or sudden death in the follow-up period since diagnosis.


6 MEASUREMENTS AND EVALUATIONS

6.1 Subject Identification and Data Collection

Data collection will include the following areas of interest: subject and parent name; date of birth; medical record number; home address; telephone numbers; referring physician information; alternative contacts and contact information; hospital where records obtained; date of first visit; diagnosis; gender, ethnicity and race; echocardiographic data, electrocardiogram data, cardiac catheterization data; CT scan and MRI data; holter monitor results; exercise test results; nuclear medicine results; medications; hospitalizations for surgery, including date of admission and discharge, date of surgery, height and weight at surgery, surgical procedure, and complications, if applicable. The annual Follow-up Form and Questionnaires will collect data regarding health status, quality of life, frequency of cardiology visits, medications, activity restrictions, exercise-related symptoms, and procedures since initial diagnosis/last follow-up.

6.2 Efficacy Evaluations

N/A

6.3 Pharmacokinetic Evaluation (only if applicable)

N/A

6.4 Safety Evaluation

There are no safety evaluations except to ensure subject confidentiality.

7 STATISTICAL CONSIDERATIONS

7.1 Primary and Secondary Endpoints

1. Our main objective is to establish a registry of AAOCA subjects. In so doing, we then aim to clarify the natural and unnatural history of AAOCA that will allow us to develop clinically predictive models to identify subsets of subjects in whom intervention is warranted. To do this, we will assess the following endpoints: signs of myocardial ischemia, subject symptoms of myocardial ischemia, or sudden death between date of surgical repair/intervention (if applicable) and any time in the follow-up period.

2. Secondary endpoints will include the following:
   a. The relationship between anatomic risk factors and surgical/interventional techniques to evidence of myocardial ischemia or sudden death after surgery.
   b. The relationship between initial and follow-up diagnostic tests and anatomic data to evidence of myocardial ischemia or sudden death in the follow-up period since diagnosis.

7.2 Statistical Methods

Descriptive statistics will be calculated, including means, standard deviations, 95% confidence intervals, medians, and minimum and maximum values for all continuous variables. Frequency
counts and percentages will be used for categorical variables. Different modes of presentation will
be described and chi-square tests used to compare symptoms with diagnosis and coronary
anatomy. Different evaluation and treatment strategies of the various institutions will be
described. Chi-square tests will be performed to determine whether differences exist between
different surgical options and post-operative morbidity and mortality, including signs/symptoms of
myocardial ischemia. Similarly, chi-square tests will be performed to determine whether
differences exist between different non-surgical treatment options (observation, exercise
restriction, beta-blockade) and morbidity and mortality, including signs/symptoms of myocardial
ischemia since date of diagnosis. A multivariate analysis of parametric models will be established
using demographic, institutional, anatomical, and surgical factors (when appropriate) and their
association with outcome (death, re-operation, exercise restriction, cardiac medication, no
limitations). These models will be used to assess different combinations of risk factors and
determine the extent of the risk factors to help predict whether certain subject or management
characteristics predict outcome. In addition, it is anticipated that this will be the first time that the
statistical methodology of Competing Risks Analysis will be applied to this subject population.

7.3 Sample Size and Power

As this is a study of a rare disease with an unknown number of subjects, our sample size will be
estimated based on numbers of known children with this at several hospitals. We estimate the
sample size to be in the range of 1,000 to 1,500 evaluable children and young adults.

For the power calculation, we will use a comparison of two proportions using a two sided test, with
an alpha of 0.05, and a power of 0.80.

We will define the reference population as those that did not have an intervention and had a
sudden cardiac death rate of 30%. Utilizing a clinically significant difference of 20%, we would need
93 subjects in each group (i.e., those that had an intervention and those that did not).

8 SAFETY MANAGEMENT

This is an observational study and does not include any drug administration, special imaging needs
or surgical intervention for research purposes. It is a minimal risk study. The only intervention will
be the annual follow-up form and questionnaires. The only risk is release of personal health
information (PHI) and loss of confidentiality. Every effort will be made to keep PHI from
unauthorized disclosure. Any breach will be reported.

9 STUDY ADMINISTRATION

9.1 Data Collection and Management

1. Privacy. Upon enrollment by the participating institutions, each subject is assigned a
unique screening number, and the Patient Enrollment Form is completed. Upon
registration at the Data Center, each subject is assigned a unique study number that is used
for all data entry and analysis purposes, and the CHSS Data Center Registration Form is
completed. After applicable written informed consent (and authorization, as applicable) is
obtained, each subject’s medical record will be reviewed for baseline and surgical (if
applicable) data. This information, including demographic information, will be collected,
and along with the consent form/assent form (and authorization, as applicable) and
completed Patient Enrollment Form will be securely transferred to the Data Center. Likewise, when the subject provides assent, and when the subject is eligible to and provides consent (and authorization, as applicable) to participate in the study him/herself the signed forms (as applicable) and any updates in contact information will be securely transferred to the Data Center as well. Similarly, subsequent follow up information and questionnaires will be securely transferred to and obtained by the Data Center. Trained dedicated personnel at the Data Center will perform all data extraction and entry of specific variables, in a de-identified manner, into a secure, password protected computerized database housed at the Data Center. A master list (key) will be kept separate from the study data. Only appointed personnel at the Data Center will be able to connect the individual subject to the data. Each CHSS member institution associated with this study will have IRB/REB approval for this study from their IRB/REB, and will utilize a Data Transfer Agreement with the CHSS Data Center to maintain the highest level of confidentiality for all study participants. The Data Center will be responsible for maintaining a log of IRB/REB approvals and checking to ensure that participating sites are not submitting records or data without the appropriate IRB/REB approval documentation on file.

2. Security. Appropriate patient identity protection safeguards will be observed by the participating CHSS member institutions, as well as the CHSS Data Center, for the transmission of the patient information (e.g., baseline and follow-up patient care charts or compact discs (CDs) or echo tapes). Secure file transfer or secure courier service will be used as appropriate. The Follow-up Form and Questionnaires will be securely provided to the subjects or parents/guardians (as applicable), and returned to the Data Center by the subjects (or parents/guardians), in a secure manner acceptable to the subjects (parents/guardians, as applicable) (e.g., mail, fax, electronically). The master list (key) and the study data will all be securely stored (using a double lock system) at the CHSS Data Center, and kept separate from each other. Likewise, the patient information sent to the Data Center, including CDs of echocardiograms, magnetic resonance images (MRIs), CT scans and cardiac catheterizations, will be securely stored separately at the Data Center. The CDs will be sent to the CHSS Data Center securely with the subject name on the outside; once at the CHSS Data Center, the name will be removed and the study number will replace the name. When possible, the scans will only contain de-identified data prior to being sent to the CHSS Data Center. However, it may not always be possible to remove identifiers from the scans. If this is the case, all attempts at keeping the subject information confidential will be made as described above.

3. De-identification. Each study participant is assigned a unique study number at the CHSS Data Center that is used for all analysis purposes. All data analysis, review, and published results will be performed in a de-identified manner.

9.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with applicable institutional policies, laws and regulations. The investigator and site personnel and the coordinating site will use the study data and records only for these study purposes. Safeguards are described under Data Collection and Management. The information collected as part of this study will be securely retained for 7 years after all study publications are completed and then it will be securely destroyed according to the applicable institutional policy effective at that time.
9.3 Regulatory and Ethical Considerations

9.3.1 Data and Safety Monitoring Plan
The study investigators will be responsible for safety monitoring. This is an observational study which involves only data collection from the hospital/institutional sources (e.g. operative notes, echocardiogram, cardiac catheterization, electrocardiogram etc.) as well as from the annual follow-up form and questionnaires sent to the subjects or parents/guardians. The study does not dictate any specific surgical treatment or medications. All the procedures performed on the patients are standard of care and the study does not involve any additional hospital visits for the subjects or parents/guardians. There is minimal safety risk with this study, mainly from the potential breach of privacy and loss of confidentiality. The investigators and site personnel and the CHSS Data Center personnel will ensure that confidential information, including PHI/identifying personal information, will be secured as described above and will not be revealed to unauthorized parties.

9.3.2 Risk Assessment
The main risk in this study is the potential breach of privacy and loss of confidentiality. There is a minimal risk of likelihood of harm. All reasonable safeguards to secure the confidentiality of information will be taken by the investigators and their research personnel and the CHSS Data Center personnel. Safeguards are described under Data Collection and Management. We believe this study overall is minimal risk.

9.3.3 Potential Benefits of Study Participation
Information collected may contribute to the care of children in the future who have the same heart condition as those that participate in this study. The information may also improve the future management of study participants. There may be no direct benefit to the subject from participation in this study.

9.3.4 Risk-Benefit Assessment
The study as a whole represents minimal risk to the subjects. The potential benefit of identifying children who may be at increased risk of ischemia and sudden death outweighs the risk of participation.

9.4 Recruitment Strategy (or Case Ascertainment)
Subjects will be identified through retrospective review of each participating hospital’s cardiology and cardiothoracic surgery databases (e.g., catheterization, echocardiography, exercise laboratory, surgical, and autopsy) and medical records from January 1, 1998 until present. Subjects will also be identified from surgeons or cardiologists caring for these subjects at the individual institutions.

9.5 Informed Consent/Assent
The phone questionnaire and chart review will be subject to verbal consent obtained by the PI or study coordinator at the individual CHSS member institutions upon initiating a telephone conversation with the parents/guardians or adult subjects. If a subject declines participation in the study, information from his/her chart will not be used in the study. Once verbal consent is obtained, a written informed consent form (and authorization, as applicable) will be mailed to the parent(s) or legal guardian of any minor child or to subjects ≥ 18 years of age. Informed assent will also be obtained from the minor child prior to participation, as appropriate. For those subjects who
are identified after the study has begun (i.e., prospective subjects), applicable written consent/assent (and authorization, as applicable) will be obtained at the time of their routine clinic visit at the CHSS member institution. As part of the study, written consent will include a combined or separate authorization (as appropriate) to have the subject’s medical information securely sent to the CHSS Data Center for data abstraction and entry into the registry. Site investigators and personnel will not allow information from the subjects’ charts to be sent to the CHSS Data Center unless applicable written consent and such authorization have been obtained. Once the parent/guardian or subject (as appropriate) has provided applicable written informed consent (and authorization (as applicable), the data can be securely sent to the CHSS Data Center. Waiver/alteration of consent and authorization (as applicable) for retrospective chart review will be maintained for decedents and subjects who cannot be located. The site PI’s phone number will be on the consent form, and the Coordinating PI’s phone number may be included as well. The subject or parent/guardian, as applicable, will keep a copy of the signed and dated consent form/assent form (and authorization, as applicable) and the original will be maintained in the subject’s confidential study records at the respective participating center. The CHSS Data Center will not register any living patient until a copy of the signed consent form and authorization (as applicable) is received.

For those subjects who turn 18 during the study, verbal consent will be obtained on or by the next follow-up contact where the subject will answer the questions (using the Adult Follow-up Form and Questionnaires) instead of the parent/guardian.

9.5.1 Waiver/Alteration of Consent

Inclusion in the study is requested for deceased patients and patients who are lost to follow up/cannot be located (who meet study eligibility criteria), and will be conducted in compliance with all applicable laws and regulations, including approval for waiver/alteration of the consent process (as applicable). Families of these patients will not be contacted for research purposes. Only the information already in the medical record will be used and only aggregated data will be reported in publications, precluding families from identifying themselves in any publication. When a participating CHSS institution sends information on a deceased patient or a patient lost to follow up, the CHSS Data Center will follow the same procedures to include them in the study that are used for those enrolled while living patient participants.

9.6 Payment to Subjects/Families

There will be no monetary payment for participation in this study.

10 PUBLICATIONS

We anticipate the results of this study will be presented at national meetings and/or published in academic journals. We will not disclose subject PHI or identifying personal information in any presentation or publication about the study.
REFERENCES


