Ischemic Stroke in Children and Young Adults With Congenital Heart Disease

Zacharias Mandalenakis, MD, PhD; Annika Rosengren, MD, PhD; Georgios Lappas, MSc; Peter Eriksson, MD, PhD; Per-Olof Hansson, MD, PhD; Mikael Dellborg, MD, PhD

Background—Patients with congenital heart disease (CHD) may be at increased risk of ischemic stroke due to residual shunts, arrhythmias, and other cardiovascular abnormalities. We studied the relative risk and potential factors for developing ischemic stroke in children and young adults with CHD in Sweden.

Methods and Results—All patients in the Swedish Patient Register with a diagnosis of CHD, born between 1970 and 1993, were identified and compared with 10 controls for each patient, matched for age, sex, and county and randomly selected from the general population. Follow-up data through 2011 were collected for both groups. Of 25,985 children and young adults with CHD (51.5% male, 48.5% female), 140 (0.5%) developed ischemic stroke. The hazard ratio for CHD patients developing ischemic stroke was 10.8 (95% CI, 8.5–13.6) versus controls. All major Marelli groups had significantly increased risk, but because of small CHD-group sizes, only atrial septal defect/patent foramen ovale, double-inlet ventricle, and aortic coarctation displayed significantly increased risk. In multivariate analysis of CHD patients, congestive heart failure carried the highest risk for developing ischemic stroke (hazard ratio 6.9 [95% CI, 4.7–10.3]), followed by hypertension and atrial fibrillation, which were also significantly associated with increased risk of ischemic stroke.

Conclusions—The risk of developing ischemic stroke was almost 11 times higher in young patients with CHD than in the general population, although absolute risk is low. Cardiovascular comorbidities were strongly associated with the development of ischemic stroke in young CHD patients. (J Am Heart Assoc. 2016;5:e003071 doi: 10.1161/JAHA.115.003071)

Key Words: epidemiology • heart defects, congenital • registry • stroke

Stroke is a leading cause of death and a major cause of adult disability in developed countries. Ischemic stroke has been shown to be relatively uncommon in children and young adults compared with older adults. However, recent studies have shown that the incidence of stroke has decreased among the elderly but increased in the young population. Traditional risk factors for ischemic stroke, such as hypertension, diabetes mellitus, and atrial fibrillation, are usually absent in children and young adults.

Congenital heart disease (CHD) is present in about 1% of live births and is the most common congenital malformation. CHD is a major risk factor for ischemic stroke and stroke recurrence in children. Patients with CHD represent about 20% of all strokes among children, and cardiac surgery in children with CHD has been shown to be associated with increased stroke risk. Previous studies have identified a strong association between cyanotic CHD and cerebral lesions, whereas a later report has failed to demonstrate any correlation. These conflicting results may be the result of more frequent surgical repair, less use of potentially harmful treatments such as phlebotomy, or use of better thromboprophylaxis.

Interestingly, a recent study showed a relatively low incidence of stroke in adults with CHD, but the risk was still estimated to be 10 to 100 times greater in CHD patients than in a healthy general population. Furthermore, a case–control study from Taiwan showed a 2.2 times increased risk of developing stroke in adults with 5 of the most common types of CHD compared to controls.

Given the increasing number of patients with CHD who are now reaching adulthood, a large number of patients will now live with their condition for a long period. Thus, even a small
relative increase in risk of stroke may, if present for a long
time, result in significant total lifetime risk. Furthermore, CHD
patients represent a conglomerate of patients with very mild
residual abnormalities, moderate but well-corrected disease,
and patients with residual shunts or complex morphology.
Each of these groups will be limited in number, highlighting
the need for very large studies to identify risks that may be
severely underestimated in a smaller study over a limited
period of time.

Sweden (current population 9.7 million) has an inpatient
register with almost complete coverage of thoracic proce-
dures since 1970. The primary objective of the present study
was to investigate the absolute and relative risks of ischemic
stroke in children and young adults with CHD in Sweden. We
also investigated possible risk factors and comorbidities
associated with the development of ischemic stroke in young
CHD patients.

Methods
Study Population
Residents in Sweden have a unique national 10-digit
registration number that includes their sex and date of birth.
Since 1987 it has been mandatory for all hospital physicians
to deliver data to the Swedish National Inpatient register. The
6 Swedish cardiothoracic surgery clinics have registered all
procedures and hospitalizations since 1970, and data from
the Hospital Outpatient register from 2000 are available. In
addition, all deaths have been reported to the national register
of Cause-Specific Deaths since 1961. All diagnoses are coded
according to the International Classification of Disease (ICD)
8th, 9th, and 10th editions. Swedish versions of the ICD were
used, and diagnoses in the present study that were originally
coded using ICD-8 were re-coded to ICD-9 to reflect the 1987
revision.

We identified 26,976 patients born between January 1970
and December 1993 who had a diagnosis of CHD at any time
during this period registered in the National Hospital Inpatient
register, Outpatient Register, or the National Cause-of-Death
register. Follow-up and comorbidity data through December
2011 were collected for all patients. Patients were included in
the study at the date of their first registration with a diagnosis
of CHD and were followed until a first diagnosis of ischemic stroke,
until death, or until the end of the study, December 31, 2011.

For each CHD patient, 10 control individuals without a
diagnosis of CHD or previous ischemic stroke were selected
from the Total Population Register in Sweden, matched by age
(calendar year of diagnosis), sex, and county. However, for 14
CHD patients only 9 controls could be matched.

Atrial shunts such as atrial septal defect (ASD) and patent
foramen ovale (PFO) have the same ICD diagnosis code;
however, PFO is commonly diagnosed at the time of ischemic
stroke during adulthood.\textsuperscript{18,19} To avoid overestimation
of ischemic stroke in this group of patients, where a PFO might
have gone undiagnosed if a stroke had not occurred, we
excluded all patients who were diagnosed with ASD and PFO
(n=554) after the age of 18 years as well as their matched
controls. Patients diagnosed with ischemic stroke before or
on the same day as the first registration with a CHD diagnosis
(n=118) and patients who died the same day they were
registered with CHD (n=319) as well as their controls were
also excluded from the present study. Controls with prior
ischemic stroke were also excluded (n=75).

To characterize our CHD cohort further, we used the
hierarchic CHD categorization recently published by Marelli
et al, which has been widely accepted.\textsuperscript{20} Educational
levels of the patients and controls were extracted from the Longitudinal Integration Database for Health Insurance and Labor Market Studies.\textsuperscript{21,22} Education
was classified as low (compulsory only), medium, or high
(university level or similar).

Definitions
CHD was defined as any patient with at least one outpatient
visit, or a hospital discharge, or a death certificate with any
ICD code, as shown in Table 1. Ischemic stroke was defined
as codes 434 or 436 (ICD-8 and ICD-9), or I63 or I64 (ICD-10).
Atrial fibrillation was defined as codes 427.92 (ICD-8), 427D
(ICD-9), or I48 (ICD-10). Hypertension was defined as codes
401-405 (ICD-8 and ICD-9) or I10-I15 (ICD-10). Congestive
heart failure was defined as codes 427.00 (ICD-8) or 428
(ICD-9) or I50 (ICD-10). Diabetes mellitus was defined as
codes 250 (ICD-8 and ICD-9) or E10-14 (ICD-10). Operations on
the cardiovascular system were classified as codes 30–32
(Classification of Operations, Swedish 6th version), or F codes
(Classification of Surgical Procedures version 1.9). The
perioperative period was defined as the interval between
the date of operation or intervention and 3 months later.

Ethics
All national registration numbers were removed and replaced
with a code in the final data set by the National Board of Health
and Welfare in Sweden. Accordingly, informed consent for this
investigation could not be provided and was therefore waived.
The study complied with the Declaration of Helsinki and was
approved by the Gothenburg Regional Research Ethics Board.

Statistics
We used SAS\textsuperscript{\textregistered} software, Version 9.4 (SAS Institute, Inc,
Cary, NC) and R software, Version 3.1 (R Foundation for
Statistical Computing, Vienna, Austria) to perform all statistical analyses. Hazard ratios (HRs) and 95% CIs estimated from the fitted regression models are presented. Only 2-sided $P$-values were used. A $P$ value $<$0.05 was considered statistically significant.

Table 1. International Classification of Disease (ICD) Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD 8</th>
<th>ICD 9*</th>
<th>ICD 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common arterial trunk</td>
<td>745.0</td>
<td>745A</td>
<td>Q20.0</td>
</tr>
<tr>
<td>Transposition of great vessels</td>
<td>745.1</td>
<td>745B</td>
<td>Q20.3</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>745.2</td>
<td>745C</td>
<td>Q21.3</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>745.4</td>
<td>745E</td>
<td>Q21.0</td>
</tr>
<tr>
<td>Atrial septal defect or patent foramen ovale</td>
<td>745.5</td>
<td>745F</td>
<td>Q21.1</td>
</tr>
<tr>
<td>Congenital tricuspid stenosis or atresia</td>
<td>746.1</td>
<td>746B</td>
<td>Q22.4</td>
</tr>
<tr>
<td>Ebstein’s anomaly</td>
<td>746.2</td>
<td>746C</td>
<td>Q22.5</td>
</tr>
<tr>
<td>Congenital stenosis of aortic valve</td>
<td>746.3</td>
<td>746D</td>
<td>Q23.0</td>
</tr>
<tr>
<td>Congenital insufficiency of aortic valve</td>
<td>746.4</td>
<td>746E</td>
<td>Q23.1</td>
</tr>
<tr>
<td>Congenital mitral stenosis</td>
<td>746.5</td>
<td>746F</td>
<td>Q23.2</td>
</tr>
<tr>
<td>Congenital mitral insufficiency</td>
<td>746.6</td>
<td>746G</td>
<td>Q23.3</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>746.7</td>
<td>746H</td>
<td>Q23.4</td>
</tr>
<tr>
<td>Congenital subaortic stenosis</td>
<td>746.81</td>
<td>746W</td>
<td>Q24.4</td>
</tr>
<tr>
<td>Cor triatriatum</td>
<td>746.82</td>
<td>746W</td>
<td>Q24.2</td>
</tr>
<tr>
<td>Infundibular pulmonic stenosis</td>
<td>746.83</td>
<td>746W</td>
<td>Q24.3</td>
</tr>
<tr>
<td>Congenital coronary vessel anomalies</td>
<td>746.85</td>
<td>746W</td>
<td>Q24.5</td>
</tr>
<tr>
<td>Congenital heart block</td>
<td>746.86</td>
<td>746W</td>
<td>Q24.6</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>747.1</td>
<td>747B</td>
<td>Q25.1</td>
</tr>
<tr>
<td>Interruption of aortic arch (atresia or stenosis of aorta)</td>
<td>747.11</td>
<td>747B</td>
<td>Q25.2, Q25.3</td>
</tr>
<tr>
<td>Other unspecified congenital malformations of aorta</td>
<td>747.2</td>
<td>747C</td>
<td>Q25.4, Q25.8, Q25.9</td>
</tr>
<tr>
<td>Congenital malformations of pulmonary artery</td>
<td>747.3</td>
<td>747D</td>
<td>Q25.5 to Q25.7</td>
</tr>
<tr>
<td>Congenital malformations of great veins</td>
<td>747.4</td>
<td>747E</td>
<td>Q26</td>
</tr>
<tr>
<td>Cor bilocular</td>
<td>745.7</td>
<td>745H</td>
<td>Q20.8</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>745.11</td>
<td>745B</td>
<td>Q20.1</td>
</tr>
<tr>
<td>Double outlet left ventricle</td>
<td>745.19</td>
<td>745B</td>
<td>Q20.2</td>
</tr>
<tr>
<td>Double inlet ventricle</td>
<td>745.3</td>
<td>745D</td>
<td>Q20.4</td>
</tr>
<tr>
<td>Discordant atrioventricular connection</td>
<td>745.12</td>
<td>745B</td>
<td>Q20.5</td>
</tr>
<tr>
<td>Isomerism of atrial appendages</td>
<td>745.8</td>
<td>745W</td>
<td>Q20.6</td>
</tr>
</tbody>
</table>

*Swedish version of ICD 9.
To estimate the HR of experiencing ischemic stroke during follow-up in patients versus matched controls, we used a stratified version of Cox regression. The proportional hazard assumption was checked through the inspection of Schoenfeld residuals. The strata in the analyses were defined by age, sex, and the year of diagnosis. These criteria were also used to match 10 random controls from the population with each patient. The time scale in our analyses was age of the first registration with a CHD diagnosis, and the time zero was not the same for all participants; as such, it was left truncated—not all patients start their follow-up at birth—a fact we corrected for in our models. Cox regression was also used when estimating HRs for factors such as sex, educational level, and comorbidities with ischemic stroke as an end point. The incidence rates of ischemic stroke were estimated as the count of the first case of ischemic stroke divided by the total person-time at risk. The comorbidities were measured at any time prior to CHD and including at the baseline visit or hospitalization (Table 2).

Figures 1 and 2 and Figure S1 show the cumulative incidence of ischemic stroke in the study population, respectively, for every Marelli group and was based on the Nelson-Aalen estimator of the cumulative hazard. The time of censoring is December 31, 2011, and death was the competing event.

### Results

A total of 25,985 CHD patients and 259,750 controls were included in the study (48.5% women). The characteristics of the study population are shown in Table 2. The mean and median ages at CHD diagnosis were 9.51 and 5.74 years, respectively; mean follow-up was 20.1 years. Educational level and proportion of individuals born in Sweden were similar among CHD patients and controls. However, diabetes and cardiovascular diseases such as congestive heart failure, hypertension, and atrial fibrillation at any time point were more common in CHD patients than in controls.

One hundred forty CHD patients (0.54%) and 137 controls (0.05%) developed ischemic stroke during a maximum of 42 years of follow-up. Median age at the time of ischemic stroke diagnosis was 23.1 years in CHD patients versus 30.5 years in controls. The HR of ischemic stroke was 10.76 (95% CI, 8.49–13.63) in CHD patients compared with controls.

Table 3 shows the HRs for ischemic stroke by Marelli classification. The first Marelli group, which represents patients with the most complex form of CHD, had an HR of 12.22 (95% CI, 7.93–18.85) for developing ischemic stroke compared with controls. However, similarly elevated HRs for developing ischemic stroke were observed in patients with less complex congenital heart malformations, such as in Marelli groups 2 and 4 (9.50 [95% CI, 6.35–14.21] and 7.12 [95% CI, 4.03–12.60], respectively).

The risks for developing ischemic stroke in patients with isolated CHD diagnoses are shown in Table 4. Patients with coarctation of the aorta had the highest risk of developing ischemic stroke, with an HR of 12.86 (95% CI, 4.79–34.56). Diagnoses of isolated double-inlet ventricle and atrial shunts (ASD or PFO) also carried a significantly elevated risk (HRs 4.49 [95% CI, 1.56–12.93] and 10.00 [95% CI, 2.02–49.55], respectively).

**Table 2. Sociodemographic Data and Comorbidities of the Study Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Congenital Heart Disease</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>12,602 (48.5)</td>
<td>125,946 (48.5)</td>
</tr>
<tr>
<td>Median age at index registration (IQR), y</td>
<td>5.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Median age at end of study period (IQR), years</td>
<td>28.6</td>
<td>29.5</td>
</tr>
<tr>
<td>Born in Sweden, n (%)</td>
<td>24,006 (92.4)</td>
<td>241,169 (92.9)</td>
</tr>
<tr>
<td>Education category at last registration *</td>
<td>Low</td>
<td>5190 (22.8)</td>
</tr>
<tr>
<td></td>
<td>Mid</td>
<td>10,685 (46.9)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>6885 (30.3)</td>
</tr>
<tr>
<td>Registration at the baseline (any diagnostic position), n (%)</td>
<td>Hypertension</td>
<td>1836 (7.1)</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td>635 (2.4)</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
<td>1325 (5.1)</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>384 (1.5)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.

*Highest attained education level during the study.

**Figure 1.** Cumulative incidence of ischemic stroke in patients with congenital heart disease and controls for up to 42 years of follow-up.
In multivariate analysis restricted to the CHD group (Table 5), a diagnosis of congestive heart failure was associated with the highest risk of developing ischemic stroke (HR 6.94 [95% CI, 4.96–10.34; \(P<0.001\))]; CHD patients with hypertension (HR 3.89 [95% CI, 2.44–6.22; \(P<0.001\)) or atrial fibrillation (HR 2.94 [95% CI, 1.78–4.83; \(P<0.001\)) were also at significantly greater risk of developing ischemic stroke. Eleven of 140 CHD patients (7.9%) developed ischemic stroke perioperatively.

Figure 1 shows the cumulative incidence of ischemic stroke in CHD patients compared with controls during the 42-year follow-up period. CHD patients older than 20 years of age showed a marked increase in the incidence of ischemic stroke, to \(\approx 1.5\%\) compared with 0.2% for the controls at the end of the study. Furthermore, the incidence of ischemic stroke was increased subsequently in all Marelli classifications; however, the highest incidence was noted in the first and the fifth Marelli patient group (Figure 2).

**Discussion**

In this large-register study, we found that in children and young adults with CHD, the risk of developing ischemic stroke was low in absolute terms but still almost 11 times higher...
Table 3. Relative Risk of Ischemic Stroke in Patients With Congenital Heart Disease Compared With Matched Control Groups by Marelli Classification

<table>
<thead>
<tr>
<th>Categorical Hierarchy Block</th>
<th>Cases (N)</th>
<th>Controls (N)</th>
<th>IS Per 100 000 Person Years, Cases (N)</th>
<th>IS Per 100 000 Person Years, Controls (N)</th>
<th>HR for IS (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marelli 1</td>
<td>5126</td>
<td>51 240</td>
<td>35.0 (45)</td>
<td>2.9 (40)</td>
<td>12.22 (7.93–18.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marelli 2</td>
<td>11 286</td>
<td>112 810</td>
<td>21.0 (46)</td>
<td>2.2 (50)</td>
<td>9.50 (6.35–14.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marelli 3</td>
<td>249</td>
<td>2490</td>
<td>15.9 (1)</td>
<td>—</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Marelli 4</td>
<td>4749</td>
<td>47 450</td>
<td>24.3 (20)</td>
<td>3.4 (31)</td>
<td>7.12 (4.03–12.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marelli 5</td>
<td>4513</td>
<td>45 096</td>
<td>47.8 (27)</td>
<td>2.7 (16)</td>
<td>17.16 (9.24–31.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All CHD</td>
<td>25 985</td>
<td>259 750</td>
<td>28.4 (140)</td>
<td>2.6 (137)</td>
<td>10.76 (8.49–13.63)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Marelli group 1 defined as diagnosis of common arterial trunk, transposition of great vessels, double-inlet ventricle, hypoplastic left heart syndrome, tetralogy of Fallot, or atriovenous septal defect. Marelli group 2 defined as atral septal defect, ventricular septal defect, patent ductus arteriosus, coarctation of aorta, or Ebstein anomaly. Marelli group 3 defined as diagnosis of unspecified congenital malformations of cardiac septum. Marelli group 4 defined as diagnosis of congenital malformations of pulmonary artery, congenital malformations of tricuspid valve, congenital malformations of aortic valve, congenital malformations of mitral valve, or congenital malformations of great veins. Marelli group 5 defined as diagnosis of other unspecified congenital malformations of aorta, other specified and unspecified congenital malformations of the heart, or unspecified congenital malformations of circulation. CHD indicates congenital heart disease; HR, hazard ratio.

Table 4. Relative Risk of Ischemic Stroke in Patients With Various Isolated Congenital Heart Diseases Compared With Controls

<table>
<thead>
<tr>
<th>CHD Diagnosis</th>
<th>Ischemic Stroke in CHD Patients/Total CHD Patients</th>
<th>Ischemic Stroke in Controls/Total Controls</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CHD</td>
<td>140/25 985</td>
<td>137/259 750</td>
<td>10.76 (8.49–13.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial septal defect or patent foramen ovale</td>
<td>3/879</td>
<td>3/8790</td>
<td>10.00 (2.02–49.55)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>5/2924</td>
<td>20/29 215</td>
<td>2.50 (0.94–6.65)</td>
<td>0.068</td>
</tr>
<tr>
<td>Tetralogy of Fallot*</td>
<td>2/699</td>
<td>9/6687</td>
<td>2.20 (0.47–10.16)</td>
<td>0.315</td>
</tr>
<tr>
<td>Atrioventricular septal defect</td>
<td>0/162</td>
<td>0/1619</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Common arterial trunk</td>
<td>1/200</td>
<td>4/2000</td>
<td>3.33 (0.35–32.05)</td>
<td>0.297</td>
</tr>
<tr>
<td>Ebstein’s anomaly†</td>
<td>0/108</td>
<td>0/1079</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Transposition of great vessels†</td>
<td>1/238</td>
<td>2/2379</td>
<td>4.85 (0.14–11.87)</td>
<td>0.997</td>
</tr>
<tr>
<td>Double inlet ventricle</td>
<td>5/1326</td>
<td>11/13 258</td>
<td>4.49 (1.56–12.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>1/2377</td>
<td>11/23 766</td>
<td>0.93 (0.17–7.23)</td>
<td>0.947</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>0/54</td>
<td>0/540</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Coarctation of aorta†</td>
<td>9/1823</td>
<td>6/18 204</td>
<td>12.86 (4.79–34.56)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CHD indicates congenital heart disease; HR, hazard ratio.

*Defined as tetralogy of Fallot diagnosis even if ventricular septal defect and pulmonary valve stenosis exist.
†Defined as Ebstein’s diagnosis even if ventricular septal defect or atrial septal defect or patent foramen ovale or patent ductus arteriosus diagnosis exists.
‡Defined as transposition of great vessels diagnosis even if ventricular septal defect or atrial septal defect or patent foramen ovale or patent ductus arteriosus diagnosis or pulmonary valve stenosis or tricuspid valve stenosis/atresia diagnosis exists.
§Defined as coarctation of the aorta even if secondary hypertension exists.
our study population, in which we recorded only a 0.5% incidence of ischemic stroke during a mean follow-up of ≈20 years. However, the Euro Heart Survey was a cross-sectional study that focused mainly on patients with more complex heart malformations and had a relatively short follow-up period compared with the present study.

In a study of 3267 adults with 5 of the most common types of CHD compared with 6534 controls, the risk of developing ischemic stroke was 2.2 times higher in adults with CHD compared to controls. Furthermore, a recent study investigated 2.5 million children in a North California Integrated Healthcare Plan and CHD was identified in 15 of 412 total pediatric stroke cases. The risk of stroke in children with CHD was 19 times higher than in randomly selected controls and the risk in children who had cardiac surgery remained elevated (13-fold) also after the perioperative period. These findings support our results demonstrating that CHD is a risk factor for ischemic stroke, with a low absolute risk and a high relative risk.

Cardiovascular factors other than congenital malformation per se may also influence the risk of stroke. The prevalence of atrial fibrillation has been reported to be as high as 15% of the total CHD population and associated with a more than doubled risk of morbidities such as stroke. We found that the risk of ischemic stroke in CHD patients with cardiovascular comorbidities such as atrial fibrillation, heart failure, and hypertension was up to 6-fold greater than that of CHD patients without these comorbidities.

In our study, we may have underestimated the risk of ischemic stroke because of the exclusion of all patients who were diagnosed with ASD or PFO during adulthood; however, patients with isolated ASD or PFO diagnosis before the age of 18 were still at 10 times greater risk of developing ischemic stroke than controls. Even so, these young patients do not, as a rule, approach the risk level at which anticoagulation is indicated (eg, atrial fibrillation). However, as the CHD population increases and becomes older, more CHD patients will likely reach that point and develop an indication for preventive antithrombotic treatment.

Studies with CHD patients are frequently limited in size and the results may not be representative of or applicable to groups or subgroups of CHD patients. Thus, a strength of the present study is that we identified virtually all CHD patients and drew matched controls from the same background population. Because of the high coverage of the Swedish registers, there is very limited loss to follow-up, but transient ischemic attacks and minor strokes may not have been recognized.

### Limitations

One of the limitations is that the study is based solely on registers and that no echocardiographic, heart morphologic, or clinical data were available for further analysis. With respect to the validity of CHD diagnoses, including the Marelli classification, children and adults with CHD are generally managed in a few highly specialized units, which should help to minimize misclassification, even though, due to the legal requirement to use only coded data, we were unable to validate the CHD diagnoses.

With respect to ischemic stroke, computed tomographic scans have been available and routinely used since the early 1980s in Sweden, so the distinction between hemorrhagic and ischemic stroke is probably valid. Furthermore, major cardiovascular diseases have been validated externally and by individual researchers with the overall positive predictive value of diagnoses in the register of about 85% to 95%.

Previous studies have reported that clinically silent ischemic strokes are quite common postoperatively in children as well as adult patients. Our study was limited to clinically evident ischemic strokes and clinically silent strokes were not included in the present study.
Table 3 shows the risk of patients with isolated CHD diagnoses of developing ischemic stroke in the present study; however, this analysis cannot be extrapolated to patients with multiple CHD diagnoses.

Another limitation is that outpatient data are available only from 2000 in Sweden; cases managed only on an outpatient basis before that time could not be identified. Also, data from the primary care were not available, but it is unlikely that young patients with CHD and even minor ischemic stroke were not hospitalized. Finally, coding as well as ascertainment bias may be present in the current national registry study.

Conclusions
The risk of ischemic stroke in children and young adults with CHD is significantly higher than in the general population. Cardiovascular comorbidities, such as congestive heart failure, atrial fibrillation, and hypertension, increased the risk of ischemic stroke; therefore, these patients should be targeted for intervention as they grow older. Further research is needed to clarify when and how to institute prevention for ischemic stroke.

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Disclosures
None.

References