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

S troke is a leading cause of death and a major cause of adult disability in developed countries.[1] Ischemic stroke has been shown to be relatively uncommon in children and young adults compared with older adults.[2] However, recent studies have shown that the incidence of stroke has decreased among the elderly but increased in the young population.[3,4] Traditional risk factors for ischemic stroke, such as hypertension, diabetes mellitus, and atrial fibrillation, are usually absent in children and young adults.[5]

Congenital heart disease (CHD) is present in about 1% of live births and is the most common congenital malformation.[6] CHD is a major risk factor for ischemic stroke and stroke recurrence in children.[7–9] Patients with CHD represent about 20% of all strokes among children,[10] and cardiac surgery in children with CHD has been shown to be associated with increased stroke risk.[9,11] Previous studies have identified a strong association between cyanotic CHD and cerebral lesions,[12,13] whereas a later report has failed to demonstrate any correlation.[14] 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.[15]

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.[16] 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.[17]

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 procedures 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.[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.[20]

Educational levels of the patients and controls were extracted from the Longitudinal Integration Database for Health Insurance and Labor Market Studies.[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® software, Version 9.4 (SAS Institute, Inc, Cary, NC) and R software, Version 3.1 (R Foundation for

Table 1. International Classification of Disease (ICD) Diagnosis

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

Continued

Table 1. Continued

Diagnosis	ICD 8	ICD 9*	ICD 10
Unspecified congenital malformations of cardiac chambers	746.9	746X	Q20.8, Q20.9
Atrioventricular septal defect	745.6	745G	Q21.2
Aortopulmonary septum defect	745.8	745W	Q21.4
Other congenital malformations of cardiac septum	745.8	745W	Q21.8
Unspecified congenital malformations of cardiac septum	745.9	745X	Q21.9
Pulmonary valve atresia	746.01	746A	Q22.0
Congenital stenosis of pulmonary valve	746.02	746A	Q22.1
Congenital pulmonary valve insufficiency	746.09	746A	Q22.2
Other congenital malformations of pulmonary valve	746.00	746A	Q22.3
Hypoplastic right heart syndrome	746.1	746B	Q22.6
Other congenital malformations of tricuspid valve	746.1	746B	Q22.8, Q22.9
Other congenital malformations of aortic and mitral valves	746.89	746W	Q23.8, Q23.9
Congenital phlebectasia	747.89	747G	Q27.4
Other specified congenital malformations of the heart	746.89	746W	Q24.8
Unspecified congenital malformations of the heart	746.9	746X	Q24.9
Patent ductus arteriosus	747.0	747A	Q25.0
Unspecified congenital malformations of circulation	747.9	747X	Q28.9
Sequestration of lung	748.5	748F	Q33.2
Secondary hypertension	405	405	I15.8, I15.9
Vitium organicum cordis (VOC)	421, 424	421, 424	I33 to 37

*Swedish version of ICD 9.

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.

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.

Table 2. Sociodemographic Data and Comorbidities of the Study Population

Characteristic	Patients With Congenital Heart Disease n=25 985	Controls n=259 750
Women, n (%)	12 602 (48.5)	125 946 (48.5)
Median age at index registration (IQR), y	5.7	5.7
Median age at end of study period (IQR), years	28.6	29.5
Born in Sweden, n (%)	24 006 (92.4)	241 169 (92.9)
Education category at last registration *		
Low	5190 (22.8)	49 586 (19.6)
Mid	10 685 (46.9)	117 343 (46.4)
High	6885 (30.3)	86 075 (34.0)
Registration at the baseline (any diagnostic position), n (%)		
Hypertension	1836 (7.1)	1412 (0.5)
Atrial fibrillation	635 (2.4)	431 (0.2)
Congestive heart failure	1325 (5.1)	160 (0.06)
Diabetes	384 (1.5)	2065 (0.8)

IQR indicates interquartile range.
*Highest attained education level during the study.

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).
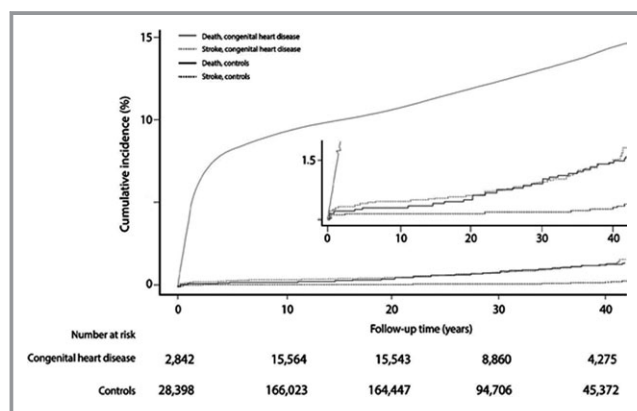
Figure 1. Cumulative incidence of ischemic stroke in patients with congenital heart disease and controls for up to 42 years of follow-up.
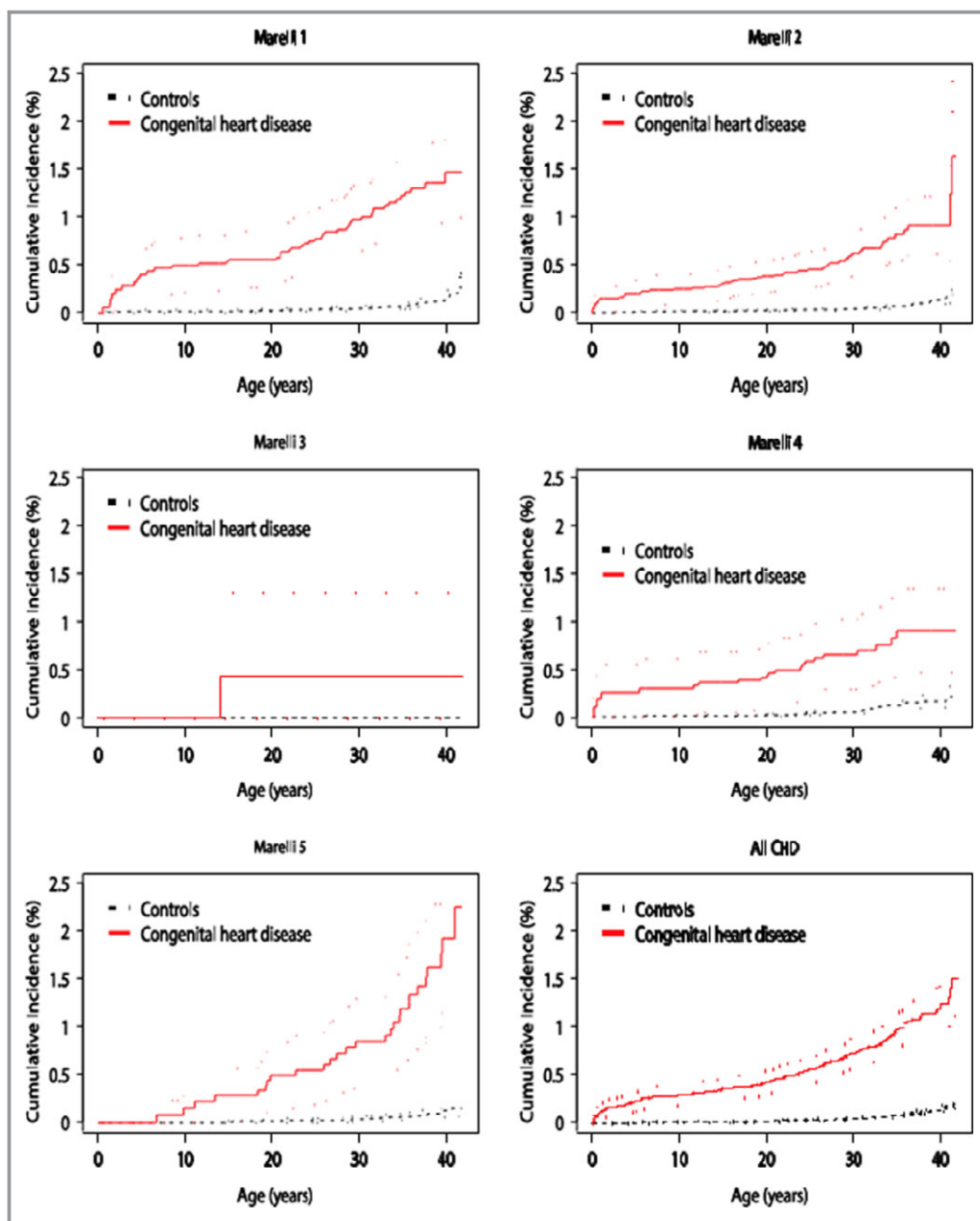
Figure 2. Cumulative incidence of ischemic stroke in overall and Marelli groups of patients with congenital heart disease (CHD) and controls for up to 42 years of age.

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 ≈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

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

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 atrioventricular septal defect. Marelli group 2 defined as atrial 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 pulmonary valve, 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 (by measurement unit and defined by age, sex, and year of diagnosis); IS, ischemic stroke.

than in matched controls. The elevated risk was most marked in, but not restricted to, patients with the most complex heart malformations. We found that isolated diagnoses of coarctation of the aorta, double-inlet ventricle, and ASD or PFO placed patients at significantly higher risk of developing ischemic stroke than controls. These findings, taking into account the complexity and heterogeneity of congenital heart lesions, are clinically important.

A previous study evaluated the risk of ischemic stroke in CHD patients, and while the results varied, the risk of ischemic stroke was estimated to be from 10 to 100 times greater in samples of CHD patients of European or Canadian origin compared with published incidence data for young adults in the United States.[16] No previous study has compared the risk of ischemic stroke in CHD patients with that of controls from the same background population.

A report from the Euro Heart Survey showed that the incidence of cerebrovascular accidents (including transient ischemic attacks) was 4% in 4000 adults with CHD during 5 years of follow-up.[23] This rate was much higher than that in

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

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

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.

Table 5. Univariate and Multivariable Analysis of Factors Associated With Ischemic Stroke in 25 985 Patients With Congenital Heart Disease

Variables	Univariate Analysis			Multivariable Analysis*		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Female sex (yes/no)	0.88	0.63 to 1.23	0.55	0.97	0.69 to 1.36	0.86
Birth year[†]	1.16	0.72 to 1.89	0.52	1.12	0.95 to 1.32	0.18
Atrial fibrillation (yes/no)	6.94	4.39 to 10.95	<0.001	2.93	1.78 to 4.83	<0.001
Diabetes (yes/no)	3.03	1.33 to 6.86	<0.001	1.30	0.55 to 3.06	0.55
Hypertension (yes/no)	4.65	3.02 to 7.16	<0.001	3.89	2.44 to 6.22	<0.001
Congestive heart failure (yes/no)	10.39	7.25 to 14.88	<0.001	6.94	4.70 to 10.34	<0.001

HR indicates hazard ratio by measurement unit.

*Cox regression analysis was adjusted for age, Marelli classification (by stratification), and comorbidities at the baseline.

[†]Range of birth year is years from the first study year (0–23 years).

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,[17] 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.[9] 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.[24] 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%.[25]

Previous studies have reported that clinically silent ischemic strokes are quite common postoperatively in children as well as adult patients.[8,26,27] 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 need to clarify when and how to institute prevention for ischemic stroke.

Sources of Funding

Disclosures

None.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER III, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics C, Stroke Statistics S. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28–e292.

2. Biller J. Stroke: improving characterization of childhood cerebral arteriopathies. *Nat Rev Cardiol*. 2009;6:395–397.

3. Rosengren A, Giang KW, Lappas G, Jern C, Toren K, Bjorck L. Twenty-four-year trends in the incidence of ischemic stroke in Sweden from 1987 to 2010. *Stroke*. 2013;44:2388–2393.

4. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995–2008. *Ann Neurol*. 2011;70:713–721.

5. Poisson SN, Schardt TQ, Dingman A, Bernard TJ. Etiology and treatment of arterial ischemic stroke in children and young adults. *Curr Treat Options Neurol*. 2014;16:315.

6. Khoshnood B, Lelong N, Houyel L, Thieulin AC, Jouannic JM, Magnier S, Delezoide AL, Magny JF, Rambaud C, Bonnet D, Goffinet F; Group ES. Prevalence, timing of diagnosis and mortality of newborns with congenital heart defects: a population-based study. *Heart*. 2012;98:1667–1673.

7. Mackay MT, Wiznitzer M, Benedict SL, Lee KJ, Deveber GA, Ganesan V; International Pediatric Stroke Study G. Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. *Ann Neurol*. 2011;69:130–140.

8. Rodan L, McCrindle BW, Manlhiot C, MacGregor DL, Askalan R, Moharir M, deVeber G. Stroke recurrence in children with congenital heart disease. *Ann Neurol*. 2012;72:103–111.

9. Fox CK, Sidney S, Fullerton HJ. Community-based case-control study of childhood stroke risk associated with congenital heart disease. *Stroke*. 2015;46:336–340.

10. Dowling MM, Hynan LS, Lo W, Licht DJ, McClure C, Yager JY, Dlamini N, Kirkham FJ, Deveber G, Pavlakis S; International Paediatric Stroke Study G. International Paediatric Stroke Study: stroke associated with cardiac disorders. *Int J Stroke*. 2013;8(suppl A100):39–44.

11. Domi T, Edgell DS, McCrindle BW, Williams WG, Chan AK, MacGregor DL, Kirton A, deVeber GA. Frequency, predictors, and neurologic outcomes of vaso-occlusive strokes associated with cardiac surgery in children. *Pediatrics*. 2008;122:1292–1298.

12. Berthrong M, Sabiston DC Jr. Cerebral lesions in congenital heart disease, a review of autopsies on 162 cases. *Bull Johns Hopkins Hosp*. 1951;89:384–406.

13. Phornphutkul C, Rosenthal A, Nadas AS, Berenberg W. Cerebrovascular accidents in infants and children with cyanotic congenital heart disease. *Am J Cardiol*. 1973;32:329–334.

14. Perloff JK, Marelli AJ, Miner PD. Risk of stroke in adults with cyanotic congenital heart disease. *Circulation*. 1993;87:1954–1959.

15. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009;124:1001–1008.

16. Hoffmann A, Chockalingam P, Balint OH, Dadashev A, Dimopoulos K, Engel R, Schmid M, Schwerzmann M, Gatzoulis MA, Mulder B, Oechslin E. Cerebrovascular accidents in adult patients with congenital heart disease. *Heart*. 2010;96:1223–1226.

17. Lin YS, Liu PH, Wu LS, Chen YM, Chang CJ, Chu PH. Major adverse cardiovascular events in adult congenital heart disease: a population-based follow-up study from Taiwan. *BMC Cardiovasc Disord*. 2014;14:38.

18. Homma S, Sacco RL. Patent foramen ovale and stroke. *Circulation*. 2005;112:1063–1072.

19. Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, Drobinski G, Thomas D, Grosgogeat Y. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med*. 1988;318:1148–1152.

20. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. 2007;115:163–172.

21. Olen O, Bihagen E, Rasmussen F, Ludvigsson JF. Socioeconomic position and education in patients with coeliac disease. *Dig Liver Dis*. 2012;44:471–476.

22. Lind M, Svensson AM, Kosiborod M, Gudbjornsdottir S, Pivodic A, Wedel H, Dahlqvist S, Clements M, Rosengren A. Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med*. 2014;371:1972–1982.

23. Engelfriet P, Boersma E, Oechslin E, Tijssen J, Gatzoulis MA, Thilen U, Kaemmerer H, Moons P, Meijboom F, Popelova J, Laforest V, Hirsch R, Daliento L, Thaulow E, Mulder B. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. The Euro Heart Survey on adult congenital heart disease. *Eur Heart J*. 2005;26:2325–2333.

24. Bouchardy J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Bottega N, Marelli AJ. Atrial arrhythmias in adults with congenital heart disease. *Circulation*. 2009;120:1679–1686.

25. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.

26. Floyd TF, Shah PN, Price CC, Harris F, Ratcliffe SJ, Acker MA, Bavaria JE, Rahmouni H, Kuersten B, Wiegers S, McGarvey ML, Woo JY, Pochettino AA, Melhem ER. Clinically silent cerebral ischemic events after cardiac surgery: their incidence, regional vascular occurrence, and procedural dependence. *Ann Thorac Surg*. 2006;81:2160–2166.

27. Chen J, Zimmerman RA, Jarvik GP, Nord AS, Clancy RR, Wernovsky G, Montenegro LM, Hartman DM, Nicolson SC, Spray TL, Gaynor JW, Ichord R. Perioperative stroke in infants undergoing open heart operations for congenital heart disease. *Ann Thorac Surg*. 2009;88:823–829.