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ORIGINAL RESEARCH

Ischemic Stroke in Adults With Congenital Heart Disease: A Population-Based Cohort Study

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***Background*—**Congenital heart disease (CHD) is associated with risk factors for ischemic stroke including cardiac arrhythmias and heart failure. However, few long-term follow-up data exist on ischemic stroke risk and associated mortality in adults with CHD.

***Methods and Results*—**Using Danish nationwide registries, we identified individuals aged ≥18 years diagnosed with CHD, at any age, from 1963 to 2017 and a sex and birth year-matched (1:10) general population comparison cohort. We computed risks, as well as sex and birth year-adjusted hazard ratios (aHRs) for ischemic stroke and 30-day post-stroke mortality in CHD adults compared with the general population. Analyses were stratified according to age <60 years (young) and ≥60 years (older). We identified 16 836 adults with CHD. The risk of ischemic stroke at age 60 years was 7.4% in the CHD cohort and 2.9% in the general population cohort. The adjusted hazard ratios for ischemic stroke compared with the general population was 3.8 (95% CI: 3.3–4.3) in young CHD adults and 1.6 (95% CI: 1.4–1.9) in older CHD adults. The adjusted hazard ratios for post-stroke mortality compared with the general population was 2.3 (95% CI: 1.2–4.4) in young CHD adults and 1.3 (95% CI: 0.9–1.9) in older CHD adults.

***Conclusions*—**Both younger and older CHD adults have an increased risk of ischemic stroke and by 60 years of age 7.4% of CHD adults will have had an ischemic stroke. Post-stroke mortality was also increased in CHD adults compared with the general population. **(*J Am Heart Assoc*. 2019;8:e011870. DOI: 10.1161/JAHA.118.011870.)**

Key Words: congenital heart disease • population-based • prognosis • stroke

The prevalence of adults living with a congenital heart disease (CHD) is increasing, resulting in a greater need to research the long-term prognosis of this patient group.[1] Risk of ischemic stroke is one such outcome in need of additional discovery. Adults with CHD are at greater risk of cardiac arrhythmias and congestive heart failure,[2,3] both well described risk factors for ischemic stroke in the general population.[4,5] Heart surgery with implantation of mechanical heart valves is another risk factor for ischemic stroke in the adult CHD population.[6,7]

A previous study investigated the risk of ischemic stroke in CHD children and young adults compared with a general population cohort, however, data on ischemic stroke risk among older patients with CHD are limited.[8,9] Additionally, CHD is a heterogeneous disease with varying comorbidities. Thus, identifying subgroups of CHD adults at particular high risk of ischemic stroke is of clinical relevance.[10]

We therefore estimated the risk of ischemic stroke in the adult CHD population in Denmark compared with the general population, overall and according to CHD-related risk factors. Moreover, we estimated the incidence of ischemic stroke in the adult CHD population in relation to CHA_2DS_2VASc scores and evaluated the use of antithrombotic therapy in the adult CHD population. Finally, we compared 30-day post-stroke mortality in the adult CHD population with that of the general population cohort.

Methods

Setting

Our study was conducted within the entire Danish population of ≈5.7 million individuals. All Danish citizens are provided

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011870

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Clinical Perspective

What Is New?

- In this nationwide population-based cohort study of 16 836 congenital heart disease (CHD) adults, the lifelong risk and mortality of ischemic stroke was elevated compared with a sex- and birth year-matched comparison cohort, especially in those aged <60 years.
- Traditional stroke risk factors ie, heart failure, atrial arrythmia, and mechanical heart valve replacement further increased this risk, despite the indication of a high prevalence of anticoagulation therapy use in CHD adults.
- In CHD adults a CHA_2DS_2VASc score of ≥1 indicated a higher risk of ischemic stroke compared with a score of 0.

What Are the Clinical Implications?

- The lifelong increased risk of ischemic stroke and increased ischemic stroke mortality in CHD adults triggers a need for targeted and timely intervention by clinicians to identify those at highest risk.
- The CHA_2DS_2VASc score could be a usable supplemental tool in identifying CHD adults at risk of ischemic stroke.

tax-supported health care through the Danish National Health Service, which encompasses universal and free access to both hospital care and primary health care, including care for CHD and ischemic stroke. No informed written consent or permission from the Scientific Ethical Committee is required for register-based studies in Denmark. The data will not be made available to other researchers for purpose of reproducing the results as that would be a violation of the Danish General Data Protection Regulation. Analytic methods are described below.

Data Linkage

Since 1968, the Central Office of Civil Registration has assigned all residents in Denmark a unique 10-digit civil personal registration number, which is used to track residents across all Danish registries.[11] This system allowed for unambiguous individual-level linkage of data from all sources used in this study and provided us with virtually complete follow-up for death, emigration, and the outcome under study.[11]

Study Population

Congenital heart disease cohort

We identified all Danish individuals diagnosed with CHD during 2 separate periods. As described previously, we used medical record reviews[12] to identify patients diagnosed in the period 1963 to 1974 and the DNPR (Danish National Patient Registry) to identify those diagnosed between 1977 and 2017. Individuals exclusively diagnosed with CHD between 1974 and 1977 were not captured in this study. The DNPR contains information on all hospital admissions in Denmark and includes individuals' civil personal registration numbers, dates of admission and discharge, surgical procedures, one primary diagnosis per hospital admission and additional relevant secondary diagnoses, coded by physicians according to the *International Classification of Diseases* (*ICD*)[13]. The *Eighth Revision* of the *ICD* was used until the end of 1993 and the *Tenth Revision* thereafter.

We categorized CHD severity into broad categories: mild to moderate, severe, and unclassified complexity.[14–16] Mild and moderate CHD types were exclusively of biventricular physiology and included lesions commonly classified as simple (including atrial and ventricular septal defects, coarctation, patent ductus arteriosus, and isolated pulmonic stenosis). Mild and moderate types were separate according to procedural intervention history such that those classified as mild had no history of cardiothoracic surgical or procedural history. Severe CHD was classified as complex biventricular physiology (including tetralogy of Fallot, pulmonary atresia, atrioventricular septal defects, transposition of the great arteries), or a history of single-ventricle diagnoses or palliative surgery such as Norwood, Glenn, and Fontan. The category of unclassified complexity included only those diagnoses that could not readily be assigned a severity category.

Work-up after an ischemic stroke may, in the optimal setting, include an echocardiography that may unmask an asymptomatic CHD, such as a small atrial septal defect, that would otherwise gone unnoticed. To avoid overestimating the risk of ischemic stroke in CHD adults we excluded individuals who were registered with both CHD and an ischemic stroke diagnosis within the same 12-month period (n=183).

General population comparison cohort

We used the Civil Registration System[11] to identify a general population comparison cohort. We matched on sex and birth year at a ratio of 10 general population individuals without a CHD per 1 CHD adult. If an individual from the general population cohort was diagnosed with CHD during follow-up this individual would move to the CHD cohort and be matched with 10 general population individuals.

Outcomes

Ischemic stroke and post-ischemic stroke mortality

Within the CHD cohort and the general population comparison cohort, we identified patients with a primary discharge diagnosis of first-time ischemic stroke in the DNPR (Table S1). We defined post-stroke mortality as death within 30 days of a first-time ischemic stroke diagnosis in the DNPR.

Antithrombotic therapy

We obtained data on the use of antithrombotic therapy from the National Prescription Registry.[17] This database provides detailed information on all redeemed drug prescriptions dispensed from all Danish pharmacies and is complete since 1995. We used Anatomical Therapeutic Chemical Classification codes to identify antithrombotic medications (Table S1). We grouped the medications into the following categories: Vitamin K antagonists, non-vitamin K oral antagonists and platelet aggregation inhibitors. Use of antithrombotic therapy was assessed as the number of filled prescriptions between January 1, 2015 until December 31, 2016 in CHD cohort adults and general population comparison cohort members that were alive on December 31, 2016.

Covariables

CHA_2DS_2VASc score

To establish the CHA_2DS_2VASc score[18] of CHD adults during the time of follow up, we identified dates of first-time diagnoses of congestive heart failure, hypertension, diabetes mellitus, thromboembolism, hemorrhagic stroke, and vascular disease in the DNPR. We defined thromboembolic disease as a diagnosis of prior transitory ischemic attack or systemic embolism (Table S1). Prior ischemic stroke was not included in the score because the study outcome was first-time ischemic stroke. We defined vascular disease as a diagnosis of myocardial infarction, atherosclerosis or history of a previous coronary bypass operation, coronary thrombendarteriectomy, recanalization of the coronary artery or reconstruction of the coronary artery but not reconstruction of an anomalous coronary artery (Table S1). Based on these covariate definitions, individuals were assigned one point for congestive heart failure, hypertension, age 65 to 74 years, diabetes mellitus, and vascular disease. One point was assigned for female sex, but only in presence of $\geq$1 of the other covariates. Two points were given for age $\geq$75 years and previous thromboembolic disease. We defined CHA_2DS_2VASc score categories as 0, 1, and $\geq$2 points.[19]

Mechanical heart valves

We obtained data on the presence of mechanical heart valves in the aortic or mitral position from the DNPR. Surgical procedural codes are presented in Table S1.

Statistical Analysis

Longitudinal follow-up was determined according to the same design between the CHD cohort and general population comparison cohort. Specifically, follow-up started either from the age of 18 years, date of CHD diagnosis (index date for matched general population comparison cohort members) or initiation of the DNPR in 1977, whichever came last. Follow up for both the CHD cohort and general population comparison cohort ended on date of first diagnosis of ischemic stroke, death, emigration or end of study (January 1, 2017). There were 183 CHD individuals excluded from the study because they had a registered CHD diagnosis and ischemic stroke diagnosis within the same 12-month period. To address stroke risk relative to age, we stratified the analyses according to age <60 years (young) or $\geq$60 years (older). As an estimate of absolute risk, we computed cumulative incidences of ischemic stroke for the adult CHD cohort, as well as the general population cohort using the method of Fine and Gray[20] to account for death as a competing risk.

We estimated median age at stroke diagnosis in the CHD cohort and the general population comparison cohort. We computed overall incidence rates of ischemic stroke, as well as incidence rates of ischemic stroke according to the presence of congestive heart failure, atrial fibrillation (AFib), and mechanical heart valves.

We used Cox proportional hazards regression analysis to compute sex and birth year adjusted hazard ratios (aHRs) as estimates of the relative risk of ischemic stroke in adults with CHD compared with the general population. In a sensitivity analysis, we excluded the "unspecific stroke" diagnosis code (*ICD-10*: I64) from the stroke definition. In subgroup analyses, we computed aHRs of ischemic stroke in CHD adults with congestive heart failure, AFib and mechanical heart valves, respectively, compared with their sex- and birth year-matched members of the general population comparison cohort. In these subgroup analyses follow-up started on the date of diagnosis for congestive heart failure, or AFib, or on date of mechanical heart valve operation. A corresponding index date for matched general population comparison cohort members was selected to determine the initiation of the time to event analysis period.

We scored CHD adults according to the presence of CHA_2DS_2VASc score covariates (0, 1, and $\geq$2), and computed incidence rates of ischemic stroke in each score category and hazard ratios (HRs) comparing risk of ischemic stroke of CHD cohort adults with CHA_2DS_2VASc scores of 1 or $\geq$2, respectively, with that of CHD cohort adults with a score of 0. Scores were included in the Cox models as time-varying covariates.

Furthermore, 30-day post-stoke mortality was assessed using the Kaplan Meier estimator. We computed aHRs of 30-day post-stroke mortality in the CHD cohort compared with the general population cohort according to age categories. We checked assumptions of proportional hazards graphically.

Finally, we assessed the prevalence of filled antithrombotic therapy prescriptions during 2015 to 2016 in CHD cohort adults and general population comparison cohort members that were alive on December 31, 2016. All analyses were performed using STATA 14 (StataCorp LP, College Station, Texas).

Results

We identified 16 836 CHD adults, 49% male, diagnosed between 1963 and 2017 that were alive and living in Denmark at the age of 18 years. We identified 168 360 general population individuals (Table 1).

During the follow-up period, 522 CHD adults and 3039 individuals from the general population cohort received an ischemic stroke diagnosis. Median age at ischemic stroke diagnosis was 53 years (interquartile range: 40–67) in the CHD cohort and 69 years (interquartile range: 55–78) in the general population comparison cohort. The risk of ischemic stroke by age 30 years was 0.7% (95% CI: 0.6%–0.9%) in the CHD cohort and 0.1% (95% CI: 0.1%–0.1%) in the general population comparison cohort. By 60 years of age, the risk of ischemic stroke was 7.4% (95% CI: 6.6%–8.3%) in the CHD cohort and 2.9% (95% CI: 2.7%–3.1%) in the general population comparison cohort (Figure 1).

In the young age category, the overall incidence rate of ischemic stroke was 1.5 per 1000 person-years for CHD adults and 0.4 per 1000 person-years in the general population comparison cohort. In the older age category, the incidence rate of ischemic stroke was 10.2 per 1000 person-years for CHD adults and 7.2 per 1000 person-years in the general population. The overall aHR for ischemic stroke in CHD adults compared with the general population comparison cohort were 3.8 (95% CI: 3.3–4.3) in the young category and 1.6 (95% CI: 1.4–1.9) in the older category. Excluding the *ICD* diagnosis of "unspecified stroke" left the aHR unchanged (young: 3.8, 95% CI: 3.3–4.5 and older: 1.6, 95% CI: 1.3–1.9). The aHRs of ischemic stroke according to CHD severity categories are presented in Table 2.

In subgroup analyses, comparing CHD adults with AFib, or congestive heart, or a mechanical heart valve to their sex- and birth year-matched controls, we found increased aHRs of ischemic stroke in both the young and older categories (Table 2).

In the CHD cohort, we found increasing incidence of ischemic stroke with increasing CHA_2DS_2VASc-scores (Table 3). The HR comparing ischemic stroke risk among those

Table 1. Characteristics of 16 836 Congenital Heart Disease Adults and 168 360 General Population Adults Diagnosed in Denmark 1963 to 2017

	Congenital Heart Disease Cohort	General Population Comparison Cohort
	n (%)	n (%)
All	16 836 (100)	168 360 (100)
Male sex	8207 (49)	82 070 (49)
Birth, y		
1910 to 1939	1356 (8)	13 560 (8)
1940 to 1959	2704 (16)	27 040 (16)
1960 to 1982	6279 (37)	62 790 (37)
1983 to 1998	6497 (39)	64 970 (39)
CHD severity		
Mild/moderate	10 332 (61)	. . .
Severe	4247 (25)	. . .
Severity not classified	2257 (13)	. . .
Age at first CHD diagnosis		
0 to 10 y	9942 (59)	. . .
>10 y	6894 (41)	. . .
Major CHD diagnoses		
Atrial septal defect	3568 (21)	. . .
Ventricular septal defect	3946 (23)	. . .
Patent ductus arteriosus	1534 (9)	. . .
Truncus arteriosus	76 (<1)	. . .
Coarctation of the aorta	971 (6)	. . .
Tetralogy of fallot	626 (4)	. . .
Transposition of the great arteries	363 (2)	. . .
Other*	5828 (35)	. . .
Comorbidity		
Atrial fibrillation	2066 (12)	4765 (3)
Chronic heart failure	1945 (12)	3403 (2)
Mechanical heart valve	455 (3)	100 (<1)

CHD indicates congenital heart disease; mild to moderate, simple biventricular with and without history of surgical intervention; severe, complex biventricular physiology, history of single-ventricle diagnoses, or palliative surgery such as Norwood, Glenn, and Fontan. *All other CHD subtypes such as hypoplastic heart syndrome, tricuspid atresia, and atrioventricular canal defect, as well as all unclassifiable subtypes.

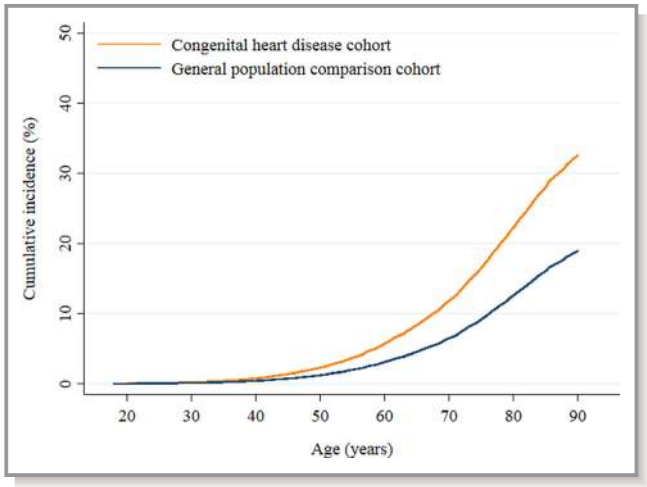

Figure 1. Cumulative incidence of ischemic stroke with death as competing risk in congenital heart disease adults (n=16 836) diagnosed in Denmark from 1963 to 2017 and general population adults (n=168 360).

with a score of 1 to those with a score of 0 was 3.7 (95% CI: 2.5–5.4). The HR for those with a score of ≥2 compared with those with a score of 0 was 4.5 (95% CI: 3.6–5.7).

When we examined 30-day post-ischemic stroke mortality, we found the following results. In the young category, 30-day post-stroke mortality was 5% (95% CI: 3%–8%) in the CHD cohort and 2% (95% CI: 2%–3%) in the general population comparison cohort (Figure 2). In the older category, 30-day post-stroke mortality was 15% (95% CI: 11%–21%) in the CHD cohort and 13% (95% CI: 11%–14%) in the general population comparison cohort (Figure 2). The corresponding aHRs of dying within 30 days of an ischemic stroke were 2.3 (95% CI: 1.2–4.4) in the young category and 1.3 (95% CI: 0.9–1.9) in the older category.

Analysis of antithrombotic therapy demonstrated that as of December 31, 2016, 14 259 CHD adults and 151 000 general population comparison cohort members were alive. Table 4 shows the proportions of CHD adults and general population comparison cohort members that had filled 1 to 4 prescriptions or ≥5 prescriptions of vitamin K antagonists, non-vitamin K oral antagonists, and platelet aggregation inhibitors between January 1, 2015 and December 31, 2016. The prevalence of filled prescriptions was greater in the CHD cohort for all 3 medication categories.

Discussion

We found an increased relative risk of ischemic stroke among CHD adults compared with the general population. The relative risk increase was particularly high among younger adults, representative of both increased risk and the low stroke incidence in the young adult general population. Having a mechanical heart valve implant was associated with a higher relative risk of ischemic stroke in young adults with CHD, as was a diagnosis of heart failure and atrial fibrillation. In addition, a CHA_2DS_2VASc score greater than zero was associated with an increased risk of ischemic stroke in the CHD population. Finally, we found an increased risk of dying within 30 days of a first-time ischemic stroke in the CHD cohort, compared with the general population, regardless of age.

Table 2. Incidence Rates and Adjusted Hazard Ratios of Stroke in Congenital Heart Disease Adults Compared With the General Population

	Young Category			Older Category		
	Incidence Rate* (95% CI)			Incidence Rate* (95% CI)		
	Congenital Heart Disease Cohort	General Population Comparison Cohort	Adjusted HR† (95% CI)	Congenital Heart Disease Cohort	General Population Comparison Cohort	Adjusted HR† (95% CI)
Overall	1.5 (1.3–1.6)	0.4 (0.4–0.5)	3.8 (3.3–4.3)	10.2 (8.9–11.8)	7.2 (6.9–7.5)	1.6 (1.4–1.9)
Sex						
Male	1.4 (1.2–1.6)	0.5 (0.4–0.5)	3.4 (2.8–4.1)	12 (10.0–15.0)	7.9 (7.4–8.4)	1.7 (1.4–2.1)
Female	1.5 (1.3–1.8)	0.4 (0.4–0.4)	3.8 (3.3–4.3)	9.0 (7.4–10.9)	6.7 (6.3–7.1)	1.6 (1.4–1.9)
Severity						
Mild/Moderate	1.2 (1.0–1.5)	. . .‡	3.2 (2.6–3.8)§	9.7 (7.7–12.3)	. . .‡	1.5 (1.3–1.9)§
Severe and UVH	2.2 (1.9–2.7)	. . .‡	6.3 (5.0–7.9)§	10.6 (7.7–14.5)	. . .‡	1.9 (1.3–2.7)§
Unclassified	1.4 (1.0–1.8)	. . .‡	2.8 (2.0–3.9)§	10.9 (7.4–16.0)	. . .‡	1.8 (1.2–2.8)§
Birth, y						
1910 to 1939	5.1 (3.1–8.5)	0.8 (0.5–1.1)	6.6 (3.4–12.7)	12.4 (10.5–14.8)	9.2 (8.8–9.7)	1.5 (1.2–1.8)
1940 to 1959	2.7 (2.2–3.3)	1.0 (0.9–1.1)	2.9 (2.3–3.6)	7.6 (6.0–9.7)	4.2 (4.6)	1.9 (1.5–2.5)
1960 to 1982	1.2 (1.0–1.4)	0.3 (0.3–0.4)	4.0 (3.3–4.7)	. . .‖	. . .‖	. . .‖
1983 to 1998	0.8 (0.6–1.1)	0.08 (0.05–0.1)	10.8 (6.5–18.0)	. . .‖	. . .‖	. . .‖
Atrial fibrillation	3.6 (2.9–4.4)	0.7 (0.6–0.8)	6.0 (4.5–7.9)§	12.7 (10.5–15.2)	7.7 (7.2–8.2)	1.8 (1.5–2.3)§
Congestive heart failure	4.2 (3.4–5.2)	0.6 (0.5–0.7)	8.1 (6.0–10.8)§	12.5 (10.1–15.5)	7.9 (7.4–8.4)	1.8 (1.4–2.3)§
Mechanical heart valve	3.7 (2.5–5.3)	0.4 (0.3–0.6)	6.6 (4.2–10.5)§	8.2 (3.7–18.2)	5.6 (4.2–7.4)	1.7 (0.7–4.1)§

Older indicates ≥60 years; UVH, univentricular heart; Young, <60 years.
*Per 1000 Person-Years.
†Adjusted for sex and birth year.
‡Not applicable.
§Sex- and birth year-matched controls.
‖No observations.

Table 3. Incidence Rates of Ischemic Stroke in Congenital Heart Disease Adults According to CHA_2DS_2VASc Score

	CHA_2DS_2VASc Score			
	0	1	≥2	Total
No. of events	210	34	278	522
Rate per 1000 PY (95% CI)	1.0 (0.9–1.2)	5.6 (4.0–7.8)	9.4 (8.3–10.5)	2.2 (2.0–2.3)
Hazard ratio (95% CI)	1 (reference)	3.7 (2.5–5.4)	4.5 (3.6–5.7)	. . .

One point for female sex, if in presence of ≥1 of the other covariates. Two points for age ≥75 years and previous thromboembolic disease.
$CHA_2DS2VASc$ score indicates one point for congestive heart failure, hypertension, age 65 to 74 years, diabetes mellitus, and vascular disease; PY, person-years.

Lanz et al[9] examined stroke risk in a Canadian CHD population. At 64 years of age the cumulative incidence of ischemic stroke was 6.1% (95% CI: 5.0–7.0) for female CHD adults and 7.7% (95% CI: 6.4–8.8) for male CHD adults, both estimates that are similar to our cumulative incidence for CHD adults at 60 years of age. Mandalenakis et al[8] evaluated the risk of stroke in a relatively young CHD population compared with a general population comparison cohort. They followed subjects until a maximum of 42 years of age, at which point the cumulative incidence of stroke was 1.5% in the CHD population and 0.2% in the general population. These incidences equated to an HR of 10.8 for ischemic stroke in CHD subjects. The higher HR, compared with our results, is likely owing to a younger age at end of follow-up (42 years versus 60 years of age for our young category). The study by Lanz et al[9] reported a 30-day mortality of 5.1% for ischemic stroke, comparable with our finding for CHD adults in the older category (5%, 95% CI: 3%–8%). When considering both of these studies relative to our own, it is important to note some of the differences in study design and study populations. In particular, Lanz et al[9] did not include a comparison cohort, which precluded the ability to determine the relative risk in the CHD population. While the study by Mandalenakis et al[8] did include a comparison cohort, the study population represented children and young adults with CHD. Our findings add to those findings by following the CHD adults into older ages, when the stroke risk is more substantial in the general population. In addition, our study adds information about the ischemic stroke risk relative to measurable clinical factors such as atrial fibrillation, as well as providing a description of present day antithrombotic therapy practices.

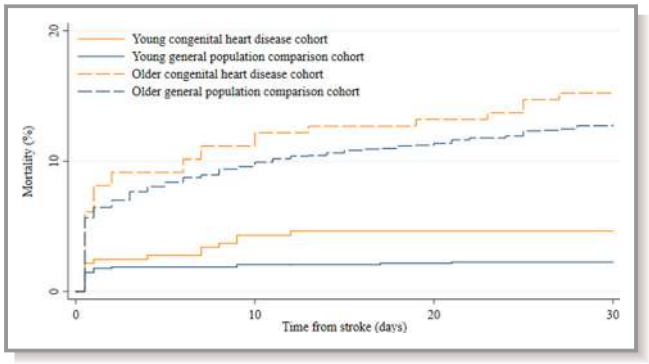

Figure 2. Thirty-day post-ischemic stroke mortality in congenital heart disease adults and the general population according to young (<60 years) and older age (≥60 years).

Heart failure is a well-established risk factor for stroke in the general population, commonly explained by hemodynamic changes that potentially lead to thrombus formation.[21] In line with this, we found that the aHR of ischemic stroke in young CHD adults compared with their sex- and birth year-matched controls was higher among those with a diagnosis of chronic heart failure. This finding suggests that chronic heart failure worsens an already challenging situation. The same applies for atrial arrhythmias and mechanical heart valves, which are also well-known stroke risk factors.[2,7]

Previous attempts to use the CHA_2DS_2VASc score to predict thromboembolic risk in CHD patients suffering from AFib have shown conflicting results.[22,23]. The different distribution of age and type of supraventricular arrhythmia in these studies may to some extent explain this inconsistency. Our study demonstrates an increasing incidence of ischemic stroke in CHD adults, including those without AFib, with a CHA_2DS_2VASc score above 0. While the "CONgenital COR vitia" study found an association between a CHA_2DS_2-VASc score of 2 or above and stroke[23], we demonstrate an increased relative risk of ischemic stroke in CHD adults with a score of ≥1 (HR=3.1, 95% CI: 2.1–4.5). Further research is necessary to determine the clinical prospective value of the CHA_2DS_2VASc score when evaluating and attempting to predict the ischemic stroke risk of adults with CHD.

Strengths and Limitations

The main strengths of this study are the large sample size, duration of follow up, and the limited selection bias afforded by the nationwide coverage and virtually complete follow-up in the Danish registries.

The positive predictive value in the DNPR of an overall CHD diagnosis is ≈90%.[12,24] However, we do not know the positive

Table 4. Proportions of Individuals, Living in Denmark on December 31, 2016, Filling in Prescriptions of Antithrombotic Therapy during 2015–2016

	Proportion, % (95% CI)			
	Congenital Heart Disease Cohort (n=14 856)		General Population Comparison Cohort (n=157 505)	
Antithrombotic therapy	1 to 4 prescriptions	≥5 prescriptions	1 to 4 prescriptions	≥5 prescriptions
Vitamin K antagonist	1% (1.0–2.0)	7% (6.9–7.7)	0.2% (0.2–0.2)	0.8% (0.7–0.8)
Non-vitamin K antagonist	1% (1.0–1.4)	2% (1.3–2.0)	0.4% (0.4–0.4)	0.5% (0.5–0.6)
Platelet aggregation inhibitors	4% (3.4–4.1)	5% (4.6–5.3)	2% (1.8–1.9)	3% (3.2–3.4)

predictive value of the specific CHD defects and misclassification of specific CHD diagnosis, and therefore also CHD complexity, may be present. Furthermore, in some cases *ICD*-codes were insufficiently specific to conclude CHD severity.

The positive predictive value of an ischemic stroke diagnosis in the DNPR is reportedly between 88% and 97%.[25,26] Up to 69% of "unspecified strokes" are also ischemic strokes.[26] The known positive predictive values of the CHA_2DS_2VASc-score covariates in the DNPR are as follows: congestive heart failure 76%,[27] arterial hypertension 92%,[27] prior transitory ischemic attack 60% to 68%,[25,26] hemorrhagic stroke 66% to 74%,[25,26] diabetes mellitus 96%,[28] atherosclerosis 69%,[29] and myocardial infarction 92% to 97%.[27]

In this study we include descriptive data on the use of antithrombotic therapy in CHD adults as well as the general population. We included this data to accommodate criticism of previous studies.[10] However, on the basis of this data our ability to understand the impact on ischemic stroke risk in the CHD population is limited. Future studies may investigate how use of antithrombotic therapy affect the risk of ischemic stroke in adult CHD patients.

A potential limitation of the study includes the possibility of surveillance bias given that CHD adults may enter the healthcare system more frequently relative to the general population cohort. However, because ischemic stroke is an acute clinical diagnosis, which often appears spontaneously without warning symptoms, there is less likelihood that frequent visits to the doctor will affect the detection of ischemic stroke compared with other acquired conditions. We therefore do not believe that surveillance bias can explain the observed difference in ischemic stroke risk.

We classified simple CHD as patients who had not undergone cardiac surgery. However, because our data spread across several decades some patients may not have received operation because they were deemed inoperable at the time, causing us to include some potentially high-risk individuals in our simple CHD category.

We included adults in the CHD cohort at the time of CHD diagnosis. Thus, ischemic strokes could potentially for some individuals be left-censored before 1977. Patients born before 1977 who also had a stroke before 1977, may represent high-risk individuals which may cause us to overestimate the association between CHD and ischemic stroke in the early birth categories. However, to the extent that CHD adults experiencing a fatal ischemic stroke before 1977, estimates of the association between CHD and ischemic stroke are conservative. Importantly, this limitation did not pertain to the analyses on subgroups born after 1977.

We assessed post-stroke mortality as all-cause mortality within 30 days of an ischemic stroke. Our data do not allow us to seek out the exact cause of death but given the short window of time between ischemic stroke event and death allows us to infer that a substantial number of deaths within 30 days of stroke will be stroke related.

We considered cardiovascular disease as an intermediate step in a potential causal pathway between CHD and ischemic stroke. As such, to avoid underestimation of any potential association between CHD and ischemic stroke, no cardiovascular diseases were included in the regression model as potential confounders. Documentation of stroke-associated lifestyle factors such as overweight/obesity, smoking habit, and alcohol consumption is generally lacking in our databases. In addition, complete data on the degree and duration of cyanosis were not available. Lastly, we are limited to addressing only clinically significant embolic events.[30]

Conclusions

Adults with CHD have an increased relative risk of ischemic stroke and stroke-associated mortality compared with the general population. This relative risk was particularly high in younger groups aged <60 years, as well as those with traditional stroke risk factors such as heart failure, arrhythmia, and a history of mechanical heart valve replacement. This was despite indications of a high prevalence of anticoagulation therapy use. The impact of traditional stroke risk factors, as measured by the CHA_2DS_2VASc score, seem to be substantial in the adult CHD population. Future studies may include a prospective application of the CHA_2DS_2VASc score to the population of adult CHD patients or potentially

development of a new stroke risk prediction model to predict high-risk CHD individuals for ischemic stroke.

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Disclosures

None.

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Supplemental Material

Table S1. Diagnostic and procedure codes.

	ICD-8	ICD-10
CHD	746-747, except 746.99, 747.59, 747.69, 747.89, 747.99	Q20-Q26, except Q20.9, Q21.9, Q23.1A, Q24.6, Q24.9, Q25.9, Q26.1, Q26.5, Q26.6, Q26.9, Q27
Ischemic stroke	433, 434	I63, I64
Congestive heart failure	42709, 42710, 42711, 42719, 42899, 78249	I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429
Hypertension	400, 401, 402, 403, 404	I10, I11, I12, I13, I15
Diabetes mellitus	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10, E11, E12, E13, E14, G632, H360, N083
Systemic embolism	444.0, 444.1, 444.2, 444.3, 444.4, 444.9	I74, K550, N280
Transitory ischemic attack	435.09, 435.99	G450, G451, G452, G458, G459
Hemorrhagic stroke	431	I61
Peripheral vascular disease	440, 443.99	I70, I739
Myocardial infarction	410	I21, I22
Atrial fibrillation/flutter	42793, 42794	I48

	Danish National Classification System of Surgical Procedures and Therapies	**Nordic Medico-Statistical Committee Classification of Surgical Procedures**
Mechanical mitral valve prosthetic	31130	KFKD00
Mechanical aortae valve prosthetic	31269	KFMD00
Coronary procedures		KFNA KFNB KFNC KFND KFNE KFNF KFNG KFNH
	Anatomical Therapeutic Chemical Classification codes	***Generic drug name***
Vitamin K Antagonists	B01AA03	Warfarin
	B01AA04	Phenprocoumon
Non-vitamin K antagonist	B01AF01	Rivaroxaban
	B01AF02	Apixaban
	B01AF03	Edoxaban
	B01AE07	Dabigatran etexilate
Platelet aggregation inhibitors	B01AC04	Clopidogrel
	B01AC06	Acetylsalicylic acid

B01AC22	Prasugrel
B01AC24	Ticagrelor