FACULTY OF HEALTH SCIENCE, AARHUS UNIVERSITY

Ischemic Stroke in Adults with Congenital Heart Disease: a population-based cohort study

Research Year Report

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Preface

This research year report is based on a study conducted during my research year at the Department of Clinical Epidemiology, Aarhus University Hospital, from September 2016 to August 2017.

I would like to say a massive *Thank you* to all my fellow research year students for creating a fun and supportive work environment. It has been an absolute pleasure and it would not have been the same without you.

During my research year, I have had the advantage of a tremendously competent supervisor team. Thank you, Morten Schmidt and Nicolas Madsen, for contributing with your invaluable clinical knowledge, for your positive energy and for understanding the importance of constructive feedback. A *special* thank you to my main supervisor Morten Olsen, for patiently guiding me and for continuously being available to discuss my thoughts and answer all of my questions.

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List of abbreviations

AFib	Atrial Fibrillation
aHR	adjusted Hazard Ratio
CHA_2DS_2VASc	Congestive heart failure, Hypertension, Age, Diabetes Mellitus, prior stroke, Vascular disease, Age, Sex category
$CHADS_2$	Congestive heart failure, Hypertension, Age, Diabetes Mellitus, prior stroke
CHD	Congenital Heart Disease
CPR	Civil Personal Registration
DNPR	Danish National Patient Registry
HR	Hazard Ratio
ICD	International classification of disease
IQR	Interquartile range
NOAK	Non-vitamin K Oral Anticoagulants
PPV	Positive predictive value
VKA	Vitamin-K antagonist

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Abstract (1,198 characters)

Background: Congenital heart disease (CHD) is associated with risk factors for ischemic stroke *i.e.* cardiac arrhythmias and heart failure.

Methods: Using Danish nationwide registries, we identified individuals aged ≥18 years diagnosed with CHD, at any age, from 1963 to 2017 and a gender and birth year matched (1:10) general population cohort. We computed cumulative incidences and hazard ratios adjusted for gender and birth year (aHRs) of ischemic stroke and 30-day post-stroke mortality in CHD adults compared with the general population.

Results: We identified 16,836 adults with CHD. The risk of ischemic stroke at age 60 years were 7.4% in the CHD cohort and 2.9% in the general population cohort. The aHRs of ischemic stroke were 3.8 (95% CI: 3.3-4.3) for CHD adults <60 years of age and 1.6 (95% CI: 1.4-1.9) for those aged ≥60 years compared with the general population. Thirty-day post-stroke mortality was increased in CHD adults <60 years of age compared with the general population (aHR=2.3, 95% CI: 1.2-4.4) and for CHD adults ≥60 years of age the aHR of mortality was 1.3 (95% CI: 0.9-1.9).

Conclusion: Adults with CHD have an increased risk of ischemic stroke and stroke mortality.

Dansk resumé (1,177 anslag)

Baggrund: Medfødte hjertefejl (CHD) er associeret med risikofaktorer for apopleksi, så som hjerteflimmer og hjertesvigt.

Metode: Ved brug af danske landsdækkende registre identificerede vi voksne (≥18 år) CHD patienter, diagnosticeret mellem 1963 og 2017 og matchede dem 1:10 på køn og alder med individer fra baggrundsbefolkningen. Vi fulgte dem indtil første apopleksi diagnose, emigration eller død. Vi beregnede kumulative incidenser og justerede hazard ratioer (aHR) for apopleksi og 30-dags post-apopleksi mortalitet blandt CHD patienter i forhold til baggrundsbefolkningen.

Resultater: Vi identificerede 16,836 CHD patienter. Risikoen for apopleksi ved 60 års alderen var 7,4% blandt CHD patienter og 2,9% i baggrundsbefolkningen. aHR for apopleksi var 3,8 (95% CI: 3,3-43) for CHD patienter <60 år og 1,6 (95% CI: 1,4-1,9) for CHD patienter ≥60 år. Tredive-dags mortalitet var øget hos CHD patienter <60 år sammenlignet med baggrundsbefolkningen (aHR=2,3, 95% CI: 1,2-4,4) og aHR for CHD patienter ≥60 år var 1,3 (95% CI: 0,9-1,9).

Konklusion: Apopleksi risiko og 30-dags apopleksi mortalitet blandt danske CHD patienter er øget sammenlignet med baggrundsbefolkningen.

Introduction

Congenital heart disease (CHD) affects approximately 8 per 1000 live births (1). Advances in diagnosis and surgical management have substantially improved survival of children born with CHD, which increases the prevalence of adults living with CHD and the need for research on acquired, long term morbidities (2). Adults with CHD are at greater risk of cardiac arrhythmias and congestive heart failure (3,4), both risk factors for ischemic stroke in the general population (5,6). Other risk factors for ischemic stroke in the adult CHD population include paradoxical embolism (7) and heart surgery with implantation of mechanical heart valves (8,9). Previous studies on the association between CHD and ischemic stroke in adults (10,11) did not include data on mechanical heart valves or anticoagulant medication, data that may help characterize subgroups of CHD adults at particular high risk of ischemic stroke (12). Factors related to CHD, including a history of heart failure, ventricular dysfunction, arrhythmia deconditioning and non-cardiac co-morbidities, may also affect the prognosis following stroke. However, there are few published data on 30-day post-stroke mortality in the adult CHD population (10).

We estimated the risk of ischemic stroke in the adult CHD population in Denmark compared with the general population, overall and according to risk factors. Furthermore, we determined the incidence of ischemic stroke in the adult CHD population in relation to varying CHA_2DS_2VASc scores, and assessed 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 approximately 5.7 million individuals. All Danish citizens are provided tax-supported healthcare 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.

Data Linkage

Since 1968, the Central Office of Civil Registration has assigned all residents in Denmark a unique ten-digit civil personal registration (CPR) number, which is utilized to track residents across all Danish registries (13). 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 (13).

Variable Definitions

Congenital Heart Disease Cohort

We identified all Danish individuals diagnosed with CHD during two separate periods. We utilized medical record reviews, that have been describes previously (14), between the years 1963-1974, as well as the Danish National Patient Registry (DNPR) to identify those diagnosed between 1977-2017. The DNPR contains information on all hospital admissions in Denmark and includes individuals' CPR 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) (15). The 8th edition of the ICD was used until the end of 1993 and the 10th edition thereafter.

We categorized CHD severity as mild/moderate, severe and unclassified complexity. Mild/moderate CHD was classified as atrial septal defect, ventricular septal defect, coarctation of the aorta and patent ductus arteriosus without or with a history of surgical or procedural intervention, respectively. Severe CHD was classified as all defects of greater complexity, such as tetralogy of Fallot and transposition of the great arteries, as well as univentricular CHD.

The diagnostic work up for patients with ischemic stroke may include an echocardiographic examination. In order to minimize potential information bias, we excluded

those who were registered with both a CHD and an ischemic stroke diagnosis within the same 12-month period.

General Population Comparison Cohort

We used the Civil Registration System (13) to identify a general population comparison cohort. We matched on gender and birth year in a ratio of 10 general population individuals per 1 CHD adult.

Ischemic Stroke

Within our cohorts, we identified patients with a primary discharge diagnosis of first-time ischemic stroke in the DNPR (Supplementary table 1).

Mechanical valves

We obtained data on the presence of mechanical valves in the aortic or mitral positon from the DNPR. Surgical procedural codes are presented in Supplementary table 1.

CHA_2DS_2VASc Score Covariates

To establish the CHA_2DS_2VASc score (16) of study subjects during the time of follow up, we identified dates of first-time diagnoses of congestive heart failure, hypertension, diabetes mellitus, thromboembolism and vascular disease in the DNPR (Supplementary table 1). We defined thromboembolic disease as a diagnosis of prior transitory ischemic attack or systemic embolism. We defined vascular disease as a diagnosis of myocardial infarction, atherosclerosis or history of a previous coronary procedure (Supplementary table 1). Based on these covariate definitions, individuals were assigned one point for congestive heart failure, hypertension, age 65-74, diabetes mellitus and vascular disease. One point was assigned for female gender, but only in presence of one or more of the other covariates. Two points were given for age greater than 75 years and previous thromboembolic disease. We defined CHA_2DS_2VASc score categories as zero, one, or two or more points (17).

Antithrombotic therapy

We obtained data on the use of antithrombotic therapy from the National Prescription Registry (18). 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 (Supplementary table 2). We grouped the medications into the following categories: Vitamin K antagonists (VKA), Non-vitamin K oral antagonists (NOAK) and platelet aggregation inhibitors.

Statistical analysis

We followed the CHD cohort and general population cohort from the age of 18 years, date of CHD diagnosis (index date for matched comparison cohort members) or initiation of the DNPR in 1977, which ever came last. Follow up ended on date of first diagnosis of ischemic stroke, death, emigration or end of study (1st of January 2017). We computed cumulative incidences of ischemic stroke for the adult CHD cohort, as well as the general population cohort, while accounting for death as a competing risk (19) and estimated median age at stroke diagnosis in the CHD cohort and the general population cohort. We computed overall incidence rates of ischemic stroke and incidence rates of ischemic stroke according to the presence of congestive heart failure, AFib and mechanical heart valves.

We used Cox's proportional hazards regression analysis to compute gender 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 from the stroke definition. All hazards ratios were computed according to the two categories 'below 60 years of age' and '60 years of age or older'. In subgroup analyses we computed hazard ratios (HRs) of ischemic stroke in adult CHD patients with congestive heart failure, AFib and mechanical valves compared with their gender and

birth year matched members of the general population cohort, with follow-up starting on date of diagnosis and date of operation, respectively (or corresponding index date for matched comparison cohort members). We scored adult CHD patients according to the presence of CHA_2DS_2VASc score covariates (0, 1, ≥2), and computed incidence rates of ischemic stroke in each score category and HRs comparing relative risk of ischemic stroke with a CHA_2DS_2VASc score of 1 or ≥2 compared with a score of 0 among CHD cohort individuals. Scores were included in the Cox models as time-varying covariates.

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

Finally, we assessed the prevalence of filled antithrombotic therapy prescriptions during 2015-2016 in adult CHD patients and 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. Characteristics are presented in Table 1.

During the follow-up period, 3,561 individuals received an ischemic stroke diagnosis; of these, 522 were CHD adults and 3,039 were individuals from the general population cohort. Median age at ischemic stroke diagnosis was 53 years (IQR: 40-67) in the CHD cohort and 69 years (IQR: 55-78) in the comparison cohort. The risk of ischemic stroke by age 30 years was 0.7% (95% CI: 0.6%-0.9%) in the adult CHD cohort and 0.1% (95% CI: 0.1%-0.1%) in the general population cohort. By 60 years of age the risk of ischemic stroke was 7.4% (95% CI:

6.6%-8.3%) in the adult CHD cohort and 2.9% (95% CI: 2.7%-3.1%) in the general population cohort (Figure 1).

The overall incidence rate of ischemic stroke for CHD adults below 60 years of age was 1.5 per 1000 person-years and 0.4 per 1000 person-years in the general population cohort. In CHD adults aged 60 years of age or older the incidence rate of ischemic stroke was 10.2 per 1000 person-years 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 cohort was 3.8 (95% CI: 3.3-4.3) among CHD adults below 60 years of age and 1.6 (95% CI: 1.4-1.9) among those aged 60 years of age or older. Excluding "unspecified stroke" left aHR unchanged [below 60 years of age: 3.8 (95% CI: 3.3-4.5). Above 60 years of age: 1.6 (95% CI: 1.3-1.9)].

The HR of ischemic stroke according to severity category is presented in Table 2. In subgroup analyses the HR of ischemic stroke was 8.1 (95% CI: 6.0-10.8) for CHD adults with congestive heart failure below 60 years of age and 1.8 (95% CI: 1.4-2.3) for those aged 60 years of age or older compared with their gender and birth year-matched controls. HR of ischemic stroke was 6.0 (95% CI: 4.5-7.9) for CHD adults with AFib below 60 years of age and 1.8 (95% CI: 1.5-2.3) for those aged ≥60 years of age compared with their gender and birth year-matched controls. The HR of ischemic stroke was 6.6 (95% CI 4.2-10.5) for CHD adults with a mechanical valve below 60 years of age and 1.7 (95% CI: 0.7-4.1) for those aged 60 years of age or older compared with their gender and birth year-matched controls.

Among CHD adults, we found increasing incidence of ischemic stroke with increasing CHA_2DS_2VASc-scores (Table 3). The HR comparing ischemic stroke risk among those with a score of one to those with a score of zero was 3.1 (95% CI: 2.1-4.5). The HR for those with a score of two or more compared with those with a score of 0 was 3.4 (95% CI: 2.7-4.3).

Thirty-day post ischemic stroke mortality

In individuals younger than 60 years of age at time of ischemic stroke, 30-day mortality was 5% (95% CI: 3%-8%) in the adult CHD cohort and 2% (95% CI: 2%-3%) in the general population cohort (Figure 2). In individuals aged 60 years or older at time of ischemic stroke, 30-day mortality was 15% (95% CI: 11%-21%) in the adult CHD cohort and 13% (95% CI: 11%-14%) in the general population cohort (Figure 3). The mortality rates corresponded to an aHR of dying within 30 days of an ischemic stroke of 2.3 (95% CI: 1.2-4.4) in CHD adults younger than 60 years of age and 1.3 (95% CI: 0.9-1.9) in CHD adults older than 60 years of compared with the general population.

Antithrombotic therapy

By 31st of December 2016, 14,259 CHD patients and 151,000 general population cohort members were alive. Table 4 shows the proportions of CHD adults and general population cohort members that had filled one to four or five or more prescriptions of VKA, NOAK and platelet aggregation inhibitors. The prevalence of filled prescriptions was greater in the CHD cohort in regard to all three medication categories.

Discussion

We found an increased relative risk of ischemic stroke among adults with CHD compared with the general population, in particular among younger adults. Several well described risk factors for stroke, such as heart failure and atrial fibrillation were associated with a higher risk in adults with CHD relative to the general population. CHA_2DS_2VASc scores greater than zero were also associated with higher ischemic stroke risk. In addition, we found an increased risk of dying within 30 days of a first-time ischemic stroke in the CHD population regardless of age.

Lanz *et al.* (10) examined stroke risk in a Canadian CHD population. At 64 years of age (maximum follow-up) 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.* (11) evaluated the risk of stroke in a young adult CHD population compared with a general population 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 a HR of 10.8 for ischemic stroke in CHD subjects. The study by Lanz *et al*. reported a 30-day mortality of 5.1% for ischemic stroke, comparable to our finding for CHD adults younger than 60 years of age [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 follow-up time. In particular, Lanz *et al*. 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.* did include a comparison cohort, the follow up time was limited to a maximum of 42 years of age. Consequently, the findings may over-estimate the lifetime risk by limiting the comparison to a period of time when the general population cohort is healthy. In addition, neither study was able to explore in more depth stroke associated variables such as the presence of a mechanical valve or antithrombotic therapy.

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 (20). A study from Holland found that the incidence admission due to heart failure in young CHD adults is 1.2 per 1000 years (median age at admission: 46.7 years), while the incidence is 0.1 per 1000 years in the general population of the same age (21). As not all patients with heart failure are admitted to the hospital, the true incidence of heart failure is likely higher. In the present study, we found that a diagnosis of chronic heart failure resulted in a further increased HR of ischemic stroke in CHD adults younger than 60 years of age compared with

their gender and birth year matched controls, suggesting that chronic heart failure worsens an already challenging situation. Supraventricular arrhythmias are common among CHD adults with a prevalence around 15% and the lifetime risk by the age of 70 years is 47% (3). Structural abnormalities, surgical implants and scarring as well as hemodynamic stress in the malformed heart may all work as substrate for supraventricular arrhythmias (22,23). Supraventricular arrhythmias are seen across a spectrum of CHD severity and even milder lesions such as atrial septum defects increase the risk (24-26). Among CHD individuals, atrial arrhythmias increase risk of stroke (3) just as we observe that a diagnosis of AFib results in a further increased HR of ischemic stroke for CHD adults younger than 60 years of age. Implantation of a mechanical heart valve introduces a thrombogenic surface into heart. Mechanical heart valves therefore require life-long anticoagulation therapy in all patients. In the present study, we observe that the HR of ischemic stroke is further increased in adult CHD patients with a mechanical valve in either the aortic or mitral position. In the general population, warfarin therapy after mechanical valve implantation reduces the incidence of major embolisms from 4% per year to 1% per year (9). However, achieving a consistent anticoagulated state with warfarin can be difficult. Moreover, CHD patients requiring valve transplantation may differ from other CHD patients in regard to comorbidity and ischemic stroke risk profile.

Previous attempts to use the CHA_2DS_2VASc score to predict thromboembolic risk in CHD patients suffering from AFib have shown conflicting results (27,28). The different distribution of age and type of supraventricular arrhythmia in these studies may to some extent explain the conflicting results. Our study demonstrates an increasing incidence of ischemic stroke in CHD adults with a CHA_2DS_2VASc score above 0. While the CONCOR study found an association between a CHA_2DS_2VASc score of ≥ 2 and stroke (28), we demonstrate an increased relative risk of ischemic stroke in CHD patients with a score ≥ 1 [HR=3.1 (95% CI: 2.1-4.5)]. Further research is necessary to determine if clinicians may consider 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 virtually complete follow-up in the Danish registries.

The positive predictive value (PPV) of an overall CHD diagnosis in the DNPR is reportedly approximately 90% (14,29). The positive predictive value of ischemic stroke in the DNPR is between 87.7%-97.0% (30,31). The same studies report that up to 69% of "unspecified strokes" are also ischemic strokes. The known positive predictive values of the CHA_2DS_2VASc-score covariates in the DNPR are as follows: congestive heart failure 76% (32), arterial hypertension 92% (32), prior transitory ischemic attack 60-68% (30,31), diabetes mellitus 96% (33), atherosclerosis 69% (34), and myocardial infarction 92-97% (32).

A potential limitation of the study includes the possibility of surveillance bias given that CHD adults may enter the health care 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 included adults in the CHD cohort at the time of CHD diagnosis, and for adults born before the initiation of the DNPR in 1977, we cannot know if they experienced an ischemic stroke before 1977. If so, estimates from the early birth year categories may overestimate the association between CHD and ischemic stroke. On the other hand, CHD adults who experienced ischemic stroke before 1977 may very well have died before 1977 given the

associated mortality, in which case our estimates of the association between CHD and ischemic stroke are conservative.

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 lifestyle factors such as overweight/obesity, smoking habit and alcohol consumption is generally lacking in our databases. These lifestyle factors are all associated with ischemic stroke but because of incomplete documentation of these covariates, we cannot comment on any potential confounding effect. In addition to this, our database does not allow for cyanosis to be accurately assessed and we are limited to addressing only clinical significant embolic events even though subclinical embolic event may be highly prevalent in some CHD subgroups (35).

Conclusions

Adults with CHD have an increased risk of ischemic stroke and stroke mortality compared with the general population. This risk is particularly high in younger groups and in those with traditional stroke risk factors such as heart failure, arrhythmia, and a history of mechanical valve replacement. Predicting which CHD adults are at risk of ischemic stroke may be aided by use of the CHA_2DS_2VASc score.

Supplementary information

The following section contains additional background information on stroke as well as methodological and statistical considerations and a discussion of strengths and limitations of my study.

Extended background

Stroke: epidemiology, pathogenesis and risk factors

Stroke is the fourth leading cause of death in the western world. The incidence of stoke in Denmark is approximately 12.000/year. Mortality is high with a 30-days post-stroke mortality of up to 15% and considerable morbidity among survivors (36). Stoke classifies into two major categories: ischemic stroke and hemorrhagic stroke. Ischemic stroke accounts for around 80-85% of all stoke in Denmark. Hemorrhagic stroke encompasses intracranial- and subarachnoid bleeding and accounts for 10-15% of stroke in Denmark (37).

Generally, there are two major causes of ischemic stroke: embolic disease and thrombotic disease both associated with atherosclerotic disease. Thrombotic stroke is the result of thrombus formation based on arteriosclerosis in large cervical and cerebral arteries, obstructing blood flow to downstream brain tissue (38). Embolic stroke occurs when an embolus travels with the bloodstream to the brain. In the brain, the embolus travels though the blood vessels until space is too narrow causing obstruction of the vessel and ischemia of downstream brain tissue. Origin of such clots can potentially be anywhere in the body but most commonly from the heart, the aortae or precerebral arteries such as the bifurcate of the common carotid artery (37). Small vessel disease in the brain causes lacunar infarctions (37). A third, less common, cause of stroke is hypoperfusion during cardiac surgery where lack of sufficient blood perfusion to the brain resulting in ischemia of brain tissue and transient or permanent brain damage.

In an optimal setting, stroke patients are thoroughly evaluated to establish ischemic stroke subtype. This includes evaluation of the patient's clinical presentation, neuroimaging and an assessment of the patients vascular and cardiac condition with vascular imagine of the carotid arteries, 12-lead ECG, to look for recent myocardial infarction or undetected AFib, and a transthoracic echocardiography to look for any cardiac embolic source (38).

Risk factors for ischemic stroke includes basic risk factors such as increasing age and male sex but also a variety of acquired diseases and lifestyle related factors such as smoking, excessive alcohol consumption and obesity. Acquired risk factors of ischemic stroke in the general population also includes hypertension, diabetes, ischemic heart disease, arteriosclerosis, chronic heart failure and AFib (38).

Stroke and congenital heart disease

Many risk factors of ischemic stroke in the CHD population are identical to those acquired in the general population, including AFib and heart failure. Residual shunts, such as a patent foramen ovale, atrial septal defect, or atrial-venous lung shunt, carries the risk of ischemic stroke caused by a paradoxical embolism. The end-organ effects of severe CHD disease include thrombophilia, hypoxia and secondary erythocytosis, associated with Fontan circulation and Eisenmenger syndrome, all of which increase the risk of thrombosis though increased blood viscosity. Iatrogenic causes of ischemic stroke include the risk of hypoperfusion during heart surgery and the risk of embolic stroke in relation to catheterization and electrophysiological studies, not to mention the risk associated with pacemaker implantations, mechanical valves and baffle leaks (12).

CHA_2DS_2VASc-score

The CHA_2DS_2VASc-score is a thromboembolic risk-stratification model used in a clinical setting to evaluate AFib patients' risk of thromboembolic disease and their need for

anticoagulation therapy. CHA_2DS_2VASc is an acronym of congestive heart failure, hypertension, age [≥75 years], diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age [65-74 years], sex category. Age [≥75 years] and previous Stroke/transient ischemic attack weights double in the risk scoring. The score ranges from 0-9 points, with 0 points indicating low risk of thromboembolic disease, 1 point indicating intermediate risk and ≥2 points indicating high risk of thromboembolic disease. Female gender is not perceived as a risk factor for ischemic stroke in the setting of lone AFib in a patient younger than 65 years of age (39). The score is especially relevant when choosing anticoagulation therapy to patients with nonvalvular AFib. Anticoagulation therapy is initiated with a score of 1 or ≥2, while a score of 0 does not require any medical therapy (38). The score is an updated version of the older $CHADS_2$-score that did not include vascular disease, age [65-74 years] and sex category. Studies show that the CHA_2DS_2VASc-score is better than the $CHADS_2$-score at identifying patients truly at low risk of thromboembolic disease and it has now replaced the $CHADS_2$-score in the clinical evaluation of AFib patients (40).

Methodological and statistical considerations

Study design

A cohort study is an observational study in which two or more groups of individuals (cohorts) are followed over time to investigate whether an outcome of interest occurs. Cohorts are characterized by a difference in exposure status of the exposure of investigation (41). The case-control study is another example of an observational study. Cases are chosen bases on their outcome status and controls are characterized by not having the outcome. Controls should be selected from the same source population as the cases and they should have the same risk of exposure as cases. The frequency of an exposure of interest is assessed in both cases and controls and a relative risk can be estimated (41). When exposure status is collected retrospectively there is an increased risk of recall-bias (41). The main pitfalls of observational

studies such as the case-control and the cohort study, is the potential effect of confounding factors and in the case of register based epidemiological studies, the dependency on the precise disease coding in our administrative databases (41). However, as will be elaborated on later, confounding in observational studies can be limited by taking certain precautions in both the design- and the analysis phase of the study. The randomized trial is known for its high place in the hierarchy of research designs, as successful randomization results in an evenly distribution of both known and unknown confounders between study groups (41). Nevertheless, it would be an absurd study design in the case of the present study as it would mean inflicting a group of people with CHD, which would be unethical, if at all possible.

This study was conducted as a cohort study using prospectively collected data from nationwide Danish medical registries. We matched CHD adults 1:10 on gender and birth year with individuals from the general Danish population, minimizing a potential confounding effect of these covariates. Cohorts were dynamic meaning that throughout follow-up individuals could move between cohorts: If an individual from the general population cohort was diagnosed with a CHD during follow-up this individual would move to the exposed cohort of adult CHD patients.

Survival analyses

The study outcome of interest was time until first-time ischemic stroke diagnosis registered in the DNPR, in which setting time-to-event methodology is appropriate. CHD subjects were considered at risk from 18 years of age, from date of CHD diagnosis or the initiation of the DNPR in 1977, whichever came last, known as left truncation or delayed entry. Follow-up continued until first-time diagnosis of ischemic stroke, emigration, death or administrative end of follow-up (1st of January 2017), whichever came first. A general assumption of survival

analysis is independent censoring: censored individuals are representative of those still in the study. Independent censoring cannot be checked statistically but must be assumed (42). The Cox proportional hazard regression is a commonly used method of regression analysis of survival data. In Cox proportional hazard regressions, censoring must be independent given covariates. Moreover, Cox regressions assume proportional hazards. In other words, hazard ratios are constant during follow-up (42).

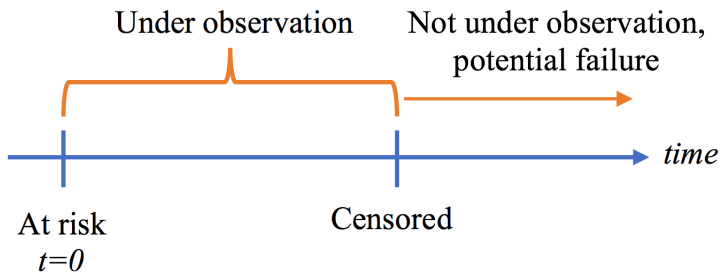
We computed cumulative incidence proportions of ischemic stroke in adult CHD patients and the general population comparison cohort as an absolute outcome measure. This was done as a competing risk analysis as we had to account for death as competing risk rather than censoring. Had we used the Kaplan-Meier estimator, death would be treated as censoring. That is, people who died during follow-up would still be at potential risk of ischemic stroke, which would be absurd. We used the Kaplan-Meier estimator to assess 30-day post-stroke mortality in the two cohorts. As all-cause mortality has no competing risk it was appropriate to use the Kaplan-Meier estimator in this setting (42). We used Cox's proportional hazards regression analysis to compute aHRs as estimates of the relative risk of ischemic stroke in adults with CHD compared with the general population. Futhermore, we conducted subgroup analyses comparing CHD patients with certain risk factors to their 10 matched controls: We computed HRs of ischemic stroke in adult CHD patients with congestive heart failure, AFib and mechanical valves compared with their matched individuals from the general population cohort. In these subgroup analyses, follow-up starting on date of diagnosis for congestive heart failure of AFib and date of operation for those with left sided mechanical heart valves, or the corresponding index date for matched comparison cohort members. When we compare these HR to the overall aHR of ischemic stroke, we see how these risk factors alter the hazard ratios of ischemic stroke in CHD adults. To obtain a deeper understanding of the ischemic stroke risk in younger CHD adults we stratified all analyses according to the two categories 'below 60

years of age' and 'Above 60 years of age, as estimates would otherwise be diluted by the age-related increasing risk of stroke.

Because ischemic stroke is an uncommon event (<15%) we interpret aHR's as relative risks. We assume that the assumption of independent censoring given covariates was fulfilled. We assessed hazard proportionality graphically using log-minus-log plots.

Right censoring and left truncation

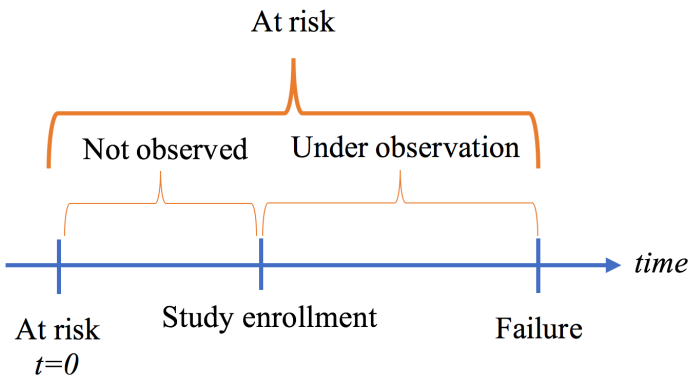
Data is right censored when a study subject is followed for a period and then at one point is no longer observed because of *i.e.* end of follow-up, loss to follow up or prematurely drop out (Supplementary figure 1) (43).



Supplementary figure 1 *Right censoring: A study subject is observed for a period and then at one point is no longer observed but will potential experience the failure event in the future.*

This happens often, as it would require a very long follow-up time to observe the failure event/death in all study subjects. As such, for these individuals, we do not know the actual time from study entry to failure event/death, but we know that they were event free/alive at the end of study and will potentially at some point after the study ends experience the failure of interest/die. We just do not know when. In the present study, we censored individuals who emigrated during follow-up, were lost to follow-up or were failure-free at the administrative end of follow-up on 1st of January 2017.

Sometimes study subjects are at risk of the failure event before they enroll in the study. This phenomenon is called left truncation or delayed entry, and happens when we have incomplete observation prior to study enrollment (Supplementary figure 2) (43).



Supplementary figure 2 *Delayed entry/left truncation: The study subject is at risk of the failure event before enrolling in the study causing incomplete observation on the left side of the timeline.*

In present study, patients entered the CHD cohorts at any time from 18 years of age. If a patient is diagnosed with a CHD at 52 years of age, they entered the CHD cohort. As you are born with a CHD, the patient has been at risk, but not under observation, since the age of 18 years (inclusion criteria). For patients born after the initiation of the DNPR in 1977 this is not a big problem, as we excluded individuals with ischemic stroke prior to their CHD diagnosis. However, as we included patients born from 1910, these patients do not come under observation until 1977. Theoretically, the oldest of these individuals could turn 67 years before entering observation. If a major proportion of our CHD patients had an ischemic stroke before 1977 and this lead to their CHD diagnosis, by including these patients, we include a potentially high-risk CHD population in our study. This would lead to an over-estimation of association between CHD and stroke. If instead a substantial proportion of the CHD patients that experience an ischemic stroke before 1977 also dies before coming under observation in 1977, our estimates of the association between CHD and ischemic stroke are conservative. Either

way delayed entry does not affect the estimates of later birth categories in which we have close to complete follow-up from birth.

Strengths and limitations

The strengths of this study include 1) long-term follow-up, which ensures that enough study individuals experience the outcome of interest 2) The population based nature that minimizes selection bias 3) The general population cohort makes it possible for us to compare CHD patients with non-CHD patients providing an important perspective in interpretation of our results.

Nonetheless, the study is not without limitations. Like all other observational studies, cohort studies are susceptible to random- and systematic error (bias). These determine the study's internal validity.

Random error

Random error is the normal variation on an estimate that is not attributable to systematic error. It is a variation in data ascribed to chance that results in measurement variation and it is reducible by increasing study power (44).

Systematic error

Systemic error, so called bias, is not attributable to chance and is insensitive to increasing study power (41). Systemic error consists of selection bias, information bias and confounding.

Selection bias

Selection bias is introduced when the association between exposure and outcome differs between study participants and non-participants/drop-outs (44). Close-to-complete follow-up for death, emigration and ischemic stroke provided by the Civil Registration System and the DNPR reduces the risk of selection bias due to loss to follow-up. Furthermore, these medical registries cover the entire Danish population that has universal and free access to primary- and

hospital healthcare services. Still, if patients with undiagnosed CHD differ in regard to risk of ischemic stroke from patients with a CHD diagnosis, this could lead to selection bias. As follow-up start at 18 years of age, a proportion of CHD patients will have died before start of follow-up. We do not know how their ischemic stroke risk would be had they lived long enough. If the risk of ischemic stroke is greater among these than the CHD patients that we observe in the study, it reduces the generalizability of our results to this population.

Work-up after an ischemic stroke may, in the optimal setting, include an echocardiographic that could potentially unmask an asymptomatic CHD. To avoid wrongfully selecting patients into the CHD cohort because of an ischemic stroke diagnosis we exclude patients who receive both a CHD and an ischemic stroke diagnosis within the same 12-month period. This may have led to exclusion of some individuals who received a CHD and ischemic stroke diagnosis independently but by chance within the same 12-month period.

Information bias

When a study participant is incorrectly classified (misclassified) in regard to either exposure or outcome variable we risk introducing information bias to our study. When misclassification distributes equally between exposure/outcome groups, we say it is non-differential misclassification which leads to bias towards no association. Misclassification that is differential between the two exposure/outcome groups introduces bias on our estimates (41).

The validity of exposure and outcome variables is crucial to minimize bias in research studies based on medical registries. Validity is a term used to describe data's ability to measure what is intended (45). The positive predictive value (PPV) of a diagnosis describes the probability that a patient diagnosed with a disease truly has the disease (41). The PPV is a commonly used measure of diagnose validity in the DNPR. True disease status is typically assessed through medical record reviews.

We identified adult CHD patients though the DNPR. Our results therefor depend on the validity of the CHD and ischemic stroke diagnosis in the DNPR. The positive predictive value of an overall CHD diagnosis in the DNRP is reportedly approximately 90% (14,29). The specific CHD diagnoses have not been validated yet. We expect any potential misclassification of CHD to be non-differential in regard to the study outcome, as data was registered prospectively, mandatorily and independently from the study outcome. The positive predictive value of the ischemic stroke diagnosis in the DNPR is high, reportedly between 87.7%-97.0% (30,31). The same studies report that up to 69% of "unspecified strokes" are also ischemic strokes. We did a sensitivity analysis in which we excluded patients with ICD-10 code I64 to see if excluding patient with "unspecified strokes" affected our estimate. As this was not the case, these patients were kept in the study to increase power in our analysis but at the expense of loss of specificity on our outcome diagnose.

Confounding

Confounding is bias caused by confusion of effects, in the sense that the effect of an exposure can be completely or partially explained by the effect of another variable, the confounder (44). To be a confounder variable, the variable must be 1) associated with the exposure, 2) associated with the outcome of interest independently from the exposure variable and 3) not be an intermediate step in the causal pathway between exposure and outcome.

There are multiple ways to deal with confounding both in the phase of designing the study and during data analysis. In clinical trials, the aim of randomization of patients to experimental groups is to create groups with a similar distribute of characteristics. Randomization can control both known and unknown confounding factors. Restriction can control for known confounding factors by excluding it/them from the study. In cohort studies matching on confounding factors, such as age or gender, between the exposed and unexposed cohorts can control known confounders (44). In the present study, we used individual matching

to control for gender and age as confounding factors. We selected ten unexposed individuals from the general population per one CHD patients, matched on gender and age. Confounding can also be dealt with during data analysis through stratification and by adjusting in regression models (44).

Arguably, an increased risk of ischemic stroke in the CHD population could be caused by factors other than the CHD. Both AFib, congestive heart failure and left-sided mechanical valves are risk factors for ischemic stroke and associated with CHD. However, we considered these factors as intermediate steps in a potential causal pathway between CHD and stroke. As such, to avoid underestimation of any potential association between CHD and stroke, we did not include these factors in the regression models as potential confounders. In the main analysis, we adjusted for gender and age in our cox regression analyses.

Clinical perspectives and future studies

The increasing survival of children born with congenital heart diseases has resulted in a population of adult CHD patients that is growing and aging. Because of this, it is increasingly important to understand the long-term morbidity associated with growing old with a CHD. Ischemic stroke is a severe disease that carries high mortality and morbidity. However, proper anticoagulation therapy reduces the risk of ischemic stroke in patients for whom it is relevant.

Our study results, along with previous studies on CHD and stoke (10,11) highlights the elevated stoke risk among adult CHD patients and the need for a targeted intervention by clinicians to identify potential high-risk CHD patients. As such, this study aids a better clinical understanding of the risk of ischemic stroke associated with living with a congenital heart disease. Furthermore, our study indicates that the CHA_2DS_2VASc score could be a usable tool in identifying adult CHD patients at risk of ischemic stroke. Forthcoming studies might elucidate this correlation, possibly improving preventive therapy for this patient group.

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Tables

TABLE 1: Cohort characteristics	Congenital Heart Disease Cohort		General Population Cohort	
	N	%	N	%
All	16,836	100	168,360	100
Gender				
Male	8,207	49	82,070	49
Female	8,629	51	86,290	51
Birth year				
1910-1939	1,356	8	13,560	8
1940-1959	2,704	16	27,040	16
1960-1982	6,279	37	62,790	37
1983-1998	6,497	39	64,970	39
CHD Severity				
Mild/moderate	10,332	61	-	-
Severe incl. univentricular heart	4,247	25	-	-
Severity not classified	2,257	13	-	-
Age at first CHD diagnosis				
0 - 10 years	9,942	59	-	-
Above 10 years	6,894	41	-	-
Major CHD diagnoses				
Atrial septal defect	3,568	21	-	-
Ventricular septal defect	3,946	23	-	-
Patent ductus arteriosus	1,534	9	-	-
Truncus Arteriosus	76	<1	-	-
Coarctation of the aorta	971	6	-	-
Tetralogy of Fallot	626	4	-	-
Transposition of the great arteries	363	2	-	-
Other	5,828	35	-	-
Comorbidity				
Atrial fibrillation	2,066	12	4,765	3
Chronic heart failure	1,945	12	3,403	2
Mechanical valve implant	455	3	100	<1

TABLE 2: Incidence rates and relative risk of stroke in adult CHD patients compared with the general population

	Below 60 years of age			60 years of age or older		
	Incidence rate per 1000 (95% CI)		aHR* (95% CI)	Incidence rate per 1000 (95% CI)		aHR* (95% CI)
	Congenital heart disease cohort	General population cohort		Congenital heart disease cohort	General population cohort	
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)
Gender						
Male	1.4 (1.2-1.6)	0.5 (0.4-0.5)	3.4 (2.8-4.1)	12.2 (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 year						
1910-1939	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)
1940-1959	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)
1960-1982	1.2 (1.0-1.4)	0.3 (0.3-0.4)	4.0 (3.3-4.7)	-[†]	-[†]	-[†]
1983-1998	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 valves	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)[‡]

[*]Adjusted for gender and birth year
[†]No observations
[‡]Gender and birth year matched controls
[§]Not applicable
CHD: Congenital heart disease
UVH: Univentricular heart

TABLE 3: Incidence rates of ischemic stroke in adult CHD patients according to CHA_2DS_2VASc score

		CHA_2DS_2VASc score*		
	Total	0	1	≥ 2
Failures, n	522	239	36	247
Person-time	242,185	208,137	6,313	27,735
Rate/1000 (95% CI)	2.2 (2.0-2.3)	1.1 (1.0-1.3)	5.7 (4.1-7.9)	8.9 (7.9-10.1)
Hazard ratio (95% CI)	-	1 (reference)	3.1 (2.1-4.5)	3.4 (2.7-4.3)

*Congestive heart failure, Hypertension, Age >65 years, Diabetes Mellitus, prior stroke, Vascular disease, Age >70 years, Sex category

TABLE 4: Proportions of individuals, living in DK on the 31st of December 2016, filling in prescriptions of anticoagulation therapy during 2015-2016

	Proportion, % (95% CI)			
	Congenital Heart Disease Cohort (n= 14,856)		General Population Cohort (n=157,505)	
Anticoagulation therapy	1-4 prescriptions	≥ 5 prescriptions	1-4 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)

Figures

FIGURE 1: Ischemic stroke risk in congenital heart disease adults and general population individuals

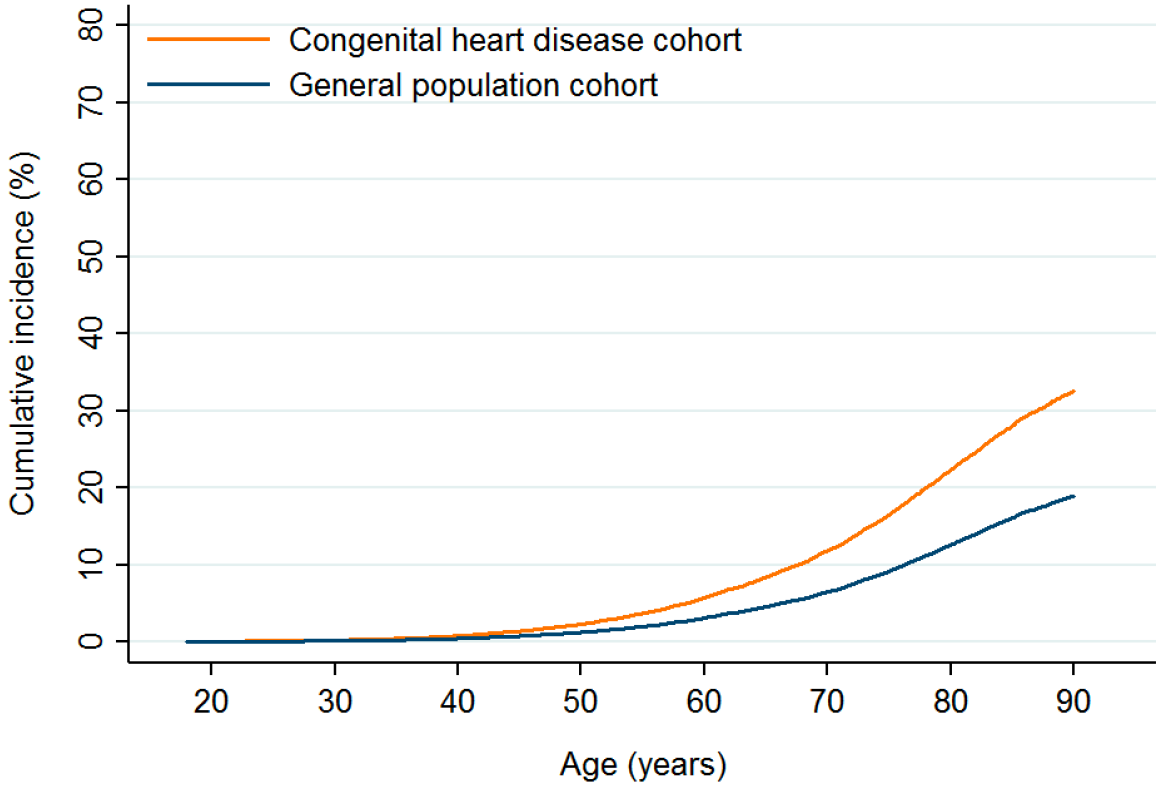
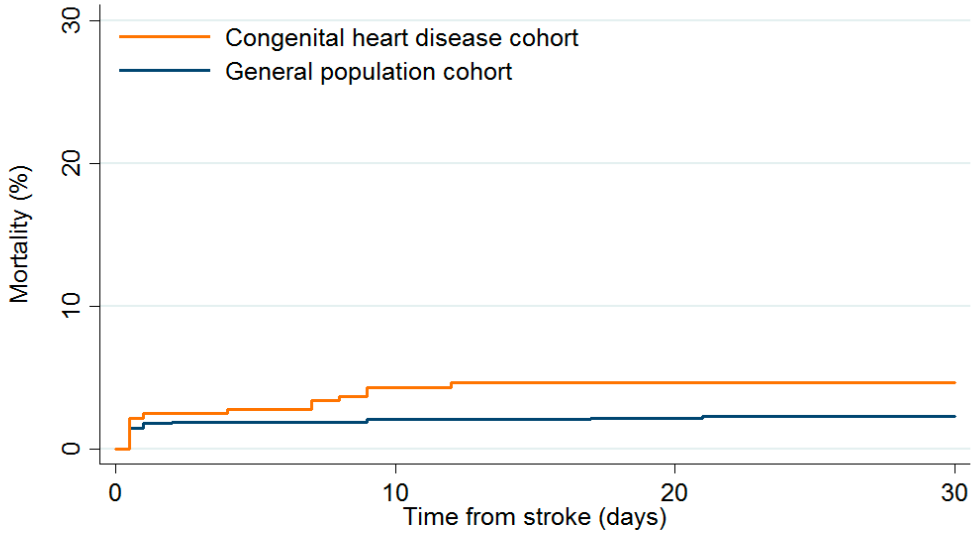
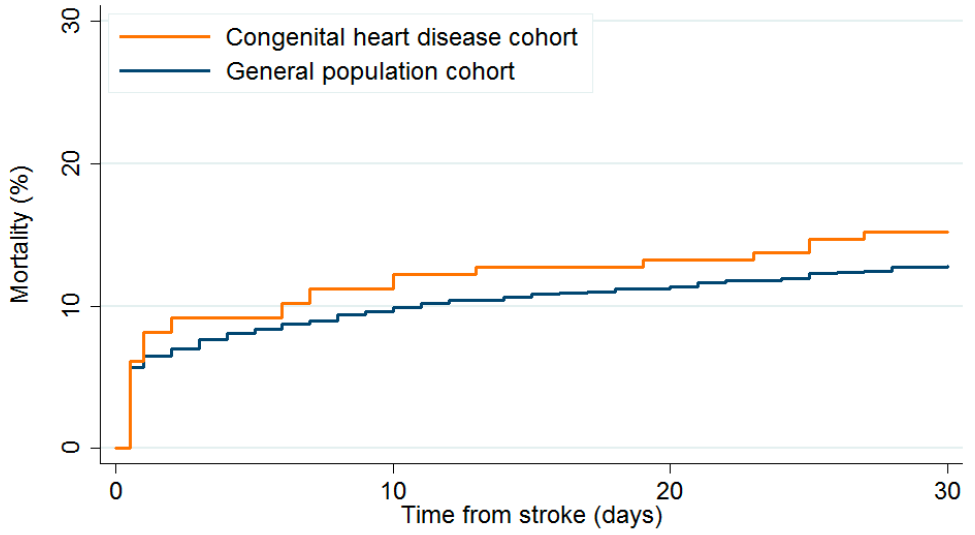


FIGURE 2: 30-day post-ischemic stroke mortality in congenital heart disease adults and general population individuals below 60 years of age



Number at risk				
General population cohort	1024	1001	999	998
Adult CHD cohort	325	311	309	308

FIGURE 3: 30-day post-ischemic stroke mortality in congenital heart disease adults and general population individuals aged 60 years or older



Number at risk				
General population cohort	2015	1818	1780	1747
Adult CHD cohort	197	175	171	167

Appendix

Supplementary table 1: Diagnostic and procedure codes

	ICD-8	ICD-10
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
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		KFN

Supplementary table 2: Anatomical Therapeutic Chemical Classification codes

	ATC-code	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