Stroke in Adults With Congenital Heart Disease
Incidence, Cumulative Risk, and Predictors

Jonas Lanz, MD, MSc; James M. Brophy, MD, PhD; Judith Therrien, MD; Mohammed Kaouache, PhD; Liming Guo, MSc; Ariane J. Marelli, MD, MPH

Background—Stroke is an important cause of morbidity and mortality, although there is a lack of comprehensive data on its incidence, cumulative risk, and predictors in patients with adult congenital heart disease.

Methods and Results—This retrospective study of 29,638 Quebec patients with adult congenital heart disease aged 18 to 64 years between 1998 and 2010 was based on province-wide administrative data. The cumulative risk of ischemic stroke estimated up to age 64 years was 6.1% (95% confidence interval [CI], 5.0–7.0%) in women and 7.7% (95% CI, 6.4–8.8%) in men; the risk of hemorrhagic stroke was 0.8% (95% CI, 0.4–1.2%) and 1.3% (95% CI, 0.8–1.8%), respectively. Compared with rates reported for the general Quebec population, age-sex standardized incidence rates of ischemic stroke were 9 to 12 times higher below age 55 years and 2 to 4 times higher in the age group 55 to 64 years; hemorrhagic stroke rates were 5 to 6 times (age <55 years) and 2 to 3 times higher. Using a combination of stepwise model selection and Bayesian model averaging, the strongest predictors of ischemic stroke were heart failure (odds ratio for age group 18–49 years, 5.94 [95% CI, 3.49–10.14], odds ratio for age group 50–64 years, 1.68 [95% CI, 1.06–2.66]), diabetes mellitus (odds ratio, 2.33 [95% CI, 1.66–3.28]), and recent myocardial infarction (odds ratio, 8.38 [95% CI, 1.77–39.58]).

Conclusions—Among patients with adult congenital heart disease, 1 in 11 men and 1 in 15 women experienced a stroke between ages 18 and 64 years. Stroke incidence was considerably higher than in the general population, especially at a younger age. The most important predictors of ischemic stroke were heart failure, diabetes mellitus, and recent myocardial infarction. Additional research is required to see whether advances in the management of adult congenital heart disease may reduce this substantial stroke rate.

(Circulation. 2015;132:2385-2394. DOI: 10.1161/CIRCULATIONAHA.115.011241.)

Key Words: epidemiology ■ heart defects, congenital ■ incidence ■ risk factors ■ stroke

A

approximately 1% of live births are affected by a defect of the heart or great vessels.1 Advances in congenital heart disease (CHD) management have improved survival,2,3 but paradoxically they have highlighted unique needs arising from lifelong comorbidities.4,5

Clinical Perspective on p 2394

There is a growing body of evidence that the heart-brain axis constitutes an important source of neurodevelopmental impairment in patients with CHD.4 Adult CHD (ACHD) patients are thus susceptible to a multitude of factors that may result in cumulative neurologic impairment. In this study we turn our attention to the understanding of the frequency and predictors of stroke. In the ACHD population, stroke may be related to paradoxical embolization through right-to-left shunts,7 previous palliative and corrective surgeries,8 infective endocarditis,9 cyanotic heart defects,10 or rheological problems, as well as to acquired risk factors for stroke.11 Although there are numerous stroke case studies,11-13 comprehensive data on stroke in patients with ACHD is lacking. Thus, the objective of this study was 3-fold: (1) to estimate the incidence rate and cumulative risk of ischemic and hemorrhagic stroke in a population-based ACHD cohort, (2) to compare these findings with the general adult population, and (3) to identify the strongest predictors of stroke in patients with ACHD.

Methods

Data Sources
In Quebec, a unique healthcare number is assigned to all individuals at birth and is systematically linked to all diagnoses and health services rendered for the duration of a patient’s life. At the McGill Adult Unit for Congenital Heart Disease Excellence, 3 administrative databases (the physicians’ services and drug claim database [Régie de l’Assurance Maladie du Québec], the hospital discharge summary database [Med-Echo], and the Quebec Health Insurance Board) have been merged to create the Québec Congenital Heart Disease...
Database, a province-wide, population-based CHD data source.\textsuperscript{6} It encompasses more than 84,000 patients with ACHD containing comprehensive longitudinal, demographic, diagnostic, and therapeutic records of patient-linked encounters with the healthcare system in Quebec between January 1, 1983, and March 31, 2010. By law, attestation of death is sent to the Quebec Health Insurance Board, increasing the likelihood of capture of death. Approval for the construction and use of the database was granted by the McGill University Health Center ethics board and the Quebec government agency responsible for privacy of access.

**Variable Definitions**

**Congenital Heart Disease**

Diagnostic codes for CHD adhered to the *International Classification of Disease (ICD)*, ninth and tenth revisions. Patients with CHD were identified if they had at least 1 diagnostic code for CHD in the database or if they had undergone a CHD-specific surgical procedure billed by a cardiovascular surgeon based on a previously defined and validated hierarchical algorithm.\textsuperscript{7} Endocardial cushion defects, lesions with single ventricle physiology, tetralogy of Fallot, transposition complex, and truncus arteriosus were classified as severe, because they are the lesions most likely to be cyanotic at birth.\textsuperscript{8} The remaining lesions were categorized based on pathophysiological and anatomic criteria (Table I in the online-only Data Supplement). Defects of septal closure between the right and left sides of the heart and anatomic criteria (Table I in the online-only Data Supplement). The defects of septal closure between the right and left sides of the heart and anatomic criteria (Table I in the online-only Data Supplement). The defects of septal closure between the right and left sides of the heart and anatomic criteria (Table I in the online-only Data Supplement). The defects of septal closure between the right and left sides of the heart and anatomic criteria (Table I in the online-only Data Supplement). The defects of septal closure between the right and left sides of the heart and anatomic criteria (Table I in the online-only Data Supplement).

**Stroke**

The outcome of interest was first hospital admission for ischemic or hemorrhagic stroke based on principal discharge diagnoses. Before 2005, stroke was ascertained by ICD-9 codes (ischemic: 434, 436; hemorrhagic: 431) and afterward by corresponding ICD-10 codes (ischemic: I63, I64; hemorrhagic: I61). For these codes, high positive predictive values have been reported in the general population.\textsuperscript{9,10} An additional code for computed tomography or magnetic resonance imaging of the head or a duplex ultrasound of the carotid arteries at the time of the index hospitalization was required to increase specificity of our stroke definition. For exclusion of patients with previous stroke, ICD-9 code 438 (late effects of cerebrovascular disease) and ICD-10 code I69 (sequelae of cerebrovascular disease) were used in addition. The term stroke used in the sections below refers to first hospital admission for stroke.

**Comorbidities, Surgeries, and Interventions**

Comorbidities were ascertained based on ICD-9 and -10 codes from inpatient (Med-Echo) and outpatient (Régie de l’Assurance Maladie du Québec) data (Table II in the online-only Data Supplement). If codes originated from outpatient data, at least 2 corresponding codes were required for a positive covariate status to increase specificity.\textsuperscript{11} Surgeries and interventions were identified based on procedural billing codes submitted by eligible specialists (Table III in the online-only Data Supplement). Cardiac surgery was defined as any surgery on the heart or aorta; high-risk surgery additionally included interventions on the carotid artery.\textsuperscript{12}

**Study Population and Design**

**Cumulative Risk Cohort**

This is a retrospective, population-based cohort study. Inclusion criteria for the cumulative risk cohort were the assignment of a specific CHD diagnosis and the contribution of any person-time within the age-range from 18 to 64 years between January 1, 1998, and March 31, 2010. Patients with a stroke in the 10 years before meeting the inclusion criteria were excluded to rule out pre-existing disease (washout period).

Because the echocardiographic workup after a stroke or transient ischemic attack frequently leads to detection of a patent foramen ovale (PFO),\textsuperscript{13} and because the same ICD-codes (ICD-9: 745.5, ICD-10: Q21.1) are used for PFOs and ostium secundum type atrial septal defects (ASDs), these patients may be selected into the database conditional on having had a stroke or transient ischemic attack. Therefore, patients receiving their first-ever ICD-9 code 745.5 or ICD-10 code Q21.1 within a year of a stroke or transient ischemic attack were excluded to reduce selection bias. Sensitivity analyses were conducted to assess the extent of potential underestimation or overestimation of cumulative risks introduced by this exclusion criterion. For sensitivity analysis A, person-time for ASD/PFO patients was only counted from the time of first assignment of a corresponding ICD code in the database. Therefore, temporality between discovering the lesion and experiencing the outcome was assured and the selection bias removed; however, this reduced person-time, because CHD is by definition present from birth, independent of the age at diagnosis. Sensitivity analysis B was directed at assessing the impact of potentially excluding not only PFO but also some true patients with ASD. Therefore, a random sample of 10\% of the excluded patients was re-included based on the assumption that the ratio of PFO versus ASD lesions among stroke patients would be no less than 9:1. This ratio is reasonable considering the prevalence proportions of PFO and ASD lesions observed in the general population\textsuperscript{20} and in stroke patients.\textsuperscript{7,21}

Additional sensitivity analyses were performed to assess the impact of including patients with unspecified lesions, the impact of changing from ICD-9 to ICD-10 coding, and the impact of applying a 15-year instead of a 10-year stroke-free washout period. For comparison of incidence rates with rates observed previously in the general population by Mayo et al.,\textsuperscript{22} a cohort starting at age 15 years was used, only ICD-9 codes were considered, and no additional imaging codes were required to enable a contrast using the same definitions.

**Nested Case–Control Subcohort**

A nested case–control design was used to assess the ability of lesion categories, comorbidities, and interventions to predict ischemic stroke. For hemorrhagic stroke, the number of events per variable was too low for reliable statistical inferences.\textsuperscript{23} Ischemic stroke cases were matched 1:4 with control patients on exact calendar day and age (caliper matching within 6 months). Matching on calendar time ensures approximation of the incidence rate ratio (IRR) by the odds ratio (OR)\textsuperscript{24} and accounts for any temporal trends in stroke incidence\textsuperscript{25} matching on age effectively controls for the most important confounder. Within the nested case–control cohort, baseline comorbidities were ascertained in the 5 years preceding the index hospitalization of the case, and acute conditions (myocardial infarction or endocarditis) and recent high-risk surgery were determined in the 90 days prior. For surgical history, the longest possible ascertainment window of 15 years was applied. In addition, the proportion of cases with a high-risk surgery, acute myocardial infarction or acute endocarditis during the index hospitalization and 30-day mortality of stroke patients were identified. Furthermore, the prevalence of generally long-standing comorbidities diagnosed in the year after ischemic stroke was determined and compared with proportions obtained at baseline to assess the possibility of an underdetection of risk factors before the stroke.

**Propensity Score–Matched Subcohort**

The effect of incident heart failure on the risk of stroke was assessed using a propensity score–matched subcohort settled within the cumulative risk cohort. This design enabled calculation of absolute risks of stroke by means of Kaplan–Meier analysis while adjusting for confounders. Incident heart failure was defined as the first appearance of a diagnostic code for heart failure in the database. This was assured by applying a 10-year washout period before matching and excluding patients with pre-existing heart failure. For each patient, the propensity of receiving a first diagnosis of heart failure was calculated by means of a time-dependent logistic regression model.\textsuperscript{26} Patients with myocardial infarction, endocarditis, or high-risk surgery in the 90 days before or at the time of the heart failure diagnosis were
excluded, because the strong association of these covariates with heart failure would impede balanced groups. All of the other covariates potentially associated with the outcome according to the nested case–control analysis, as well as "coronary artery disease" and "history of left valve replacement," were included in the model.\textsuperscript{26} Patients with incident heart failure were matched 1:1 on calendar time and propensity score to patients without heart failure (nearest neighbor matching). If the logit of the propensity for cases and matched control subjects differed by >0.2 SDs, the pair was dropped from the analysis.\textsuperscript{27} Sensitivity analyses were conducted to assess the impact of excluding strokes, which occurred within 90 days of acute events (myocardial infarction, endocarditis, or high-risk surgery), on the results of the nested case–control and the propensity score–matched cohort.

Statistical Analysis

Incidence rates were compared by the use of direct standardization. For comparison with the general population of Quebec in 2002,\textsuperscript{22} incidence rates were age and sex standardized to the midyear Quebec population of 2002. The analysis of the cumulative risk of stroke over the course of adulthood accounted for the competing risk of death.\textsuperscript{28} Baseline characteristics and comorbidities of the nested case–control cohort were presented as proportions for categorical variables and median and interquartile ranges for continuous ones. The distributions of covariates within strata of the outcome were compared using univariate conditional logistic regression. Predictors of stroke were first evaluated using a stepwise procedure with a high stay and a low entry threshold \( P \) value of 0.3 to exclude covariates with virtually no probability of an effect and enhance computational efficiency of the following steps. Interaction terms with age were tested for significance at an \( \alpha \) level of 0.05. The selected covariates were implemented in a freely available macro for Bayesian model averaging.\textsuperscript{29} All \( 2^k \) \((k = number \ of \ covariates)\) possible models were considered equally likely a priori and posterior probabilities (PrPs) calculated using the Bayesian information criterion approximation to Bayes factor.\textsuperscript{30} The \( \beta \) coefficient of each candidate variable was calculated as a weighted average of the coefficients from all of the models that included the variable in question with weights equal to posterior model probabilities. Posterior parameter estimates (mean OR), 95% credible intervals (95% CIs), and PrPs where the regression coefficients are non-0 were reported. Bounds for categorization of PrPs were defined at 50%, 75%, 95%, and 99%, corresponding with weak, positive, strong, and very strong evidence for an association with the outcome.\textsuperscript{30}

Baseline characteristics after propensity score matching were assessed using standardized differences.\textsuperscript{31} The impact of incident heart failure on the risk of ischemic stroke was evaluated using Cox proportional hazard models stratified on the matched sets. Time 0 for a given matched pair corresponded with the date of first diagnosis of heart failure. An interaction term with follow-up time was added to test the proportionality assumption. Kaplan–Meier curves contrasting stroke-free survival in patients with incident heart failure and non-heart failure were compared by a stratified log-rank test.\textsuperscript{32} The maximum follow-up period was 10 years, at which surviving subjects were right censored. All of the statistical analyses were conducted using SAS software 9.3 (SAS Institute Inc, Cary, NC).

Results

We identified 30200 eligible patients, of whom 297 had a stroke during the washout period and 265 patients with PFO were excluded (Figure 1). A total of 358 strokes (311 ischemic and 47 hemorrhagic) occurred in the remaining 29638 patients with ACHD over 258045 person-years of follow-up time between January 1, 1998, and March 31, 2010.

Incidence Rates

For women, age-specific incidence rates of ischemic stroke ranged from 29 (age group 18–24 years) to 292 (age group 75–84 years) per 100000 person-years, for men 16 to 304 per 100000 person-years (Table 1). The IRR contrasting age-standardized rates for men and women was 1.35 (95% confidence interval [CI], 1.08–1.69). Rates for hemorrhagic stroke were 5 to 34 per 100000 person-years in women and 10 to 54 per 100000 person-years in men (IRR, 1.69 [95% CI, 0.95–3.02]). The sensitivity analyses aimed at assessing the impact of excluding PFO patients (Table IV in the online-only Data Supplement).

Figure 1. Derivation of the study population and subcohorts. *To exclude pre-existing disease. †Patent foramen ovale (PFO) patients are assigned the same International Classification of Disease (ICD) codes (ICD-9: 745.5, ICD-10: Q21.1) as ostium secundum type atrial septal defects (ASD). Because PFOs are frequently searched for after the occurrence of a stroke or transient ischemic attack (TIA), their inclusion is conditional on the outcome (or a precursor) causing selection bias. Thus, patients receiving their first congenital heart disease (CHD) diagnosis based on 1 of these 2 ICD codes within a year of a stroke or TIA were excluded. N indicates number.
Supplement) or unspecified lesions (Table V in the online-only Data Supplement) from the main cohort, contrasting the change from ICD-9 to ICD-10 coding (Table VI in the online-only Data Supplement) and using a 10-year versus a 15-year wash-out period (Table VII in the online-only Data Supplement), showed IRRs with statistically nonsignificant $P$ values.

IRRs comparing ischemic stroke rates age standardized to the Quebec 2002 midyear population with the rates reported previously for the general 2002 Quebec population were 12.12 (95% CI, 10.41–14.11) in women and 9.37 (95% CI, 8.34–10.52) in men for age group 15 to 54 years; corresponding IRRs for age group 55 to 64 years were 4.23 (95% CI, 3.73–4.80) in women and 2.06 (95% CI, 1.85–2.30) in men (Table VIIIA in the online-only Data Supplement). Results for hemorrhagic stroke are reported in Table VIIIB in the online-only Data Supplement.

**Cumulative Risks**

For an 18-year-old woman, the overall cumulative risk of ischemic stroke over the course of adulthood up to age 64 years was on average 6.8% (95% CI, 5.7–7.8%) and for an 18-year-old man 8.9% (95% CI, 7.6–10.1%). Stratified by stroke type, cumulative risks in women were 6.1% (95% CI, 5.0–7.0%) for ischemic and 0.8% (95% CI, 0.4–1.2%) for hemorrhagic stroke; in men, 7.7% (95% CI, 6.4–8.8%) and 1.3% (95% CI, 0.8–1.8%), respectively (Figure 2A). Intermediate- and long-term mortality-adjusted

---

**Table 1. Age- and Sex-Specific Incidence Rates of Ischemic and Hemorrhagic Stroke**

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strokes, n</td>
<td>Person-Time, y</td>
</tr>
<tr>
<td>Ischemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–24</td>
<td>11</td>
<td>37,871</td>
</tr>
<tr>
<td>25–34</td>
<td>18</td>
<td>42,228</td>
</tr>
<tr>
<td>35–44</td>
<td>29</td>
<td>30,039</td>
</tr>
<tr>
<td>45–54</td>
<td>41</td>
<td>20,955</td>
</tr>
<tr>
<td>55–64</td>
<td>51</td>
<td>17,481</td>
</tr>
<tr>
<td>Crude rate</td>
<td>150</td>
<td>148,574</td>
</tr>
<tr>
<td>Age-adjusted rate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Hemorrhagic |       |       |                    |       |       |                    |
| 18–24       | 2     | 37,871| 5 (1–19)           | 3     | 30,396| 10 (2–29)         |
| 35–44       | 4     | 30,039| 13 (4–34)          | 6     | 19,058| 31 (12–69)        |
| 45–54       | 6     | 20,955| 29 (11–62)         | 7     | 17,789| 39 (16–81)        |
| 55–64       | 6     | 17,481| 34 (13–75)         | 9     | 16,757| 54 (25–102)       |
| Crude rate  | 20    | 148,574| 13 (8–21)         | 27    | 109,471| 25 (16–36)        |
| Age-adjusted rate |       |       | 14 (9–22)          |       |       | 24 (16–35)        |
cumulative risks at different index ages are presented in Table IX in the online-only Data Supplement. Stratified by lesion category, severe (8.9% [95% CI, 6.0–11.5%]) and left-sided lesions (9.5% [95% CI, 7.8–11.1%]) conveyed the highest cumulative risk of stroke during adulthood, whereas estimates for shunt- and right-sided lesions were lower, at 7.0% (95% CI, 5.8–8.0%) and 4.0% (95%-CI, 1.2–6.5%; Figure 2B).

Baseline and Clinical Characteristics
For the nested case–control subcohort, all 311 ischemic stroke cases were matched on age and calendar time with 12,440 control patients (1:40 ratio). In Table 2, the distribution of baseline characteristics, comorbidities, and interventions is shown for case and control subjects. The median age at the time of stroke was 49.9 years. The burden of baseline comorbidities and previous interventions was throughout higher in ischemic stroke than control patients (Table 2). A total of 13.4% of the strokes occurred in the setting of a high-risk surgery, 5.8% in relation to an acute myocardial infarction, and 8.0% in the context of acute endocarditis during the index hospitalization. Thirty-day mortality was 5.1% for patients with ischemic stroke and 27.7% for those with hemorrhagic stroke.

<table>
<thead>
<tr>
<th>Table 2. Baseline and Clinical Characteristics of Nested Case–Control Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Age at matching</td>
</tr>
<tr>
<td>Sex (men), %</td>
</tr>
<tr>
<td>Lesion categories, %*</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Shunt</td>
</tr>
<tr>
<td>Left sided</td>
</tr>
<tr>
<td>Right sided</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Comorbidities/lifestyle</td>
</tr>
<tr>
<td>Hypertension*</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Myocardial infarct, recent*</td>
</tr>
<tr>
<td>Peripheral artery disease*</td>
</tr>
<tr>
<td>Atrial arrhythmia*</td>
</tr>
<tr>
<td>Heart failure*</td>
</tr>
<tr>
<td>PH (2°)</td>
</tr>
<tr>
<td>Endocarditis, recent*</td>
</tr>
<tr>
<td>Chronic kidney disease*</td>
</tr>
<tr>
<td>Polycythemia (2°)</td>
</tr>
<tr>
<td>DVT/PE*</td>
</tr>
<tr>
<td>Obesity*</td>
</tr>
<tr>
<td>Alcohol abuse*</td>
</tr>
<tr>
<td>Tobacco abuse*</td>
</tr>
<tr>
<td>Cocaine abuse</td>
</tr>
<tr>
<td>Interventions</td>
</tr>
<tr>
<td>Cardiac surgery</td>
</tr>
<tr>
<td>Left-sided valve replacement</td>
</tr>
<tr>
<td>Right-sided valve replacement</td>
</tr>
<tr>
<td>Pacemaker/ICD procedure</td>
</tr>
<tr>
<td>Catheter intervention</td>
</tr>
<tr>
<td>High-risk surgery, recent*</td>
</tr>
</tbody>
</table>

Ischemic stroke cases are matched on age and calendar time to control subjects (1:40). Results are shown as proportions (%) for categorical and median and interquartile range (IQR) for continuous variables. Odds ratios were derived from univariate conditional logistic regression; for lesion categories shunt lesions served as the reference. ACHD indicates adult congenital heart disease; 95% CI, 95% confidence interval; PH, pulmonary hypertension; 2°, secondary; recent, occurring in 90 days before the time of hospital admission of case.

*Variables were selected for Bayesian model averaging by stepwise selection.
In the year after ischemic stroke, a significant rise in the proportion of patients diagnosed with hypertension, coronary artery disease, atrial arrhythmia, and tobacco use was noted (Table X in the online-only Data Supplement).

**Predictors of Stroke**

Fourteen covariates (listed in Table 2) were selected by the stepwise method and implemented into the Bayesian model averaging macro, which thus averaged over $2^{14} = 16384$ possible models. Interaction terms of age with heart failure and severe lesions were statistically significant and age dichotomized as a categorical variable (age groups 18–49 and 50–64 years) rendered the most parsimonious models based on the Bayesian information criterion. Figure 3 displays the results of the Bayesian model averaging as a forest plot.

There was very strong evidence for an effect of heart failure and diabetes mellitus on the risk of ischemic stroke with PrPs >99%. Heart failure had a greater relative impact at younger age, with a mean OR of 5.94 (95% credible interval, 3.49–10.14) for age group 18 to 49 years and an OR of 1.68 (95% credible interval, 1.06–2.66) for age group 50 to 64 years. The mean OR comparing diabetic with nondiabetic subjects was 2.33 (95% credible interval, 1.66–3.28). A positive association was noted for recent myocardial infarction (OR, 8.38 [95% credible interval, 1.77–39.58]; PrP, 93.6%). Recent high-risk surgery was a weak predictor of ischemic stroke (OR, 1.84 [95% CI, 0.60–5.63]; PrP, 59.7%). All of the other covariates showed PrPs <50%, and consequently 95% credible intervals of posterior parameter estimates included the null effect. Heart failure and diabetes mellitus remained the strongest predictors even if strokes were excluded, which occurred in the setting of acute myocardial infarction, endocarditis, or high-risk surgery (Figure I in the online-only Data Supplement).

**Stroke Risk After First Diagnosis of Heart Failure**

For 1379 patients of the cumulative risk cohort, a first diagnosis of heart failure was recorded between January 1, 1998, and March 31, 2010. A total of 284 patients were excluded because of high-risk surgery, endocarditis, or myocardial infarction in the 90 days prior and 4 patients, because no control patient was available within 0.2 SDs of the logit of the propensity score. Thus, the final propensity score–matched cohort consisted of 1091 matched pairs. Twenty patients with incident heart failure and 10 patients without heart failure experienced an ischemic stroke. Exposure status was well balanced between heart failure and nonheart failure patients for all of the covariates (Table XI in the online-only Data Supplement). The interaction term between heart failure and follow-up time was significant and therefore incorporated into the Cox model. The hazard ratio for ischemic stroke comparing patients with incident heart failure and nonheart failure was 8.83 (95% CI, 2.17–65.01) at 1 year, 5.90 (95% CI, 1.80–31.23) at 2 years, and 3.95 (95% CI, 1.42–15.613) at 3 years; thereafter, CIs turned inconclusive. The absolute risk of ischemic stroke at 1 year was 0.6% (95% CI, 0.3–1.4%) in patients with heart failure versus 0% in patients without heart failure, at 2 years 1.2% versus 0.2%, at 3 years 1.5% versus 0.8%, and at 10 years 4.2% versus 2.3% (P value of stratified log-rank test comparing survival curves, 0.0499; Figure 4). If strokes that occurred in the setting of acute events are excluded, the comparison loses statistical significance but a trend toward a higher stroke rate in patients with heart failure persists (15 versus 6 ischemic strokes, P value of stratified log-rank test, 0.1083; Figure II in the online-only Data Supplement).

**Discussion**

In this ACHD population, incidence rates ranged from 0.02% (age 18–24 years) to 0.30% (age 55–64 years) per year for

---

**Figure 3.** Predictors of ischemic stroke assessed by means of Bayesian model averaging. Presented are odds ratios (OR) derived from posterior-parameter estimates (mean), 95% credible intervals (95% CrI), and the posterior probability (PrP) that the regression coefficient for each covariate is non-0 given the data for all covariates with a PrP >25%. *In 90 days before time of hospital admission of case. †In reference to shunt lesions.
ischemic and from 0.01% to 0.05% for hemorrhagic stroke. In comparison with the general population, incidence of ischemic stroke was roughly 9 to 12 times higher below age 55 years and 2 to 4 times higher between age 55 and 64 years; hemorrhagic stroke rates were 5 to 6 times (below age 55 years) and 2 to 3 times (between age 55 and 64 years) higher. Among patients with ACHD reaching age 18 years, 8.9% of men and 6.8% of women experienced at least 1 stroke before age 65 years. With regard to lesion categories, patients with severe and left-sided lesions had the highest cumulative risk of stroke during adulthood. Thirty-day mortality after ischemic stroke was 5.1%, after hemorrhagic stroke the rate was 27.7%. Heart failure, diabetes mellitus, and recent myocardial infarction were the strongest predictors of ischemic stroke. The risk of ischemic stroke conveyed by heart failure was especially pronounced in younger patients and during the first 3 years after its initial diagnosis, although the latter finding lacked power to reach statistical significance in a sensitivity analysis.

The only large-scale, population-based study in this field published up to now mainly reported prevalence measures, and comparison with the general population was based on an estimated prevalence ratio with a wide range. A crude incidence rate of stroke was reported (0.05% per year), but age-specific incidence rates could not be generated and recurrent strokes were not excluded. Furthermore, inferences on associations between clinical characteristics and stroke were only possible at a descriptive level. Other studies predominately reported prevalence proportions as the measure of outcome. The IRR comparing stroke rates in men and women in our ACHD cohort (1.35) was very similar to what had been reported for the general population in a meta-analysis of 44 studies (pooled IRR, 1.33). Our ability to make a direct comparison of cumulative risks to the general population was limited, because no cumulative risk estimates had been published for the corresponding age range. However, incidence rates of stroke based on the same hospital discharge data source were reported for the general population of Quebec by Mayo et al. For comparison, we used the same definitions for stroke and age standardized our rates to the general population. Age-adjusted incidence rates of ischemic and hemorrhagic strokes were throughout higher in patients with ACHD than in the general population, in particular at a younger age. Thirty-day mortality of ischemic and hemorrhagic stroke was comparable with rates reported for the general Quebec population.

Heart failure, which showed a high predictive ability for ischemic stroke in our study, is an established risk factor for stroke in the general population. However, its effect is generally difficult to separate from closely associated cardiovascular risk factors and comorbidities, such as hypertension, coronary artery disease, and especially atrial arrhythmia, which are frequently clinically undetected. Suggested mechanisms of stroke in patients with heart failure are thrombus formation because of blood stasis or structural defects, neuroendocrine or hemostatic disorders associated with heart failure, or a combination of these factors. Cardiac surgeries constitute another mediator on the causal pathway between heart failure and stroke; however, heart failure remained the strongest predictor even after excluding strokes, which occurred in the setting of high-risk surgery. Our propensity score–matched analysis supports the role of heart failure as a risk factor for ischemic stroke in the setting of incident heart failure. Similar to our findings in the propensity score–matched subcohort, an attenuation of the risk of stroke with follow-up time after incident heart failure has been observed in the general population. Whether subgroups of patients with heart failure and sinus rhythm could benefit from an antithrombotic treatment is a matter of ongoing research in the general population and based on our findings may warrant further investigation in patients with ACHD. Additional predictors of stroke in our ACHD cohort were diabetes mellitus and recent myocardial infarction, which are well-known risk factors of ischemic stroke in the general population. Classic risk factors such as hypertension, hypercholesterolemia, and atrial arrhythmia showed no conclusive evidence of a predictive role in this ACHD population; however, it is important to note that...
this does not rule out an independent contribution of these factors, but rather means that, in our cohort, other covariates were stronger predictors of ischemic stroke. Furthermore, the increase in the prevalence of patients diagnosed with hypertension, coronary artery disease, atrial arrhythmia, and tobacco use in the year after ischemic stroke may indicate that these risk factors were undiagnosed before the event; consequently, earlier detection of these risk factors may represent a potential target in the prevention of stroke in ACHD. Moreover, atrial arrhythmia lost part of its predictive ability because of a correlation with heart failure. The lesion categories assessed were not strong predictors either, possibly because heart failure serves as a better proxy for severity of disease.

The strength of this study is its comprehensiveness and thorough analysis. The study population encompassed the CHD population of a large Canadian province and was based on all healthcare-related patient encounters over a period of >2 decades. Our study design and numerous sensitivity analyses have attempted to capture and reduce information and selection biases. For example, ascertainment of incident stroke cases was limited to hospital discharge data preceded by a 10-year washout period before inclusion, and additionally an imaging modality associated with the diagnostic workup for stroke was required. For comorbidity status based on outpatient data, 2 diagnoses were required to reduce misclassification.17 We attempted to correct for selection bias introduced by differential inclusion of patients with PFO into our cohort conditional on stroke and assessed the impact by means of sensitivity analyses. The nested case-control design used to evaluate predictors of ischemic stroke is a valid alternative to a Cox model assessing time-dependent exposure with superior computational efficiency.42 It thus allowed inferences by means of Bayesian model averaging, which is known to take into account model uncertainty and to render better predictive accuracy than classic selection methods.30,43

Despite our efforts to minimize misclassification, information bias remains a limitation, as is inherent to all administrative databases.44 Another drawback is the lack of clinical detail.45 Information on some potential confounders could not be adequately captured (eg, tobacco, alcohol, and drug abuse), was not detailed (eg, left- versus right-sided heart failure and bioprosthetic versus mechanical valve replacement not distinguishable), or was not available (medication use, family history, and lifestyle factors). The lack of detailed information inherent to administrative data, left truncation of information such as on correctional surgeries dating back >15 years, and power considerations also precluded meaningful inferences for specific defects. Because data are limited to the province of Quebec, migration cannot be excluded as a potential source of bias either; however, a previous analysis showed that at least the prevalence of CHD should not be relevantly affected by this.2 Regarding the comparison with the general population, we used the same data sources and definitions; however, a possible surveillance bias leading to a different detection rate of stroke in patients with ACHD as opposed to the general population cannot be excluded.

Despite these limitations, the presented study constitutes a comprehensive analysis of the incidence and cumulative risk of stroke in patients with ACHD and yields important information on the predictive role of potential risk factors for ischemic stroke. In summary, 1 in 11 men and 1 in 15 women with CHD is expected to experience at least 1 stroke during the course of adulthood (age 18–64 years). Patients with severe and left-sided lesions had the highest cumulative risk of stroke. In patients with ACHD aged <55 years, ischemic stroke was approximately 9 to 12 times higher and in patients aged 55 to 64 years 2 to 4 times higher than in the general population; hemorrhagic stroke rates were 5 to 6 times (below age 55 years) and 2 to 3 times higher. Heart failure, diabetes mellitus, and recent myocardial infarction were the comorbidities with the strongest predictive ability for stroke. For patients with heart failure, the risk of stroke was in particular high at younger age and in the first 3 years after its first diagnosis. Additional research is required to see whether early detection of risk factors and advances in the management of ACHD may reduce this substantial stroke rate.

Sources of Funding
Dr Marelli receives funding from the Heart and Stroke Foundation of Quebec, the Fonds de Recherche en Santé Québec, and the Canadian Institute of Health Research. Dr Brophy is a funded scholar of the Fonds de Recherche en Santé Québec.

Disclosures
None.

References
Stroke in Adults With Congenital Heart Disease


CLINICAL PERSPECTIVE

The present study documents for the first time in a population-based cohort the magnitude of the risk of stroke in adults with congenital heart disease (ACHD). Almost 7% of female and 9% of male patients with ACHD experienced a stroke over the course of their adult life before reaching age 65 years. Rates were highest in patients with severe lesions and defects primarily affecting the left heart. In comparison with the general adult population, incidence rates of stroke were up to 12 times higher in patients with ACHD. Thirty-day mortality after stroke was comparable with the general population, with 5.1% after ischemic and 27.7% after hemorrhagic stroke. Heart failure, a common complication of congenital heart disease, and diabetes mellitus, a common acquired cardiovascular risk factor, represent the strongest predictors of ischemic stroke in this cohort. The risk conveyed by heart failure was especially pronounced in younger patients and during the first 3 years after its initial diagnosis. Sensitivity analyses indicate that some classic stroke risk factors, such as atrial arrhythmia and hypertension, could be underdetected in ACHD. In view of the substantial impact that stroke has on quality of life and morbidity, our findings should inform urgent efforts aimed at medical strategies to specify the ACHD phenotypes most likely to benefit from primary prevention and reduce stroke rates in this rapidly growing population.
Stroke in Adults With Congenital Heart Disease: Incidence, Cumulative Risk, and Predictors
Jonas Lanz, James M. Brophy, Judith Therrien, Mohammed Kaouache, Liming Guo and Ariane J. Marelli

_Circulation_. 2015;132:2385-2394; originally published online November 23, 2015;
doi: 10.1161/CIRCULATIONAHA.115.011241
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/132/25/2385

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2015/11/20/CIRCULATIONAHA.115.011241.DC1
http://circ.ahajournals.org/content/suppl/2017/07/10/CIRCULATIONAHA.115.011241.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/
### Supplemental Table 1. Categorization of CHD-lesions

<table>
<thead>
<tr>
<th>Lesion category</th>
<th>Specific lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe lesions</strong></td>
<td>Endocardial cushion defect</td>
</tr>
<tr>
<td></td>
<td>Single ventricle physiology</td>
</tr>
<tr>
<td></td>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td></td>
<td>Transposition complex</td>
</tr>
<tr>
<td></td>
<td>Truncus arteriosus</td>
</tr>
<tr>
<td><strong>Shunt lesions</strong></td>
<td>Atrial septal defect</td>
</tr>
<tr>
<td></td>
<td>Ventricular septal defect</td>
</tr>
<tr>
<td></td>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td></td>
<td>Unspecified defects of septal closure</td>
</tr>
<tr>
<td><strong>Left-sided lesions</strong></td>
<td>Congenital mitral stenosis</td>
</tr>
<tr>
<td></td>
<td>Congenital mitral insufficiency</td>
</tr>
<tr>
<td></td>
<td>Congenital aortic stenosis</td>
</tr>
<tr>
<td></td>
<td>Congenital aortic insufficiency</td>
</tr>
<tr>
<td></td>
<td>Aortic coarctation</td>
</tr>
<tr>
<td><strong>Right-sided lesions</strong></td>
<td>Ebstein anomaly</td>
</tr>
<tr>
<td></td>
<td>Congenital tricuspid valve disease</td>
</tr>
<tr>
<td></td>
<td>Anomalies of the pulmonary artery</td>
</tr>
<tr>
<td></td>
<td>Anomalies of the pulmonary valve</td>
</tr>
<tr>
<td><strong>Other lesions</strong></td>
<td>Anomalies of great veins</td>
</tr>
<tr>
<td></td>
<td>No single leading CHD lesion*</td>
</tr>
</tbody>
</table>

*Categorization of congenital heart defects (CHD) according to severity and patho-anatomical criteria. * Patients with more than one specific lesion belonging to different lesion categories.*
<table>
<thead>
<tr>
<th>Covariates</th>
<th>ICD-9 codes</th>
<th>Disease</th>
<th>ICD-10 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>401.x</td>
<td>Essential hypertension</td>
<td>I10.x</td>
<td></td>
</tr>
<tr>
<td>402.x</td>
<td>Hypertensive heart disease</td>
<td>I11.x</td>
<td></td>
</tr>
<tr>
<td>403.x</td>
<td>Hypertensive chronic kidney disease</td>
<td>I12.x</td>
<td></td>
</tr>
<tr>
<td>404.x</td>
<td>Hypertensive heart and chronic kidney disease</td>
<td>I13.x</td>
<td></td>
</tr>
<tr>
<td>405.x</td>
<td>Secondary hypertension</td>
<td>I15.x</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>249.x</td>
<td>Secondary diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250.x</td>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus due to underlying condition</td>
<td>E08.x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug or chemical induced diabetes mellitus</td>
<td>E09.x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 1 diabetes mellitus</td>
<td>E10.x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes mellitus</td>
<td>E11.x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malnutrition-related diabetes mellitus</td>
<td>E12.x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other specified diabetes mellitus</td>
<td>E13.x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unspecified diabetes mellitus</td>
<td>E14.x</td>
<td></td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>272.0</td>
<td>Pure hypercholesterolemia</td>
<td>E78.0</td>
</tr>
<tr>
<td>272.2</td>
<td>Mixed hyperlipidemia</td>
<td>E78.2</td>
<td></td>
</tr>
<tr>
<td>272.4</td>
<td>Other and unspecified hyperlipidemia</td>
<td>E78.4</td>
<td></td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>414.0x</td>
<td>Coronary atherosclerosis</td>
<td>I25.1x</td>
<td></td>
</tr>
<tr>
<td>414.2x</td>
<td>Chronic total occlusion of coronary artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>414.3x</td>
<td>Coronary atherosclerosis due to lipid rich plaque</td>
<td></td>
<td></td>
</tr>
<tr>
<td>414.8x</td>
<td>Other specified forms of chronic ischemic heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>414.9x</td>
<td>Chronic ischemic heart disease, unspecified</td>
<td>I25.9x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis of coronary artery bypass graft(s) and coronary artery of transplanted heart with angina pectoris</td>
<td>I25.7x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other forms of chronic ischemic heart disease</td>
<td>I25.8x</td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial infarct</strong></td>
<td>410.x</td>
<td>Acute myocardial infarction</td>
<td>I21.x</td>
</tr>
<tr>
<td></td>
<td>ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction</td>
<td>I22.x</td>
<td></td>
</tr>
<tr>
<td><strong>Peripheral artery disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>440.2x</td>
<td>Atherosclerosis of native arteries of the extremities</td>
<td>I70.2x</td>
<td></td>
</tr>
<tr>
<td>440.3x</td>
<td>Atherosclerosis of bypass graft of the extremities</td>
<td>I70.3x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis of unspecified type of bypass graft(s) of the extremities</td>
<td>I70.4x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis of autologous vein bypass graft(s) of the extremities</td>
<td>I70.5x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis of nonautologous biological bypass graft(s) of the extremities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Code</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>--------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerosis of nonbiological bypass graft(s) of the extremities</td>
<td>I70.6x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerosis of other type of bypass graft(s) of the extremities</td>
<td>I70.7x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic total occlusion of artery of the extremities</td>
<td>I70.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease, unspecified</td>
<td>I73.9x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Atrial arrhythmia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>I48.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>I48.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure, unspecified</td>
<td>I48.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left heart failure</td>
<td>I50.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic heart failure</td>
<td>I50.2x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic heart failure</td>
<td>I50.3x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined systolic and diastolic heart failure</td>
<td>I50.4x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure, unspecified</td>
<td>I50.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary hypertension</strong> (secondary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension, secondary or not otherwise specified</td>
<td>I27.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other secondary pulmonary hypertension</td>
<td>I27.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other specified pulmonary heart diseases incl. Eisenmenger's complex, syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endocarditis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute and subacute endocarditis</td>
<td>I33.x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis, valve unspecified</td>
<td>I38</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic kidney disease</strong> (secondary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease (CKD)</td>
<td>N18.x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Polycythemia</strong> (secondary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycythemia, secondary</td>
<td>D75.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Deep vein thrombosis/ Pulmonary embolism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebitis and thrombophlebitis of deep vessels of lower extremities</td>
<td>I80.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebitis and thrombophlebitis of lower extremities, unspecified</td>
<td>I80.4x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other venous embolism and thrombosis of inferior vena cava</td>
<td>I80.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute venous embolism and thrombosis of deep vessels of lower extremity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebitis and thrombophlebitis of femoral vein</td>
<td>I80.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebitis and thrombophlebitis of other and unspecified deep vessels of lower extremities</td>
<td>I80.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embolism and thrombosis of vena cava and other thoracic veins</td>
<td>I82.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism and infarction</td>
<td>I26.x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight and obesity</td>
<td>E66.x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol abuse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol dependence syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol-induced mental disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td>ICD Code</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>305.0</td>
<td>Alcohol abuse</td>
<td>F10.x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcohol related disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>305.1</td>
<td>Tobacco abuse</td>
<td>Z72.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tobacco use disorder, Tobacco dependence</td>
<td>Z71.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tobacco use</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tobacco abuse counseling</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nicotine dependence</td>
<td>F17.x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nicotine dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>304.2</td>
<td>Cocaine abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cocaine dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>305.6</td>
<td>Cocaine abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cocaine related disorders</td>
<td>F14.x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cocaine related disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICD-9 and ICD-10 codes used for the definition of comorbidities. An “x” implies that all codes were considered at the corresponding code position.
### Supplemental Table 3. Definitions of covariates – Surgeries and interventions

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Type of surgery</th>
<th>Code d’acte</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fallot repair</td>
<td></td>
<td>4342, 4548, 4584</td>
</tr>
<tr>
<td>Unifocalization MAPCAs</td>
<td></td>
<td>4629, 4635, 4636, 4642</td>
</tr>
<tr>
<td>Fontan procedure</td>
<td></td>
<td>4253, 4573</td>
</tr>
<tr>
<td>Cavo-pulmonary anastomosis</td>
<td></td>
<td>4364, 4638</td>
</tr>
<tr>
<td>Norwood procedure</td>
<td></td>
<td>4372, 4591</td>
</tr>
<tr>
<td>Atrial baffle procedure (incl. Senning, Mustard)</td>
<td></td>
<td>4365, 4572, 4336</td>
</tr>
<tr>
<td>Blalock-Hanlon procedure</td>
<td></td>
<td>4004</td>
</tr>
<tr>
<td>Rashkind procedure</td>
<td></td>
<td>4005</td>
</tr>
<tr>
<td>Arterial switch</td>
<td></td>
<td>4354, 4590</td>
</tr>
<tr>
<td>Rastelli</td>
<td></td>
<td>4252, 4579, 4581</td>
</tr>
<tr>
<td>Closure of systemic-pulmonary shunt</td>
<td></td>
<td>4405, 4643</td>
</tr>
<tr>
<td>Systemic arterial to pulmonary shunt</td>
<td></td>
<td>4362, 4637, 4363, 4598</td>
</tr>
<tr>
<td>ASD closure</td>
<td></td>
<td>4331, 4568, 4600</td>
</tr>
<tr>
<td>ASD creation or enlargement</td>
<td></td>
<td>4567</td>
</tr>
<tr>
<td>Sinus venosus defect repair/pulmonary veins</td>
<td></td>
<td>4334, 4437, 4571, 4640, 4621, 4627</td>
</tr>
<tr>
<td>VSD closure</td>
<td></td>
<td>4206, 4338, 4576, 4577, 4577</td>
</tr>
<tr>
<td>VSD creation or enlargement</td>
<td></td>
<td>4578</td>
</tr>
<tr>
<td>Atrioventricular canal repair</td>
<td></td>
<td>4332, 4333, 4569, 4570</td>
</tr>
<tr>
<td>Patent ductus ligation</td>
<td></td>
<td>4382, 4383, 4633, 4644</td>
</tr>
<tr>
<td>Tricuspid or mitral commissurotomy</td>
<td></td>
<td>4328, 4330</td>
</tr>
<tr>
<td>Tricuspid valve surgery</td>
<td></td>
<td>4556, 4559, 4854, 4856, 4558</td>
</tr>
<tr>
<td>Tricuspid valve replacement</td>
<td></td>
<td>4557, 4855</td>
</tr>
<tr>
<td>RVOT procedure</td>
<td></td>
<td>4340, 4582</td>
</tr>
<tr>
<td>Pulmonary artery banding</td>
<td></td>
<td>4348, 4370, 4633</td>
</tr>
<tr>
<td>Pulmonary artery unbanding</td>
<td></td>
<td>4634</td>
</tr>
<tr>
<td>Pulmonary artery repair</td>
<td></td>
<td>4641</td>
</tr>
<tr>
<td>Pulmonary valve surgery</td>
<td></td>
<td>4327, 4335, 4561</td>
</tr>
<tr>
<td>Surgical reintervention on pulmonary valve</td>
<td></td>
<td>4564</td>
</tr>
<tr>
<td>Pulmonary valve replacement</td>
<td></td>
<td>4562, 4563</td>
</tr>
<tr>
<td>Mitral valve surgery without replacement</td>
<td></td>
<td>4550, 4552, 4554, 4555, 4847, 4849, 4554</td>
</tr>
<tr>
<td>Mitral valve replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- not specified</td>
<td></td>
<td>4848, 4551</td>
</tr>
<tr>
<td>- homograft/xenograft</td>
<td></td>
<td>4553, 4850</td>
</tr>
<tr>
<td>Aortic sub-/supravalvular stenosis repair</td>
<td></td>
<td>4325, 4583</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- not specified</td>
<td></td>
<td>4326, 4543, 4545</td>
</tr>
<tr>
<td>- homograft/xenograft</td>
<td></td>
<td>4308, 4329</td>
</tr>
<tr>
<td>Valvuloplasty (unspecific)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valvuloplasty, replacement of mitral or tricuspid valve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic root replacement, valve sparing</td>
<td></td>
<td>4594, 4645</td>
</tr>
<tr>
<td>Replacement of aortic root and aortic valve</td>
<td></td>
<td>4355, 4592, 4593</td>
</tr>
<tr>
<td>(unspecified whether mechanical or bioprosthesis)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aortoplasty or aortic annuloplasty 4544
Ross procedure 4546
Konno procedure 4269, 4547
Coarctation repair 4225, 4226, 4227, 4272, 4630
Aortic Arch repair 4356, 4595, 4596, 4631, 4534, 4647, 4027, 4026
Vascular ring repair 4371, 4632
Aortic aneurysm repair 4218, 4219, 4220, 4221, 4207, 4208, 4647, 4648
Aortic dissection repair 4223, 4369, 4209, 4687
Aortopulmonary window repair 4639
Sinus valsalva, aneurysm repair 4344, 4587
Pulmonary embolectomy 4010, 4655
Pericardiectomy 4200, 4201, 4000, 4165, 4539, 4540
Correction of anomalous coronary artery 4610
CABG 4351, 4352, 4353, 4313, 4314, 4315, 4316, 4228, 4601, 4602, 4603, 4604, 4605, 4606, 4607, 4608, 4860, 4861, 4862, 4863, 4864, 4865
Cardiac tumor resection 4160, 4163, 4164, 4537, 4538
Repair of Right/Left Ventricular Aneurysm 4343, 4585, 4803, 4804
Surgical arrhythmia procedures 4270, 4271, 4620, 4622, 4623, 4624, 4625, 4309, 4311, 4203, 4204, 4205
Mechanical heart support 4511, 4513, 4497
Heart transplantation 4320, 4528
Transplantation of heart and lungs 4806, 4529, 4574

Left-sided valve replacement
Mitral valve replacement - not specified 4848, 4551
- homograft/xenograft 4553, 4850
Aortic valve replacement - not specified 4326, 4543
- homograft/xenograft 4545
- aortic root and aortic valve replacement (valve type not specified) 4355, 4592, 4593

Right-sided valve replacement
Pulmonary valve replacement 4562, 4563
Tricuspid valve replacement 4557, 4855

Pacemaker/ICD-procedure
Pacemaker/ICD implantation/related procedure 4300, 4301, 4302, 4307, 4613, 4614, 4318, 4306, 4361, 4614, 4490, 4491, 4493, 4494, 4495, 4541, 4549, 4495, 4303, 4304, 4239, 4615, 4616, 4617, 4618, 4628, 4832, 4834, 4835, 4836, 4837, 4839, 4825, 4826, 4827, 4829, 4830, 4840, 4841, 4842, 4843, 4023, 4024, 4025, 20531, 20532, 20577,
### Catheter-interventions
- Percutaneous coronary intervention: 9301, 9302, 9303, 20520, 20521, 20522, 20523
- Angioplasty of cardiac valve or large intrathoracic vessel, shunts or conduits: 9360
- Closure of persistent ductus arteriosus or septal defect with umbrella device: 9419
- Rashkind septostomy: 542
- Endovascular extraction of foreign body: 20524
- Septal embolization in hypertrophic cardiomyopathies: 20525
- Device closure of valvular or perivalvular insufficiency: 20526
- Percutaneous valve replacement: 20527
- Transapical valve replacement: 20576
- Transseptal arrhythmia ablation: 291, 9422, 323
- Arrhythmia ablation with three-dimensional mapping: 9471

### High-risk surgery
- Codes for cardiac surgery (see above) plus:
  - Repair of a thoraco-abdominal aortic aneurysm: 4650, 4651, 4652
  - Aorto-subclavian or aorto or aorto-innominate artery bypass: 4656
  - Thromb-endarterectomy or bypass of thoracic, thoraco-abdominal or abdominal aorta: 4357, 4274, 4377, 4378, 4339, 4375, 4414, 4668, 4669, 4693, 4694, 4695, 4696, 4697, 4699
  - Extraction of infected vascular prosthesis of aorta: 4677, 4678, 4679, 4683, 4684, 4685
  - Thromb-endarterectomy of carotid or vertebral artery: 4360, 4418, 4423, 4424, 4710, 4727
  - Removal of carotid body (tumor): 4230, 4246, 4674
  - Suture of carotid artery laceration: 4266
  - ECMO procedure: 4393, 4508, 4510, 4514, 4517, 4518, 4560, 4812, 4821

Codes d’acte of the Régie de l’Assurance Maladie du Québec, Canada, used for the definition of surgeries and interventions.
**Supplemental Table 4.** The impact of different approaches to address selection bias caused by patients with patent foramen ovale on the incidence of ischemic stroke.

<table>
<thead>
<tr>
<th>Stroke-type</th>
<th>Analysis</th>
<th>Cases (N)</th>
<th>Person-time (years)</th>
<th>IRR* (95%-CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>Main</td>
<td>311</td>
<td>258045</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensitivity analysis A</td>
<td>248</td>
<td>237962</td>
<td>0.89 (0.75-1.05)</td>
<td>0.163</td>
</tr>
<tr>
<td></td>
<td>Sensitivity analysis B</td>
<td>336</td>
<td>258227</td>
<td>1.08 (0.92-1.26)</td>
<td>0.384</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>Main</td>
<td>47</td>
<td>258045</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensitivity analysis A</td>
<td>43</td>
<td>237954</td>
<td>1.02 (0.67-1.54)</td>
<td>0.9424</td>
</tr>
<tr>
<td></td>
<td>Sensitivity analysis B</td>
<td>48</td>
<td>258213</td>
<td>1.02 (0.68-1.53)</td>
<td>0.9223</td>
</tr>
</tbody>
</table>

For the main analysis patients with a first assignment of an ICD-9 745.5 or ICD-10 Q21.1 code within a year after a stroke or transient ischemic attack were excluded, for sensitivity analysis A person-time for patients was only counted starting from the time of first assignment of one of the corresponding ICD-codes and for sensitivity analysis B a random sample of 10% of the patients, which were excluded in the main analysis, was re-included. * Incidence rate-ratios (IRR) comparing age-sex-standardized incidence rates of the corresponding sensitivity analysis to the main analysis.

**Supplemental Table 5.** The impact of including patients with unspecified lesions into the cohort.

<table>
<thead>
<tr>
<th>Stroke-type</th>
<th>Sex</th>
<th>Cases (N)</th>
<th>Person-time (years)</th>
<th>IRR* (95%-CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>Women</td>
<td>216</td>
<td>192394</td>
<td>0.99 (0.80-1.22)</td>
<td>0.9397</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>262</td>
<td>160835</td>
<td>0.89 (0.73-1.09)</td>
<td>0.2646</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>Women</td>
<td>27</td>
<td>192394</td>
<td>0.94 (0.53-1.69)</td>
<td>0.8427</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>39</td>
<td>160835</td>
<td>0.84 (0.51-1.38)</td>
<td>0.488</td>
</tr>
</tbody>
</table>

Number of strokes and person-time in a cohort including patients with ICD-9 or -10 codes for unspecified congenital heart disease lesions, stratified by stroke-type and sex. * Incidence rate-ratios (IRR) comparing age-standardized incidence rates of the sensitivity analysis to rates of the main analysis, for which patients with unspecified lesions were excluded.

**Supplemental Table 6.** Contrasting the change from ICD-9 to ICD-10 coding.

<table>
<thead>
<tr>
<th>Stroke-type</th>
<th>Analysis</th>
<th>Cases (N)</th>
<th>Person-time (years)</th>
<th>IRR* (95%-CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>ICD-9</td>
<td>200</td>
<td>163907</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD-10</td>
<td>111</td>
<td>96257</td>
<td>1.05 (0.83-1.33)</td>
<td>0.6785</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>ICD-9</td>
<td>32</td>
<td>163907</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD-10</td>
<td>15</td>
<td>96257</td>
<td>0.90 (0.48-1.68)</td>
<td>0.7468</td>
</tr>
</tbody>
</table>

### Supplemental Table 7. Contrasting a 10-year to a 15-year washout period.

<table>
<thead>
<tr>
<th>Stroke-type</th>
<th>Analysis</th>
<th>Cases (N)</th>
<th>Person-time (years)</th>
<th>IRR* (95%-CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>10-years</td>
<td>197</td>
<td>163290</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-years</td>
<td>196</td>
<td>162984</td>
<td>1.00 (0.82-1.22)</td>
<td>0.9788</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>10-years</td>
<td>33</td>
<td>163290</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-years</td>
<td>32</td>
<td>162984</td>
<td>1.03 (0.63-1.67)</td>
<td>0.9090</td>
</tr>
</tbody>
</table>

Sensitivity analyses contrasting a 10- to a 15-year washout period prior to inclusion in a sub-cohort starting at January 1, 2003 (since the earliest available inpatient data starts in 1988). *Incidence rate-ratios comparing the rates of the two coding periods by means of age-sex-standardization.

### Supplemental Table 8. The incidence of ischemic (A) and hemorrhagic (B) stroke in ACHD compared to the general population.

**A. Ischemic stroke**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age-group (years)</th>
<th>Rate per 100,000 py in ACHD*</th>
<th>Rate per 100,000 in general population†</th>
<th>IRR‡ (95%-CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>15-54</td>
<td>101.5</td>
<td>8.4</td>
<td>12.12 (10.41-14.11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>304.3</td>
<td>71.9</td>
<td>4.23 (3.73-4.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men</td>
<td>15-54</td>
<td>134.7</td>
<td>14.4</td>
<td>9.37 (8.34-10.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>250.6</td>
<td>121.4</td>
<td>2.06 (1.85-2.30)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**B. Hemorrhagic stroke**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age-group (years)</th>
<th>Rate per 100,000 py in ACHD*</th>
<th>Rate per 100,000 in general population†</th>
<th>IRR‡ (95%-CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>15-54</td>
<td>13.5</td>
<td>2.6</td>
<td>5.27 (3.95-7.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>33.8</td>
<td>9.7</td>
<td>3.48 (2.44-4.94)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men</td>
<td>15-54</td>
<td>23.9</td>
<td>3.7</td>
<td>6.44 (5.10-8.13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>44.8</td>
<td>20.1</td>
<td>2.23 (1.71-2.91)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Ischemic and hemorrhagic stroke was defined according to the same ICD-9 codes from hospital discharge data as in the reference study by Mayo et al. Incidence rates of stroke in adults with congenital heart disease (ACHD) were age-standardized to the mid-year population of Quebec in 2002 and are presented per 100,000 person-years (py). Age-group specific incidence rates of stroke per 100,000 population in Quebec in 2002 as published by Mayo et al. Incidence rate ratios (IRR) with 95% confidence intervals comparing incidence rates for ischemic (A) and hemorrhagic (B) stroke in ACHD to rates reported for the general population.
### Supplemental Table 9. Intermediate- and long-term mortality-adjusted cumulative risks of ischemic (A) and hemorrhagic (B) stroke in ACHD.

<table>
<thead>
<tr>
<th>A. Ischemic stroke</th>
<th>Sex</th>
<th>Index age (years)</th>
<th>Cumulative risk of stroke, % (95%-CI)</th>
<th>10-year</th>
<th>20-year</th>
<th>30-year</th>
<th>up to age 65</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>18</td>
<td>0.3 (0.1-0.4)</td>
<td>0.8 (0.5-1.1)</td>
<td>2.1 (1.6-2.6)</td>
<td>6.1 (5.0-7.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>0.4 (0.2-0.6)</td>
<td>1.4 (1.0-1.8)</td>
<td>3.3 (2.6-4.0)</td>
<td>5.9 (4.8-6.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td>1.0 (0.6-1.4)</td>
<td>2.9 (2.2-3.6)</td>
<td>5.5 (4.5-6.5)</td>
<td>5.5 (4.5-6.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45</td>
<td>2.0 (1.4-2.6)</td>
<td>4.6 (3.6-5.5)</td>
<td>.</td>
<td>4.6 (3.6-5.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>55</td>
<td>2.8 (2.0-3.5)</td>
<td>.</td>
<td>.</td>
<td>2.8 (2.0-3.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>18</td>
<td>0.2 (0.1-0.4)</td>
<td>0.9 (0.5-1.2)</td>
<td>3.4 (2.6-4.1)</td>
<td>7.7 (6.4-8.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>0.6 (0.3-1.0)</td>
<td>2.6 (1.9-3.3)</td>
<td>5.2 (4.1-6.1)</td>
<td>7.7 (6.4-8.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td>2.0 (1.3-2.6)</td>
<td>4.6 (3.6-5.6)</td>
<td>7.2 (6.0-8.4)</td>
<td>7.2 (6.0-8.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45</td>
<td>2.8 (2.0-3.5)</td>
<td>5.5 (4.4-6.5)</td>
<td>.</td>
<td>5.5 (4.4-6.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>55</td>
<td>2.9 (2.1-3.7)</td>
<td>.</td>
<td>.</td>
<td>2.9 (2.1-3.7)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Hemorrhagic stroke</th>
<th>Sex</th>
<th>Index age (years)</th>
<th>Cumulative risk of stroke, % (95%-CI)</th>
<th>10-year</th>
<th>20-year</th>
<th>30-year</th>
<th>up to age 65</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>18</td>
<td>0.0 (0.0-0.1)</td>
<td>0.1 (0.0-0.3)</td>
<td>0.3 (0.1-0.4)</td>
<td>0.8 (0.4-1.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>0.0 (0.0-0.1)</td>
<td>0.2 (0.0-0.3)</td>
<td>0.5 (0.2-0.7)</td>
<td>0.8 (0.4-1.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td>0.1 (0.0-0.3)</td>
<td>0.4 (0.1-0.7)</td>
<td>0.7 (0.4-1.1)</td>
<td>0.7 (0.4-1.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45</td>
<td>0.3 (0.1-0.5)</td>
<td>0.6 (0.2-1.0)</td>
<td>.</td>
<td>0.6 (0.2-1.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>55</td>
<td>0.3 (0.1-0.6)</td>
<td>.</td>
<td>.</td>
<td>0.3 (0.1-0.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>18</td>
<td>0.1 (0.0-0.2)</td>
<td>0.2 (0.0-0.3)</td>
<td>0.5 (0.2-0.8)</td>
<td>1.3 (0.8-1.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>0.1 (0.0-0.2)</td>
<td>0.4 (0.1-0.7)</td>
<td>0.8 (0.4-1.1)</td>
<td>1.2 (0.7-1.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td>0.3 (0.1-0.6)</td>
<td>0.7 (0.3-1.1)</td>
<td>1.2 (0.7-1.7)</td>
<td>1.2 (0.7-1.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45</td>
<td>0.4 (0.1-0.7)</td>
<td>0.9 (0.4-1.3)</td>
<td>.</td>
<td>0.9 (0.4-1.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>55</td>
<td>0.5 (0.2-0.9)</td>
<td>.</td>
<td>.</td>
<td>0.5 (0.2-0.9)</td>
<td></td>
</tr>
</tbody>
</table>

Intermediate- and long-term mortality-adjusted cumulative risks of first hospital admission for ischemic (A) and hemorrhagic (B) stroke at different index ages stratified by sex. Prior to the index age adults with congenital heart disease (ACHD) were free of stroke for at least 10 years.
Supplemental Table 10. Generally long-lasting comorbidities in patients with ischemic stroke (N=311) at time of the stroke and one-year after the event.

<table>
<thead>
<tr>
<th>Comorbidities / Lifestyle</th>
<th>Baseline</th>
<th>One year after stroke</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>31.2%</td>
<td>39.6%</td>
<td>0.0019</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.0%</td>
<td>19%</td>
<td>0.2008</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>7.7%</td>
<td>10.9%</td>
<td>0.1138</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>11.3%</td>
<td>17.7%</td>
<td>0.0012</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1.9%</td>
<td>1.9%</td>
<td>1.0</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>15.4%</td>
<td>23.8%</td>
<td>0.0005</td>
</tr>
<tr>
<td>Heart failure</td>
<td>17.0%</td>
<td>15.8%</td>
<td>0.6171</td>
</tr>
<tr>
<td>PH (2°)</td>
<td>3.2%</td>
<td>2.6%</td>
<td>0.5271</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>4.8%</td>
<td>6.1%</td>
<td>0.1573</td>
</tr>
<tr>
<td>Polycythemia (2°)</td>
<td>0.6%</td>
<td>1.6%</td>
<td>0.2568</td>
</tr>
<tr>
<td>Obesity</td>
<td>6.1%</td>
<td>5.1%</td>
<td>0.5316</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>4.2%</td>
<td>3.9%</td>
<td>0.7963</td>
</tr>
<tr>
<td>Tobacco abuse</td>
<td>8.7%</td>
<td>14.2%</td>
<td>0.0243</td>
</tr>
<tr>
<td>Cocaine abuse</td>
<td>0.3%</td>
<td>0.6%</td>
<td>0.3173</td>
</tr>
</tbody>
</table>

Status of generally long-standing comorbidities at time of ischemic stroke (Baseline, ascertained based on ICD-codes in the 5-year period prior to the event) and one year after stroke (based on ICD-codes recorded since the stroke event). Results are shown as proportions (%), p-values are derived from McNemar’s tests. N, number. PH, pulmonary hypertension. 2°, secondary.
**Supplemental Table 11.** Baseline and clinical characteristics of propensity-score matched heart failure and non-heart failure patients.

<table>
<thead>
<tr>
<th></th>
<th>Heart failure (N=1,338)</th>
<th>Non-heart failure (N=1,338)</th>
<th>Standardized difference of the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at matching</td>
<td>48.5 (±12.1)</td>
<td>48.8 (±12.4)</td>
<td>-0.0189</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>54.7%</td>
<td>54.8%</td>
<td>-0.0018</td>
</tr>
<tr>
<td><strong>Lesion-categories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>19.0%</td>
<td>18.4%</td>
<td>-0.0141</td>
</tr>
<tr>
<td>Shunt</td>
<td>37.2%</td>
<td>37%</td>
<td>0.0037</td>
</tr>
<tr>
<td>Left-sided</td>
<td>38.8%</td>
<td>38.9%</td>
<td>-0.0018</td>
</tr>
<tr>
<td>Right-sided</td>
<td>3.9%</td>
<td>4.6%</td>
<td>-0.0317</td>
</tr>
<tr>
<td>Others</td>
<td>1.1%</td>
<td>1.1%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>36.1%</td>
<td>37.9%</td>
<td>-0.0363</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14.6%</td>
<td>13.8%</td>
<td>0.0209</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>17.5%</td>
<td>16.5%</td>
<td>0.0269</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1.5%</td>
<td>1.7%</td>
<td>-0.0215</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>29.9%</td>
<td>29.9%</td>
<td>0</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5.1%</td>
<td>4.3%</td>
<td>0.0378</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>1.9%</td>
<td>2.0%</td>
<td>-0.0072</td>
</tr>
<tr>
<td>Obesity</td>
<td>11.6%</td>
<td>12.0%</td>
<td>-0.0143</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>2.8%</td>
<td>2.7%</td>
<td>0.011</td>
</tr>
<tr>
<td>Tobacco abuse</td>
<td>7.4%</td>
<td>6.6%</td>
<td>0.0321</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left valve replacement</td>
<td>7.3%</td>
<td>7.7%</td>
<td>-0.0140</td>
</tr>
</tbody>
</table>

Presented are proportions (%) for categorical variables, mean and standard deviation for continuous covariates as well as standardized differences for incident heart-failure cases and propensity-score matched non-heart failure patients. Covariates are well balanced between the propensity-score matched heart failure and non-heart failure patients.
Supplemental Figure 1. Predictors of ischemic stroke - Sensitivity analysis excluding strokes occurring within 90 days of an acute myocardial infarction, endocarditis or high-risk surgery from the nested case-control cohort. Predictors were assessed by means of Bayesian model averaging. Presented are odds-ratios (OR) derived from posterior-parameter estimates (mean), 95%-credible intervals (95%-CrI) and the posterior probability (PrP) that the regression coefficient for each covariate is non-zero given the data for all covariates with a PrP > 25%. Heart failure and diabetes remain the strongest predictors with posterior probabilities of 98.2% and 75.2% respectively.
Supplemental Figure 2. Risk of ischemic stroke in incident heart failure - Sensitivity analysis excluding strokes occurring within 90 days of an acute myocardial infarction, endocarditis or high-risk surgery from the propensity-score matched cohort. Kaplan Meier curve showing ischemic stroke-free survival curves for patients with first diagnosis of heart failure and propensity-score matched non-heart failure patients. The numbers of patients at risk are provided above the x-axis. In the incident heart failure cohort 15 ischemic strokes occurred, in the non-heart failure cohort 6. The log-rank test was stratified on the matched sets (p=0.1083).
References

恶性心脏肿瘤的特征及生存期

原发性心脏恶性肿瘤（primary malignant cardiac tumors, PMCT）是相当罕见的心脏源疾病，组织病理多变，生物学上表现具有攻击性。本研究旨在调查 PMCTs 相关的发病率，组织病理学，人口统计学和生存期。

本研究调查了 1973 年到 2011 年国立癌症研究所确诊 PMCTs 患者的监测情况、流行病学和 18 项最终结果登记资料（SEER）。从 SEER 登记的共 7384 580 例癌症病例中，识别出 551 例 PMCTs（0.008%），PMCTs 发生率为每 1 亿人中有 34 个患者，且随着时间延续发生率有所增长（1973-1989 年为 25.1 个，1990-1999 年为 30.2 个，2000-2011 年为 46.6 个）。大多数患者为女性（54.1%）及白人（78.6%）。

最常见的 PMCTs 是肉瘤（n=357, 64.8%），其次是淋巴瘤（n=150, 27%），间皮瘤（n=44, 8%）。经 80 个月（中位数）的随访，413 名患者死亡。PMCTs 中最致命的是心脏肉瘤和间皮瘤。二者 1、3、5 年生存率分别为 47%，16% 和 11% 及 51%，26% 和 23%。（时序检验 p<0.001）心室淋巴瘤和肉瘤患者都较年轻，且比类似组织病理学的心外疾病患者生存率更低（p<0.001）。

综上，PMCT 极其罕见且与不良预后相关。过去 50 年中，确诊 PMCTs 的患者发生率和存活率都有增加。与类似组织病理学的心外疾病患者相比，PMCT 患者往往更年轻且生存率更差。


先天性心脏病成人患者：休克发病率、累积危险度及预测因子

约有 1%的人出生起就面临心脏或大血管缺损。先天性心脏病（congenital heart disease, CHD）管理的改善能提高存活率，但与此矛盾的是，突显了终身并发症所带来的独特需求。休克是 CHD 成
年患者（Adult CHD，ACHD）发病和死亡的一个重要原因，尽管其发病率、累积危险度及预测数据目前比较缺乏。

本研究目的包括3方面，(1) 评估ACHD中缺血性休克和出血性休克的发生率和危险度；(2) 与一般人群比较这些数据；(3) 界定ACHD患病的最强预测因子。

本回顾性研究入组了1998-2010年共29638例魁北克市ACHD，年龄在18-64岁，罹患先天性心脏病的成人。64岁以下的女性，其缺血性休克的累积危险度估计为6.1%（95%置信区间[CI]，5.0-7.0%），男性为7.7%（95%CI，6.4-8.8%）；出血性休克的危险度男性、女性则分别为0.8%（95%CI，0.4-1.2%）和1.3%（95%CI，0.8-1.8%）。

结合阶梯式模型选择和贝叶斯模型平均，发现最可能导致缺血性休克的是心竭（18-49岁组的优势比OR为5.94[95%CI，3.49-10.14]，50-64岁组的OR为1.68[95%CI，1.06-2.66]），糖尿病（OR为2.33[95%CI，1.66-3.28]），及近期发生的心梗（OR为8.38[95%CI，1.77-39.58]）。

综上，在ACHD中，每11位男性或15位女性中会有1人有过休克经历，年龄在18-64岁。该人群休克发生率高于一般人群，尤其是年轻人。最可能导致缺血性休克的预测因子是心竭、糖尿病及近期发生的心梗。对ACHD加以管理是否能改善这种高休克率还需进一步的研究来予以确认。


**美国静脉血除铅的使用和不良预后趋势**
静脉血除铅（Transvenous lead removal，TLR）在科技创新上取得了显著进步，然而，在大量应用TLR之外关于其使用和不良预后趋势的数据则比较有限。本研究旨在检查其使用模式，不良事件发生频率及对并发症住院量的影响。

本研究采用全国住院患者样本，筛选出91890台TLR手术，绝大部分在男性（60.8%）和白人（65.8%）中进行，中位年龄73岁。调查了TLR相关常见的并发症，其中充血性心衰占39.5%，高血压占59.3%，糖尿病占28.2%，外周血管病占7.6%。