Stroke in Adults With Coarctation of the Aorta: A National Population-Based Study

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Background—Adults with repaired coarctation of the aorta (CoA) have reduced long-term survival compared with the general population. This study aimed to determine whether CoA is independently associated with premature ischemic and hemorrhagic stroke in the contemporary era.

Methods and Results—This was a cross-sectional study utilizing the National Inpatient Sample database from 2005 to 2014. We hypothesized that patients with CoA are hospitalized with ischemic and hemorrhagic stroke at a younger age compared with the general population. To test this hypothesis, we compared the age at stroke in patients with and without a diagnosis of CoA using simple and multivariable weighted linear regression. Among 4,894,582 stroke discharges, 207 had a diagnosis of CoA. Patients with CoA had strokes at significantly younger age compared with patients without CoA: 18.9 years younger for all-cause stroke (P < 0.001), 15.9 years younger for ischemic stroke (P < 0.001), and 28.5 years younger for hemorrhagic stroke (P < 0.001), after adjusting for potential confounders. There was no significant difference in the proportion of ischemic strokes between those with and without CoA (79.2% versus 83.0%, P = 0.50). However, CoA patients had a higher proportion of subarachnoid hemorrhage (11.8% versus 4.8%, P = 0.039) than those without CoA. Among patients who had a hemorrhagic stroke, the prevalence of unruptured intracranial aneurysms was higher in patients with CoA compared with those without CoA (23.3% versus 2.5%, P = 0.002).

Conclusions—Patients with CoA have both ischemic and hemorrhagic strokes at significantly younger ages compared with the general population. (J Am Heart Assoc. 2018;7:e009072. DOI: 10.1161/JAHA.118.009072.)

Key Words: adult congenital heart disease • coarctation of the aorta • intracranial aneurysm • stroke

Despite adequate relief of aortic arch obstruction, adults with coarctation of the aorta (CoA) have reduced long-term survival compared with the general population. Case reports and single-center series suggest that stroke may be an important contributor to premature morbidity and mortality in CoA. Proposed mechanisms include long-term vascular dysfunction and a high prevalence of systemic hypertension and intracranial aneurysms. However, there are limited data on age at, risk factors for, or type of stroke (ischemic versus hemorrhagic) in adults with CoA. The Quebec Congenital Heart Disease Registry reported an increased hazard of stroke in patients with left-sided lesions, but they did not further specify CoA. A study from the Swedish Patient Register found an increased risk of ischemic stroke in CoA. However, there were few events and this study did not include analysis of hemorrhagic stroke.

Studies limited to tertiary medical centers are limited by the relatively low incidence of stroke and variable follow-up duration of CoA patients. Therefore, evaluating the burden of stroke in adults with CoA necessitates the use of population-based data. There are no existing US population-based studies of stroke in CoA. Prospective registries or longitudinal databases of sufficient size or with adequate follow-up duration are also not available. Therefore, we utilized the National Inpatient Sample (NIS) database, the largest all-payer inpatient database representing >95% of the US population.
primary aim was to determine whether CoA is independently associated with premature stroke in the contemporary era. Our secondary aims were to delineate the proportions of hemorrhagic and ischemic stroke and the prevalence of unruptured intracranial aneurysms.

Methods

Because of limitations of the NIS data use agreement and availability of the data directly from the Agency for Healthcare Research and Quality, the data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design

A cross-sectional study utilizing discharge data from the NIS database, provided by the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality, was performed for the period 2005 to 2014. Each year of the NIS includes data from an estimated 35 million annual discharges. Patients ≥18 years of age were included in our study. Our primary hypothesis was that patients with CoA are hospitalized with all-cause, ischemic, and hemorrhagic stroke at a younger age compared with the general population. Secondary outcomes included proportion of stroke types, prevalence of unruptured intracranial aneurysm, mortality, and discharge disposition in those with and without CoA. Because of the use of publicly available anonymized data, the Boston Children’s Hospital Institutional Review Board exempted the study and waived the requirement for informed consent.

Definitions

CoA was defined as International Classification of Diseases, Ninth Revision (ICD-9) code 747.1. Observations were excluded if there was a concomitant ICD-9 code indicating infective endocarditis (421.x), complex congenital heart disease (Table 1), or pregnancy as designated by Healthcare Cost and Utilization Project. Ischemic stroke was defined by ICD-9 codes of 433.x1, 434.x (excluding 434.x0, “without mention of infarction”), or 436.x. Hemorrhagic stroke was defined by ICD-9 code 430.x (subarachnoid hemorrhage) or 431.x (intracerebral hemorrhage). Unruptured intracranial aneurysm was defined by ICD-9 code 437.3. The median income quartiles based on ZIP code are provided by Healthcare Cost and Utilization Project; the upper limit of quartile 1 is 150% of the federal poverty level. Per Healthcare

Table 1. International Classification of Diseases, Ninth Revision (ICD-9) Codes for Complex Congenital Heart Disease

| ICD-9  | Diagnosis                                      |
|--------|-----------------------------------------------|
| 745.0  | Common truncus                                |
| 745.1  | Transposition of great vessels                |
| 745.2  | Tetralogy of Fallot                           |
| 745.3  | Common ventricle                              |
| 745.4  | Ventricular septal defect                     |
| 745.6  | Endocardial cushion defects                   |
| 745.7  | Cor bilocular                                 |
| 746.0  | Anomalies of pulmonary valve                  |
| 746.1  | Tricuspid atresia and stenosis                |
| 746.2  | Ebstein’s anomaly                              |
| 746.5  | Congenital mitral stenosis                    |
| 746.6  | Congenital mitral insufficiency               |
| 746.7  | Hypoplastic left heart syndrome               |
| 746.8  | Other congenital anomalies of heart (includes Shone’s) |
| 747.3  | Anomalies of pulmonary artery                 |
| 747.4  | Anomalies of great veins                      |
Cost and Utilization Project, race includes both race and ethnicity; in the case that the source data supplied both, ethnicity takes precedence over race. For example, if a patient is coded as being both black and Hispanic, then race is defined as Hispanic.

### Statistical Analysis

To test our primary hypothesis, we compared the age at the time of stroke hospitalization in patients with and without a diagnosis of CoA using simple and multivariable weighted linear regression. Covariates included sex, race, long-term anticoagulation or antiplatelet use, atrial fibrillation or flutter, chronic kidney disease, coronary artery disease, diabetes mellitus, heart failure, hyperlipidemia, hypertension, tobacco use, and median income by ZIP code. Sample weights were applied to patient-level discharge observations to generate a nationally representative estimate of US hospitalizations per recommendations from the Healthcare Cost and Utilization Project Methods Series. To account for a change in sampling frame in 2012, revised trend weights supplied by the Agency for Healthcare Research and Quality were used. Stata statistical software (version 14.2) svy commands were used to account for sample weights and clustering in the NIS survey design.

In both primary and secondary analyses, 2 models were evaluated, 1 excluding and 1 including potential intermediates in the causal pathway (hypertension, heart failure, anticoagulation, atrial fibrillation or flutter, and chronic kidney disease). Interaction between hypertension and CoA was also assessed using an interaction term for hypertension. Since income was missing in 2.2% of observations and race in 14.7%, multiple imputation was used to impute the incomplete observations based on the values of all other covariates (Stata mi commands). Multinomial regression was used for both variables, and 10 imputed data sets were created. Weighted linear regression models were run for each of the imputed data sets and combined to give the final results. Relationships between secondary outcomes and patient characteristics were assessed using logistic regression. For all analyses, the statistical significance level was set at 0.05 and hypothesis tests were 2-sided.

### Sensitivity Analyses

In 2009, the number of secondary diagnosis codes used in the NIS database increased from 15 to 25. To evaluate the potential effect of this change, we explored inclusion of only the first 15 diagnostic codes for all years, as compared with 15 diagnostic codes from 2005 to 2008 and 25 diagnostic codes from 2009 to 2014. Codes for bicuspid aortic valve (BAV), which is present in >50% of patients with CoA, has limited accuracy in administrative databases. It may be coded as either bicuspid aortic valve/congenital aortic insufficiency (746.4) or congenital aortic stenosis (746.3). To determine the impact of inclusion of observations with BAV on the independent association of CoA with age at stroke, we repeated the analyses adjusting for the presence of these codes.
Results
Among 4,894,582 discharges with a primary diagnosis of stroke, 207 had a concomitant, secondary diagnosis of CoA. Characteristics of these patients are summarized in Table 3. Patients with and without a CoA diagnosis were similar with respect to sociodemographic characteristics and most clinical comorbidities. However, CoA patients were less likely to have diabetes mellitus (16.9% versus 34.3%, \( P = 0.023 \)) and more likely to be Hispanic (23.2% versus 7.9%, \( P < 0.001 \)). Hypertension was highly prevalent in patients with and without CoA (86.4% versus 78.7%, \( P = 0.22 \)).

Table 3. Characteristics of Patients With Stroke

| Variable                        | CoA (%) (N=207) | Non-CoA (%) (N=4,894,582) | \( P \) Value |
|---------------------------------|-----------------|---------------------------|--------------|
| Female                          | 88 (42.5)       | 2,582,648 (52.8)          | 0.18         |
| Anticoagulation/antiplatelet use | 17 (8.3)        | 393,080 (8.0)             | 0.95         |
| Atrial fibrillation or flutter   | 27 (13.2)       | 1,073,518 (21.9)          | 0.17         |
| Chronic kidney disease          | 15 (7.1)        | 553,109 (11.3)            | 0.40         |
| Coronary artery disease         | 51 (24.5)       | 1,117,803 (22.8)          | 0.80         |
| Diabetes mellitus               | 35 (16.9)       | 1,679,633 (34.3)          | 0.023        |
| Heart failure                   | 39 (18.7)       | 639,178 (13.1)            | 0.28         |
| Hyperlipidemia                  | 91 (43.8)       | 2,205,330 (45.1)          | 0.87         |
| Hypertension                    | 179 (86.4)      | 3,853,648 (78.7)          | 0.22         |
| Tobacco use                     | 59 (28.5)       | 1,194,034 (24.4)          | 0.54         |
| Race                            |                 |                           | 0.007*       |
| White                           | 122 (61.6)      | 2,611,344 (69.6)          |              |
| Black                           | 20 (10.2)       | 623,224 (16.3)            |              |
| Hispanic                        | 46 (23.2)       | 296,274 (7.9)             |              |
| Asian or Pacific Islander       | –               | 113,386 (3.0)             |              |
| Native American                 | –               | 18,164 (0.5)              |              |
| Other                           | \(^*\)          | 102,909 (2.7)             |              |
| Median income by ZIP code       |                 |                           | 0.34         |
| Quartile 1                      | 81 (41.3)       | 1,111,341 (29.2)          |              |
| Quartile 2                      | 45 (21.5)       | 965,552 (26.3)            |              |
| Quartile 3                      | 29 (16.4)       | 880,522 (23.7)            |              |
| Quartile 4                      | 43 (20.9)       | 807,885 (20.8)            |              |

CoA indicates coarctation of the aorta.

\(^*\) Significance because of higher percent Hispanic in CoA group. Total numbers (N) are weighted estimates rounded to the nearest whole number. There were no CoA patients of Asian, Pacific Islander, or Native American race, denoted by "---".

\(^\dagger\) Healthcare Cost and Utilization Project data use agreement prohibits reporting of fewer than 11 observations.

CoA and Age at Stroke
A comparison of age at stroke in patients with and without a diagnosis of CoA is shown in Figure 1. The median age at stroke was significantly lower in CoA patients (52 years; interquartile range 31–64) compared with those without CoA (72 years; interquartile range 60–82; \( P < 0.001 \)). The association between CoA and age at stroke remained significant in multivariable models adjusting for sociodemographic and clinical comorbidities (Table 4). In addition, there was no change in the association after inclusion of potential intermediaries in the model (Table 4). The interaction term for hypertension and CoA was not significant (\( P = 0.41 \)), and therefore was excluded from the final models.

Types of Stroke
The relative proportions of stroke types are depicted in Figure 2. There was no significant difference in the proportion of ischemic strokes between patients with and without CoA (79.2% versus 83.0%, \( P = 0.50 \)). However, CoA patients had a higher proportion of subarachnoid hemorrhage (11.8% versus 4.8%, \( P = 0.039 \)) than those without CoA (Figure 2). Patients with CoA had both ischemic and hemorrhagic stroke at a younger age than those without CoA (57 versus 73 years and 27 versus 67 years, respectively, \( P < 0.001 \)) (Figure 1). The median age of subarachnoid hemorrhage in patients with CoA was 23 years, 35 years younger than in those without CoA (\( P < 0.001 \)). The association between CoA and age at ischemic and hemorrhagic stroke remained significant in multivariable...
models adjusting for sociodemographic and clinical comorbidities (Table 4). Inclusion of potential intermediaries in the model (atrial fibrillation or flutter, long-term anticoagulation or antiplatelet use, chronic kidney disease, heart failure, and hypertension) did not significantly attenuate the association of CoA with age at ischemic or hemorrhagic stroke (Table 4).

### Intracranial Aneurysm

As summarized in Figure 3, unruptured intracranial aneurysms were more prevalent in stroke patients with CoA than in those without CoA (9.7% versus 1.1%, \(P<0.001\)). Among patients who had a hemorrhagic stroke, the prevalence of unruptured intracranial aneurysms was higher in patients with CoA compared with those without CoA (23.3% versus 2.5%, \(P=0.002\)). On further subanalysis, 40% of CoA patients who had a subarachnoid hemorrhage were found to have an unruptured intracranial aneurysm. None of the CoA patients with intracerebral hemorrhage had an unruptured aneurysm.

### In-Hospital Mortality and Disposition

The overall in-hospital mortality was 4.9% for ischemic stroke and 24.6% for hemorrhagic stroke. There were no in-hospital deaths in the CoA group. There were no statistically significant differences in hospital discharge disposition between those with and without CoA. Following ischemic stroke, 41.6% of patients with CoA and 43.1% of patients without CoA were discharged to a skilled nursing or intermediate care facility \((P=0.86)\). Following hemorrhagic stroke, 31.8% of patients with CoA and 38.9% of patients without CoA were discharged to a skilled nursing or intermediate care facility \((P=0.66)\).

### Sensitivity Analyses

To explore whether the increase in the number of diagnostic codes from 15 to 25 in 2009 may have confounded our results, we explored the inclusion of only the first 15 codes for all years. The association between CoA and age at admission for stroke remained unchanged \((\beta = -18.7, 95\% \text{ confidence interval, } -24.2, -13.3, \ P<0.001)\). Therefore, all reported analyses included 15 diagnostic codes from 2005 to 2008 and 25 diagnostic codes from 2009 to 2014.
Only 6.7% of patients with CoA had a code for BAV or congenital aortic stenosis, which is significantly less than the established prevalence of BAV of at least 50% in patients with CoA. To determine the impact of inclusion of observations with codes for BAV or congenital aortic stenosis on the independent association of CoA with age at stroke, we repeated the analyses adjusting for the presence of these codes. There was no significant change in the association of CoA with age at stroke; therefore, reported analyses do not adjust for BAV.

Discussion

Our results indicate that patients with CoA in the United States have ischemic and hemorrhagic stroke at a substantially younger age than the general population, even after accounting for traditional cerebrovascular risk factors. To the best of our knowledge, this is the largest study to date examining ischemic and hemorrhagic stroke in adults with CoA.

CoA and Age At Stroke

Our finding that patients with CoA have ischemic strokes at a younger age than the general population is consistent with prior studies. Lanz et al reported a median age of 49.9 years for ischemic stroke for patients with all types of congenital heart disease and an increased risk among patients with left-sided lesions, though they did not further specify CoA. Mandalenakis et al found that a diagnosis of CoA conferred a significantly increased risk of ischemic stroke compared with the general population. However, presumably because of limited sample size with only 9 events, they did not account for potential confounders in the CoA subgroup. Inclusion of potential confounders and intermediaries in our models did not significantly attenuate the estimate for CoA, supporting the independent association of CoA with age at stroke.

While there are multiple single-center reports of individual patients with CoA who sustained a hemorrhagic stroke during the second and third decades of life, to the best of our knowledge, this is the first population-based study of hemorrhagic stroke in CoA patients in the contemporary era. We found that CoA patients were 28 years younger at the time of admission for hemorrhagic stroke compared with those without CoA, independent of other risk factors. These results are consistent with those of Lanz et al, who reported that the age- and sex-standardized incidence rate of hemorrhagic stroke in all types of congenital heart disease was 5 to 6 times higher compared with the general population. The high in-hospital mortality rate in patients with hemorrhagic stroke seen in our data set is consistent with prior studies. Our finding that none of the patients with CoA died during hospitalization may be related to the significantly younger age of patients with CoA.

In our analyses, we considered only isolated CoA, excluding those with complex associated lesions, such as congenital mitral valve disease. We were unable to completely account for the effect of BAV in this population, which is present in >50% of CoA patients, because of the known limitations of accurately identifying patients with BAV in administrative databases. However, when we adjusted for BAV in our sensitivity analysis, there was no change in our estimate of the association of CoA with age at ischemic or hemorrhagic stroke.

Notably, the association of CoA with age at stroke was not significantly attenuated by inclusion of hypertension in the model, nor with the inclusion of an interaction term. These results suggest that blood pressure management alone may not be sufficient to mitigate the risk of stroke in this population. However, we cannot exclude the role that hypertension may play in the pathogenesis of stroke in this patient population because it is a well-established risk factor for intracranial aneurysm formation and rupture in the general population and is present in 86% of CoA patients with stroke. Although CoA is a known risk factor for hypertension, the prevalence of hypertension in our data set was similar in patients with or without CoA. This is not unexpected in a population of stroke patients, because hypertension is a known risk factor for stroke, independent of CoA.

There is the potential for selection bias, because only those patients who survive long enough to have a stroke are included in the analyses. Therefore, younger age of stroke in those with CoA may in small part be because of early mortality of patients with CoA compared with the general population. However, prior analyses have found only a 5- to 10-year reduction in life expectancy for patients with CoA, in large part because of cerebrovascular disease. Therefore, it is unlikely that underlying differences in population age distributions explain our findings of CoA patients having all-cause stroke at ages 20 years younger and hemorrhagic stroke at ages 28 years younger than the general population.

There are multiple proposed contributors to the early age of stroke in patients with CoA. Long-term vascular dysfunction and increased carotid intima-medial thickness may increase the risk of ischemic stroke. In addition, CoA patients are more likely to be male and have hyperlipidemia. There is a high prevalence (10%–12%) of intracranial aneurysms, which may predispose to hemorrhagic stroke. The high prevalence of systemic hypertension (>50%) increases the risk of both hemorrhagic and ischemic stroke.

Intracranial Aneurysm

Our findings that patients with CoA have hemorrhagic stroke 28 years younger than the general population, independent of
risk factors such as hypertension or anticoagulation use, and have a high prevalence of unruptured intracranial aneurysms (40% in those with subarachnoid hemorrhage) suggest that the cause of hemorrhagic stroke in patients with CoA may be a result of early development and subsequent rupture of intracranial aneurysms. Risk factor reduction alone may not sufficiently reduce the risk of early hemorrhagic stroke. Independent of the cause of the initial stroke, the presence of an unruptured aneurysm may pose increased risk for a subsequent event if untreated. Notably, the prevalence of unruptured intracranial aneurysm in CoA patients in the entire stroke cohort (9.7%) was similar to the reported prevalence of 10% to 12% in cross-sectional surveillance studies.11,12

Limitations
Many of the limitations of this study are intrinsic to the use of an administrative database. First, we were unable to determine type or timing of CoA repair or the presence of residual arch obstruction, which may contribute to the age at stroke. Second, information regarding medication use for comorbidities such as hypertension was not available. Third, body mass index could not be ascertained given the poor predictive value of ICD-9 codes for obesity.12 Fourth, it is likely that CoA is not routinely coded in all admitted patients with CoA, resulting in an underestimation of its prevalence, though this would not affect the estimates of age at stroke. Finally, it should be noted that we are reporting the difference in age at stroke between those with and without CoA, adjusting for other comorbidities, but not the absolute or relative risk of stroke among those with CoA.

Conclusions
Questions remain regarding the optimal strategy to reduce the premature morbidity and mortality related to stroke in patients with CoA. Our findings suggest that traditional risk factor reduction alone may not be sufficient and other approaches should be investigated. Nevertheless, our results support the recommendation of the 2008 guidelines for the management of adult congenital heart disease to regularly monitor patients with repaired CoA for resting and exercise-induced systemic hypertension, to treat aggressively when hypertension and other established risk factors are identified, and to screen for intracranial aneurysms.1

In conclusion, patients with CoA in the United States have ischemic and hemorrhagic stroke at substantially younger ages compared with the general population. Further research is needed to investigate appropriate surveillance and treatment strategies to reduce the premature morbidity of stroke in patients with CoA.

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