Title

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Journal

Journal of the American Heart Association, 13(17)

ISSN

2047-9980

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Publication Date

2024-09-03

DOI

10.1161/jaha.124.036458

Editorial: Congenital Heart Disease, Atrial Fibrillation and Ischemic Stroke Risk

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Key words: Editorials, atrial fibrillation, congenital heart disease, ischemic stroke

Word count: 1845

Over the past several decades, major advances in the medical and surgical management of infants and children with congenital heart disease (CHD) have led to the improving survival of these vulnerable patients beyond childhood. Later in life, however, dysrhythmias become a prevalent comorbidity. Adults with CHD tend to develop atrial fibrillation (AF) at younger ages than the general population because of abnormal cardiac anatomy, displaced or malformed sinus nodes or AV conduction systems, other cardiac diseases, medications, and genetics.[1] A prior large study found that atrial arrhythmias increased the risk of death and heart failure but not ischemic stroke in adults with CHD.[2] Despite this finding, ischemic stroke remains a major concern for adults with CHD and AF.

Extensive prior studies have led to the development of guidelines and clinical scores to stratify stroke risk related to atrial fibrillation in the general population.[3] Clinical scores, such as CHA_2DS_2-VASc, help medical providers determine when to initiate anticoagulation for stroke prevention.[3-5] Currently, only limited data are available to guide decision-making about anticoagulation for stroke prevention in adults with CHD and AF.[6,7] The CHA_2DS_2-VASc score does not take into account the presence or severity of CHD, and is thought to have only modest stroke predictive value in adults with CHD.[6,7] Nonetheless, guidelines suggest that it should be one of the factors that influence decision-making for anticoagulation of patients with CHD in clinical practice.[8] Whether AF confers similar ischemic stroke risk in people with CHD as in the general population remains a gap in knowledge.

In this issue of the Journal of the American Heart Association (JAHA), Holmgren et al report the results of a Swedish, population-based retrospective study that takes a step towards addressing this gap.[9] The authors performed a register-based study using diagnostic codes to identify patients born between 1970 and 2017 with AF and CHD from the Swedish National Patient Registry and the Swedish Cause of Death Register. For each patient with AF and CHD, age and sex-matched controls with AF and without CHD were identified. Cases and controls were followed from the onset of AF until ischemic stroke, death, or the end of the study. By study definition, the primary outcome of ischemic stroke had to occur after the date of AF diagnosis. Patients who sustained an ischemic stroke before AF was diagnosed were excluded.

Out of 71,942 patients with CHD, 951 developed AF. Out of 714,462 controls without CHD, 606 developed AF. Among these patients with AF, ischemic stroke was infrequent overall: only 28 ischemic strokes were identified among AF patients with CHD and only 3 ischemic strokes among controls with AF and no CHD. The stroke risk was greater for patients with CHD and AF despite a higher proportion of treatment with anti-coagulation therapy both before and after the onset of AF. The hazard ratio for ischemic stroke after the onset of AF was estimated to be more than 3 times higher in people who had non-complex CHD. In patients with complex CHD, the risk was more than 6 times higher. The magnitudes of these hazard ratios were even greater (adjusted hazard ratio of 8.3 for patients with complex CHD) in

a statistical model that included several components of the CHA_2DS_2-VASc score, including sex, age, hypertension, and heart failure. Diabetes, ischemic heart disease and myocardial infarction were not included in the models because of a low number of these co-morbidities.

Children were eligible for inclusion in the study, but most of the patients were adults, and the study results are primarily applicable to older age groups with CHD. The cohort born after 1990 (who were younger than 28 years old in 2017, at the end of the study) had very few ischemic strokes. The lower incidence rate of ischemic stroke for those born after 1990 may reflect lower stroke risk at younger ages or could reflect improving stroke prevention strategies among people with CHD in more recent decades.

One of the strengths of the study was its large size, with the inclusion of patients from hospitals nationwide over an entire population rather than a potentially skewed subset of patients seen at tertiary care centers or a single institution. Health care in Sweden is decentralized and health care expenditure is relatively high compared to other countries, and these factors should be kept in mind before generalizing these results to other populations.

The study had several additional limitations that should be kept in mind. The hazard ratios were calculated from only a small number of cases and controls who had ischemic stroke. With this small number of events, a few misclassified or excluded patients with ischemic stroke due to AF could swing the results by a large margin. By study design, patients who had an ischemic

stroke diagnosed before the onset of AF were excluded. This was potentially significant because 43 patients with CHD and six patients without CHD were excluded for an ischemic stroke that occurred before AF was diagnosed. Some of these patients could have had an AF-related stroke, with AF detected during diagnostic work-up prompted by stroke. The precision of the hazard ratios, therefore, should be interpreted cautiously, and future studies are needed to confirm the findings.

The implications of the Holmgren study are that ischemic stroke risk in adults with AF and CHD could be 3 to 8 times higher than in adults with AF in the general population, and that the risk of stroke is modified by the severity of the underlying heart lesion. The reasons for increased stroke risk in the setting of AF and CHD are not clear. One explanation is that CHD exposes people to non-AF stroke risks more frequently. The Holmgren study adjusted for heart failure identified by diagnostic codes when it was present prior to AF onset, but this strategy likely missed heart failure in some patients. The authors did not adjust for cardiac catheterization, cardiac surgery, ventricular assist devices, or extracorporeal life support.

In addition to extrinsic cardiac devices and procedures, stroke risk factors inherent to the heart may be more common in people with CHD. The mechanisms of AF-associated stroke are not straightforward but rather tightly intertwined with underlying endothelium dysfunction, atrial fibrosis, impaired myocyte function, and other atrial cardiopathy.[10] How these vary in

different congenital heart lesions is complex but must be considered as future stroke prevention strategies are developed.

AF is estimated to affect more than half of adults with CHD by 50 years of age.[1] With the rising number of adults with AF and CHD, clinical decision-making tools and antithrombotic stroke prevention strategies for this group of patients must be optimized. Prospective studies are needed to verify its findings, but the Holmgren study suggests that AF-related stroke risk assessment should not be directly extrapolated from the general population to people with CHD. If verified, a further implication is that stroke prevention strategies developed for AF in the general population may not work well if applied to adults with AF and CHD. More research is needed to understand underlying stroke mechanisms in this growing group of patients. Improving stroke prevention for adults with AF and CHD should be considered a specific, distinct research priority.

Conflict of Interest Disclosures:

Dr. Fox receives grant funding from the NIH (1R01NS119896-01A1, 1UG3NS119702) and the American Heart Association/Bugher Foundation (23BFHSCP1176240, and 814692). She served on a data safety and monitoring board for the NIH-NHLBI (the PumpKIN Trial). She receives royalties from UpToDate for pediatric stroke topics. She served as a consultant for Competitive Drug Development International.

Dr. Kamel served in a PI role in the ARCADIA trial, which received in-kind study drug from the BMS-Pfizer Alliance for Eliquis and ancillary study support from Roche Diagnostics; a Deputy Editor role for *JAMA Neurology*; clinical trial steering/executive committee roles for the STROKE-AF (Medtronic), LIBREXIA-AF (Janssen), and LAAOS-4 (Boston Scientific) trials; consulting or endpoint adjudication committee roles for AbbVie, AstraZeneca, Boehringer Ingelheim, and Novo Nordisk; and household ownership interests in TETMedical, Spectrum Plastics Group, and Ascential Technologies.

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