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RESEARCH LETTER

Association of Hypertension With Early-Onset Cryptogenic Ischemic Stroke by the Presence of Patent Foramen Ovale: A Case–Control Study

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Cryptogenic ischemic stroke (CIS) in the young represents a crucial area of research due to its substantial clinical burden and increasing incidence.[1] Hypertension stands as the most prevalent well-documented stroke risk factor. However, there are limited and conflicting data on the prevalence of hypertension and associations of hypertension with ischemic stroke in young patients with cryptogenic pathogenesis.[2,3] Although patent foramen ovale (PFO) is an important phenotypic feature of CIS, the association of hypertension in patients with CIS with or without PFO has not been specifically addressed in previous studies. These studies may have mixed PFO cases between cardioembolic and undetermined pathogenetic subgroups. Young patients with CIS and PFO are less likely to have hypertension and other traditional risk factors, and most recent evidence suggests that specific high-risk features of PFO (atrial septal aneurysm or a large-sized shunt) substantially increase the causality of PFO.[4] We determined the sex- and age-specific prevalence and association of hypertension in early-onset CIS stratified by the high-risk PFO (HR-PFO) phenotype.

We included 523 consecutive young patients aged 18 to 49 years with CIS (median age, 40.8 [interquartile range, 34.1–45.8]; 47.2% women) from the Searching for Explanations for Cryptogenic Stroke in the Young study and 1:1 age- and sex-matched stroke-free controls across 19 European centers. Data on HR-PFO were unavailable for 23 of the initial 546 patients because shunt size was not reported due to various reasons, such as poor visibility and technical difficulties. Ethical

Key Words: blood pressure ■ foramen ovale, patent ■ hypertension ■ ischemic stroke ■ risk factors

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approval was obtained from local committees and written informed consent from all participants. The data that support the findings of this study are available from the corresponding author upon reasonable request. Patients underwent standardized pathogenetic examinations as detailed before.[5] Hypertension was defined as a prior diagnosis, prior antihypertensive medication use, or a mean of 2 office blood pressure measures ≥140/90 at study visit (median 6 days from stroke onset in patients). Comorbidities included cardiovascular disease, diabetes, hypercholesterolemia, current smoking, abdominal obesity, physical inactivity, unhealthy diet, heavy alcohol use, psychosocial stress, and depression. HR-PFO in patients with CIS was assessed by local investigators and defined as PFO with atrial septal aneurysm or PFO with a large-sized right-to-left shunt (≥25 microbubbles crossing the atrial septum), identified through transthoracic or transesophageal echocardiogram, often supported by transcranial Doppler bubble test. In patients with CIS, we assessed the association of hypertension with the absence of HR-PFO with logistic regression, adjusting for demographics and all other comorbidities. Using all stroke-free controls, we constructed logistic regression models to assess the association of hypertension with (1) CIS without HR-PFO and (2) CIS with HR-PFO, stratifying by sex and age group (18–39 and 40–49 years). We also tested for sex and age interactions. Adjustments included demographics alone, demographics with standardized modifiable stroke risk factors (cardiovascular disease, diabetes,

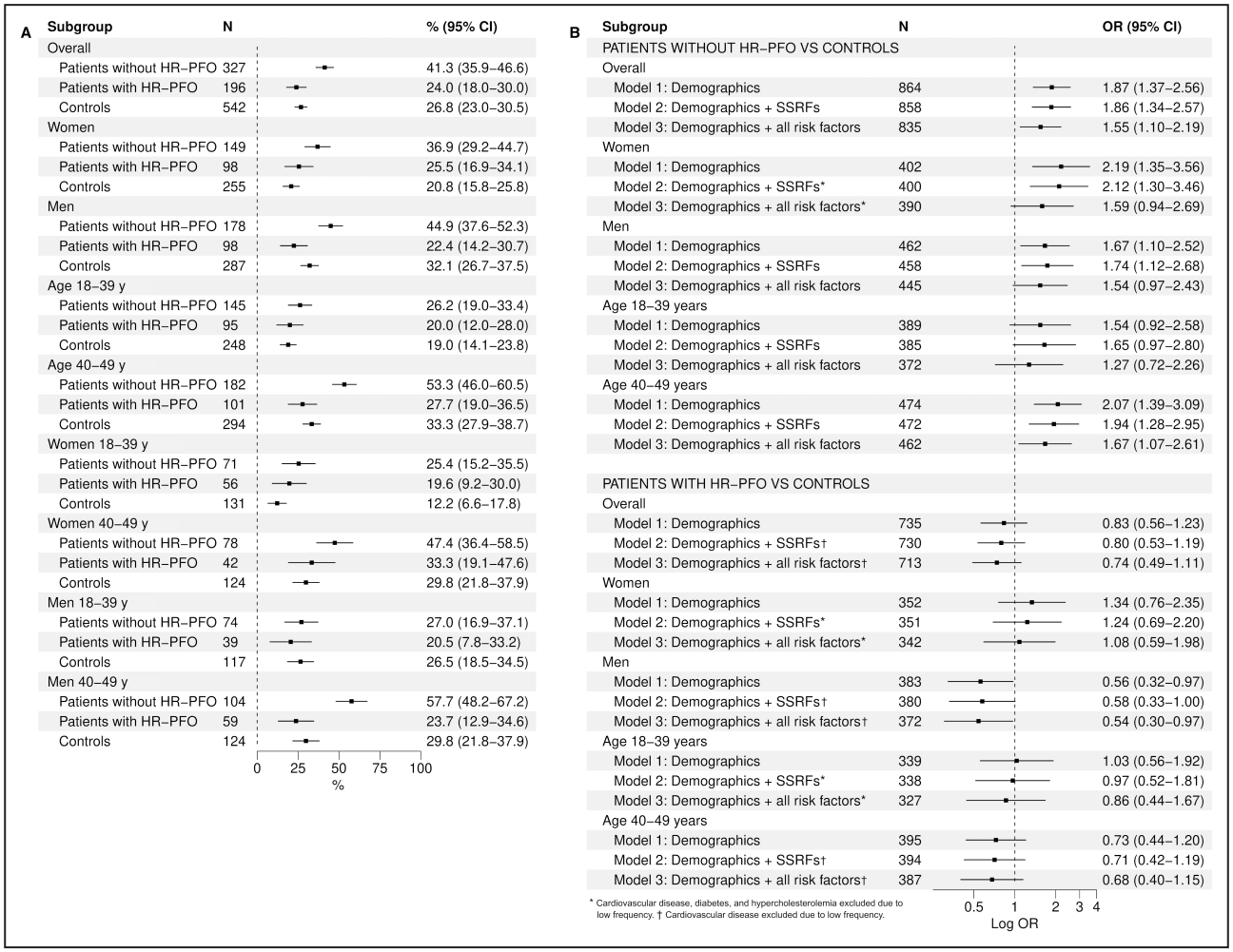

Figure. Frequencies of hypertension in the study population and multivariable analysis of the association between hypertension and early-onset cryptogenic ischemic stroke.

A, Frequencies and 95% CIs of hypertension in patients with cryptogenic ischemic stroke without high-risk patent foramen ovale (HR-PFO), patients with HR-PFO, and stroke-free controls, shown for the overall cohort and by demographic subgroups. **B**, Odds ratios (ORs) with 95% CIs for the association of hypertension with cryptogenic ischemic stroke in the overall cohort, women, men, those aged 18 to 39 years, and those aged 40 to 49 years, stratified by the presence of HR-PFO in patients. Model 1 is adjusted for demographics (age, sex, and level of education). Model 2 is adjusted for demographics and standardized stroke risk factors (SSRFs) including cardiovascular disease, diabetes, hypercholesterolemia, and current smoking, when frequency allowed. Model 3 was further adjusted for abdominal obesity, physical inactivity, unhealthy diet, heavy alcohol use, psychosocial stress, and depression.

hypercholesterolemia, and current smoking), and demographics with all comorbidities. Statistical analyses used IBM SPSS Statistics 29.0 and R (R Core Team 2023).

Compared with patients with CIS without hypertension (n=359 [65.2%]), patients with hypertension (n=182 [34.8%]) were older (43.8 versus 39.2 years), and more frequently had cardiovascular disease (4.4% versus 1.2%), diabetes (4.9% versus 1.8%), hypercholesterolemia (5.5% versus 0.6%), abdominal obesity (79.1 versus 48.7%), and low physical activity (34.6% versus 26.0%), and more often they reported psychosocial stress (57.1% versus 45.3%). Patients with hypertension less frequently had HR-PFO (25.8% versus 43.7%). Among patients with CIS, hypertension was associated with absence of HR-PFO (odds ratio, 2.11 [95% CI, 1.36–3.27]).

Compared with all stroke-free controls (n=542), patients without HR-PFO (n=327 [62.5%]) more frequently had hypertension in the overall cohort, across sexes, and in the older age group overall and in men. Among women in both age groups, there was a trend of higher hypertension prevalence in patients without HR-PFO, although the confidence intervals overlapped. No significant differences emerged between patients with HR-PFO (n=196) and controls (Figure [A]).

In multivariable case–control analyses, hypertension showed a significant association for CIS without HR-PFO across all models in the overall cohort, whereas no association emerged for CIS with HR-PFO. The strength of the association between hypertension and CIS without HR-PFO tended to diminish when behavioral risk factors were included in the models. In sex-specific analyses, we initially observed an association between hypertension and CIS with HR-PFO with less stringent adjustment, which did not persist after full adjustment, with no interaction by sex (P=0.545). Age-specific models adjusted for all relevant confounders showed association for CIS without HR-PFO specifically among individuals aged 40 to 49 years (Figure [B]), with no formal interaction observed by age (P=0.469).

The main findings of this study were that hypertension was highly prevalent in patients with early-onset CIS without PFO across sexes and with age, and that the independent association between hypertension and CIS considered only the patients without HR-PFO but not those with HR-PFO, a phenotype most likely connected to CIS through paradoxical embolism. The overall prevalence of hypertension in our patients with CIS without HR-PFO aligns with the range reported in larger series of unselected young patients with ischemic stroke.[2,3] In contrast, those with HR-PFO exhibited a prevalence below the range reported, but aligning (that shown) in pooled data set results of all-aged patients with PFO from randomized trials.[4] Hypertension was independently associated with CIS without HR-PFO, without interaction for age and sex, although in demographic subgroups our power to show significant differences was limited. However, our results expand previous case–control studies involving unselected young patients with ischemic stroke, which indicated a stronger association between hypertension and age.[2,3] Hypertension probably contributes to early-onset CIS (assuming most events are not related to atherosclerotic disease) in patients without HR-PFO through various cardiac and arterial mechanisms, including left ventricular hypertrophy, left atrial stiffness, vulnerability to paroxysmal atrial fibrillation, endothelial dysfunction, reduced fibrinolytic capacity, and cerebral hemodynamic alterations. The attenuation of the association's strength following further adjustments in our models may indicate that behavioral risk factors beyond smoking significantly contribute to early-onset CIS, potentially through processes involved in the development of hypertension.

The most notable strengths of our study are the relatively large sample of prospectively and consecutively identified young patients with CIS, detailed characterization of participants, and extensive adjustment for relevant confounders. Limitations include restricted sample size for subgroup analyses and those inherent to case–control studies, such as possible selection bias with controls. However, the prevalence of comorbidities, including hypertension among control subjects, is in line with contemporary estimates.

ARTICLE INFORMATION

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Disclosures

Dr Putaala is a board member of the Finnish Hypertension Association. Dr Fonseca is a speaker for Novo Nordisk. The remaining authors have no disclosures to report.

Supplemental Material

Data S1

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