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Temporal trends in hypertension-related ischaemic stroke risk in atrial fibrillation from 2007 to 2018: a nationwide cohort study

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Atrial fibrillation (AF) is a major cause of ischaemic stroke (IS), with the risk varying considerably between individuals based on their clinical characteristics.[1] Hypertension, in turn, is one of the most common medical conditions and a leading risk factor for cardiovascular diseases.[2] In the presence of AF, hypertension is a well-documented risk factor for IS and it is included in the commonly used IS risk scores.[3]

Over the past decades, progress in medical research has resulted in substantial changes in the management of both hypertension and AF.[4–6] While the interplay between hypertension and AF has been extensively studied, there is a paucity of information regarding the temporal trends in their coexistence and whether hypertension still continues to be a similar risk factor for IS in AF. Considering the evolution in the management of hypertension, we hypothesized that the IS risk associated with it has attenuated over time.

The Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) Study (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845) is a nationwide retrospective cohort study that includes all patients documented with an AF diagnosis code I48 in Finland from 2007 to 2018.[7] Patients were identified using all available national healthcare registers, including hospitalizations and outpatient specialist visits, primary healthcare, and the National Reimbursement Register. The present sub-study was conducted within a previously established cohort of patients with incident AF.[6] Follow-up started from the initial AF diagnosis and continued until the occurrence of an IS event, death, or 31 December 2018. Additionally, since it is the non-anticoagulated IS risk that drives the clinical decision-making of oral anticoagulant (OAC) therapy, we performed separate analyses covering only the follow-up time without OAC therapy.

Patients were classified as having hypertension if they had recorded hypertension codes (ICD-10 codes I10-I15 or ICPC-2 codes K85-K87) in the healthcare registers and hypertension medication reimbursement codes or had redeemed antihypertensive medications. However, beta-blockers and calcium channel blockers were not considered if the patient had a diagnosis of coronary artery disease, and renin–angiotensin–aldosterone system inhibitors were not considered if the patient had a diagnosis of heart failure or cardiomyopathy. In patients without a prior history of IS before the first AF diagnosis, IS event was considered to occur on the first date of a recorded I63 or I64 ICD-10 diagnosis code in the hospital care register after the AF diagnosis. In patients with prior IS, the event was considered to occur on the date of the first new hospitalization with I63 or I64 ICD-10 code as the main diagnosis with at least a 90-day gap from the prior event. The I64 code of unspecified stroke was included in the outcome measure, since it has been shown that 87% of all strokes recorded with ICD-10 code of I64 are ischaemic.[8]

We calculated incidence rates and incidence rate ratios (IRRs) with 95% confidence intervals for IS using Poisson regression. Adjusted IRRs accounted for the following variables: age, calendar year period, sex, heart failure, diabetes, prior IS, vascular disease, dyslipidaemia, prior bleeding, alcohol use disorder, renal failure, liver cirrhosis or failure, dementia, income level (divided into tertiles), and OAC use. Anticoagulant exposure was considered to start from the first purchase of an OAC and continue until 120 days after the last OAC purchase. Subsequently, the models were fitted with an interaction term between the calendar year period and hypertension to assess changes in the impact of hypertension on IS over time.

We identified 229 565 patients with new-onset AF (50.0% female; mean age 72.7 years; mean follow-up time 4.0 years), of whom 74.2% had hypertension. Compared with patients without hypertension, those with hypertension were older (74.7 vs. 67.2 years) and had a higher prevalence of comorbidities, which reflected also in their higher stroke risk scores (mean CHA_2DS_2-VASc score 4.0 vs. 1.9) The prevalence of hypertension exhibited a steady increase from 66.8% in 2007–2008 to 79.0% in 2017–2018. This increase was observed consistently in all ages, so that by 2017–2018, 62.5%, 78.5%, and 85.5% of patients aged under 65, 65–74, and 75 years or more had hypertension, respectively.

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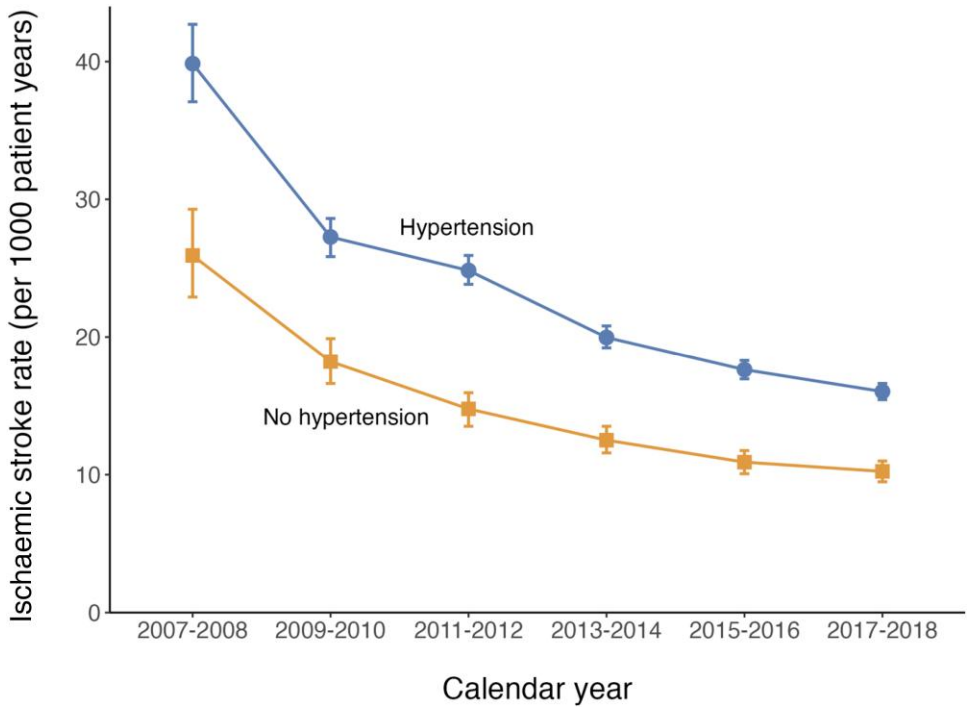

Figure 1 Temporal trends of the crude ischaemic stroke rates with 95% confidence intervals in patients with and without hypertension during the entire follow-up.

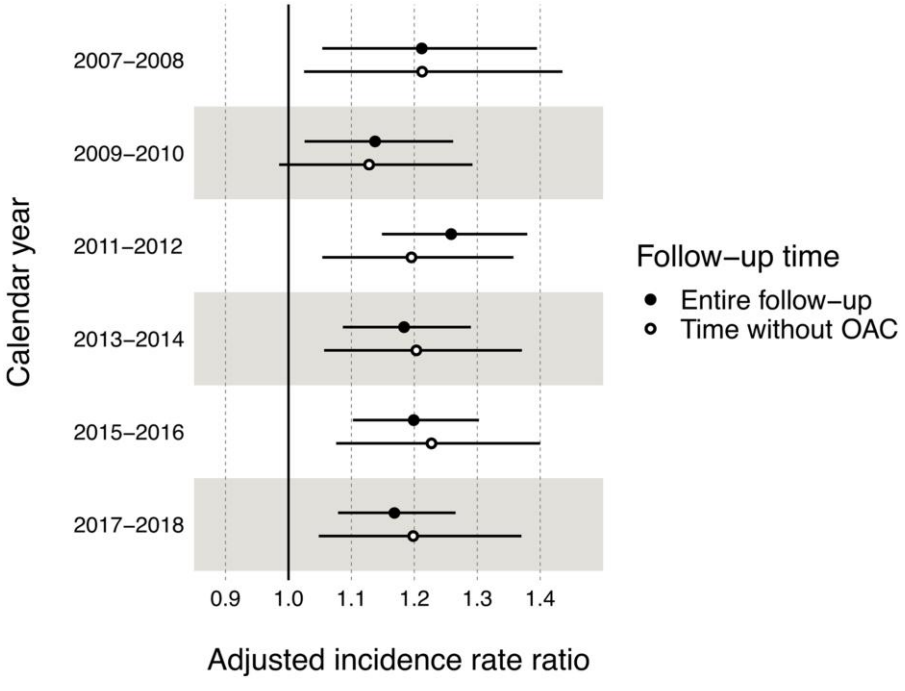

Figure 2 Adjusted incidence rate ratios with 95% confidence intervals of ischaemic stroke in the entire follow-up and in the analyses covering only time without oral anticoagulant use comparing patients with hypertension to those without (vertical reference line) in each calendar year period. OAC, oral anticoagulant.

When the entire follow-up was included in the analyses, IS was observed in 12 823 (7.5%) patients with hypertension and in 3 473 (5.9%) patients without hypertension. The crude IS rates decreased continuously during the study period, particularly in patients with hypertension (*Figure 1*). Hypertension was associated with a higher IS rate both in the unadjusted and adjusted analyses [respective IRRs with 95% confidence intervals 1.57 (1.51–1.63) and 1.19 (1.15–1.24)]. No significant interaction between the calendar year period and hypertension was observed (*P*-value for interaction = 0.77), indicating that the independent impact of hypertension on IS remained stable over time (*Figure 2*). When only follow-up time without OAC therapy was analysed, the results remained uniform to those covering the entire follow-up time [adjusted IRR with 95% confidence interval 1.19 (1.13–1.27); *P*-value for interaction = 0.97; *Figure 2*].

The most important limitations of our study are the challenges in identifying patients with hypertension using administrative data and the lack of information on blood pressure measurements and control of hypertension.[9] To improve sensitivity in detecting patient with hypertension, we linked data from all national health registries, also including pharmacy claims data. Particular strengths of our study include the long observation period and the comprehensive nationwide coverage, encompassing uniquely all levels of care. Additionally, the well-validated hospital care register enhances the reliability of the observed IS events.[10]

Considering the high prevalence of hypertension in patients with AF, the associated multi-morbidity, and the fact that hypertension itself is a modifiable IS risk factor in AF, our findings underscore the importance of cardiovascular and comorbidity risk optimization in the treatment of AF, aligning with the 'C' component of the ABC pathway in the current guidelines.[1] Moreover, while there has been a substantial decrease in the absolute IS rate in patients with AF between 2007 and 2018, the relative IS risk associated with hypertension continues to be of similar magnitude, emphasizing the relevance of maintaining hypertension as a factor in the clinically used IS risk scores.

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Data availability

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Finnish national register holders (KELA, Finnish Institute for Health and Welfare, Population Register Center and Tax Register) through Findata (https://findata.fi/en/).

Author contribution

All authors contributed to the conception and design of the work. K.T. and O.H. contributed to the acquisition and analysis of the data for the work. K.T. and V.L. contributed to the interpretation of the data and drafted the manuscript. K.E.J.A., E.K., J.J., O.H., J.H., J.P., M.L., P.M., J.H., and M.L. critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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