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ORIGINAL RESEARCH

Heart Failure and Stroke Risk in Atrial Fibrillation: Temporal Trends From a Nationwide Cohort Study

Eero Jalli, MD; Ville Langén, MD, PhD; Jussi Jaakkola, MD, PhD; K. E. J. Airaksinen, MD, PhD; Olli Halminen, DSc; Jukka Putaala, MD, PhD; Pirjo Mustonen, MD, PhD; Jari Haukka, PhD; Juha Hartikainen, MD, PhD; Miika Linna, PhD; Mika Lehto, MD, PhD; Konsta Teppo, MD, PhD

BACKGROUND: Heart failure (HF) is a well-recognized risk factor for ischemic stroke (IS) in patients with atrial fibrillation (AF). Advancements in medical research have significantly improved the detection and management of both AF and HF. However, limited data are available on whether these changes have modified the stroke risk associated with HF in patients with AF. This nationwide retrospective cohort study aims to evaluate temporal trends in HF-related IS risk among patients with AF.

METHODS: The FinACAF (Finnish AntiCoagulation in Atrial Fibrillation) registry-linkage study includes all patients in Finland with incident AF from 2007 to 2018.

RESULTS: We identified 229 565 patients with incident AF of whom 17.4% had HF at the time of AF diagnosis. Crude IS rates decreased both in patients with and without HF over the study period. HF was independently associated with a 30% to 50% higher IS rate in 2007 to 2010, but this association attenuated to only 10% to 15% higher in 2015 to 2018. This reduction in HF-related stroke risk was observed primarily in patients without a history of myocardial infarction (MI) (incident rate ratio in 2015–2018, 1.08 [95% CI, 0.95–1.22]), while stroke risk associated with HF remained unchanged in patients with prior MI (incident rate ratio during the entire study period, 1.23 [95% CI, 1.07–1.41]).

CONCLUSIONS: Stroke risk associated with HF has decreased among patients with AF, driven by a decline in HF-related stroke risk in patients without a history of MI. However, HF remains an important stroke risk factor in patients with AF with a history of MI.

Key Words: atrial fibrillation ■ cohort study ■ heart failure ■ stroke

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting up to 5.2% of the adult population.[1] It is a major risk factor for ischemic stroke (IS), with the risk of stroke varying considerably among individuals on the basis of their comorbidities and other clinical characteristics.[2,3] Accurate stratification of stroke risk and identification of individuals who would benefit from oral anticoagulant (OAC) therapy for stroke prevention are essential in managing patients with AF.

Heart failure (HF) is a clinical syndrome that can arise from various underlying conditions, with coronary artery disease and hypertension being the most common causes in developed countries. Traditionally, it has been divided into different phenotypes based on measurements of left ventricular ejection fraction (EF).[4] The incidence of HF has been rising, largely due to the aging population, while prevalence has risen even more, likely attributable to longer survival.[5] AF is a common comorbidity in patients with HF, affecting

Correspondence to: Eero Jalli, Turku University Hospital and University of Turku, Turku, Finland. Email: eero.o.jalli@utu.fi

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CLINICAL PERSPECTIVE

What Is New?

- This nationwide retrospective cohort study reveals that the stroke risk associated with heart failure has decreased among patients with atrial fibrillation.
- The reduction in heart failure–related ischemic stroke risk is primarily driven by a decreasing association between heart failure and ischemic stroke among patients without a history of myocardial infarction.

What Are the Clinical Implications?

- Further investigation is needed to inform clinical decisions on stroke prevention, promoting more personalized treatment approaches.

Nonstandard Abbreviations and Acronyms

FinACAF	Finnish AntiCoagulation in Atrial Fibrillation
IRR	incidence rate ratio
IS	ischemic stroke
OAC	oral anticoagulant

55.1% of individuals with HF.[6] In the presence of AF, HF is a well-documented risk factor for IS, and it is also included in the CHA_2DS_2-VASc score, the currently recommended tool for evaluating stroke risk and determining the need for OAC therapy. Additionally, HF is reported as the most common cause of death among patients with AF.[7]

The past few decades have brought significant advancements in the diagnosis and treatment of both AF and HF, particularly among older adults, where diagnosis rates have increased.[5,8,9] Treatment of HF has improved considerably in recent years as new drugs, device therapies, and catheter ablation have become integral to routine care. The awareness and treatment of comorbidities and risk factors for HF such as hypertension and coronary artery disease have also improved.[8,9]

Although the link between HF and risk of stroke in AF is well established, data on temporal trends are lacking. Given the recent improvements in the management of patients with HF and AF, we hypothesize that the IS risk associated with HF has decreased over time. Therefore, we conducted a nationwide retrospective cohort study with the aim of examining temporal trends in the stroke risk associated with HF among patients with AF.

METHODS

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/).

Study Population

The FinACAF (Finnish AntiCoagulation in Atrial Fibrillation) Study (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845) is a nationwide retrospective cohort study that includes all patients documented with AF in Finland from 2004 to 2018.[10] Patients were identified using all available national health care registers, including hospitalizations and outpatient specialist visits (Hilmo), primary health care (Avohilmo), and the National Reimbursement Register maintained by the Social Insurance Institute (KELA). The cohort inclusion criterion was the *International Classification of Diseases*, *Tenth Revision* (*ICD-10*) diagnosis code I48, encompassing atrial fibrillation and atrial flutter, collectively referred to as AF, recorded between 2004 and 2018. Exclusion criteria were permanent emigration abroad before December 31, 2018, and age <20 years at the time of AF diagnosis. The present substudy was conducted within a cohort of patients with incident AF from 2007 to 2018, established in previous studies of the FinACAF cohort.[11–13]

IS risk is dynamic, and patients' risk categories may evolve over time due to advancing age and incident comorbidities during longer follow-up, typically shifting from lower to higher categories.[14,15] Relatedly, HF is associated with a higher incidence of AF and vice versa. To mitigate the bias from new incident HF diagnoses and other comorbidities, we restricted follow-up to a maximum of 1 year after the initial AF diagnosis. This also prevents large variations in follow-up times across the study period, which could complicate the interpretation of stroke trends. Follow-up began on the first date of AF diagnosis and continued until the occurrence of an IS event, death, the end of the observation period on December 31, 2018, or a maximum of 1 year from the first AF diagnosis, whichever occurred first. Additionally, since the nonanticoagulated IS risk drives clinical decision making regarding stroke prevention with OACs, we performed separate analyses on IS rates covering only the follow-up period without OAC therapy, with follow-up continuing until the first OAC purchase; IS; death; December 31, 2018; or a maximum of 1 year from the first AF diagnosis. Separate analyses were also performed with follow-up extended to a maximum of 2 years, with and without the period after the first OAC purchase. Data on baseline comorbidities were obtained from the aforementioned health care registers. The cohort construction process is summarized in Figure S1, and the definitions of baseline comorbidities are presented in Table S1.

Definition of Heart Failure

Patients were classified as having HF if they had recorded HF codes (*ICD-10* codes I50, I11.0, I13.0, or I13.2, or *International Classification of Primary Care, Second Edition*, code K77) in the hospital or primary care registers, or HF reimbursement codes in the National Reimbursement Register. Previous studies have shown that using hospital-level data alone can underestimate disease prevalence, so we therefore combined available national health registry data to improve the detection of patients with HF. The administrative data lacked information on left ventricular EF, making further categorization into HF with preserved EF or HF with reduced EF unfeasible. However, the HF definition used aligns with the "C" in the CHA_2DS_2-VA score, which considers both HF with preserved EF and HF with reduced EF. Moreover, we separately assessed patients with HF with and without prior myocardial infarction (MI; *ICD-10* codes I21–I22). Additionally, sensitivity analyses were performed without using *International Classification of Primary Care, Second Edition*, codes for HF, as these may be less reliable than *ICD-10* codes.

Outcomes

In patients without a prior history of IS before the first AF diagnosis, an 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 cohort entry. 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 that had occurred before AF diagnosis.

Study Ethics

The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Helsinki, Helsinki, Finland (No.. 15/2017) and received research permission from the Helsinki University Hospital (HUS/46/2018). Respective permissions were obtained from the Finnish register holders (KELA 138/522/2018; THL 2101/5.05.00/2018; Population Register Centre VRK/1291/2019-3; Statistics Finland TK-53-1713-18/u1281; and Tax Register VH/874/07.01.03/2019). Patients' personal identification numbers were pseudonymized, and the research group received individualized but unidentifiable data. Informed consent was waived due to the retrospective registry nature of the study. The study conforms to the Declaration of Helsinki, as revised in 2013.

Statistical Analysis

We calculated incidence rates and incidence rate ratios (IRRs) for IS using a Poisson regression model. The model used a Lexis-type data structure, incorporating 2 time scales: follow-up time from AF diagnosis and calendar year.[16] This statistical approach aligns outcomes with each calendar-year period. The 12-year observation period was divided into 4-year intervals. Age and calendar year were treated as categorical variables. Adjusted IRRs accounted for the following variables: age, calendar-year period, sex, hypertension, diabetes, prior IS, vascular disease, dyslipidemia, prior bleeding, alcohol use disorder, renal failure, liver cirrhosis or failure, dementia, income level (divided into tertiles), and OAC use. OAC use was treated as a time-varying variable, initiated by the first purchase of an OAC and continuing until 120 days after the last drug purchase. In Finland, individuals are reimbursed for up to 90 days of medication per purchase. We used the 120-day interval to encompass this 90-day period and an additional 30-day grace period, to account for potential stockpiling and variations in warfarin dosing. When only time without OAC therapy was investigated, OAC use was not included in the adjusted analyses. Subsequently, the models were fitted with an interaction term between calendar-year period and HF to assess changes in the impact of HF on IS over time. Separate analyses compared patients with HF and MI with those without HF, patients with HF without MI with those without HF, and patients with HF with MI with those without MI. Additionally, to assess the impact of differing definitions for IS in individuals with or without prior stroke events, we performed sensitivity analyses by excluding patients with a prior stroke event before the first AF diagnosis. These analyses were conducted with a 1-year follow-up, both with and without including the period of anticoagulant use. Baseline variables were compared using the χ^2 test, Student's *t* test, and ANOVA. Statistical analyses were conducted using IBM SPSS Statistics software version 28.0 (SPSS, Inc., Chicago, IL) and R version 4.0.5 (R Core Team, Vienna, Austria; https://www.R-project.org).

RESULTS

We identified 229 565 patients with new-onset AF (50.0% women, mean age, 72.7 years), of whom 17.4% had HF at the time of AF diagnosis. The HF group had a higher proportion of women (55.6% versus 48.8%; $P<0.001$) and was generally older compared with the group without HF (mean age, 79.0 versus 71.4; P<0.001). Patients with HF had lower income, a higher burden of comorbidities, and a higher mean CHA_2DS_2-VA score (4.4 versus 2.6; P<0.001) compared with patients without HF (Table 1). The history of MI among patients with HF increased continuously from 16.5% to 20.6% during the study period, and similar trends in the prevalence of other major comorbidities were observed in both patients with HF and those without (Table S2). The proportion of patients initiating OACs within 1 year after AF diagnosis increased between the first and last calendar-year periods in both those with HF and those without (from 53.3% to 68.9% and from 44.3% to 71.6%, respectively; Table S3).

The prevalence of HF decreased from 18.0% in 2007 to 2010 to 16.7% in 2015 to 2018. This decline was particularly notable in the older age groups, whereas among patients aged <65 years, the prevalence increased slightly, rising from 7.6% in 2007 to 2010 to 8.9% in 2015 to 2018 (Figure 1). However, the absolute number of patients with HF did not fall in any age group during the study period.

The crude IS incidence rate decreased steadily throughout the study period, with a decline observed in both patients with HF and those without (Figure 2). However, the IS rate remained consistently higher in patients with HF (Figure 2). Among patients with HF, the crude IS rate declined in patients with HF and MI, as well as in those with HF without MI. Notably, the decline was most pronounced in patients with HF and no MI (Figures S2 and S3).

HF was associated with a higher IS rate in both the unadjusted and adjusted analyses (adjusted IRRs, 1.20 [95% CI, 1.12–1.28] for 1-year follow-up and 1.22 [95% CI, 1.15–1.28] for 2-year follow-up). When the analysis was limited to follow-up time without OAC therapy, the results remained consistent with those from the 1- or 2-year follow-up including OAC treatment (Table 2). Importantly, the magnitude of the IS risk related to HF decreased over time similarly across all analyses, although the interaction between HF and calendar-year period did not reach statistical significance in analyses without OAC therapy (P values for interaction: 0.003, 0.093, 0.021, and 0.152 in the 1-year analysis with and without OAC therapy, and in the 2-year analysis with and without OAC therapy, respectively; Figure 3 and Figure S4). The findings were also similar in the sensitivity analyses excluding patients with IS events before AF (Figure S5).

Patients with HF and a history of MI had slightly higher stroke rates than patients with HF and no MI throughout the study period (unadjusted IRR,1.20 [95% CI, 1.05–1.38] in analysis with OAC therapy; Table S4). The association between IS and HF in patients with prior MI remained unchanged during the observation period (Figure S6). However, in those with HF but no prior MI, a significant decline in the adjusted IS risk was observed (adjusted IRRs in analysis with OAC use in 2007–2010, 1.32 [95% CI, 1.18–1.48] and in 2015–2018, 1.08 [95% CI, 0.95–1.22]; P=0.0004 for decline; Figure 4). Correspondingly, when patients with HF with MI were compared with those with HF but no MI, the IS risk was similar at the beginning of the study period. However, by the last calendar-year period, the adjusted IS risk appeared higher in those with prior MI, although this trend did not reach statistical significance (adjusted IRRs in analysis with OAC use, 0.96 [95% CI, 0.73–1.26) versus 1.18 [95% CI, 0.92–1.50]; P=0.50; Figure S7).

Table 1. Baseline Characteristics of the Study Cohort According to the Presence of Heart Failure

	No heart failure	Heart failure
	n=189 648	n=39 917
Demographics		
Age, y	71.4±13.2	79.0±11.1
Female sex	48.8	55.6
Income quartiles		
First (lowest)	30.7	50.2
Second	32.7	31.6
Third (highest)	36.6	18.2
Comorbidities		
Any vascular disease	24.0	47.3
Prior MI	6.6	18.6
Diabetes	19.7	30.7
Dyslipidemia	46.7	52.7
Hypertension	73.7	76.2
Prior IS	10.1	11.4
Abnormal liver function	0.5	0.8
Abnormal renal function	2.8	9.7
Alcohol use disorder	4.0	3.8
Dementia	4.4	8.5
Prior bleeding	9.8	14.9
Risk scores		
Modified HAS-BLED score	2.5±1.0	2.7±1.1
CHA_2DS_2-VASc score	3.1±1.8	5.0±1.7
CHA_2DS_2-VA score	2.6±1.6	4.4±1.5

Values denote proportions (%) or means±SD. All differences P<0.001, except alcohol use disorder (P=0.097). CHA_2DS_2-VASc score indicates congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes (1 point), history of stroke or transient ischemic attack (2 points), vascular disease (1 point), age 65–74 years (1 point), sex category (female) (1 point); CHA_2DS_2-VA score same as CHA_2DS_2-VASc score but without sex category; modified HAS-BLED score, hypertension (1 point), abnormal renal or liver function (1 point each), prior stroke (1 point), bleeding history (1 point), age>65 years (1 point), alcohol abuse (1 point), concomitant antiplatelet/nonsteroidal anti-inflammatory drugs (1 point) (no labile international normalized ratio, maximum score 8). IS indicates ischemic stroke; and MI, myocardial infarction.

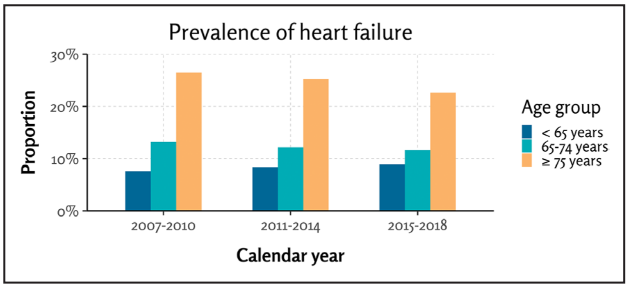

Figure 1. Prevalence of heart failure in different age groups between 2007 and 2018 in the study population.

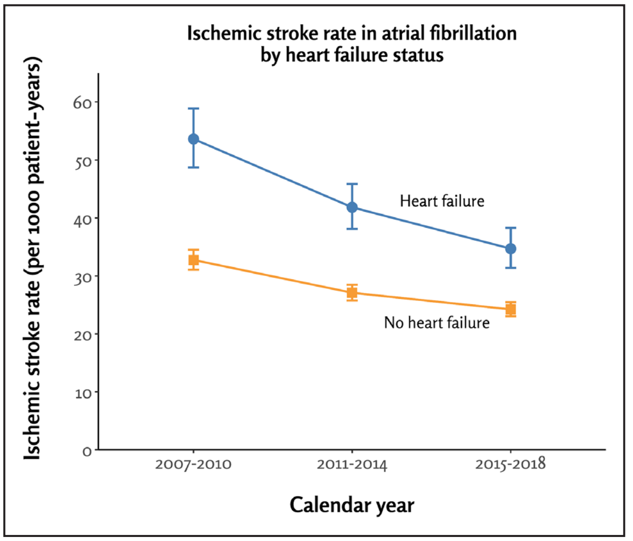

Figure 2. Trends in crude ischemic stroke rate with 95% CIs between 2007 and 2018 in the entire study population.

DISCUSSION

This nationwide retrospective cohort study assessing temporal trends in the burden of HF among patients with AF from 2007 to 2018 yielded 3 main findings: (1) Crude IS rates declined in both patients with and patients without HF; (2) the association between HF and IS risk attenuated; and (3) this reduction in HF-related IS risk is predominantly driven by a decreasing association between HF and IS among patients without a history of MI.

The overall prevalence of HF among patients with AF decreased during the study period, primarily due to a reduction in HF among those aged >65 years, while a slight increase was observed in younger patients. This finding aligns with previous literature on temporal trends in comorbidities among patients with AF.[17] However, it is notable that although the proportional share of HF among patients with AF has decreased, the absolute number of patients with both HF and AF has actually increased. Thus, the rise in AF incidence over recent decades appears to have been proportionally more pronounced in patients without HF. This trend may be explained by increased detection of paroxysmal forms of AF and patients with lower AF burden, due to advancements in diagnostics and increased screening of asymptomatic AF. Nevertheless, considering the rising number of patients with coexisting HF and AF, and the multimorbidity associated with HF, our findings underscore the importance of cardiovascular and comorbidity risk optimization in the treatment of AF, aligning with the "C" component of the AF-CARE pathway in the current European clinical practice guidelines.[18]

The observed decrease in IS rates among patients with AF with HF is concordant with previous findings of improving prognosis in patients with AF.[11] Moreover, the observed 20% to 30% higher IS risk associated with HF during the entire study period is consistent with the pooled risk estimate of a recent meta-analysis.[19]

Table 2. Incidence of Ischemic Stroke in Patients With or Without Heart Failure From 2007 to 2018

	Events	Patient-years (1000 y)	Incidence per 1000 patient-years (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
1-y follow-up with OAC use					
No heart failure	4609	168.1	27.4 (26.6–28.2)	Reference	Reference
Heart failure	1300	30.7	42.3 (40.0–44.7)	1.54 (1.45–1.64)	1.20 (1.12–1.28)
1-y follow-up without OAC use					
No heart failure	2793	74.2	37.7 (36.3–39.1)	Reference	Reference
Heart failure	834	10.9	76.5 (71.4–81.8)	2.03 (1.88–2.19)	1.29 (1.18–1.40)
2-y follow-up with OAC use					
No heart failure	6671	308.2	21.6 (21.1–22.2)	Reference	Reference
Heart failure	1831	53.5	34.2 (32.7–35.8)	1.58 (1.50–1.67)	1.22 (1.15–1.28)
2-y follow-up without OAC use					
No heart failure	3675	125.6	29.3 (28.3–30.2)	Reference	Reference
Heart failure	1038	16.5	62.8 (59.1–66.8)	2.15 (2.00–2.30)	1.30 (1.21–1.40)

IRR indicates incidence rate ratio; and OAC, oral anticoagulation.

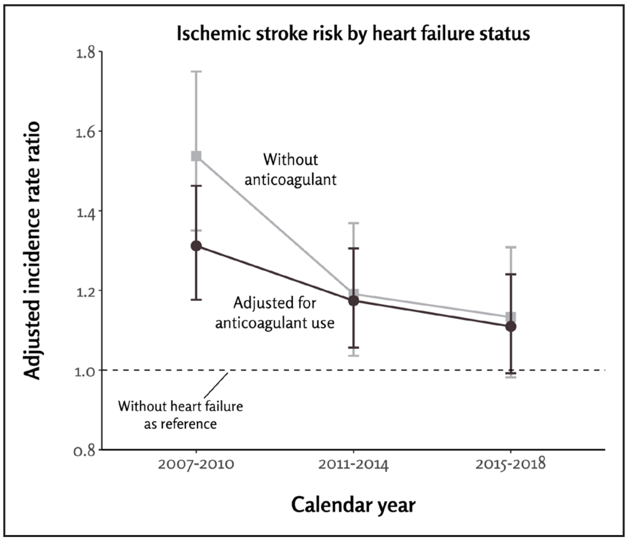

Figure 3. Adjusted incidence rate ratios for ischemic stroke with 95% CIs, comparing patients with and without heart failure.

The 2 line graphs represent results from 2 separate models: 1 covering only follow-up without anticoagulation and another also including time with anticoagulants and adjusted for their use. Both analyses considered a 1-year follow-up after the diagnosis of atrial fibrillation. Interaction between calendar years and heart failure: P=0.003 (adjusted for anticoagulant use) and P=0.093 (follow-up without anticoagulants).

However, a novel finding of the current study is that the magnitude of this risk has changed over time. HF was independently associated with a 30% to 50% higher stroke risk at the beginning of the study period, while in more contemporary patients, this risk was reduced to only 10% to 15% higher. This change was primarily driven by a reduction in stroke risk among patients with HF and no history of MI, whereas stroke risk associated with HF remained unchanged in patients with a history of MI. At the start of the observation period, the IS risk associated with HF was similar in patients with and without prior MI. However, by the last calendar-year period, HF with a history of MI carried a higher stroke risk than HF without prior MI.

Previous studies have generally reported a comparable stroke risk associated with HF in patients with both reduced and preserved left ventricular EF.[20] While the current study lacks detailed data on EF, our findings highlight important granularity in the stroke risk related to HF. Whether the observed divergent trends in stroke risk for HF with and without prior MI translate into similar trends for HF with reduced versus preserved EF warrants further investigation. In previous studies, the stroke risk associated with HF with reduced and preserved EF has appeared similar, but more contemporary data are needed in this regard. According to our data, HF, specifically in the absence of a prior MI, may not markedly increase the risk of stroke in contemporary patients with AF. However, although clearly decreasing trends were observed, it is important to note that not all interaction terms between HF and calendar year were statistically significant, and the 95% CIs for the rate ratio estimates between the first and last calendar year periods mostly overlapped. Our study highlights the need for further investigation into the factors driving the increased stroke risk in the interplay between HF and AF. These insights may inform clinical decisions on stroke prevention, promoting more individualized treatment approaches.

Factors underlying the observed trends are likely multifactorial, and not all are captured by the current data. While previous studies have indicated a decreasing overall prevalence of HF in the general population, the prevalence of HF with preserved EF has been increasing.[21] Although this trend is partly attributable to increasing age and a greater burden of cardiometabolic disorders, it may also stem from better awareness of HF and improved detection of milder forms of the condition. In parallel with substantial advances in treatment, these factors may contribute to previously reported improvements in HF prognosis.[22] These changes may also explain the observed decline in the role of HF as a stroke risk factor in patients with AF in the current study. However, it is notable that, although

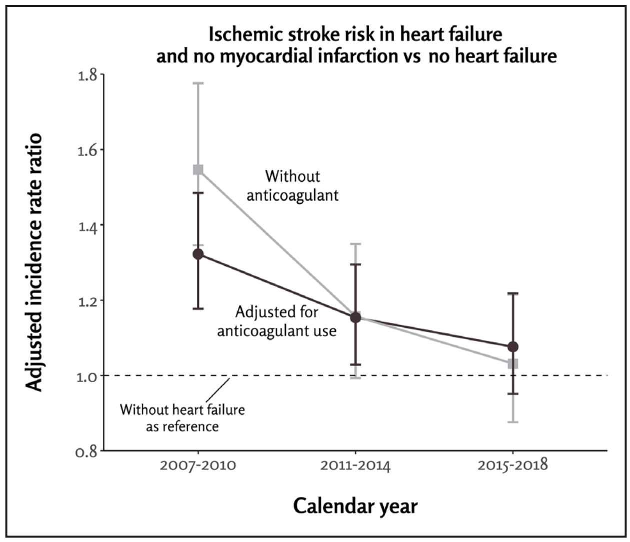

Figure 4. Adjusted incidence rate ratios with 95% CIs for ischemic stroke in patients with heart failure and no myocardial infarction, compared with those without heart failure.

The analyses considered a 1-year follow-up period after the diagnosis of atrial fibrillation. The 2 line graphs represent results from 2 separate models: 1 covering only follow-up without anticoagulation and another also including time with anticoagulants and adjusted for their use. Interaction between calendar years and heart failure: P=0.0004 (adjusted for anticoagulant use) and P=0.048 (follow-up without anticoagulants).

most HF treatments are more effective in cases with reduced EF, and improvements in MI management have reduced the burden of postinfarction ventricular dysfunction, our study suggests that HF with prior MI remains a significant risk factor of similar magnitude for in patients with stroke with AF. Increasing use of direct OACs may influence the results, including follow-up with OAC therapy, and adjust for it. However, we assume this has not significantly affected the association between HF and stroke, as the results remained consistent in analyses that considered follow-up time without OAC therapy.

The retrospective registry-based design of our study has some limitations that should be considered. Importantly, our study lacked information on EF and valvular diseases, limiting a more in-depth characterization of cases of HF. However, the HF definition used is concordant with the "C" of the CHA_2DS_2-VA score, allowing us to assess temporal trends in the importance of this risk factor. Similarly, information bias due to missing or inaccurate recording of diagnostic codes may have affected the identification of patients with HF, as well as the reliability of stroke outcomes. To improve accuracy, we linked the data from all national health registries. We also lacked data on the subtype and pathogenesis of the strokes. Moreover, our results represent associations and not necessarily causal relationships between HF, calendar years, and outcomes. The cohort construction process, along with the exclusion of patients with prior OAC use or emigration after AF diagnosis, may introduce selection bias. Moreover, while the lack of a fixed lookback period could cause bias in our results, by influencing, for example, the HF prevalence trends, the primary focus on the HF and IS association is unlikely to be significantly affected. Finally, despite adjusting for multiple variables, some residual confounding may remain in the results, such as the lack of adjustment for rhythm control therapies. Nevertheless, our study has the advantage of a comprehensive nationwide coverage through linked national registries, encompassing uniquely all patients with incident AF in Finland from all levels of care. The use of the well-validated hospital care register enhances the reliability of the observed IS outcomes, and the medication information is derived from complete nationwide pharmacy data on redeemed prescriptions.[23]

In conclusion, this nationwide cohort study demonstrated that IS risk associated with HF in patients with AF has declined, driven by a decreasing stroke risk in those without prior MI. HF remains an important stroke risk factor in contemporary patients with AF with a history of MI, but in those without, its role as a stroke risk factor appears to have decreased. Further research is needed to provide more granular information on the risk of IS in patients with HF in the absence of MI.

ARTICLE INFORMATION

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Affiliations

Heart Centre (E.J., K.E.A., K.T.), Division of Medicine (E.J., V.L., K.T.) and Department of Geriatric Medicine, Turku University Hospital and University of Turku, Finland (V.L.), Cardiac Unit, Department of Internal Medicine, Satasairaala, Pori, Finland (J.J.); Aalto University, Espoo, Finland (O.H., M.L.); Department of Neurology, Helsinki University Hospital and University of Helsinki, Finland (J.P.); Turku University Hospital and University of Turku, Finland (P.M.); University of Helsinki, Finland (J.H.); Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland (J.H.); University of Eastern Finland, Kuopio, Finland (M.L.); and Jorvi Hospital, Department of Internal Medicine, HUS Helsinki University Hospital and University of Helsinki, Finland (M.L.).

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Supplemental Material

Tables S1–S4
Figures S1–S7

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