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ORIGINAL RESEARCH

Temporal Trends of Ischemic Stroke Risk in Patients With Incident Atrial Fibrillation Before Anticoagulation

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ABSTRACT

BACKGROUND Atrial fibrillation (AF) is a major risk factor for ischemic stroke (IS), but whether the magnitude of this risk has changed over time is unknown.

OBJECTIVES This study sought to investigate temporal trends in IS rates in patients with incident AF before oral anticoagulant agent (OAC) therapy.

METHODS The nationwide FinACAF (Finnish Anticoagulation in Atrial Fibrillation) study covers patients with AF at all levels of care in Finland from 2007 to 2018. A 4-week quarantine period from AF diagnosis was applied, and only follow-up time without OAC therapy was included. Incidence rates of IS were computed in 4-year intervals in relation to sex and non-sex CHA_2DS_2-VASc (ie, CHA_2DS_2-VA) score values.

RESULTS In total, 129,789 patients with new-onset AF were identified (49.2% women; mean age: 71.4 ± 14.5 years). Between the calendar year intervals of 2007-2010 and 2015-2018, the patients' mean CHA_2DS_2-VA score increased from 2.5 to 3.0, and concurrently the overall IS rate decreased by 25% from 36.7 to 27.6 events per 1,000 patient-years. This trend was driven by a 32% decrease of IS rate in women, particularly among those with higher age and CHA_2DS_2-VA scores. The IS rate in patients with a CHA_2DS_2-VA score of 1 was 8.2 events per 1,000 patient-years and remained stable across the study period.

CONCLUSIONS The initial IS risk in AF patients, before the initiation of OAC therapy, has decreased by 25% between 2007 and 2018 despite an increase in both age and stroke risk scores. The decrease has been most pronounced in older women with high stroke risk scores. (JACC Clin Electrophysiol. 2024;■:■–■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

DOAC = direct oral anticoagulant agent

ICD-10 = International Classification of Diseases-10th Revision

IS = ischemic stroke

OAC = oral anticoagulant agent

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting up to 5.2% of the adult population.[1] It is a major cause of ischemic stroke (IS), with the risk varying considerably among individuals based on their comorbidities and other characteristics.[2,3] Accurate stratification of IS risk is essential to identify the patients who will benefit from oral anticoagulant agent (OAC) therapy, as well as those for whom the potential benefits of stroke prevention are outweighed by the bleeding risks associated with OAC therapy.

Current guidelines endorse the use of the CHA_2DS_2-VASc scoring system to estimate the risk of IS. Patients with 2 or more nonsex risk factors (CHA_2DS_2-VASc score of ≥2 in men and ≥3 in women) are considered to have a high risk of IS and are generally recommended to receive stroke prevention with OACs. For the moderate risk category (CHA_2DS_2-VASc score of 1 in men and 2 in women), current guidelines recommend consideration of OAC treatment, either with a vitamin K antagonist or with a direct OAC (DOAC).[4-6]

Previous studies have reported decreasing trends in AF-related strokes as well as in overall stroke rate. [7-9] This improving prognosis of AF has occurred concurrently with increasing use of OAC therapy.[9] However, it is unknown whether the initial risk of IS, before OAC therapy, has also changed over time in patients diagnosed with AF. Furthermore, wide variation in the reported IS rates exists between the validation studies of the CHA_2DS_2-VASc score, most likely reflecting differences in study designs and populations studied, which have mainly been restricted to hospital-diagnosed patients.[10] To inform clinical decision making and future contemporary guidelines, there is a need for more comprehensive data on the initial IS rates and their temporal trends among patients diagnosed with AF before the initiation of OAC therapy.

Thus, we conducted a nationwide cohort study covering all patients with incident AF from all levels of care in Finland between 2007 and 2018 to explore time trends of IS in patients with AF in relation to sex and nonsex CHA_2DS_2-VASc (ie, CHA_2DS_2-VA) score values.

METHODS

FinACAF (Finnish Anticoagulation in Atrial Fibrillation Study, NCT04645537; ENCePP [European Network of Centres for Pharmacoepidemiology & Pharmacovigilance], EUPAS29845) is a nationwide retrospective cohort study that includes all patients documented with AF in Finland from 2004 to 2018.[11] 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 an International Classification of Diseases-10th Revision (ICD-10) diagnosis code of I48, encompassing AF and atrial flutter, collectively referred to as AF, recorded between 2004 and 2018. The exclusion criteria were permanent emigration abroad before December 31, 2018, and age of younger than 20 years at AF diagnosis. The present substudy was conducted within a cohort of patients diagnosed with incident AF during 2007 to 2018 that was established in previous studies of the FinACAF cohort.[9,12,13] In this cohort, to include only patients with newly diagnosed AF, a washout period was applied by excluding those with a recorded AF diagnosis or OAC purchases during 2004 to 2006, because a medical history of less than 2 years was considered too short to reliably exclude the presence of a prior AF diagnosis. Additionally, those with a fulfilled OAC prescription within a year before the first AF diagnosis were excluded.

To accurately assess long-term risks, it is important to ensure a stable study population at the start of the observation period. Therefore, we applied a quarantine period with the follow-up beginning 28 days after the initial AF diagnosis. Quarantine periods, often used in registry studies, involve an initial blanking period following the index diagnosis to delay the counting of days at risk.[14-16] In registry-based studies, the incidence of IS, as well as mortality, typically appears to be higher right after the initial AF diagnosis, subsequently attenuating to a more stable level.[10,16,17] Thus, without the use of a blanking period, the long-term IS rate may be overestimated.[16] The choice of the 28-day quarantine period is based on a previous study from the FinACAF cohort in which the IS rates were observed to plateau after a period of approximately 4 weeks.[18] IS events during this blanking period were not considered as outcomes but were included in the baseline comorbidities. Patients experiencing death, initiating OAC therapy, or reaching the end of the study period within this 28-day period were excluded.

We were interested in the risk of IS in untreated patients and, thus, concentrated on time without OAC therapy. Follow-up ended when they initiated OAC treatment, marked by the first observed pharmacy purchase of either warfarin or a DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban). This method

has been recommended for estimating event rates in untreated populations.[10,16] Moreover, a patient's risk category may evolve over time because of advancing age and incident comorbidities during a longer follow-up, usually changing from lower to higher categories.[19] To mitigate this bias in risk group classification, we restricted the follow-up to a maximum of 2 years after the initial AF diagnosis. This also prevents significant variations in follow-up times across the study period, which might complicate the interpretation of the rate trends. Thus, follow-up continued until the first IS event; the first OAC purchase; death; end of study period on December 31, 2018; or a maximum of 2 years after AF diagnosis, whichever came first.

Data on baseline comorbidities were obtained from the aforementioned health care registers from all levels of care. The process of cohort construction is summarized in Supplemental Figure 1, and the definitions of baseline comorbidities are presented in Supplemental Table 1.

DEFINITION OF IS. In patients without prior IS, an event was considered to occur on the first date of a recorded I63 or I64 ICD-10 diagnosis code in the hospital care register. In patients with an IS before the end of the quarantine period, an IS event was considered to occur on the date of the first new hospitalization with the I63 or I64 ICD-10 code as the main diagnosis. The I64 code of unspecified stroke was included in the outcome measure because it has been shown that 87% of all strokes recorded with an ICD-10 code of I64 are ischemic.[20] Only IS diagnoses from the hospital register were included to ensure that the event of interest was truly major and clinically relevant. Additionally, in sensitivity analyses, we also included the I74 ICD-10 code of arterial thromboembolism to the outcome measure.

STUDY ETHICS. The study protocol was approved by the Ethics Committee of the Medical Faculty of Helsinki University, Helsinki, Finland (no. 15/2017) and received research permission from 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; 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 because of the retrospective registry nature of the study. The study conforms to the Declaration of Helsinki as revised in 2013.

STATISTICAL ANALYSES. We estimated trends in IS incidence rates and incidence rate ratios using the Poisson regression with a Lexis-type data structure based on 2 timescales: follow-up time and calendar year split into 4-year intervals.[21] This statistical approach was chosen to calculate IS rates for each calendar year interval during follow-up. IS rates were also calculated for the entire study period from 2007 to 2018. We computed trend curves for IS rates and juxtaposed them with the previously estimated tipping points representing the IS rates above which the benefits of OACs in reducing stroke risk outweigh the elevated risk of bleeding. In this study, we used the tipping point thresholds estimated in the study by Eckman et al[22]: 17 events per 1,000 patient-years for warfarin and 9 events per 1,000 patient-years for DOACs, although specifically this estimate included only dabigatran data for the modeling. Because female sex is considered a risk modifier in the presence of other risk factors rather than an independent risk factor, we used the non-sex CHA_2DS_2-VASc (ie, CHA_2DS_2-VA) score to classify patients.[23] IS rates were calculated for the entire cohort and separately for men and women. Patients with a CHA_2DS_2-VA score of 6 or more were combined into a single group because of the limited number of patient-years and events without OAC use in the highest risk categories. Additionally, patients were categorized based on their age at baseline. Mortality rates were calculated similarly to the IS rates. However, unlike the main analysis, patients who experienced an IS within the quarantine period were not excluded from the mortality assessment cohort.

Additionally, to mitigate the effect of possible selection arising from both the use of the quarantine period and the initiation of OAC therapy, we performed sensitivity analyses covering the cohort of all patients with incident AF without the quarantine period and also including time with OAC therapy (Supplemental Figure 1). Thus, in these sensitivity analyses, follow-up started from the first AF diagnosis and continued until the first IS event; death; end of the study period on December 31, 2018; or a maximum of 2 years after AF diagnosis, whichever came first. We computed incidence rate ratios for the calendar year periods with Poisson regression, and to control for the effect of OACs, the regressions were adjusted for OAC exposure, which was considered to start from the first OAC purchase and continue until 120 days after the last drug purchase. The 120-day interval was chosen because, in Finland, it is possible to purchase drugs with reimbursement for a maximum of 90 days, and an additional 30-day grace

period was allowed to cover possible stockpiling and differences in warfarin dosing.

Statistical significance was evaluated by the 95% CIs of the incidence rates and incidence rates ratios. The chi-square test and analysis of variance were used to compare baseline variables. Statistical analyses were performed with IBM SPSS Statistics software version 28.0 (SPSS, Inc) and R version 4.0.5 (R Core Team).

DATA AVAILABILITY STATEMENT. 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.

RESULTS

Overall, of the 229,565 patients with incident AF, 129,789 were included in the main analyses after the quarantine period (60.1%, 47.3%, and 62.1% of all incident patients in calendar periods 2007-2010, 2011-2014, and 2015-2018, respectively) (Supplemental Figure 1). Baseline age and the prevalence of the comorbidity components of the CHA_2DS_2-VA score increased over the study period, especially in men, leading to a rise in the mean overall score (**Table 1**, Supplemental Table 2). The use of statins, oral diabetes medications, antiplatelets, and antihypertensives at baseline increased concurrently (Supplemental Table 3). Follow-up ended because of an IS event in 4,060 (3.1%) patients, death in 14,671 (11.4%) patients, and initiation of OAC therapy in 52,906 (40.8%) patients. The mean follow-up times were 1.4, 1.3, and 0.5 years for patients diagnosed in 2007-2010, 2011-2014, and 2015-2018, respectively, and when the follow-up was split into these calendar year intervals, the total patient-years of follow-up were 28,534; 50,646; and 51,266, respectively.

When the entire study cohort with all risk categories was included in the analysis, the incidence of IS decreased by 25% during the study period. The decline was driven by a 32% decrease of IS incidence in women, whereas in men, a nonsignificant 7% decrease was observed (**Table 2**). Correspondingly, in the sensitivity analyses covering all patients with incident AF, without the quarantine period and adjusting for OAC use, the overall IS rate declined by 29%, with 35% and 16% declines observed in women and men, respectively (Supplemental Table 4).

TABLE 1 Baseline Characteristics of the Study Cohort According to the Calendar Year Intervals

	2007-2010 (n = 39,372)	2011-2014 (n = 36,746)	2015-2018 (n = 53,671)
Congestive heart failure	14.4	15.4	15.2
Hypertension	66.9	70.6	77.1
Age of 65-74 y	21.1	23.4	27.9
Diabetes	15.8	18.7	24.1
Prior IS or TIA	18.7	19.3	19.8
Any vascular disease	25.8	26.7	27.8
Age of 75 y or older	45.5	43.6	49.4
Female	51.0	48.1	48.7
Mean age, y	70.4	70.3	72.9
Mean CHA_2DS_2-VASc	3.0	3.2	3.5
Mean CHA_2DS_2-VA	2.5	2.7	3.0
CHA_2DS_2-VA = 0	14.1	13.3	8.0
CHA_2DS_2-VA = 1	18.4	18.1	13.2
CHA_2DS_2-VA = 2	17.6	17.0	17.9
CHA_2DS_2-VA = 3	21.4	19.3	22.7
CHA_2DS_2-VA = 4	14.7	14.7	17.4
CHA_2DS_2-VA = 5	8.6	10.3	12.0
CHA_2DS_2-VA ≥6	5.2	7.3	8.8
Mean modified HAS-BLED	2.1	2.4	2.7
Prior bleeding	9.1	12.2	13.2
Antiplatelets[a] or NSAIDs	32.4	30.5	29.5
Alcohol use disorder	3.2	5.8	5.5
Abnormal renal function	2.6	4.2	5.1
Abnormal liver function	0.5	0.7	0.6

Values are % unless otherwise indicated. All differences between calendar year intervals: $P < 0.001$. [a]Antiplatelets: anatomic therapeutic code B01AC.

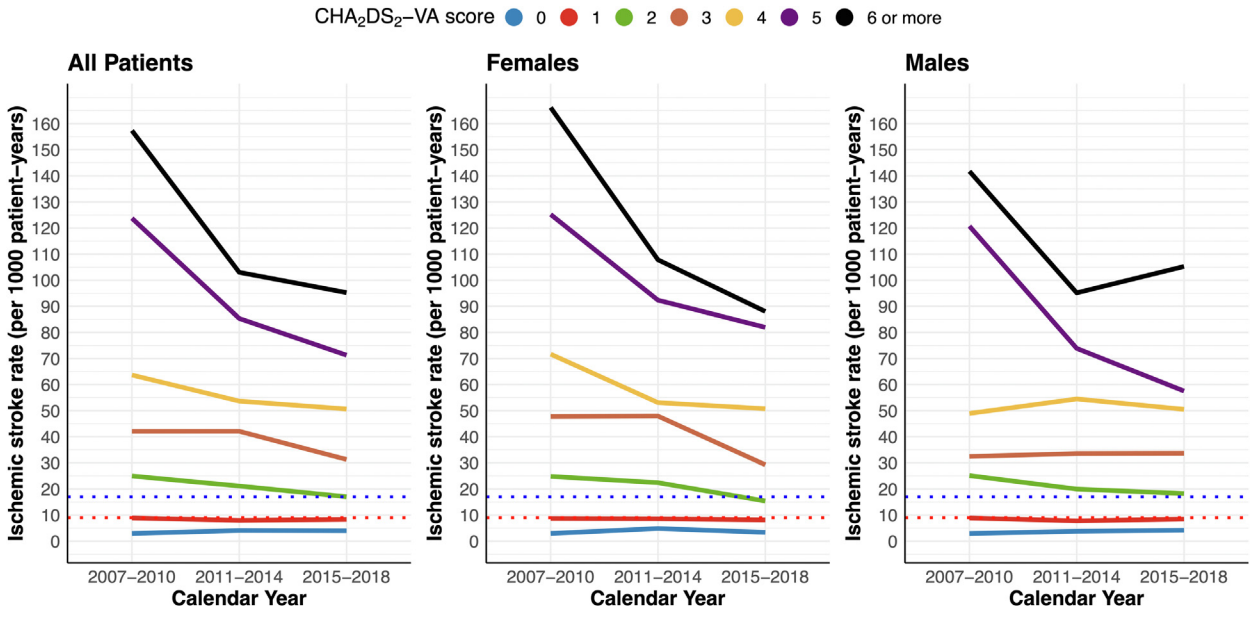
IS = ischemic stroke; NSAID = nonsteroidal anti-inflammatory drug; TIA = transient ischemic attack.

IS rates increased gradually with higher CHA_2DS_2-VA scores in both men and women (**Figure 1**, Supplemental Tables 5 and 6). In patients without any CHA_2DS_2-VA factors, IS rates were consistently low: 3.8 (95% CI: 3.1-4.7) events per 1,000 patient-years during the entire study period. Likewise, in patients with a CHA_2DS_2-VA score of 1, the IS rates remained

TABLE 2 Ischemic Stroke Incidence Rates Covering the Entire Study Cohort With All Risk Categories According to the Calendar Year Intervals

	Calendar Year Period	Incidence Rate per 1,000 Years (95% CI)	Incidence Rate Ratio (95% CI)
All patients	2007-2010	36.7 (34.5-39.0)	Reference
	2011-2014	31.6 (30.0-33.2)	0.86 (0.80-0.93)
	2015-2018	27.6 (26.1-29.0)	0.75 (0.69-0.81)
Male patients	2007-2010	25.4 (22.8-28.1)	Reference
	2011-2014	23.6 (21.8-25.5)	0.93 (0.82-1.06)
	2015-2018	23.5 (21.8-25.4)	0.93 (0.82-1.05)
Female patients	2007-2010	48.3 (44.8-52.1)	Reference
	2011-2014	40.3 (37.8-42.9)	0.83 (0.76-0.92)
	2015-2018	32.8 (30.5-35.3)	0.68 (0.61-0.75)

FIGURE 1 **Temporal Trends of Ischemic Stroke Rates According to the CHA_2DS_2-VA Score**



Treatment thresholds for warfarin (blue broken line) and direct oral anticoagulant agents (red broken line).[22]

stable without a significant temporal change, with an overall rate of 8.2 (95% CI: 7.2-9.4) events per 1,000 patient-years. In individuals with a CHA_2DS_2-VA score of 2, IS rates decreased linearly by 32% during the study period, with a decreasing trend observed in both men and women. In patients with a CHA_2DS_2-VA score of 3, the overall IS rate decreased by 26%, driven by a 39% decrease in women, whereas in men no change was observed. Similarly, in patients with a CHA_2DS_2-VA score of 4, the overall IS rate decreased by 20%, driven by a 29% decrease in women. In women with a CHA_2DS_2-VA score of 5, the rates declined by 35%, and in men, they approximately halved. In the combined group of patients with a CHA_2DS_2-VA score of 6 or more, the overall IS rate declined by as much as 39%, driven by decreasing trends in women, whereas in men a nonsignificant and nonlinear 26% decrease was observed (**Figure 1**, Supplemental Table 6).

In the sensitivity analyses, which also included arterial thromboembolisms in the outcome measure, the trend patterns were similar to those of the main analyses, but the incidence rates were overall slightly higher. The incidence rate for the composite outcome decreased by 26%, and the overall point rate estimates during the entire study period in patients with CHA_2DS_2-VA scores of 0 and 1 were 4.0 and 9.1 events per 1,000 patient-years, respectively. In patients with a CHA_2DS_2-VA score of 2, the rate of the composite outcome decreased to 18.2 events per 1,000 patient-years (Supplemental Tables 7 and 8).

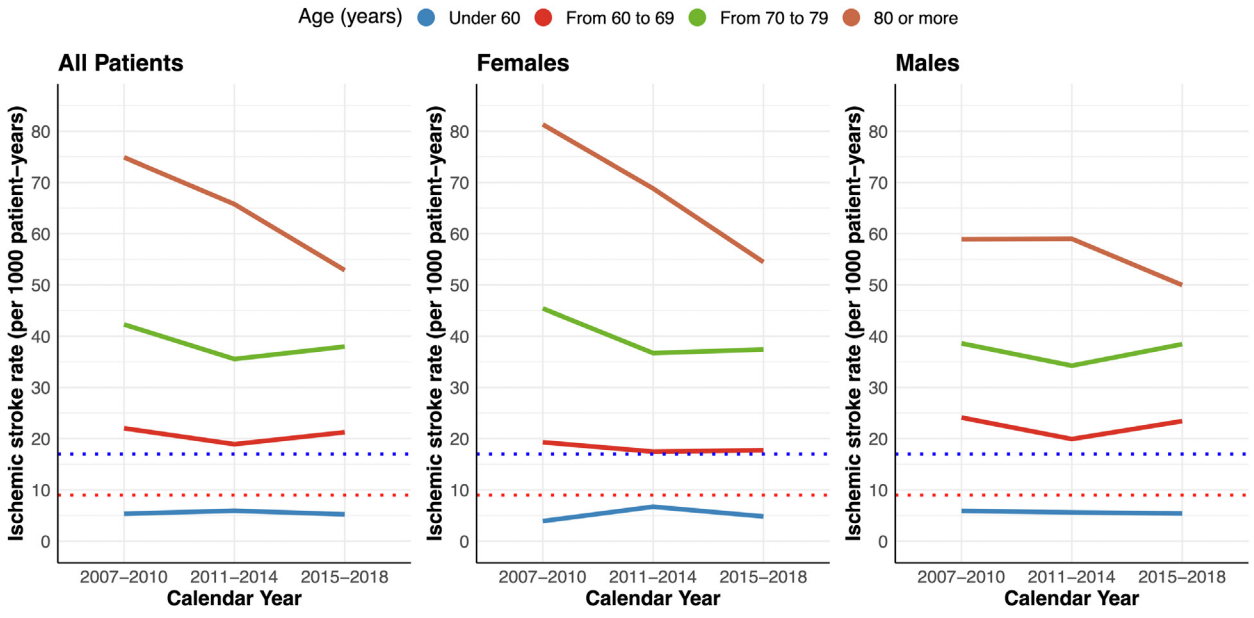
IS rates increased continuously with advancing age. Some nonlinear variability in IS rates was observed over time across different age categories, but the changes were nonsignificant in patients younger than 80 years. The majority of events occurred in patients aged 80 years or older, among whom an overall 29% decrease in IS rates was observed. This reduction was more pronounced in women, with a 33% decrease, whereas in men, there was a 15% nonsignificant decrease (**Figure 2**, Supplemental Table 9).

Similar to the IS rates, mortality rates were also observed to decline during the study period, but the magnitude of the change was smaller. The overall mortality rate declined by 6% between the first and last calendar year intervals, and although a decreasing trend was seen broadly across different CHA_2DS_2-VA score categories, the decline was slightly more pronounced in patients with lower risk score values (Supplemental Table 10).

DISCUSSION

This nationwide cohort study explored temporal trends of initial IS risk before anticoagulation in

FIGURE 2 **Temporal Trends of Ischemic Stroke Rates According to Age**



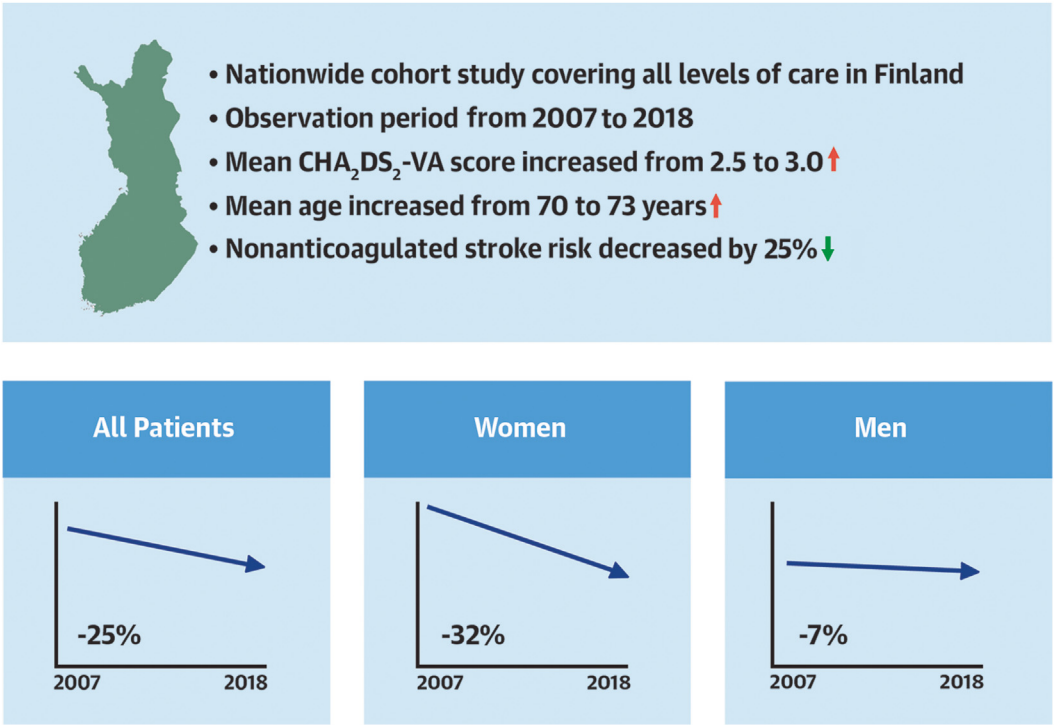
Treatment thresholds for warfarin (blue broken line) and direct oral anticoagulant agents (red broken line).[22]

patients diagnosed with AF between 2007 and 2018. The study has 3 main findings: 1) despite a rising mean age and stroke risk scores, the overall IS rates decreased by 25%; 2) this trend was driven by declining IS rates particularly in older women with high stroke risk scores; and 3) the IS rates for patients with a nonsex CHA_2DS_2-VASc (ie, CHA_2DS_2-VA) score of 1 have remained stable and approximately at the threshold at which the potential benefits and harms of DOAC therapy have been estimated to overlap (**Central Illustration**).[22]

To the best of our knowledge, this is the first study to investigate temporal trends in the initial IS risk among OAC-naive patients diagnosed with AF. Although there have been several previous validation studies on the CHA_2DS_2-VASc score, with substantial variability in the reported IS risk estimates, methodologic disparities among these studies hinder the interpretation of the results and render temporal comparisons impossible.[16,24] Furthermore, many previous studies had limited data on patients with AF diagnosed in the primary care setting, which may cause some selection bias and limit the generalizability of previous rate estimates to the many patients treated in primary care, notwithstanding the fact that eventual hospitalizations may be common in this group. Additionally, many prior studies have reported risk estimates based on the CHA_2DS_2-VASc score without necessarily differentiating between men and women.[15,25] This may further complicate the interpretation of previous findings, because sex is a risk modifier when combined with other risk factors rather than an independent risk factor per se.[23] Thus, the comprehensive nationwide data from all levels of care in the current study provides robust new data on IS rates and their trends in patients with AF.

The most pronounced temporal change in our study was the decrease in IS rates among women with a CHA_2DS_2-VA score of 2 or higher. In total, this resulted in an approximately 32% overall reduction in the IS rate in women during the study period. In men as well, declining IS rates were observed particularly in patients with high stroke risk scores, although the overall 7% reduction in men did not reach statistical significance. The diminishing differences in stroke rates between men and women are in line with the recently reported decrease in the IS risk associated with female sex.[26] Notably, overall IS rates have decreased, despite the continuously increasing mean age of the population and stroke risk scores. Similar to the IS rates, mortality rates also decreased during the study period, although the 6% change was smaller than the decline observed in IS rates. The reduction in the risk of IS seemed to be driven by trends occurring among patients aged 80 years or older, in whom the majority of events were observed. This finding aligns

CENTRAL ILLUSTRATION **Decreasing Nonanticoagulated Stroke Risk in Atrial Fibrillation Patients Despite Rising Age and Stroke Risk Scores**



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with the previously reported decreasing overall stroke rates particularly among older individuals during the past decades.[27] Moreover, in light of the current study's findings, the previously reported reduction in AF-related strokes appears not to be solely attributed to enhanced stroke prevention with OACs but seems to be partially explained by the initially lower untreated risk of IS among patients newly diagnosed with AF, especially in women.[9] Furthermore, although the prevalence of AF is rising, the observed decrease in the risk of IS may substantially alleviate the overall burden it imposes on health care systems.[1,28,29]

Despite the observed decrease in IS rates, they remained well above the OAC therapy thresholds in a vast majority of patients. In patients with a CHA_2DS_2-VA score of 2, IS rate declined to 17 events per 1,000 patient-years, reaching the treatment threshold for warfarin therapy yet remaining significantly above that of DOACs. Notably, the rate fell within the range of 10 to 20 events per 1,000 patient-years, which is actually considered to represent a "moderate" stroke risk in recent guidelines.[5] On the other hand, patients without any score components appear to be clearly below the treatment thresholds. Indeed, regarding the risk of IS and need for anticoagulation in these patients with either a CHA_2DS_2-VA score of ≥2 or 0, our findings align with the recommendations of the current guidelines.[4,5,30]

The challenge arises in patients classified as having a so-called "moderate" risk with a nonsex CHA_2DS_2-VASc (ie, CHA_2DS_2-VA) score of 1, in whom the need for OAC therapy is not obvious, and existing guidelines differ in nuances.[4-6,31] In the current study, we found no significant temporal change in the untreated IS risk in this patient group, and their overall point rate estimate in the main analysis (8.2 events per 1,000 patient-years) was below the treatment threshold of DOACs, although the confidence interval exceeded the treatment threshold of 9 events per 1,000 patient-years. Also, the rate was slightly higher in the analyses also considering other arterial thromboembolisms but remained considerably lower than those reported in many prior studies, including the large Danish registry-based studies on hospitalized patients with AF, where the rate estimates in this

risk category have varied approximately between 15 to 20 events per 1,000 patient-years.[10,15,23,32] Overall, our findings suggest that contemporary IS risk in this category might be lower than generally assumed, and stroke prevention, especially with warfarin, may not necessarily be reasonable.

The observed trends in IS rates are likely related to several factors. First, increased screening and awareness of AF may have led to a diagnosis at an earlier stage of the disease in some individuals, and irrespective of stroke risk scores, atrial myopathy may thus be less advanced, resulting in a lower risk of thromboembolism. In fact, IS rate in patients with subclinical AF episodes detected from implanted cardiac device memory has appeared to be low in recent studies.[33,34] Moreover, improved diagnosis and management of comorbidities may explain the seemingly rising stroke risk scores, although it may actually have enabled better and more proactive treatment of these comorbidities and, consequently, a decrease in IS risk. Indeed, the use of preventive medications increased in our study cohort, and improvements in cardiovascular prevention efforts and the move toward a holistic approach to AF management have been associated with reductions in IS and mortality.[35] Improved detection of comorbidities may also have resulted in a shift of lower-risk patients to higher risk categories, possibly reflecting in the dramatic reduction in IS rates of the highest categories, although this reclassification does not explain the decrease in the overall IS rate. Additionally, favorable changes in lifestyle-related factors, such as decreased smoking, may have also contributed to the reduced IS rates.[36,37]

STUDY STRENGTHS AND LIMITATIONS. Our data uniquely covers all levels of care nationwide and, compared to most previous studies in the field, is not restricted to only hospitalized patients. This might be one explanation for the somewhat lower IS rates observed in our study when compared to, for example, the Danish cohort studies.[10,15,23,32] Additionally, this enables a comprehensive assessment of patients' stroke risk factors and, underestimation of the risk scores could in part explain the high IS rates observed in previous studies among patients with low scores. Furthermore, lower rates may in part result from the fact that our outcome measure did not include transient ischemic attack or pulmonary embolism, as in some studies.[15,38] Moreover, inadequate use of quarantine periods in some studies may have led to an overestimation of the long-term IS rates.[16] Additionally, a particular strength of the current study is the well-validated hospital care register, with a relatively high diagnostic accuracy, especially regarding cardiovascular diseases.[39]

Nevertheless, the limitations of our study need to be acknowledged—the most important of which are the challenges inherent in register-based retrospective cohort studies. Hence, information bias may be present in the used administrative data, potentially affecting the precision of both the CHA_2DS_2-VA score and the outcome events. Additionally, the construction of the study cohort may have introduced some selection bias. Moreover, the increasing OAC initiation rate and the resulting shorter follow-up toward the end of the study period may have introduced bias into the results of the main analysis.[9] However, the results were similar even in the sensitivity analyses that attempted to mitigate the potential selection bias arising from the use of the quarantine period and increasing OAC use. We also lacked information on the specific subtypes of AF. Finally, the treatment thresholds used in this study are only statistically computed estimates, and although observational studies have attempted to explore treatment benefits among patient groups near these thresholds, future randomized studies are needed to conclusively address the controversies in treatment practices.[22,40,41]

CONCLUSIONS

This nationwide cohort study demonstrated that despite the increasing age and stroke risk scores in patients with incident AF, their initial untreated IS risk decreased by 25% between 2007 and 2018, driven by changes in older women with high stroke risk scores. The declining IS risk needs to be considered in clinical decision making when balancing the harms and benefits of stroke preventive therapies in contemporary patients with AF.

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Ingelheim, BMS-Pfizer, and Abbott; has served on the Advisory Board for Portola, Novo Nordisk, and Herantis Pharma; has served as a visiting editor for Terve Media; and holds stock ownership in Vital Signum. Dr Haukka has served as a research consultant for Janssen R&D and as a speaker for Bayer Finland. Dr Salmela has served as a speaker for BMS, Boehringer Ingelheim, and Pfizer; and has served on the Advisory Board for Pfizer. Dr Linna has served as a speaker for BMS-Pfizer Alliance, Bayer, and Boehringer Ingelheim. Aapo Aro has received research grants from the Finnish Foundation for Cardiovascular Research and has served as a speaker for Abbott, Johnson & Johnson, Sanofi, Bayer, and Boehringer Ingelheim. Dr Mustonen has served as a consultant for Roche, BMS-Pfizer Alliance, Novartis Finland, Boehringer Ingelheim, and MSD Finland. Dr Hartikainen has received research grants from the Finnish Foundation for Cardiovascular Research, European Union's Horizon 2020, and EU FP7; has been a member of the Advisory Board for BMS-Pfizer Alliance, Novo Nordisk, and Amgen; and has served as a speaker for Cardiome and Bayer. Dr Lehto has served as a consultant for BMS-Pfizer Alliance, Bayer, Boehringer Ingelheim, and MSD; has served as a speaker for BMS-Pfizer Alliance, Bayer, Boehringer Ingelheim, MSD, Terve Media, and Orion Pharma; and has received research grants from Aarne Koskelo Foundation, the Finnish Foundation for Cardiovascular Research, Helsinki and Uusimaa Hospital District research fund, and Boehringer Ingelheim. Dr Lip has served as a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Anthos (no fees were received personally) and is a National Institute for Health and Care Research senior investigator and co-principal investigator of the AFFIRMO project on multimorbidity in atrial fibrillation, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 899871. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This nationwide cohort study demonstrates that, despite increasing age and stroke risk scores in patients with newly diagnosed atrial fibrillation, their initial ischemic stroke risk before stroke preventive treatment decreased by 25% between 2007 and 2018, driven by changes in older women with high stroke risk scores.

TRANSLATIONAL OUTLOOK: The declining stroke risk needs to be considered in clinical decision making when balancing the harms and benefits of stroke preventive therapies in contemporary patients with atrial fibrillation.

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KEY WORDS atrial fibrillation, ischemic stroke, temporal trends

APPENDIX For supplemental tables and a figure, please see the online version of this paper.