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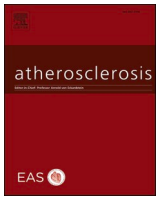

Vascular disease and ischemic stroke in patients with atrial fibrillation: Temporal trends and age-related differences

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ABSTRACT

Background and aims: We examined temporal trends and age-related differences in the prevalence of vascular diseases and in their association with ischemic stroke (IS) risk in patients with atrial fibrillation (AF).
Methods: The registry-based FinACAF study covered all patients with AF in Finland during 2007–2018. Incidence rate ratios (IRRs) of IS were computed with Poisson regression, and the interaction of vascular diseases with age and calendar year period was assessed.
Results: We identified 229,565 patients (50.0 % female; mean age 72.7 years) with incident AF. The overall prevalence of any vascular disease was 28.6 %, and the prevalence increased from 2007 to 2018, primarily among patients over 75 years. Overall, 5909 (2.6 %) patients experienced IS within the first year after AF diagnosis. Crude IS rate decreased continuously during the study period in both patients with and without vascular diseases, with the rates remaining consistently higher in patients with vascular diseases. Vascular diseases were independently associated with higher IS incidence among patients under 65 years (adjusted IRR with 95 % confidence interval 1.35 (1.10–1.66)), while among older patients, only peripheral artery disease was associated with IS, and other vascular conditions had no association with IS. No interactions between the calendar year period and vascular diseases with IS rate were observed.
Conclusions: The association between vascular diseases and IS has remained stable over time and vascular diseases were independently associated with higher incidence of IS particularly in patients with AF under the age of 65.

1. Introduction

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 of stroke varying considerably among individuals based on their specific comorbidities and other 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.

Atherosclerotic vascular diseases, in turn, are exceedingly prevalent conditions, characterized by the accumulation of fatty and fibrous material in the innermost layer of the arteries [4,5]. The pathophysiology of atherosclerosis is complex and multifactorial, involving an interplay between genetic predispositions, chronic inflammation, aging, metabolic risk factors, and lifestyle-related factors [6–9]. These diseases pose a significant burden to patients and healthcare systems, and are the leading cause of premature adult mortality worldwide [10–12].

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Atherosclerosis is itself an important etiology of IS [4]. Additionally, in the presence of AF, vascular diseases are a well-documented risk factor for cardioembolic stroke and are thus included in the CHA_2DS_2-VASc score, a widely employed tool for evaluating the risk of stroke and determining the need for OAC therapy [13,14].

Over the past decades, progress in medical research has resulted in substantial changes in the management of both atherosclerotic vascular diseases and AF. Improved prevention, awareness and treatment of vascular diseases have likely contributed to the observed decline in the overall incidence of IS and myocardial infarction, as well as the decrease in cardiovascular mortality during the past decades [15–20]. Additionally, there are reports suggesting an improvement in adverse lifestyle habits linked to cardiovascular disease and its prognosis, including a decrease in salt intake and smoking [21,22].

While the interplay between vascular diseases and AF has been extensively studied, there is a paucity of information regarding the temporal trends in their coexistence and whether vascular diseases continue to pose a similar risk for IS in AF. Moreover, previous studies have suggested age-related differences in the impact of traditional stroke risk factors, but whether the IS risk associated with vascular diseases in the presence of AF changes with age is unknown [23,24].

Therefore, we sought to examine temporal trends in the prevalence of vascular diseases in patients with AF in a nationwide cohort study, and to explore whether the association between vascular diseases and IS is dependent on patients' age or has changed over time.

2. Patients and methods

2.1. Study population

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 AF in Finland from 2004 to 2018 [25]. Patients were identified using all available national healthcare registers, including hospitalizations and outpatient specialist visits (Hilmo), primary healthcare (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 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 below 20 years at the time of AF diagnosis. The present sub-study was conducted within a cohort of patients with incident AF from 2007 to 2018, established in previous studies of the FinACAF cohort [26–28]. Patients often develop new comorbidities, including vascular diseases, after the initial diagnosis of AF, impacting the risk of IS and making it a dynamic process [29,30]. To mitigate the bias deriving from new diagnoses, we restricted the follow-up period to a maximum of one year after the initial AF diagnosis. This approach also prevents significant variations in follow-up times across the study period, which might complicate the interpretation of the rate trends. Thus, follow-up started from the initial AF diagnosis and continued until the occurrence of the first IS event, death, December 31, 2018, or a maximum of one year after AF diagnosis, whichever came first. Moreover, since it is the nonanticoagulated IS risk that drives the clinical decision making of oral OAC therapy, we performed separate analyses covering only the follow-up time without OAC therapy. Additionally, sensitivity analyses were performed focusing solely on patients without an IS or transient ischemic attack before the onset of AF, as part of these events likely had an atherothrombotic etiology.

Data on baseline comorbidities were obtained from the aforementioned healthcare registers. The process of the cohort construction is summarized in Fig. 1, and the definitions of baseline comorbidities are presented in Supplementary Table 1.

2.2. Definition of vascular disease

We concentrated on the broad concept of any vascular disease, as defined in the CHA_2DS_2-VASc score, and additionally explored the trends in the burden of coronary artery disease, prior myocardial infarction and peripheral artery disease. Patients were classified as

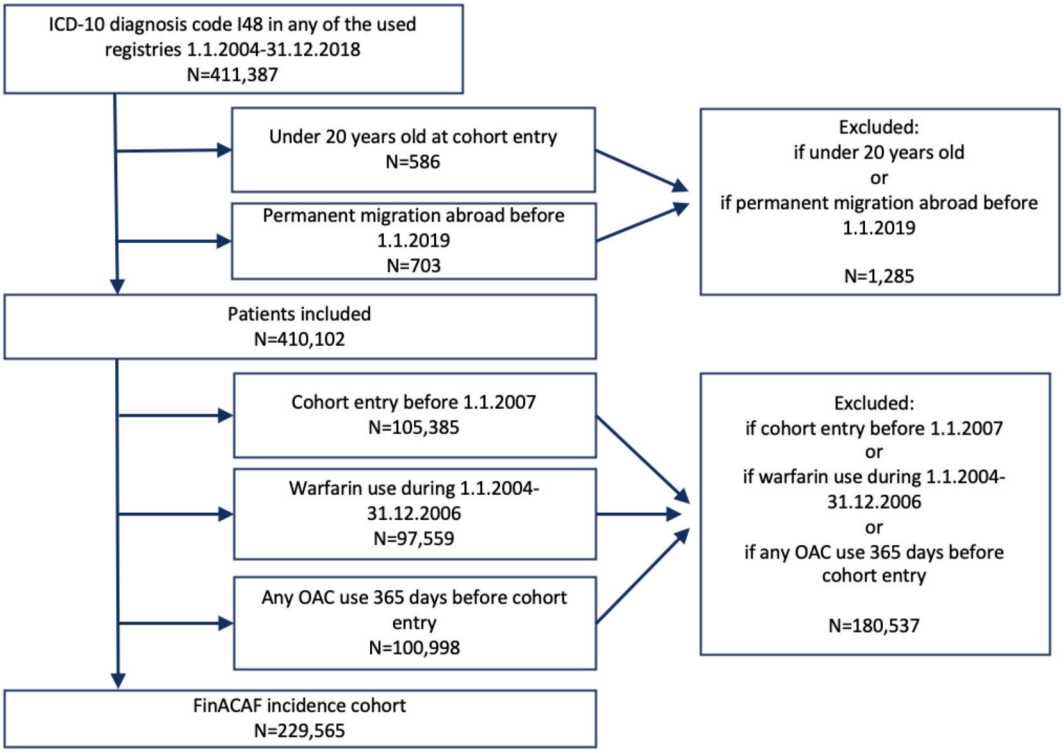

Fig. 1. Flow-chart of the patient selection process.

having any vascular disease if they had recorded codes for ischemic heart diseases or atherosclerosis in other arteries (ICD-10 codes I20-I25, I65-I66, I67.2 or I70 or International Classification of Primary Care, Second Edition codes K74-K76 or K91-K92) in the hospital or primary care registers or a reimbursement code for coronary artery disease in the National Reimbursement Register. The IS codes were excluded from this definition because prior event is considered an additional and higher risk factor than vascular disease for recurrent IS in the currently used risk stratification scores [13]. Additionally, selecting from the aforementioned ICD-10 codes, patients were separately classified to have coronary artery disease, prior myocardial infarction or peripheral artery disease.

2.3. 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 the 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 which had occurred before AF diagnosis. 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 ischemic [31]. Only IS diagnoses from the hospital register were included to ensure that the event of interest was truly major and clinically relevant.

2.4. Study ethics

The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Helsinki, Helsinki, Finland (nr. 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.March 01, 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.

2.5. Statistical analyses

We calculated incidence rates and incidence rate ratios (IRRs) for IS using the Poisson regression model. The 12-year observation period was divided into four-year intervals, and IS rates were computed for these follow-up intervals. Adjusted IRRs accounted for the following variables: age, calendar year period, sex, heart failure, diabetes, prior IS, hypertension, dyslipidemia, 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 OAC purchase and continue until 120 days after the last drug purchase. The 120-day interval was chosen since 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. Subsequently, the models were fitted with an interaction term between calendar year period and vascular diseases to assess changes in their impact on IS over time. Interaction terms between vascular diseases and age category (under 65 years, from 65 to 74 years, and 75 years or more) were fitted to the models to explore age differences in the association between vascular disease and IS. In all analyses, patients with any type of vascular disease were compared to those without any vascular disease. Baseline variables were compared using the chi-square test, Student's t-test, and analysis of variance. Statistical significance was evaluated using a *p*-value threshold of 0.05 as well as with the 95 % confidence intervals (CIs) of the IRRs. Statistical analyses were conducted using IBM SPSS Statistics software version 28.0 (SPSS, Inc., Chicago, Illinois, USA) and R version 4.0.5 (R Core Team, Vienna, Austria; https://www.R-project.org).

3. Results

We identified 229 565 patients with new-onset AF (50.0 % female; mean age 72.7 years; mean follow-up time 4.0 years). The overall prevalence of any vascular disease, coronary artery disease, prior myocardial infarction and peripheral artery disease were 28.6, 23.1, 9.1 % and 5.8 %, respectively. Patients with vascular diseases were older and had a higher overall prevalence of comorbidities than patients without vascular diseases, which also reflected in their higher stroke risk scores (Table 1). Initiation of OAC therapy during follow-up did not differ significantly between the patients with and without vascular diseases (70.6 % vs. 70.2 %, p = 0.052). Baseline use of statins, antihypertensives and oral antidiabetics increased during the study period (Supplementary Table 2).

Table 1
Baseline characteristics of the study cohort.

	No vascular disease	Any vascular disease	Coronary artery disease	Prior myocardial infarction	Peripheral artery disease
	n = 165,216	n = 64,349	n = 51,678	n = 20,017	n = 10,110
Demographics					
Mean age, years	70.8 (13.8)	77.7 (10.3)	78.1 (10.2)	77.6 (10.6)	78.4 (9.3)
Female sex	50.8	48.1	47.2	44.8	45.3
Income tertiles					
1st (lowest)	30.8	42.2	42.8	43.1	43.9
2nd	31.9	34.2	34.0	33.8	36.3
3rd (highest)	37.3	23.4	23.2	23.1	19.8
Comorbidities					
Diabetes	17.9	31.0	31.6	31.9	40.6
Dyslipidemia	36.9	75.5	78.3	76.3	76.2
Hypertension	71.5	81.0	81.0	80.0	88.5
Heart failure	12.7	29.3	31.8	37.1	32.5
Prior IS or TIA	13.3	20.9	20.6	19.8	26.5
Abnormal liver function	0.5	0.5	0.4	0.4	0.9
Abnormal renal function	2.8	7.0	7.2	8.6	12.8
Alcohol use disorder	4.2	3.3	3.0	3.6	5.0
Dementia	4.4	7.0	7.3	7.3	7.0
Prior bleeding	9.0	14.9	15.2	15.7	18.6
Risk scores					
Mean modified HAS-BLED score	2.4 (1.0)	2.9 (1.0)	2.9 (1.0)	2.9 (1.0)	3.2 (1.0
Mean CHA_2DS_2-VASc score	2.9 (1.7)	4.7 (1.7)	4.9 (1.6)	4.8 (1.7)	5.2 (1.6)

Values denote proportions (%) or means with standard deviations. CHA_2DS_2-VASc score, congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes (1 point), history of stroke or TIA (2 points), vascular disease (1 point), age 65–74 years (1 point), sex category (female) (1 point); IS, ischemic stroke; 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/NSAIDs (1 point) (no labile INR, max score 8); TIA, transient ischemic attack. *p*-values 0.17, 0.04 and 0.02 for differences in abnormal liver function when compared to any vascular disease, coronary artery disease and myocardial infarction, respectively. For all other differences *p*-values <0.001.

The prevalence of vascular diseases at cohort entry showed a consistent rise from 2007 to 2018 in the overall cohort (Fig. 2). However, this increase was primarily influenced by changes in patients aged 75 years or older, with smaller changes observed among younger patients. By the period of 2015–2018, 13.0 %, 24.8 %, and 37.4 % of patients under 65, 65 to 74, and 75 years or more had any vascular disease, respectively (Supplementary Table 3).

Overall, IS was observed in a total of 5909 (2.6 %) patients within the first year after the AF diagnosis. The crude IS rate decreased continuously during the study period in both patients with and without vascular diseases, with the rates remaining consistently higher in patients with vascular diseases (Fig. 3). When compared to patients without vascular diseases, the unadjusted incidence of IS was higher in patients with vascular diseases, most prominently in those with peripheral artery disease. In the adjusted analyses in the overall cohort, only peripheral artery disease was independently associated with a 33 % higher IS incidence, whereas no association between the other disease categories and IS rate was observed. (Table 2).

No significant interaction between the calendar year period and any of the vascular disease categories with the IS rate was observed (p-values for interaction 0.52, 0.49, 0.88 and 0.34 with any vascular disease, coronary artery disease, myocardial infarction and peripheral artery disease, respectively). Thus, while some variability in the associations between vascular diseases and IS rate were observed, no statistically significant changes were detected in any of the disease categories (Fig. 4).

An interaction with age and vascular diseases was observed (p-values for interaction with all vascular disease categories <0.001). Among patients under 65 years of age, all vascular disease categories were independently associated with a higher IS rate, with the highest adjusted rate estimates observed in patients with peripheral artery disease. All these associations between vascular disease categories and IS rates attenuated in older patients. Only peripheral artery disease was independently associated with IS rate among patients aged 75 years or older,

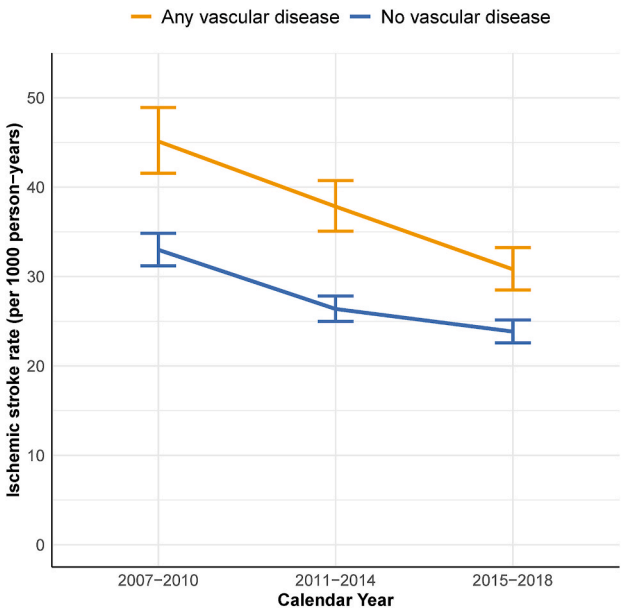

Fig. 3. Temporal trends of the crude ischemic stroke rates with 95 % confidence intervals in patients with and without vascular disease.

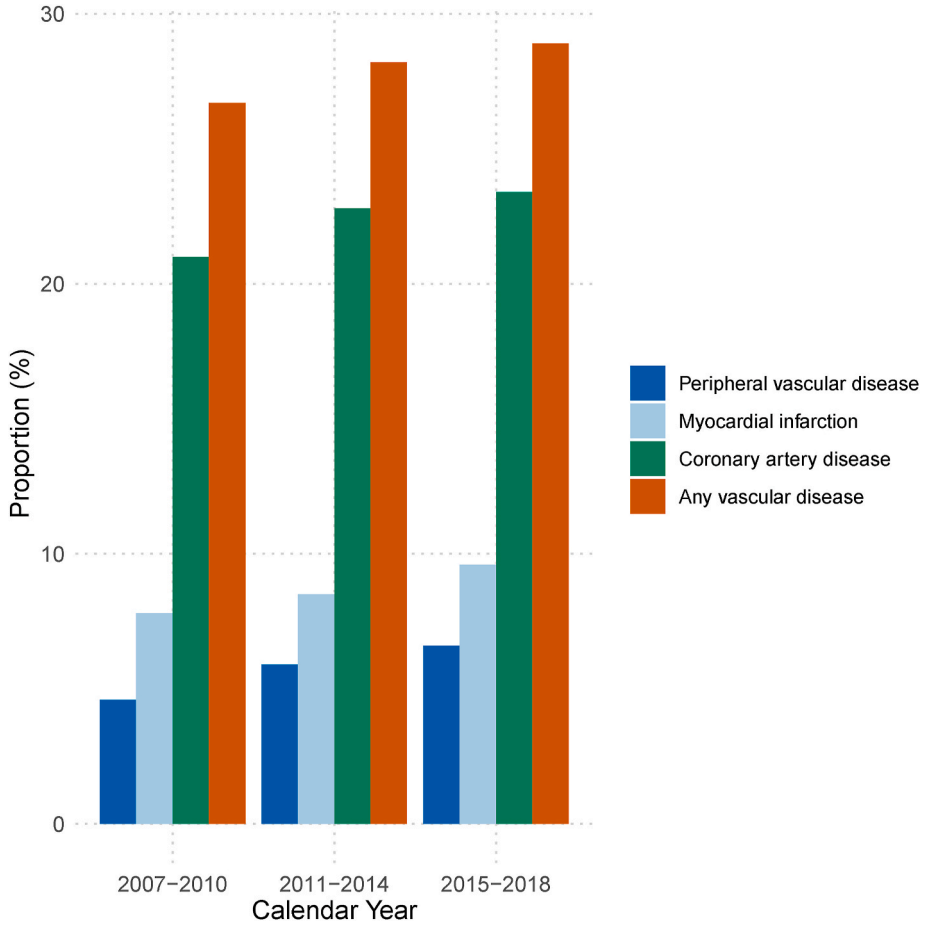

Fig. 2. Temporal trends in the prevalence of vascular diseases in patients with incident atrial fibrillation.

Table 2
Ischemic stroke rates in patients with and without vascular diseases.

	P-years (1000 years)	Events, n	Incidence (per 1000 p-years)	Unadjusted IRR	Adjusted IRR
Entire cohort					
No vascular disease	146	3957	27.2 (26.3–28.0)	(Reference)	(Reference)
Any vascular disease	53	1952	36.8 (35.2–38.4)	1.35 (1.28–1.43)	1.03 (0.97–1.09)
Coronary artery disease	42	1562	36.9 (35.1–38.8)	1.36 (1.28–1.44)	1.01 (0.95–1.08)
Prior myocardial infarction	16	616	39.2 (36.2–42.5)	1.45 (1.33–1.57)	1.05 (0.96–1.15)
Peripheral artery disease	8	400	51.3 (46.4–56.6)	1.89 (1.71–2.09)	1.33 (1.19–1.48)
Age categories					
Under 65 years					
No vascular disease	45	537	12.0 (11.0–13.0)	(Reference)	(Reference)
Any vascular disease	6	137	21.2 (17.8–25.0)	1.77 (1.47–2.14)	1.35 (1.10–1.66)
Coronary artery disease	5	101	21.0 (17.1–25.5)	1.76 (1.42–2.17)	1.39 (1.10–1.76)
Prior myocardial infarction	2	46	21.1 (15.4–28.1)	1.76 (1.30–2.38)	1.39 (1.01–1.92)
Peripheral artery disease	1	28	40.6 (27.0–58.7)	3.40 (2.32–4.97)	1.98 (1.32–2.98)
From 65 to 74 years					
No vascular disease	41	905	22.0 (20.6–23.5)	(Reference)	(Reference)
Any vascular disease	13	334	25.2 (22.6–28.0)	1.14 (1.01–1.30)	1.02 (0.89–1.17)
Coronary artery disease	10	258	25.2 (22.2–28.4)	1.14 (0.99–1.31)	1.02 (0.87–1.19)
Prior myocardial infarction	4	119	30.4 (25.2–36.4)	1.38 (1.14–1.67)	1.14 (0.93–1.40)
Peripheral artery disease	2	72	35.6 (27.9–44.9)	1.62 (1.27–2.05)	1.18 (0.92–1.53)
75 years or more					
No vascular disease	60	2515	42.1 (40.5–43.8)	(Reference)	(Reference)
Any vascular disease	33	1481	44.4 (42.1–46.7)	1.05 (0.99–1.12)	0.98 (0.92–1.05)
Coronary artery disease	27	1203	44.1 (41.6–46.6)	1.05 (0.98–1.12)	0.97 (0.90–1.04)
Prior myocardial infarction	10	451	46.9 (42.7–51.5)	1.12 (1.01–1.23)	0.99 (0.89–1.10)
Peripheral artery disease	5	300	59.0 (52.5–66.1)	1.40 (1.24–1.58)	1.30 (1.15–1.48)

Values in parentheses denote 95 % confidence intervals. IRR, incidence rate ratio; P-year, patient-year. IRRs estimated with Poisson regression and adjusted for age, sex, calendar year, heart failure, prior ischemic stroke, hypertension, dyslipidemia, prior bleeding, alcohol use disorder, renal failure, liver cirrhosis or failure, dementia, income level and anticoagulant use.

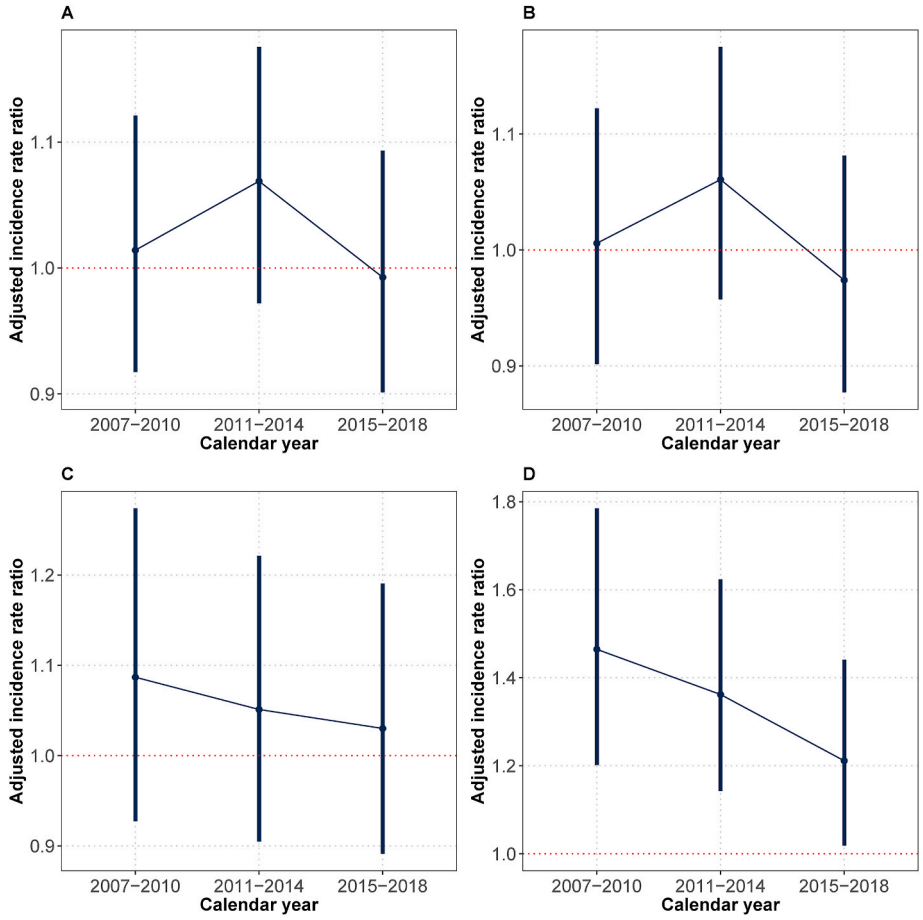

Fig. 4. Adjusted incidence rate ratios with 95 % confidence intervals of ischemic stroke comparing patients with any vascular disease (A), coronary artery disease (B), myocardial infarction (C), and peripheral artery disease (D) to those without vascular disease (horizontal reference line) in each calendar year period.

while no such associations with IS were observed with the other disease categories among the age categories over 65 years (Table 2).

In the analyses restricted to the follow-up time without OAC therapy, the crude IS rates were higher, but the adjusted rate ratios were consistent with the results of the analysis also covering the time with OAC therapy. No statistically significant interactions between the calendar year period and any of the vascular disease categories were observed (p-values for interaction 0.39, 0.36, 0.57, and 0.06 with any vascular disease, coronary artery disease, myocardial infarction, and peripheral artery disease, respectively). Moreover, a clear interaction between age and vascular diseases was present, and the point rate ratios were higher in younger patients and attenuated with age, although due to a small number of events, the associations were largely statistically nonsignificant (*p*-values for interaction with age for all vascular disease categories <0.001; Supplementary Table 4). Likewise, in the sensitivity analyses among patients without prior IS or transient ischemic attack, the results were concordant with those of the analyses conducted in the overall cohort (*p*-values for interaction with calendar year period 0.18, 0.25, 0.74 and 0.26 for any vascular disease, coronary artery disease, myocardial infarction and peripheral artery disease, respectively; *p*-values for interaction with age for all vascular disease categories <0.001; Supplementary Table 5).

4. Discussion

This nationwide retrospective cohort study observed a considerable decrease in the incidence of IS among AF patients with vascular diseases, in parallel with those without vascular diseases. Notably, a significant interaction between age and vascular diseases was observed in relation to the risk of IS. Vascular diseases were independently associated with higher IS incidence in patients below the age of 65, but among older patients, only peripheral artery disease was independently associated with IS, whereas no association with IS was observed with other vascular disease categories. No significant changes in the associations between vascular diseases and IS were observed over time.

The prevalence of vascular diseases exhibited a modest increase during the study period, with nearly 30 % of patients with incident AF having comorbid vascular diseases by 2015–2018. A higher prevalence was observed in older patients, and even among those under 65 years of age, more than one in eight presented with a vascular disease. A recent meta-analysis reported a pooled vascular disease prevalence of 21 % among patients with AF, and thus the observed prevalence in the current study by the end of the study period is somewhat higher than in most previous studies [14]. Given this rising prevalence, the multimorbidity linked with vascular diseases, and their inherent nature as a modifiable IS risk factor, our findings underscore the significance of a holistic cardiovascular and comorbidity risk optimization in AF treatment, aligning with the "C" component of the ABC pathway in current clinical practice guidelines [4,13,32].

The observed decrease in IS rates among AF patients with and without vascular diseases is concordant with previous findings of improving prognosis of AF [26,33]. The increase in the use of antihypertensives, statins and oral antidiabetics has likely played a role in the improving prognosis. Despite the consistently higher crude IS rates among patients with vascular diseases compared to those without, vascular diseases, with the exception of peripheral artery disease, did not exhibit an independent association with IS in the overall cohort. This finding is somewhat discordant with the majority of studies assessing the impact of vascular diseases on the risk of IS in AF. Indeed, the above-mentioned meta-analysis reported a pooled hazard ratio of 1.21 (95 % confidence interval 1.06–1.39) for the association between vascular disease and IS [14]. That said, after the sex factor, vascular disease has often appeared to be the CHA_2DS_2-VASc component with the smallest risk magnitude, and there are also several previous studies that have not found a significantly higher IS risk associated with vascular diseases [14,34]. However, in contrast to other vascular conditions, we observed that peripheral artery disease was prominently associated with IS, likely due to its systemic nature and tendency to remain subclinical until advanced stages [35]. The observed high comorbidity burden in patients with peripheral artery disease may also reflect the fact that, when diagnosed, this condition often represents an advanced manifestation of atherosclerosis.

Importantly, a significant interaction between age and vascular diseases was observed. Among patients under the age of 65 years, those with any of the studied forms of vascular disease had a substantially higher IS incidence, and in the adjusted analyses, these conditions were all independently associated with a higher IS incidence. On the other hand, among older patients, only peripheral artery disease remained associated with IS rate. A vast majority of patients with AF are over 65 years, often justifying anticoagulation based on their age alone [13]. Indeed, the challenge in identifying those who may benefit from stroke prevention with OACs arises mainly among patients under the age of 65 years. Thus, the current finding that the IS risk associated with vascular diseases is pronounced in younger patients may have an important clinical significance. Without acknowledging this age-dependency, the risk associated with vascular diseases might be considered small and without clinical relevance, when it, in fact, appears to have a pronounced importance particularly in these challenging treatment decisions. While to our knowledge there are no prior studies investigating the age-dependency of vascular disease-related IS risk particularly in AF, our results are concordant with a previous observation of an overall decreasing role of vascular disease with advancing age in relation to other stroke risk factors [23]. Moreover, despite the advancements in the management of both AF and vascular diseases, the impact of vascular diseases appears to have remained constant during our study period, emphasizing the need of sustaining vascular diseases as a factor in the clinically used risk scores.

The observed age differences in vascular disease-related IS risk, along with previous reports on sex-related IS risk and the findings in patients without AF, propose a new concept of whether the focus on specific risk factors should shift with increasing age [23,24]. This seems reasonable concerning vascular diseases in AF, but whether this holds true for other risk factors requires further study. While the IS incidence was higher in patients with vascular disease under 65 years in relative terms, it needs to be noted that the absolute number of strokes may seem somewhat small in these patients, when compared to older patients. However, an IS occurring in younger patients may result in a significantly greater loss of quality-adjusted life years compared to a stroke in an older individual. The observed age-dependency may also reflect differences in the mechanism of IS, since cardioembolic etiologies become more prevalent with advancing age, while the relative proportion of atherothrombotic etiologies tends to decrease slightly after middle-age [36].

The observed increase in the prevalence of vascular diseases is likely multifactorial. In fact, improved preventive measures have resulted in decreasing overall cardiovascular disease incidence and mortality during the past decades [15,37]. In our study, the prevalence increased mainly among patients over the age of 75 years, and may in parts be explained by the rising age of patients diagnosed with AF [1]. Moreover, increased use of non-invasive imaging and high-sensitivity troponin assays have likely improved the detection of atherosclerosis and myocardial infarction [38–40]. The IS trend curves in patients with and without vascular diseases showed a similar pattern, suggesting shared factors underlying the improved prognosis, and thus that the improvements are not related to vascular diseases *per se,* especially since the impact of vascular diseases appears to have remained stable. Improved management of hypertension and diabetes—both prevalent and significant stroke risk factors in older adults, and crucial links between vascular diseases and IS—may partly explain the observed decline in stroke rates. However, consistent with the association between vascular diseases and IS risk, we have previously demonstrated that while both hypertension and diabetes remain important stroke risk factors, their

relative impact has remained stable over the same period [41–44].

The retrospective registry-based design of our study has some limitations that need to be considered. First, our results may be affected by information bias due to possible inaccuracies in the registry data. Second, due to the retrospective nature, out results represent associations and not necessarily causal relationships. Third, our analyses did not account for the use of aspirin, since it is frequently purchased over the counter without prescription in Finland, and thus is not reliably documented in the pharmacy claims data. It is indeed likely that patients with vascular diseases were in large parts using aspirin when they were not on OAC therapy, which might slightly attenuate their impact on IS risk. However, this setting can in fact provide important data for the estimation of the incremental burden of IS associated with vascular diseases in standard clinical practice. Fouth, OAC use was based on pharmacy claims, and whether patients actually took the medication is unknown. Finally, residual confounding cannot be excluded in the results, although the regressions were adjusted for a broad set of other variables with a potential effect on IS risk. Nevertheless, our study has the advantage of a long study period and a comprehensive nationwide coverage through linked national registries, encompassing uniquely practically all patients with incident AF in Finland from all levels of care. The utilization of the well-validated hospital care register enhances the reliability of the observed IS outcomes [45].

In conclusion, our nationwide cohort study revealed significant age-related differences in the impact of vascular disease on IS in patients with AF. In patients under the age of 65, vascular diseases are independently associated with a higher incidence of IS, but in older patients, only peripheral artery disease was linked to IS, with no such association observed for other vascular diseases.

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Data availability statement

Because of the sensitive nature of the data collected for this study, requests to access the dataset 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/).

CRediT authorship contribution statement

Konsta Teppo: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Visualization. **Elin Karlsson:** Conceptualization, Methodology, Writing – review & editing. **Tuomas Kiviniemi:** Conceptualization, Methodology, Writing – review & editing. **Olli Halminen:** Conceptualization, Data curation, Methodology, Investigation, Writing – review & editing, Project administration. **Ossi Lehtonen:** Conceptualization, Methodology, Writing – review & editing. **Elis Kouki:** Conceptualization, Writing – review & editing. **Jari Haukka:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Pirjo Mustonen:** Conceptualization, Writing – review & editing, Supervision. **Jukka Putaala:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Miika Linna:** Conceptualization, Methodology, Writing – review & editing. **Juha Hartikainen:** Conceptualization, Writing – review & editing, Supervision. **K.E. Juhani Airaksinen:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration. **Mika Lehto:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2024.118590.

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