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Temporal relations between atrial fibrillation and ischaemic stroke and their prognostic impact on mortality

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Aims Limited evidence is available on the temporal relationship between atrial fibrillation (AF) and ischaemic stroke and their impact on mortality in the community. We sought to understand the temporal relationship of AF and ischaemic stroke and to determine the sequence of disease onset in relation to mortality.

Methods and results Across five prospective community cohorts of the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) project we assessed baseline cardiovascular risk factors in 100 132 individuals, median age 46.1 (25th–75th percentile 35.8–57.5) years, 48.4% men. We followed them for incident ischaemic stroke and AF and determined the relation of subsequent disease diagnosis with overall mortality. Over a median follow-up of 16.1 years, $N = 4555$ individuals were diagnosed solely with AF, $N = 2269$ had an ischaemic stroke but no AF diagnosed, and $N = 898$ developed both, ischaemic stroke and AF. Temporal relationships showed a clustering of diagnosis of both diseases within the years around the diagnosis of the other disease. In multivariable-adjusted Cox regression analyses with time-dependent covariates subsequent diagnosis of AF after ischaemic stroke was associated with increased mortality [hazard ratio (HR) 4.05, 95% confidence interval (CI) 2.17–7.54; $P < 0.001$] which was also apparent when ischaemic stroke followed after the diagnosis of AF (HR 3.08, 95% CI 1.90–5.00; $P < 0.001$).

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Conclusion The temporal relations of ischaemic stroke and AF appear to be bidirectional. Ischaemic stroke may precede detection of AF by years. The subsequent diagnosis of both diseases significantly increases mortality risk. Future research needs to investigate the common underlying systemic disease processes.

Keywords Atrial fibrillation • Ischaemic stroke • Temporal relationship • Cohort study

What's new?

- The temporal relationship between ischaemic stroke and atrial fibrillation (AF) does not appear to be unidirectional: ischaemic stroke frequently precedes the diagnosis of AF by years.
- Subsequent diagnosis of both diseases significantly increases overall mortality risk irrespective of the first event even long term.
- Both, ischaemic stroke and AF may be the consequences of a common underlying cardiovascular pathophysiology.

Introduction

Atrial fibrillation (AF) and stroke are common diseases that have a high impact on morbidity, quality of life, and mortality.[1] The association between AF and stroke is well established and there is convincing evidence for the benefit of oral anticoagulation in the prevention of stroke in patients with documented AF.[2] The pathophysiological mechanisms of atrial dysfunction, disturbed haemodynamics, and arterial thromboembolism appear to be obvious.[3] However, there is not necessarily a direct temporal relationship between AF episodes and stroke events as demonstrated for subclinical AF.[4] The prevalence of AF in patients diagnosed with ischaemic strokes varies from 11% to 33% depending on the study design and the methods used to detect AF.[5–7] Even in patients with stroke of defined aetiology, i.e. small or large vessel strokes, the detection of incident AF exceeds 2%.[8] Prior or concurrent diagnosis of AF in stroke patients is associated with an increased relative risk of death compared to patients without AF, an association that is possibly confounded by greater severity of stroke in patients with AF.[7]

Guidelines emphasize the importance of screening for AF after stroke.[9,10] To date, these recommendations are aimed mainly at identifying the cause of the acute stroke or transitory ischaemic attack in order to take measures to prevent recurrence. However, beyond age, stroke patients often have a cardiovascular risk factor profile that indicates high susceptibility to AF.[11]

Currently, there is limited evidence on the risk of incident AF and its prognostic significance after ischaemic stroke in the community. Therefore, our goal was to examine the temporal relationship between stroke and AF and their impact on mortality across Europe in cohorts of the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) consortium.[12]

Methods

Study sample

We pooled participant-level data from five community cohorts of the BiomarCaRE project with available information on AF and stroke status at baseline and follow-up (FU) (http://www.biomarcare.eu/), the DanMONICA study, the FINRISK study, the Moli-sani study, the Northern Sweden MONICA study, and the Tromsø Study, comprising $N = 112\,537$ unique individuals.[12] Each cohort is based on representative population samples with baseline examinations between 1982 and 2010. Details on the enrolment and FU procedures of each cohort are provided in the Supplementary material online. The data from the cohorts were harmonized in the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) Project.[13]

Individuals with a positive history of AF based on self-report and/or prior diagnosis by a physician and/or prior International Classification of Diseases (ICD) coding and/or on the baseline electrocardiogram were classified as having prevalent AF and were excluded from all analyses ($N = 873$). Furthermore, individuals with a positive history of stroke (regardless of stroke subtype) based on self-report and/or prior physician's diagnosis and/or prior ICD coding for stroke were defined as having baseline stroke and were excluded ($N = 1455$).

For this study, only individuals with complete FU variables for AF, stroke and mortality and with complete information on covariates were used. Thus, $N = 100\,132$ individuals were included for analyses across all cohorts.

Definition of outcomes and follow-up

Ischaemic stroke was defined as first fatal or non-fatal cerebral infarction based on MORGAM criteria (for detailed outcome classifications see the Supplementary material online). An event was also considered as ischaemic stroke in the data analysis if there was no validation according to MORGAM criteria or validation was not possible due to insufficient data, but the routine clinical diagnoses indicated cerebral infarction (ICD-8 code of 432, 433, or 434, ICD-9 code of 443 or 434 or ICD-10 code of I63). In the context of this study, the term stroke always refers to an ischaemic stroke, unless explicitly stated otherwise.

Incident AF was defined by date of the first documentation on electrocardiogram or assignment of the relevant ICD code (427.4 for ICD-8, 427.3 for ICD-9, and I48 for ICD-10). Overall mortality was defined as mortality due to any cause during the FU time. Cardiovascular death was defined similar to the endpoint definition of the European SCORE project.[14] If the cause of death did not fulfil

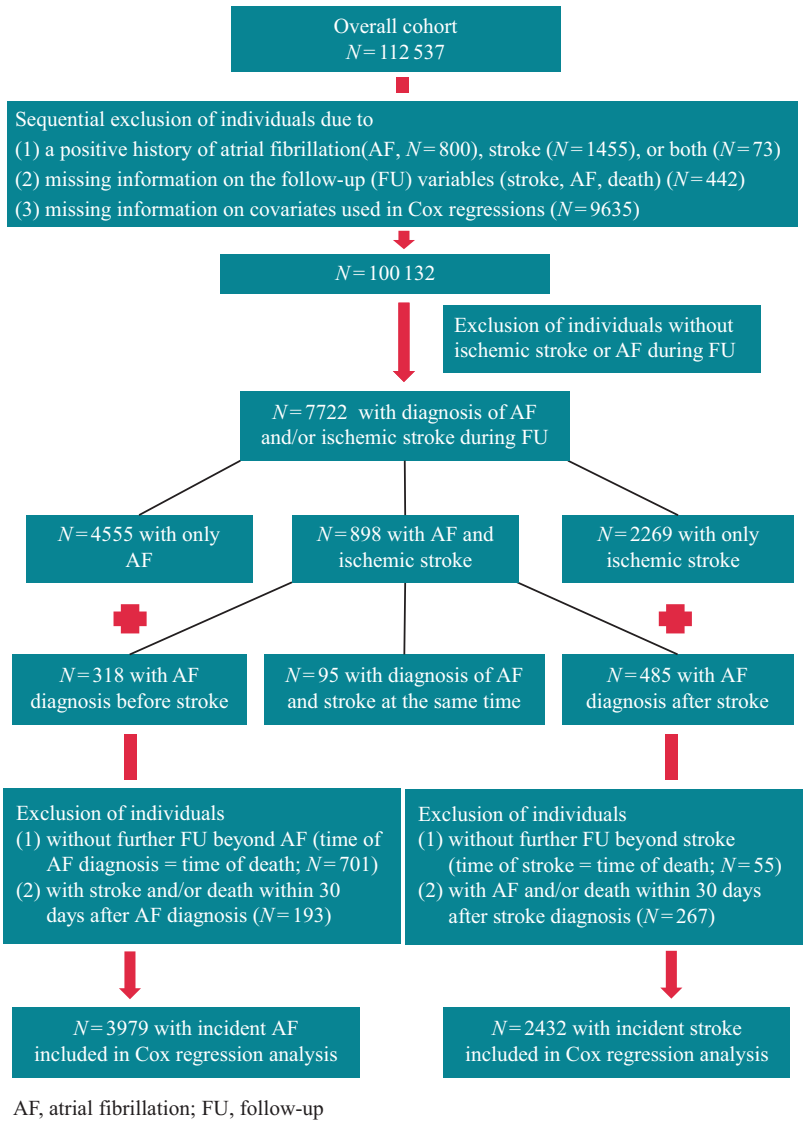

Figure 1 Flow chart for Cox regression analyses with time dependent covariates.

those criteria, the event was considered as a non-cardiovascular death.

Follow-up for ischaemic stroke and AF was based upon linkage with national hospitalization registries or administrative registries for ambulatory visits to specialized hospitals. Follow-up for mortality was obtained from central death registries.

The FU for the cohorts was completed in 2010 (DanMONICA, FINRISK, Tromsø) or 2011 (Moli-sani study, Northern Sweden).

Statistical methods

Baseline characteristics are expressed as numbers and percentages for categorical variables, medians and first and third quartiles for continuous variables. To study the temporal relationship between AF and stroke we assessed the diagnoses of AF and stroke over time in the overall cohort. We calculated a cumulative incidence curve for diagnosis of AF after stroke with death as a competing risk using the Aalen–Johansen estimator.[15] A similar analysis was performed exchanging the role of AF and stroke. The time after the initial diagnosis was used as the time scale in both cases.

To understand the prognostic impact of subsequent diagnosis of AF after stroke for all-cause mortality, we computed sex and cohort stratified Cox regressions for all-cause mortality including only those individuals that were diagnosed with stroke during FU and no diagnosis of AF up to that point. Diagnosis of AF was used as a time-dependent covariate and the models were adjusted for (i) age and (ii) additionally for cardiovascular risk factors, which were used as time fixed covariates as they were available only at baseline [total cholesterol, body mass index (BMI), daily smoking, diabetes mellitus, systolic blood pressure, antihypertensive treatment, and prevalent myocardial infarction]. This set of risk factors was used for all analyses. In order to account a potential non-linear relationship of the continuous covariates (age, total cholesterol, BMI, and systolic blood pressure)

with overall mortality, we performed an additional Cox regression analysis modelling these covariates using cubic splines. As a sensitivity analysis, we further adjusted for prevalent heart failure and peripheral artery disease. Since data on heart failure and peripheral artery disease was not systematically assessed through all cohorts, this analysis was restricted to cohorts with available information on these variables. In order to further investigate the association of a subsequent AF diagnosis after stroke with mortality, we performed additional Cox regression analyses using cardiovascular and non-cardiovascular death as the outcome of interest. Individuals for whom the date of the index stroke corresponded with the date of death were excluded from the analyses. Further individuals with diagnosis of both diseases within 30 days and individuals who died within 30 days after stroke, were excluded because the temporal relations are difficult to establish if two events are diagnosed almost concurrently (*Figure 1*). For those that were diagnosed with subsequent AF after stroke, the FU time for the Cox regression model began 30 days after the initial stroke occurred. A random coefficient for AF diagnosis after stroke was included per cohort to account for possible heterogeneity in the association with time-to-event. As a sensitivity analysis, we repeated the Cox regression analysis including individuals with diagnosis of both diseases and/or death within 30 days. Similar analyses were performed for stroke onset after diagnosis of AF. The time after the initial diagnosis was used as the time scale in all models.

The proportional hazards assumption for the subsequent diagnosis of interest (AF or stroke) was assessed by including an interaction of this variable with a cubic spline of the FU time, effectively creating a time dependent coefficient for the diagnosis of interest. To include this interaction in the models, the data had to be expanded to update the FU time of all individuals after each single death.

Table 1 Baseline characteristics of individuals that entered analyses ($n = 100\,132$)

Examination age (years)	46.1 (35.8–57.5)
Male, *N* (%)	48 423 (48.4)
Total cholesterol (mmol/L)	5.6 (4.9–6.5)
Body mass index (kg/m^2)	25.5 (22.9–28.6)
Daily smoker, *N* (%)	28 672 (28.6)
Diabetes mellitus, *N* (%)	3771 (3.8)
Systolic blood pressure (mmHg)	132 (120–146)
Antihypertensive treatment, *N* (%)	13 225 (13.2)
Prevalent myocardial infarction	2253 (2.3)

Values are medians (first and third quartiles) unless otherwise indicated.

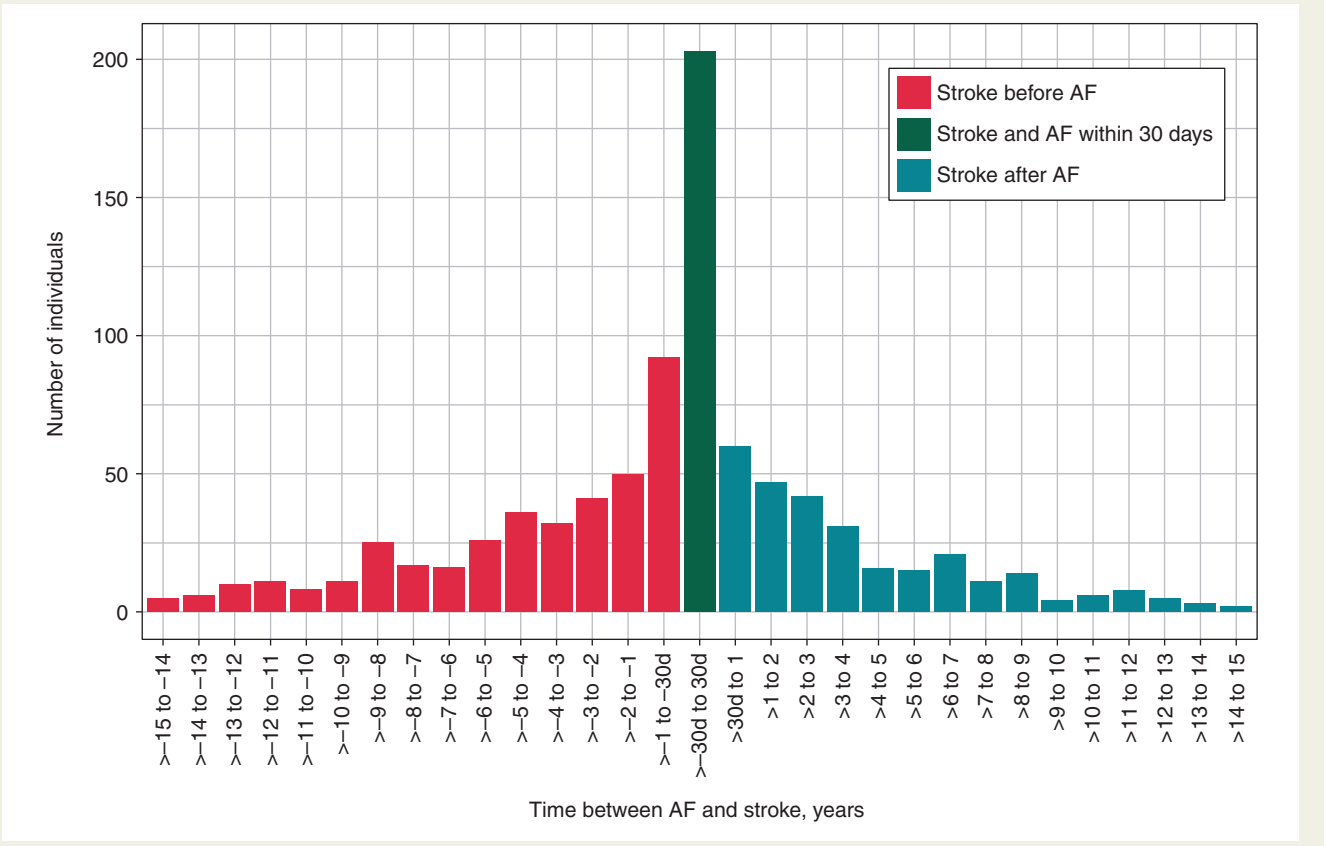

Figure 2 Temporal relations of AF and stroke. Distribution of individuals who developed both stroke and AF based on the time that elapses between diagnoses of both events. $N = 898$ individuals were diagnosed with both diseases during a median follow-up of 16.1 years. The *x*-axes are truncated at 15 years before and after diagnosis of AF, respectively. AF, atrial fibrillation.

Table 2 Baseline characteristics of individuals used in Cox regression analyses for mortality

	Index event	
	Incident ischaemic stroke ($n = 2432$)	Incident atrial fibrillation ($n = 3979$)
Examination age (years)	57.9 (49.7–63.4)	58.0 (49.1–67.5)
Male, *N* (%)	1411 (58.0)	2253 (56.6)
Total cholesterol (mmol/L)	6.3 (5.5–7.2)	6.1 (5.3–7.0)
Body mass index (kg/m^2)	26.7 (24.2–29.7)	26.8 (24.3–29.9)
Daily smoker, *N* (%)	785 (32.3)	936 (23.5)
Diabetes mellitus, *N* (%)	240 (9.9)	212 (5.3)
Systolic blood pressure (mmHg)	145 (131–162)	142 (129–159)
Antihypertensive treatment, *N* (%)	541 (22.2)	916 (23.0)
Prevalent myocardial infarction, *N* (%)	187 (7.7)	245 (6.2)

Values are medians (first and third quartiles) unless otherwise indicated.

Median FU was estimated by the Kaplan–Meier potential FU estimator. A two-sided value of $P \leq 0.05$ was considered statistically significant. All statistical analyses were conducted with R statistical software version 3.5.1 (The R Project for Statistical Computing).

Results

Incidence and temporal relationship of atrial fibrillation and ischaemic stroke

The baseline characteristics of individuals included in the analyses are presented in *Table 1*. The median age was 46.1 years (interquartile range 21.7 years) with 48% men. During a median FU of 16.1 years (with a maximum FU of 29 years), 4555 individuals were diagnosed solely with AF, 2269 individuals had a stroke but no AF, and 898 individuals developed both stroke and AF. The overall incidence rate of stroke was 0.2 per 100 person-years, while the incidence rate of AF was 0.4 per 100 person-years. Among those 898 individuals with both stroke and AF, 402 (45%) suffered a stroke at least 30 days before diagnosis of AF, in 293 (33%) AF diagnosis preceded stroke by more than 30 days, and 203 (23%) subjects were diagnosed with stroke and AF within 30 days. *Figure 2* displays the temporal relations between the diagnosis of AF and stroke.

Sequential disease occurrence and mortality

New-onset stroke occurred in $N = 2699$ individuals with no prior or concurrent diagnosis of AF and FU continuing beyond that point. Of these, $N = 2432$ were retained in the Cox regression to examine the impact of subsequent AF diagnosis on mortality after exclusion of 267 individuals due to death, diagnosis of AF or end of FU within 30 days (*Figure 1*). The median age at baseline of individuals included in this regression analysis was 57.9 years (interquartile range 13.7 years, *Table 2*). The median age of individuals at the time of stroke occurrence was 70.0 (interquartile range 14.6 years). Over a median FU time of 8.6 years after stroke diagnosis (with a maximum FU of 28.8 years), 402 (17%) individuals were diagnosed with AF and 1118 (46%) died. In 648 (58%) cases, the cause of death was considered cardiovascular. The detection rate of subsequent AF in individuals with new-onset stroke was 2.9 per 100 person-years (*Figure 3A*). Subsequent diagnosis of AF after stroke was associated with a significantly increased overall mortality in multivariable-adjusted Cox regression [hazard ratio (HR) 4.05, 95% confidence interval (CI) 2.17–7.54; $P < 0.001$] (*Table 3*; for results of the sex, cohort, and age-adjusted Cox regressions, see Supplementary material online, *Table S2*). Accounting for potential non-linear associations of continuous covariates with overall mortality did not alter the observed associations (results not shown). Inclusion of individuals in whom death, diagnosis of AF or end of FU occurred within 30 days hardly changed the observed HRs (HR 4.01, 95% CI 2.13–7.55; Supplementary material online, *Table S3*). The association of subsequent diagnosis of AF with mortality was stronger for cardiovascular death but also remained significant for non-cardiovascular death [HR 5.38 (95% CI 2.92–9.92) and 2.73 (95% CI 1.19–6.26), respectively; for more details, see Supplementary material online, *Tables S5* and *S6*].

The evaluation of the proportional hazards assumption revealed a significant interaction between the time interval from stroke to subsequent AF and its impact on overall mortality ($P < 0.001$). The effect of AF on all-cause mortality seemed to decrease with the time that elapsed before AF was diagnosed (*Figure 4* displays the time-dependent changes in HRs for overall mortality of subsequent AF and stroke).

Atrial fibrillation was diagnosed for the first time in $N = 4172$ individuals with no prior history of stroke, but for whom we have FU continuing beyond that point. After exclusion of 193 individuals due to death, stroke, or end of FU within 30 days, $N = 3979$ individuals were kept in the Cox regression examining the impact of subsequent stroke on mortality. The median age at baseline of individuals that entered this regression analysis was 58.0 years (interquartile range 18.4 years; *Table 2*). The median age of individuals at the time of AF diagnosis was 71.5 (interquartile range 15.6 years). Over a median FU of 5.9 years (with a maximum FU of 28.7 years), 293 (7%) individuals suffered a stroke, 969 (24%) died (*Figure 3B*). Four hundred and seventy-three (49%) deaths were classified as cardiovascular, while the remaining 496 were considered of non-cardiovascular origin. The incidence rate for subsequent stroke in individuals with a new diagnosis of AF was 1.4 per 100 person-years. Subsequent stroke after incident AF was associated with a significantly increased overall mortality (HR 3.11, 95% CI 1.91–5.05; $P < 0.001$; *Table 3*). With regard to the cause of death, subsequent stroke was significantly associated with cardiovascular death but not with non-cardiovascular death [HR 4.58 (95% CI 2.63–7.96) and 1.32 (95% CI 0.93–1.88), respectively; Supplementary material online, *Tables S5* and *S6*]. There was no significant interaction between the time of stroke in relation to AF diagnosis and its impact on mortality ($P = 0.22$; *Figure 4*).

The observed association of subsequent diagnosis of both diseases with overall mortality remained significant when prevalent heart failure and peripheral artery disease were added to the multivariable Cox regression (Supplementary material online, *Table S4*).

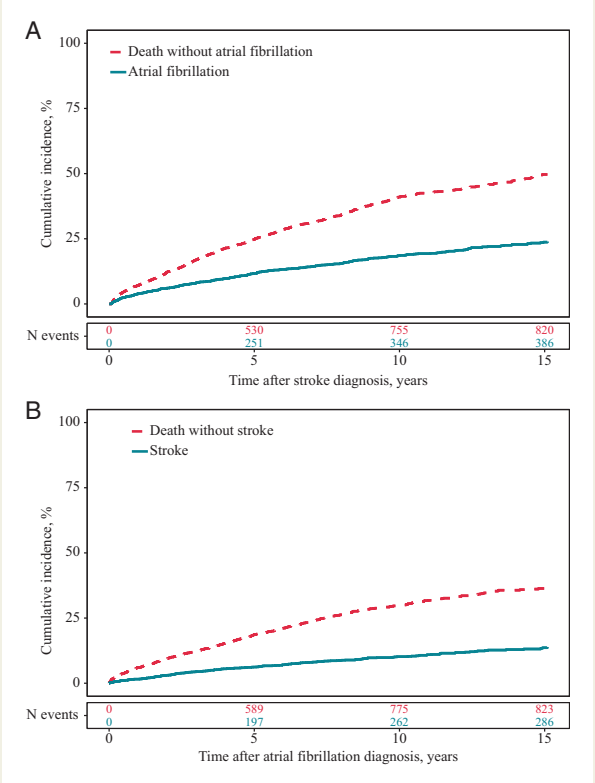

Figure 3 Cumulative incidence curves with adjustment for death as a competing risk for (*A*) diagnosis of AF after ischaemic stroke and (*B*) ischaemic stroke after diagnosis of AF. Cumulative curves for overall mortality are additional presented by dashed lines to illustrate the proportion of individuals that die before experiencing the event of interest. The *x*-axes are truncated at 15 years after diagnosis of AF or stroke, respectively. AF, atrial fibrillation.

Discussion

In our pooled analysis of community-based studies, we show a significant comorbidity from incident ischaemic stroke and AF. The risk factor profile of individuals with both diseases was very similar. Subsequent diagnosis of AF and ischaemic stroke, irrespective of which disease occurred first, was associated with a significant increase in mortality compared to individuals affected only with AF or stroke.

Both stroke and AF are relatively common diseases in middle-aged and older adults and there appears to be a clear mechanistic relationship between AF, atrial myopathy and the risk of thromboembolic stroke.[3] Studies on incident AF after stroke have focused on the short- and mid-term FU after the index event. Their goal was to detect AF as a potential source of cardiac embolism and to prevent recurrence by oral anticoagulation.[5–7] Our data extend the concept of ischaemic stroke as an indicator of AF risk. While the coincidence of ischaemic stroke and AF may not necessarily signify cardioembolic stroke, there is an increasing focus on trying to understand common underlying pathophysiological mechanisms linking the two conditions as part of a systemic disease.[8,16] Both diseases share classical cardiovascular risk factors.[10,11] We could demonstrate a similar baseline distribution of clinical risk factors such as male sex, increased BMI, and hypertension that are strongly related to disease onset. Vascular dysfunction may be a precursor of both stroke and AF and disease onset reflecting advanced cardiovascular impairment.[9,16,17] This concept is supported by recent findings during long-term continuous rhythm monitoring in which stroke and subclinical AF episodes were not temporally correlated very strongly.[4] In our sample, in nearly half of the individuals with both diseases ischaemic stroke preceded the diagnosis of AF. This observation may be due to a high proportion of individuals with AF related strokes for whom AF was missed in the diagnostic work up because AF often occurs intermittently and many episodes tend to be asymptomatic.[18,19] Prior studies on prolonged monitoring for AF after ischaemic stroke demonstrated an enhanced

Table 3 Multivariable-adjusted Cox proportional hazards regressions for mortality

Variables	Index event			
	Incident ischaemic stroke ($n = 2432$)		Incident atrial fibrillation ($n = 3979$)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Subsequent atrial fibrillation	4.05 (2.17–7.54)	<0.001	–	–
Subsequent stroke	–	–	3.08 (1.90–5.00)	<0.001
Age at diagnosis of index event (years)	1.08 (1.07–1.09)	<0.001	1.09 (1.08–1.10)	<0.001
Total cholesterol (mmol/L)	0.98 (0.93–1.03)	0.48	1.03 (0.98–1.09)	0.25
Body mass index (kg/m^2)	1.01 (0.99–1.03)	0.24	0.99 (0.98–1.01)	0.28
Daily smoker	1.60 (1.39–1.84)	<0.001	1.88 (1.61–2.18)	<0.001
Diabetes mellitus	1.30 (1.07–1.57)	0.0072	1.81 (1.41–2.32)	<0.001
Systolic blood pressure (per 10 mmHg)[a]	1.05 (1.02–1.08)	0.0026	1.07 (1.04–1.10)	<0.001
Antihypertensive treatment	1.04 (0.90–1.21)	0.57	1.18 (1.01–1.39)	0.042
Prevalent myocardial infarction	1.54 (1.25–1.89)	<0.001	1.12 (0.90–1.41)	0.31

In individuals with a first diagnosis of stroke $N = 1118$ died during follow-up; in individuals with a first diagnosis of atrial fibrillation $N = 969$ died. The Cox models are stratified for sex and cohort. Time since the index event is used as the time scale in both analyses. Subsequent atrial fibrillation and subsequent stroke are used as time-dependent covariates.
CI, confidence interval; HR, hazard ratio.
[a]Per 10 mmHg.

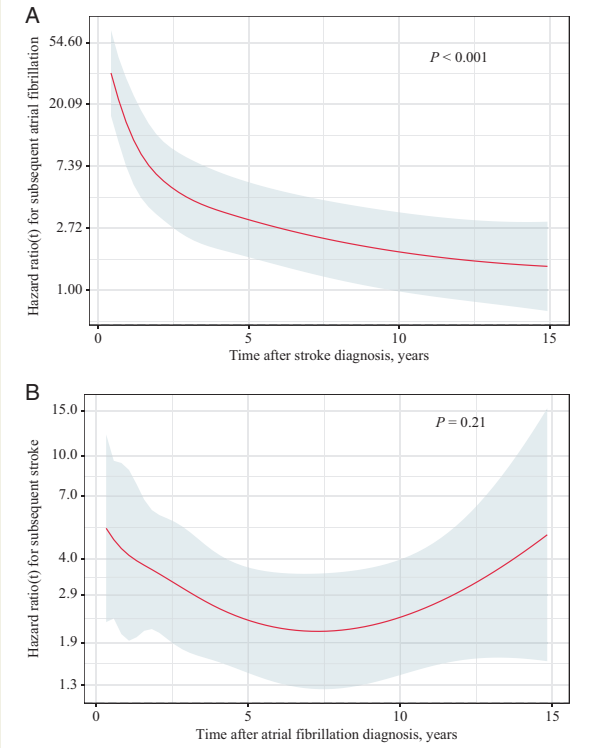

Figure 4 Time dependent hazard ratios for overall mortality for subsequent disease diagnosis. (*A*) Time dependent hazard ratios for overall mortality of subsequent AF after stroke. (*B*) Time dependent hazard ratios for overall mortality of subsequent stroke after AF. Hazard ratios are given for the impact of subsequent disease diagnosis as a function of time. The range shaded in blue provides a 95% confidence interval for the hazard ratio at each time point. The given *P*-values are for a test of the proportional hazards assumption for the variable of interest. A logarithmic scale is used on the *y*-axis. The *x*-axes are truncated at 15 years after diagnosis of AF or stroke, respectively. AF, atrial fibrillation.

AF detection rate when compared to short-term monitoring after the stroke event.[6,19] However, despite a peak of AF diagnoses in the first years after the initial stroke, the time interval to diagnosis of subsequent AF in this study shows a wide range with many cases detected long after the initial stroke. We assume that AF diagnosed later after stroke is less likely to be causal for the previous stroke but rather an indicator of systemic disease progression.

Atrial fibrillation-related strokes are usually more severe than other strokes caused by ischaemia. They are associated with a substantial increase in disability and mortality.[7] We now report that subsequent diagnosis of AF in individuals with stroke is associated with a significantly higher overall mortality after adjustment for clinical risk factors and comorbidities even in the long run, although impact on mortality seems to be higher if AF is diagnosed shortly after stroke. This can possibly be explained by the fact that some of the AF cases detected close to the stroke might actually represent AF-related stroke rather than new-onset AF. Nevertheless, irrespective whether the first event was stroke or AF, the co-occurrence of both diseases implies higher lethality. As expected this seems to be mainly driven by an increased risk for cardiovascular death reflecting the potential progression of an underlying systemic cardiovascular disease. However, in contrast to incident stroke after AF the subsequent diagnosis of AF after stroke seems to imply an increased risk for non-cardiovascular death as well. A potential explanation might be the known association of AF with other non-cardiovascular diseases.[9,20]

Limitations and strengths

Incident AF was assessed mainly by linkage to registries and diagnosis was usually based on 12-lead electrocardiogram. Thus, the diagnosis relied on routine clinical manifestation. Individuals with paroxysmal or asymptomatic AF may have been missed and are likely underrepresented in this study.[18] The occurrence of incident stroke may result in better surveillance for AF, potentially explaining the higher rate of incident AF cases close after stroke occurrence. On the other hand, most of the search for AF after stroke is conducted during or shortly after the intra-hospital period. In line with these assumptions, the cumulative incident curve for AF with adjustment for death as a competing risk revealed a rather linear increase beyond the first year following incident stroke, suggesting that the higher rate of incident AF diagnoses in individuals with stroke is likely a consequence of a systemic underlying disease and shared risk factors (*Figure 3A*).

Classification into stroke subtypes in MORGAM is based on strict criteria, but diagnostic tests required for this strict process were often unavailable. In these cases, strokes were classified as cerebral infarctions based on routine clinical diagnosis. As a result misclassification of stroke subtype in some cases cannot be ruled out.

Another limitation of this study is that data on potential time-dependent changes of cardiovascular risk factors that were used in Cox regression were not available, so that residual cofounding cannot be ruled out. Further, we have no information on the medical treatment after diagnosis of AF or stroke. This limitation is relevant for the intake of oral anticoagulation given its well-stablished beneficial effects on stroke prevention and mortality reduction in individuals with AF.[2] However, not accounting for potential medical treatment, including oral anticoagulation, would have more likely diluted the observed association of both diseases with mortality. To understand the relations and the long-term impact of AF and stroke, the survey years of some cohorts date back more than two decades. Therefore, temporal trends in disease diagnostics and treatment including the introduction of non-vitamin K antagonist oral anticoagulants are likely. To account for heterogeneity by cohort we adjusted association analyses for cohort.

Further, based on the current study, no conclusions can be drawn on the causal relationship between stroke and AF. It also remains uncertain whether subsequent diagnosis of AF after stroke is a risk factor for mortality itself or a marker of the progress of the underlying diseases.

The strength of our study is the large sample with long FU and harmonized data in which we can provide results with good power. Our results provide further evidence justifying intensified screening for AF after stroke for even longer FU periods.

Conclusions

In our cohort, stroke and AF are common comorbidities in middle-aged to older adults. They exhibit an overlapping risk factor profile. The temporal relations of disease diagnosis are bidirectional. In addition to AF constituting an intuitive pathophysiological risk factor for ischaemic stroke, stroke should also be considered as an indicator of increased AF risk. Stroke may precede detection of AF by years. The subsequent diagnosis of both diseases significantly increases mortality risk. Whether targeting modifiable risk factors or improved screening for AF after stroke in individuals from the community improves survival, needs to be determined.

Supplementary material

Supplementary material is available at *Europace* online.

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