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The individual and combined impact of heart failure and atrial fibrillation on ischaemic stroke outcomes: a prospective hospital register cohort study

Heart failure and atrial fibrillation in ischaemic stroke

Tiberiu A Pana[a]; David J McLernon PhD[a]; Mamas A. Mamas MD[b]; Joao H Bettencourt-Silva PhD[c, d]; Anthony K Metcalf MD[c]; John F. Potter MD[c, e]; Phyo K Myint MD[a, c, e, f]

[a]University of Aberdeen, Aberdeen, UK.
[b]Keele University, Stoke-on-Trent, UK.
[c]University of East Anglia, Norwich, UK.
[d]University of Cambridge, Cambridge, UK.
[e]Norfolk and Norwich University Hospital, Norwich, UK.
[f]Aberdeen Royal Infirmary, NHS Grampian, Aberdeen, UK.

Correspondence to:
Professor Phyo Kyaw Myint
Room 4:013, Polwarth Building
School of Medicine, Medical Sciences and Nutrition
Foresterhill, Aberdeen
AB25 2ZD,
Scotland, UK.
Tel: +44 (0) 1224 437841,
Fax: +44 (0) 1224 43791
Mail to: phyo.myint@abdn.ac.uk

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ABSTRACT

Aims: To determine individual and combined effects of AF (atrial fibrillation) and HF (heart failure) on AIS (acute ischaemic stroke) outcomes: in-hospital mortality, length-of-stay and post-stroke disability; long-term mortality and stroke recurrence.

Methods: Prospective cohort study of AIS patients admitted to a UK centre with catchment population of ~900,000 between 2004-2016. Exposure groups were patients with neither AF nor HF (reference group), those with AF but without HF, those with HF but without AF, and those with AF+HF. Logistic and Cox regressions were used to model in-hospital and long-term outcomes, respectively.

Results: 10,816 patients with a mean age±SD = 77.9±12.1 years, 48% male were included**.** Only 30 (4.9%) of the patients with HF but not AF were anticoagulated at discharge. Both AF (OR 1.24 95%CI 1.07-1.43), HF (OR 1.40 (1.10-1.79)) and their combination (OR 2.23 (1.83-2.72)) were associated with increased odds of in-hospital mortality. All three exposure groups were associated with increased length-of-stay, whilst only AF predicted increased disability (1.36 (1.12-1.64)). Patients were followed for a median of 4.8 and 3.7 years for mortality and recurrence, respectively. Long-term mortality was associated with AF (HR 1.45 95%CI 1.33-1.59), HF (2.07 (1.83-2.36)) and their combination (2.20 (1.96-2.46)). Recurrent stroke was associated with AF 1.50 (1.26-1.78), HF (1.33 (1.01-1.75)) and AF with HF(1.62(1.28-2.07)).

Conclusion: The AF-associated excess risk of stroke recurrence was independent of co-morbid HF. HF without AF was alsoassociated with a significant risk of recurrence. Anti-coagulation for secondary stroke prevention in patients with HF without AF may require further evaluation in a clinical trial setting.

INTRODUCTION

The relationship between heart failure (HF), atrial fibrillation (AF) and the outcomes of acute ischaemic stroke (AIS) has been previously examined. It has been previously shown that both AF and HF are not only associated with an increased risk of AIS[1-4], but also with increased post-AIS mortality and disability[5-13]. Furthermore, both AF and HF have been linked to increased risk of stroke recurrence[14-16].

Due to the natural course of the two disease entities, they frequently co-exist[17-19]. This proves particularly problematic, since the previously reported impact of HF on AIS outcomes may be influenced by AF and vice-versa. Thus, despite previous reports having analysed the individual contribution of either AF or HF on stroke outcomes, as well as the impact of AF on outcomes of stroke patients with HF[8], the combined contribution of the two remains largely unknown.

Given the current lack of understanding of the relative individual versus combined impact of these conditions on stroke outcomes, we aimed to quantify these associations using a cohort of unselected hospitalised AIS patients. Both in-hospital (death, length-of-stay (LoS), disability) and long-term (mortality and stroke recurrence) outcomes were assessed.

METHODS

Study participants and design

Participants were drawn from the Norfolk and Norwich Stroke and TIA Register (NNSTR) database using previously defined selection criteria[20,21]. The NNSTR is a prospective UK single-centre hospital-based register. The NNSTR records all stroke admission to the Norfolk and Norwich University Hospital (NNUH), the only tertiary centre in Norfolk County, England (catchment population 900,000 in 2017). Given the demographics of the region, this registry is representative of most Western European

populations. Data collection methods have been reported previously[20,21]. The register received ethical approval from the Newcastle and Tyneside National Health Service (NHS) and Research Ethics Committee (17/NE/0277) as a research database, which does not require individual patient consent. The protocol was approved by the Steering Committee of the Register. The study was conducted in accordance with the principles of the Declaration of Helsinki (1964) and later amendments.

Exclusion criteria, outcomes of interests (in-hospital mortality, LoS, disability, post-discharge long-term mortality and ischaemic stroke recurrence), and selection of study covariates were all agreed a-priori.

Patients admitted with confirmed AIS between January 2004 and December 2016 were included. In all participants, AIS was diagnosed based on patient history, neurological examination, and neuroimaging results. Follow-up data were collected in June 2017, yielding a median follow-up of 5.5 and 3.7 years for the mortality and recurrence outcomes respectively. Maximum follow-up was 5262 days (14.4 years). Record linkage with the UK NHS system ensures a robust ascertainment of co-morbidities and almost complete follow up data. Exclusion criteria were applied successively for each stage of the analysis, according to analysis-specific requirements (Figure 1). A total of 10,839 AIS patients were initially extracted from the database. Patients with missing discharge dates (n = 23) were excluded, leading to a starting cohort of 10,816.

Data collection and exposure group definition

Data on the exposure variables (HF and AF) were identified from ICD-10 codes based on clinical findings and retrieved from the hospital administration database (heart failure (I50) and atrial fibrillation and flutter (I48)). Given that our database performed electronic record linkage with primary care co-morbidity data, any diagnoses of AF or HF before,

during or after the stroke admission were extracted. Given that general practitioners in England receive financial incentives to optimise the diagnosis and treatment of certain conditions (including AF and HF)[22], co-morbidity ascertainment in our databse is robust. Any new diagnoses of HF or AF after discharge were extracted as dichotomous variables from the NNSTR along with the time when they were first diagnosed and updated in the models. For all the analyses, patients were split into 4 mutually exclusive categories: patients with neither AF nor HF, patients with AF but not HF, patients with HF but not AF and patients with both AF and HF.

Data collection and confounder selection

Potential confounders were selected based on existing literature[5,6,8-10] and clinical judgement. Data on age, sex, Oxfordshire Community Stroke Project classification (OCSP) and relevant biochemical and haematological measurements collected on admission (random plasma glucose, haemoglobin, total white cell count, albumin, creatinine, urea, CRP (C-reactive protein), and INR (International Normalised Ratio)) were collected by electronic record linkage. Information on confounding comorbidities were identified from ICD-10 codes based on clinical findings and retrieved from the hospital administration database (Supplementary Table I). Any diagnoses of a co-morbidity of interest occurring before, during or after the stroke admission were extracted. . Co-morbidities were extracted as dichotomous variables from the NNSTR along with the time when they were first diagnosed.

Data collection and outcome selection

Data regarding our outcomes of interest were extracted from the hospital database. To evaluate the stroke-related disability status, we calculated the difference between the modified Rankin Score (mRS) after and before the incident stroke and then split these values

into tertiles. Data regarding the mortality and recurrence rates were collected using the recorded date of death or AIS readmission from the database, respectively.

Statistical Analysis

Data were analysed using Stata 15.1 SE (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). The Pearson's chi-squared test was used to compare differences in categorical variables across the 4 exposure groups. The Kruskal-Wallis test and one-way ANOVA were used to compare differences in non-normally and normally distributed variables, respectively. The median follow-up time was calculated using the reverse Kaplan-Meier method[23]. The log-rank test was utilised to compare the rates of incident dementia over the follow-up period between patients with and without AF.

Handling of missing data

Thirteen variables (pre- and post-stroke mRS, OCSP, admission random plasma glucose, creatinine, sodium, albumin, cholesterol, INR, CRP, haemoglobin, white cell count and platelet count) contained missing data (Supplementary Table II). Having explored the differences between patients with missing data for each of the variables in question (Supplementary Tables III-XV), we have observed that patients with missing data were more likely to die in hospital, have a longer hospital stay and have more co-morbidities. We thus deemed the data likely to be missing-at-random[24]. Multiple imputation by chained equations algorithm with 20 iterations was implemented to impute the missing data. Biochemical and haematological variables were imputed using predictive mean matching[25]. OCSP and the mRS scores were imputed using multinomial logistic regressions. The difference between the pre- and post-stroke mRS (ΔmRS) was calculated using the imputed variables for each of the 20 iterations and then divided into tertiles, which were then utilised as the disability outcome.

As our database only recorded the National Institutes of Health Stroke Scale (NIHSS) routinely for admissions occurring after January 2015, a high frequency (86%) of missing data was observed for this variable. We performed sensitivity analyses as a separate model including the imputed NIHSS, which did not show any significant change in any of the results.

In-hospital mortality

A multivariable binomial logistic regression was performed to assess the association between the exposure groups and in-hospital deaths. The following confounders were included, based on clinical judgement and existing literature[5,6,8-10]: age, sex, OCSP, co-morbidities (Supplementary Table I), admission plasma biochemical and haematological parameters and admission antithrombotic medication.

Length of in-hospital stay and excess disability

A total of 2035 patients who died in hospital were excluded for this part of the analysis, resulting in a cohort of 8781 patients. A binomial logistic regression model was used to determine the association between exposure groups and in-hospital LoS greater than the cohort median. For the analysis of the excess disability, a multinomial logistic regression model with ΔmRS tertiles as the outcomes was utilised. In addion to the same confounders used in the in-hospital mortality analysis, the pre-stroke mRS score was also added because patients with a high pre-stroke mRS are more likely to fall in the category of patients with the lowest excess post-stroke disability.

Post-discharge mortality and AIS recurrence

A further 74 patients with missing follow-up information were excluded for the long-term mortality analysis, yielding a cohort of 8707 patients. All patients with a history of previous ischaemic stroke (n = 441) and those who suffered a recurrent stroke in hospital (n = 273) were further excluded from the AIS recurrence analysis, yielding a cohort of 7933 patients.

For both outcomes, a Cox regression model was employed to estimate the long-term mortality or recurrence risk associated with each of the exposure groups. Given the competing risk of death for the outcome of recurrent ischaemic stroke, cause-specific hazard ratios were yielded for this outcome.

The satisfaction of the proportional hazards assumption was confirmed for both analyses. The models were adjusted for age, sex, OCSP, co-morbidities (Supplementary Table I) and discharge antithrombotic agents. We additionally controlled for new co-morbidity diagnoses (including incident haemorrhagic stroke) after hospital discharge as time-updated binary variables in the regression model. The long-term mortality analysis was also adjusted for incident recurrent strokes.

RESULTS

Descriptive Statistics

Table 1 and Supplementary Table XVI display the patient characteristics at admission. The statistics for the variables with missing values are displayed for the complete cases only. The mean age (SD) was 77.9 (12.1) years and 49% were male. Patients were followed up for a median (95%CI) of 2001 (1957-2044) and 1348 (1303-1411) days for mortality and recurrence, respectively. There were 6668 out of 10,816 (61.7%) patients with neither co-morbidity, 2605 (24.1%) patients with AF only, 611 (5.7%) with HF only and 932 (8.6%) with both AF and HF. Patients with both AF and HF were the oldest group (mean±SD

= 83.5±8.8), followed by patients with only AF (82.2±8.8), patients with only HF (80.2±10.7) and patients with neither co-morbidity (75.3±12.8). Patients with AF were more likely to be female, regardless of whether they had HF. The highest in-hospital mortality was recorded for patients with both AF and HF, followed by patients with HF only and those with AF only and patients with neither disease. Among stroke admissions with neither co-morbidity, AF only, HF only, and those with both AF and HF there were 153 (2.3%), 662 (25.4%), 30 (4.9%) and 185 (19.9%) patients receiving anticoagulant medications at discharge. The patients with both HF and AF had the highest comorbidity burden, followed by those with HF only, those with AF only and those with neither HF nor AF. There were 314 (2.9%) patients with pre-existing dementia. The rates of dementia were significantly higher amongst patients with AF than in those without. Patients with AF had a significantly higher incidence of dementia in the long-term follow-up than those without ($P < 0.001$).

In-hospital mortality analysis

Table 2 and Figure 2 detail the results of the in-hospital mortality analysis. Compared to the reference group, patients with both AF and HF had the highest increase in odds (OR (95% CI) = 2.23(1.83-2.72)), followed by patients with HF only (1.40(1.10-1.79)) and those with AF only (1.24(1.07-1.43)). Sensitivity analyses adjusting for the imputed NIHSS score did not show any differences for this outcome.

In-hospital length of stay and disability analysis

Table 2 details the results of the in-hospital LoS and stroke-associated excess disability analyses. The median LoS was 8 days. Compared to the reference group, patients with only HF had a 85% increase in the odds of having a LoS greater than median (OR(95%CI) = 1.85(1.50-2.28)). Those with both HF and AF experienced an increase in their

odds of 66% (1.66(1.38-2.00)), whilst those with AF only had a 29% higher odds for this outcome (1.29(1.16-1.44)).

With membership to the 1st ΔmRS tertile as baseline, none of AF, HF or their combination predicted membership of the 2nd tertile. Only patients with AF but not HF were more likely to be part of the 3rd tertile (1.36(1.12-1.64)).

Long-term mortality analysis

Table 3 displays the numbers and rates of post-discharge deaths recorded during the follow-up period. There were 1649 (29.1%), 860 (42.9%), 229 (50.7%) and 330 (56.2%) deaths recorded in patients with neither co-morbidity, those with AF only, those with HF only and those with both AF and HF, respectively. Table 3 and Figure 2 detail the results of the long-term mortality analysis. Those with HF only and those with both HF and AF had twice the long-term mortality risk of the reference group (HR(95%CI) = 2.07(1.83-2.36) and 2.20(1.96-2.46)), respectively. Patients with AF only had a 45% increased risk of long-term mortality (HR(95% CI) = 1.45(1.33-1.59)).

Long-term stroke recurrence analysis

Table 3 displays the number and rate of recurrent ischaemic strokes recorded during the follow up. There were 550(10.5%), 233(12.7%), 52(13.0%) and 59(11.5%) recurrent events recorded in patients with neither co-morbidity, those with AF only, those with HF only, and those with both AF and HF respectively. Table 3 and Figure 2 detail the results of the long-term AIS recurrence analysis**.** Compared to the reference group, a higher risk of recurrence was associated with patients with AF alone, those with HF alone and those with both AF and HF: HR(95%CI) – 1.50(1.26-1.78), 1.33(1.01-1.75 and 1.62(1.28-2.07), respectively.

DISCUSSION

In this large, real-world stroke registry we have found a 24% and 40% increase in odds of in-hospital mortality associated with isolated AF and isolated HF, respectively. Patients with both AF and HF were over twice as likely to die in hospital compared to the reference group. This suggests that the individual effects of each co-morbidity are synergistic. Nevertheless, this effect was not identified for the post-discharge outcomes. Our long-term mortality results suggest that HF is associated with double the mortality rate regardless of whether AF co-existed. Furthermore, isolated AF was associated with a 50% excess long-term mortality. In contrast, patients with AF and HF had a 60% increase in the stroke recurrence risk, but in patients with isolated HF this only increased by 33%.

Our data show that patients with HF without AF are at a 30% higher risk of recurrence than patients without HF, after adjusting for discharge anti-thrombotics. A previous meta-analysis found that co-morbid HF is associated with a twofold increase in AIS recurrence[16]. Nevertheless, this relationship may be also driven by co-existent AF, since up to 50% of HF patients also have AF[17-19] . A previous study showed that the rate of cardiovascular events of stroke patients with HF does not differ significantly based on their AF status[8]. Whilst this outcome did include AIS recurrence, it was considered as part of a composite outcome. Consequently, we are the first to report on the rates of AIS recurrence in patients with HF without AF.

Previous clinical trials assessing anticoagulation for the prevention of AIS in patients with HF without AF have concluded that it was either not associated with better outcomes[26], or that its risks outweigh the benefits[27,28]. The latter finding may be consistent with our finding that stroke HF patients without AF had at a significant, yet lesser increase in the risk of recurrence. Clinical trial post-hoc analyses have determined that increasing severity of HF[29], lower left ventricular ejection fraction[30] and higher levels of N-terminal pro B-type

natriuretic peptide[29] were risk factors for incident stroke in HF patients without AF. Thus, it may be that within our group of patients with HF and no AF there may be certain subgroups at a higher risk of recurrent events, whilst others may be at no significantly increased risk. We were nevertheless not able to identify any such subgroups due to the lack of those parameters in our data. Nevertheless, previous trials assessed the use of anticoagulants for primary stroke prevention in HF patients, whilst our study analysed stroke recurrence. Our study identifies the need for further trials assessing secondary stroke prevention in patients with HF.

Our results show that in terms of long-term mortality there was no difference between HF patients with and without AF. This result is consistent with previous literature[8]. Our study also confirms that AF significantly increases the long-term mortality of AIS patients[5,7,8,12,13]. Unfortunately, we were not able to stratify by the TOAST classification. Given the fact that AIS events in HF and AF patients are more likely to be cardioembolic in origin[31], the observed mortality may also be driven by the fact that AIS cases of the cardioembolic subtype have an overall worse prognosis[31]. Nevertheless, we adjusted for the OCSP classification, which may be regarded as a proxy of the TOAST and have controlled for discharge anti-thrombotic medications. This finding may also be explained by the association between AF and other co-morbidities, such as dementia, that may influence survival. This relationship has been described previously[32,33] and can also be observed in our sample: patients with AF were not only more likely to have pre-existing dementia but also develop incident dementia after discharge.

Our study has several strengths. By stratifying AIS patients in four mutually exclusive groups, our study was able to provide novel insights into the real influence of AF and HF on the outcomes of AIS patients. We are the first study to report the association between these exposure groups and stroke outcomes. The cohort is a large, prospectively identified

population of consecutively hospitalised stroke patients. As a record linkage study embedded within the UK National Health Service (NHS), the ascertainment of co-morbidities throughout the study follow-up as well as discharge medication is robust and we have almost 100% follow up. Only 0.90% of our initial cohort were excluded due to missing follow-up information.We have also been able to adjust for anti-thrombotic medications at discharge, thereby minimsing the bias inherent to the non-randomised nature of observational studies.

There are some limitations worth highlighting. Our database did not record HF clinical characteristics. Thus, we have been unable to identify HF patient subgroups that may be at a higher risk of recurrent AIS independent of the effects of AF. There was a large proportion of missing data for NIHSS, given that routine collection of this variable only occurred after 2015. Nevertheless, our sensitivity analyses including the imputed NIHSS yield similar results. Furthermore, we controlled for surrogate markers of stroke severity, such as the OCSP classification and the post-stroke mRS score. The study population is ethnically homogenous. However, both AF and HF are unlikely to have different impact in other ethnic groups, as underlined by a Greek study showing similar results[8]. Furthermore, differences may exist in HF case ascertainment and management along the patient recruitment timeline. Given the long follow-up time of our cohort, post-discharge changes in medication regimens may have been missed, including antithrombotics. This is likely to affect patients with more severe strokes, since those are most likely to be initiated on oral anticoagulation with a longer delay from the index event[34]. Our results may thus underestimate the recurrence risk in these patients. We may have only been able to account for chronic AF in our analyses, since asymptomatic paroxysmal episodes of AF may be missed without 24h cardiac rhythm monitoring. Nevertheless, this remains an inherent limitation of any large-scale long term follow-up observational study in the absence of implantable monitors. According to the REVEAL AF study, up to 40% of patients at a high

risk for developing AF experienced at least one episode of AF (>6 minutes) over 30 months follow-up[35].Nevertheless, our study represents the real-world setting, where patients are not routinely under continuous cardiac monitoring. Thus, short episodes of paroxysmal AF may remain unrecognised and the required anticoagulant therapy may not be prescribed. Recurrent events were ascertained using only the register data, but this is likely to have a high accuracy, since it is based on the NHS record system.

Our study may have several important implications for clinical practice. This study shows that HF patients with co-existent AF are at an almost double risk of post-stroke in-hospital death when compared to their counterparts without AF. Whilst it has been shown before on non-stroke cohorts that patients with HF have a worse prognosis when AF co-exists[19], our study indicates that this effect is synergistic in patients with AIS. This warrants that special consideration needs to be paid to those patients in the context of stroke care. Whether these high-risk patients may benefit from the adoption mechanical endovascular recanalization strategies, given that intravenous thrombolysis is more likely to fail in this patient subgroup[36], remains to be established by further studies.

CONCLUSION

Our study shows that patients with both AF and HF are at increased risk of mortality during their acute stroke admission, with double the risk of those with AF or HF in isolation. Subsequently, it may be the case that this subgroup of patients may benefit from personalised therapeutic options. Furthermore, our study shows that the excess risk of recurrent AIS associated with AF is independent of co-morbid HF and that HF in isolation is also associated with recurrent events . Thus, anti-coagulation strategies in stroke patients with HF but without AF may require further evaluation in a clinical trial setting. In the meantime, our study provides real-world prognostic information for AIS patients with these conditions.

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CONTRIBUTIONS

PKM and JFP are the co-PIs of the NNUSTR. JHB-S performed data linkage. TAP and PKM conceived the study. Data were analysed by TAP under the supervision of DJM and PKM. TAP and PKM drafted the paper and all of the authors contributed in writing the paper. PKM is the guarantor.

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DISCLOSURES

None.

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FIGURE LEGENDS

Figure 1. Selection criteria and resulting cohorts used in each analysis.

Figure 2. Graphical representation of the results of the analyses of the long-term AIS outcomes.

TABLES

Table 1. Patient characteristics in hospital, stratified by group membership.

	Total	Neither HF nor AF	AF only	HF only	Both AF and HF	*P* value*
N	10,816	6668	2605	611	932	
Age, mean (SD)	77.9(12.1)	75.3(12.8)	82.2(8.8)	80.1 (10.7)	83.5(8.8)	<0.001
Sex, N(%)						
M	5192(48.0)	3371(50.6)	1128(43.3)	307(50.3)	386(41.4)	<0.001
F	5624(52.0)	3297(49.5)	1477(56.7)	304(49.8)	546(58.6)	
			Outcomes			
In-hospital mortality, N (%)	2035(18.8)	951(14.3)	586(22.5)	158(25.9)	340(36.5)	<0.001
Length of stay median (IQR)	8.0(3.0-17.0)	7.0(3.0-15.0)	10.0(4.0-20.0)	11.0(4.0-21.2)	10.3(5.0-22.0)	<0.001
mRS admission median (IQR)	0.0(0.0-2.0)	0.0(0.0-1.0)	0.0(0.0-2.0)	1.0(0.0-2.0)	1.0(0.0-3.0)	<0.001
mRS discharge median (IQR)	3.0(1.0-6.0)	2.0(1.0-4.0)	4.0(2.0-6.0)	4.0(2.0-6.0)	5.0(3.0-6.0)	<0.001
ΔmRS median (IQR)	2.0(0.0-3.0)	1.0(0.0-3.0)	2.0(1.0-4.0)	2.0(1.0-4.0)	3.0(1.0-4.0)	<0.001
			OCSP classification			
LACS	2484(24.4)	1733(27.6)	458(18.8)	136(23.2)	157(17.9)	<0.001
PACS	3681(36.2)	2204(35.1)	934(38.4)	215(36.7)	328(37.4)	
POCS	1611(15.8)	1112(17.7)	320(13.2)	85(14.5)	94(10.7)	
TACS	1954(19.2)	949(15.1)	625(25.7)	122(20.8)	258(29.5)	
Unknown, N (%)	442(4.4)	278(4.4)	97(4.0)	28(4.8)	39(4.5)	
			Admission anti-thromobotic medication			
Antiplatelets admission	3135(29.0)	1709(25.6)	854(32.8)	240(39.3)	332(25.6)	<0.001
Anticoagulants admission	740(6.8)	93(1.4)	424(16.3)	11(1.8)	212(22.8)	<0.001

			Discharge anti-thrombotic medication			
Antiplatelets discharge	7203(66.6)	4691(70.4)	903(34.7)	346(56.6)	262(28.1)	<0.001
Anticoagulants discharge	1030(9.5)	153(2.3)	662(25.4)	30(4.9)	185(19.9)	<0.001
			Pre-existing co-morbidities			
Coronary Heart Disease, N(%)	2933(27.1%)	1282(19.2%)	756(29.0%)	373(61.0%)	522(56.0%)	<0.001
Peripheral Vascular Disease, N(%)	430(4.0%)	196(2.9%)	107(4.1%)	51(8.3%)	76(8.2%)	<0.001
Transient Ischaemic attack, N(%)	530(4.9%)	278(4.2%)	138(5.3%)	40(6.5%)	74(7.9%)	<0.001
Hypertension, N(%)	6405(59.2%)	3580(53.7%)	1725(66.2%)	417(68.2%)	683(73.3%)	<0.001
Diabetes, N(%)	1901(17.6%)	1094(16.4%)	434(16.7%)	164(26.8%)	209(22.4%)	<0.001
Chronic Kidney Disease, N(%)	693(6.4%)	274(4.1%)	152(5.8%)	102(16.7%)	165(17.7%)	<0.001
Asthma, N(%)	987(9.1%)	557(8.4%)	214(8.2%)	87(14.2%)	129(13.8%)	<0.001
Chronic Obstructive Pulmonary Disease, N(%)	868(8.0%)	435(6.5%)	173(6.6%)	109(17.8%)	151(16.2%)	<0.001
Cancers, N(%)	1683(15.6%)	968(14.5%)	429(16.5%)	111(18.2%)	175(18.8%)	<0.001
Liver disease, N(%)	167(1.5%)	107(1.6%)	27(1.0%)	10(1.6%)	23(2.5%)	0.02
Dementia, N(%)	314(2.9%)	147(2.2%)	106(4.7%)	22(3.6%)	39(4.2%)	<0.001
Charlson co-morbidity index, median (IQR)	3(1-4)	2(1-4)	2(1-4)	5(3-6)	4(3-6)	<0.001

Continous normally distributed variables displayed as mean (standard deviation). Non-normally variables displayed as mean (inter-quartile range). Categorical variables displayed as frequency (percentage).

* One-way ANOVA, the Kruskal-Wallis test and the Chi-squared test were used to test differences across groups for normally distributed, non-normally distributed and categorical variables respectively.

Table 2. Results of the in-hospital anlayses.

	No NIHSS adjustment		NIHSS adjustment	
	In-hospital death			
	OR[95%CI]	*P* value	OR[95%CI]	*P* value
No AF; No HF	1 (reference)		1 (reference)	
AF only	**1.24[1.07-1.43]**	**0.004**	**1.23[1.06-1.42]**	**0.005**
HF only	**1.40[1.10-1.79]**	**0.007**	**1.40[1.10-1.79]**	**0.007**
AF + HF	**2.23[1.83-2.72]**	**<0.001**	**2.22[1.82-2.70]**	**< 0.001**
	LoS greater than median*			
	OR[95%CI]	*P* value	OR [95%CI]	*P* value
No AF; No HF	1 (reference)		1 (reference)	
AF only	**1.29[1.16-1.44]**	**<0.001**	**1.29[1.16-1.44]**	**<0.001**
HF only	**1.85[1.50-2.28]**	**<0.001**	**1.85[1.50-2.27]**	**<0.001**
AF + HF	**1.66[1.38-2.00]**	**<0.001**	**1.66[1.38-2.00]**	**<0.001**
	Excess disability			
	2nd ΔmRS† tertile vs 1st ΔmRS tertile			
	OR[95%CI]	*P* value	OR[95%CI]	*P* value
No AF; No HF	1 (reference)		1 (reference)	
AF only	1.06[0.91-1.25]	0.451	1.07[0.91-1.24]	0.414
HF only	1.03[0.78-1.36]	0.841	1.07[0.80-1.41]	0.658
AF + HF	0.86[0.67-1.09]	0.202	0.88[0.65-1.19]	0.408
	3rd ΔmRS tertile vs 1st ΔmRS tertile			
	OR[95%CI]	*P* value	OR[95%CI]	*P* value
No AF; No HF	1 (reference)		1 (reference)	
AF only	**1.36[1.12-1.64]**	**0.002**	**1.38[1.15-1.65]**	**<0.001**
HF only	1.27[0.85-1.89]	0.238	1.25[0.88-1.78]	0.205
AF + HF	1.11[0.83-1.49]	0.470	1.14[0.82-1.58]	0.443

All models were adjusted for age, sex, OCSP classification, pre-existing co-morbidities (ischaemic heart disease, peripheral vascular disease, transient ischaemic attack, previous stroke, hypertension, diabetes mellitus, chronic kidney disease, asthma, chronic obstructive pulmonary

disease, cancers, liver disease), admission plasma biochemical parameters (random plasma glucose, creatinine, sodium, albumin, cholesterol, INR, CRP, haemoglobin, white cell count, platelet count) and admission anti-thrombotic medication.

Statistically significant results displayed in **bold**.

*LoS: in-hospital length of stay
†ΔmRS: the difference in the modified Rankin Scale after and before the index stroke.

Table 3. Results of the long-term outcome analysis.

		Mortality		
	Post-discharge deaths(%)	N*	HR[95%CI] †	*P* value
No AF; No HF	1649(29.1)	5659	1 (reference)	
AF only	860(42.9)	2007	**1.45[1.33-1.59]**	**<0.001**
HF only	229(50.7)	452	**2.07[1.83-2.36]**	**<0.001**
AF + HF	330(56.2)	589	**2.20[1.96-2.46]**	**<0.001**
		Recurrence		
	Recurrent stroke (%)	N‡	HR [95%CI] †	*P* value
No AF; No HF	550(10.5)	5247	1 (reference)	
AF only	233(12.7)	1834	**1.50[1.26-1.78]**	**<0.001**
HF only	52(13.0)	400	**1.33[1.01-1.75]**	**0.042**
AF + HF	59(11.5)	512	**1.62[1.28-2.07]**	**<0.001**

* Patients in each disease category at risk of death. The median follow-up was 5.5 years.

† Results of the Cox regression for long-term mortality and ischaemic stroke recurrence,adjusted for age, sex, pre-existing co-morbidities (ischaemic heart disease, peripheral vascular disease, transient ischaemic attack, previous stroke, hypertension, (diabetes mellitus, chronic kidney disease, asthma, chronic obstructive pulmonary disease, cancers, liver disease), discharge antithrombotic agents, the OCSP classificationand incident co-morbidities after hospital discharge (including incident haemorrhagic stroke) as time-updated binary variables in the regression model. The mortality analysis was adjusted for incident recurrent ischaemic strokes.

‡ Patients in each disease category at risk of recurrent stroke The median follow-up was 3.7 years.

FIGURES

Figure 1. Selection criteria and resulting cohorts used in each analysis.

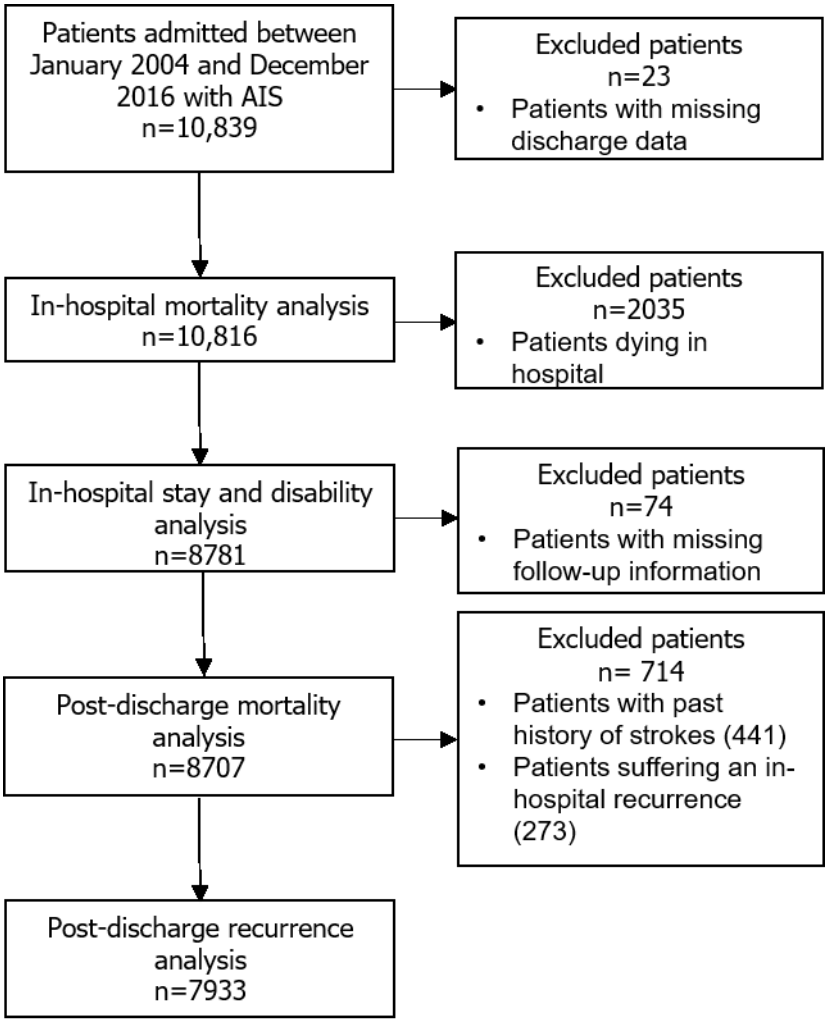

Figure 2. Graphical representation of the results of the analyses of long-term AIS outcomes.