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CLINICAL RESEARCH
Epidemiology and prevention

Incidence of ischaemic stroke and mortality in patients with acute coronary syndrome and first-time detected atrial fibrillation: a nationwide study

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Aims The aim of this study was to examine contemporary data on the 1-year prognosis of patients surviving acute coronary syndrome (ACS) and concomitant first-time detected atrial fibrillation (AF).

Methods and results Using Danish nationwide registries, we identified all patients surviving a first-time admission with ACS from 2000 to 2018 and grouped them into (i) those without AF prior to or during ACS; (ii) those with a history of AF; and (iii) those with first-time detected AF during admission with ACS. With 1 year of follow-up, rates of ischaemic stroke, death, and bleeding were compared between study groups using multivariable adjusted Cox proportional hazards analysis. We included 161 266 ACS survivors: 135 878 (84.2%) without AF, 18 961 (11.8%) with history of AF, and 6427 (4.0%) with first-time detected AF at admission with ACS. Compared to those without AF, the adjusted 1-year rates of outcomes were as follows: ischaemic stroke [hazard ratio (HR) 1.38 (95% CI 1.22–1.56) for patients with history of AF and HR 1.67 (95% CI 1.38–2.01) for patients with first-time detected AF]; mortality [HR 1.25 (95% CI 1.21–1.31) for patients with history of AF and HR 1.52 (95% CI 1.43–1.62) for patients with first-time detected AF]; and bleeding [HR 1.22 (95% CI 1.14–1.30) for patients with history of AF and HR 1.28 (95% CI 1.15–1.43) for patients with first-time detected AF].

Conclusion In patients with ACS, first-time detected AF appeared to be at least as strongly associated with the 1-year rates of ischaemic stroke, mortality, and bleeding as compared with patients with a history of AF.

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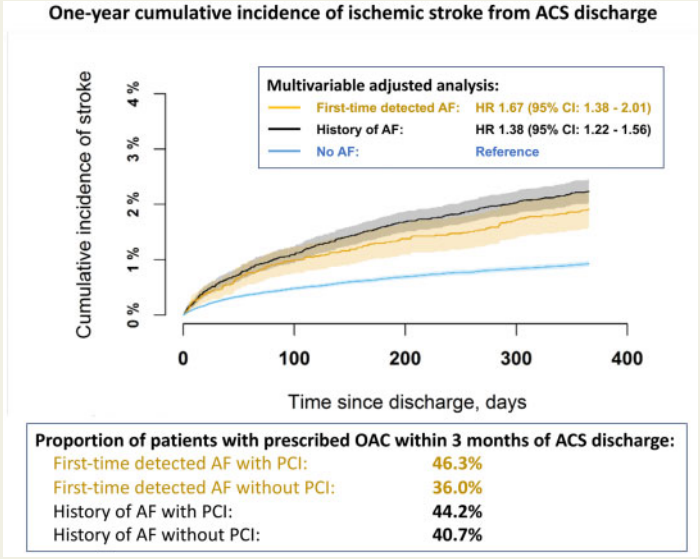
Graphical Abstract



In patients with acute coronary syndrome, first-time detected atrial fibrillation appears at least as strongly, or even higher, associated with the 1-year rates of ischaemic stroke as for patients with a history of atrial fibrillation, while <50% were treated with oral anticoagulation therapy.

Keywords Acute coronary syndrome • Atrial fibrillation • Ischaemic stroke • Myocardial infarction • Unstable angina pectoris • Bleeding

Introduction

Acute coronary syndrome (ACS) is frequently accompanied by atrial fibrillation (AF), which may be previously known or first-time detected. Previously known AF is well-recognized to further aggravate the prognosis of patients with ACS; however, contemporary, unselected data on the subgroup of patients admitted with first-time detected AF are sparsely examined, and especially missing in a nationwide setting. First-time detected AF at admission with ACS has been reported with highly variable estimates (4.1–37.0%) and has been identified with an increased associated risk of mortality, stroke, and myocardial infarction (MI).[1–11] However, the associated prognosis of first-time detected AF in ACS is yet to be further elucidated; data from previous studies on this matter have been conducted on selected study cohorts, and only few have been addressed since non-vitamin K oral anticoagulants (NOACs) were recommended more widely in AF management in 2010.[12]

To prevent ischaemic stroke in patients with AF, treatment with vitamin K antagonists (VKAs) or NOACs is indicated[13,14] but has not shown net clinical benefit in the secondary prevention of MI when bleeding is taken into account.[15,16] Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor and aspirin is proven to reduce the incidence of atherothrombotic events and stent thrombosis[14] but does not provide adequate protection against AF-related strokes.[14,17,18] Over the course of the study period, oral anticoagulant (OAC) treatment strategies have changed; first, regarding the indication for OAC and, second, the recommendations to prefer NOACs over VKAs.[19]

Thus, according to guidelines on patients with ACS treated with percutaneous coronary intervention (PCI), DAPT is indicated, but when patients present with concomitant AF, an initial period of triple therapy may be needed;[4] however, balancing the high risk of bleeding is a well-known difficult clinical scenario.[20–22]

Clarifying the 1-year rates of adverse outcomes in ACS survivors, and especially the incidence of ischaemic stroke, all-cause mortality, and bleeding, in patients with ACS based on the type of AF (history of AF vs. first-time detected AF) is of importance to understand the magnitude of the problem.[4,23] It is also a necessary step before an in-depth investigation of the optimal treatment strategy of antiplatelet/anticoagulant therapy in this patient subgroup.

In a nationwide Danish cohort, we set out to examine the associated 1-year rates of ischaemic stroke, all-cause mortality, and bleeding in patients with ACS presenting with first-time detected AF. We mapped out the practice patterns for antithrombotic therapy following ACS and investigated the associated outcomes.

Methods

Data sources

Every Danish citizen is provided with a unique identifier making it possible to link multiple nationwide registries. In the present study, we linked the following registries: (i) the Danish National Patient Registry (DNPR), which holds information on all hospital admissions since 1977 and outpatient visits since 1995, with diagnosis codes based on the International

Classification of Diseases (ICD) (ICD-8 and ICD-10 codes) and surgical procedures classified according to the Nordic Medico-Statistical Committee since 1996;[24] (ii) the Danish Civil Registration System, which holds information on sex, vital status, migration, and birthdate;[25] (iii) the Danish National Prescription Registry, which holds records on all claimed drug prescriptions since 1995;[26] and (iv) the Danish Registry of Causes of Death, which contains information on date, cause, and place of death.[27] The Danish registries are validated, previously described in detail, and of high quality.[28,29]

Study population

The study population constituted patients surviving a first-time admission with ACS from 2000 to 2018 diagnosed with unstable angina pectoris (UAP) or MI (ICD-10 codes: I200 and I21, respectively). The study population was grouped into (i) patients without AF (ICD-8 codes: 42793 and 42794; ICD-10 code: I48) prior to or during the admission with ACS; (ii) patients with history of AF; and (iii) patients with first-time detected AF. History of AF was defined by either of three criteria: (i) an inpatient or outpatient diagnosis code of AF any time prior to admission with ACS; (ii) a filled prescription of amiodarone, digoxin, dronedarone, or flecainide prior to admission with ACS; and (iii) a filled prescription of OAC agents within 6 months of ACS and without a previous diagnosis of venous thromboembolism. First-time detected AF was defined as a diagnosis code of AF during admission with ACS with no prior history of AF. The population-based diagnosis codes are previously validated with a positive predictive value (PPV) of 88% for UAP, 88–97% for MI, and 95% for AF.[29]

Covariates

Patients' medical history was assessed from the DNPR as an in- or outpatient visit with a diagnosis at any time prior to admission with ACS. Hypertension was defined from the use of claimed drug prescriptions, as done previously.[30] Concomitant pharmacotherapy was assessed from the Danish National Prescription Registry during a period of 6 months prior to admission with ACS. The estimated risk of stroke (CHA_2DS_2-VASc score) and estimated risk of bleeding [a modified HAS-BLED score (international normalized ratio was left out due to a lack of data)] were calculated according to previous studies.[31,32] Supplementary material online, *Tables S1 and S2* list all classification codes used for medical history and pharmacotherapy, respectively.

Follow-up and outcomes

The primary outcome was hospital admission with ischaemic stroke or unspecified stroke (ICD-10 codes: I63–64, respectively, previously validated with a PPV of 97%[33]). Unspecified stroke was classified as ischaemic because studies have shown that more than two-third of unspecified strokes coded in the DNPR are ischaemic.[33,34] We had three secondary outcomes: (i) all-cause mortality; (ii) hospital admission with a diagnosis of bleeding; and (iii) hospital admission with a diagnosis of MI. Bleeding was defined as an intracranial, urinary tract, respiratory, gastrointestinal, retroperitoneal, or eye bleed leading to hospital admission (Supplementary material online, *Table S1*). This definition has been validated in similar databases with a PPV of 89–99%.[35]

Patients surviving hospitalization for ACS were followed from the date of discharge until the occurrence of the respective outcomes, new-onset AF (for patients without AF), death, end of study period (31 December 2018), or a maximum of 1 year of follow-up, whichever came first.

Statistics

Baseline characteristics were compared by study groups. Categorical variables were presented as counts and percentages, and continuous variables were presented as medians with interquartile ranges (IQR). The cumulative incidence of ischaemic stroke, recurrent MI, and bleeding was examined using the Aalen–Johansen estimator assessing death as a competing risk. Differences between groups were assessed with Gray's test. Mortality was examined using Kaplan–Meier estimates. The associated rates of outcomes were examined using multivariable adjusted Cox proportional hazards analysis, including the following covariates: study groups, sex, age, calendar year, treatment with statins, and known comorbidities at admission date (including hypertension, heart failure, chronic ischaemic heart disease, previous stroke, previous transient ischaemic attack, diabetes, previous malignancy, chronic renal failure, and coronary artery bypass graft during admission). When examining the associated rate of bleeding, the model further included previous liver disease, previous bleeding disorders, treatment with non-steroidal anti-inflammatory drugs, and alcohol abuse.

The assumption of proportional hazards was investigated using Martingale's residuals. When assessing the 1-year rates of recurrent MI, the assumption of proportional hazards was violated, which is why a landmark analysis was conducted on patients surviving beyond 14 days of discharge. Additional landmark analyses were conducted at 30 and 60 days beyond ACS discharge. Age and calendar year were included as continuous variables in the regression analysis and tested for linearity. Sex and age were tested as effect modifiers on the main outcome. All statistical analyses were performed using the SAS statistical software (version 9.4, Cary, NC, USA) and R (version 3.6.1 The R Foundation, Vienna, Austria).[36] Level of statistical significance was recognized by a *P*-value <0.05.

Subgroup analysis—antithrombotic therapy and associated outcomes

In patients surviving 90 days after ACS discharge, practice patterns for prescribed antithrombotic medication were examined based on filled prescriptions within 90 days of discharge. Data were stratified on whether patients were treated with PCI or not. Antithrombotic therapy was divided into (i) no antithrombotic therapy; (ii) aspirin only; (iii) $P2Y_{12}$ inhibitors only (ticagrelor, clopidogrel, and prasugrel); (iv) DAPT (aspirin and a $P2Y_{12}$ inhibitor); (v) OAC therapy only [dabigatran, rivaroxaban, apixaban, edoxaban (NOACs), or warfarin (VKA)]; (vi) OAC and either aspirin or a $P2Y_{12}$ inhibitor; and (vii) triple therapy with DAPT and OAC. All patients who developed AF within 90 days of discharge were excluded. Incidence and adjusted rates of ischaemic stroke, mortality, and bleeding were examined in three groups: (i) those with no prescribed antithrombotic therapy; (ii) those with prescribed antiplatelet therapy (aspirin only, $P2Y_{12}$ inhibitors only, and DAPT) (reference group); and (iii) those with prescribed OAC agents (OAC only, OAC, either aspirin or a $P2Y_{12}$ inhibitor, and DAPT with OAC).

Sensitivity analyses

To test the robustness of our findings, six supplementary analyses were conducted. First, three consecutive matches on sex, age, and index date (ACS discharge) were conducted in a 1:1 ratio: (i) history of AF matched with controls without AF; (ii) first-time detected AF matched with controls without AF; and (iii) first-time detected AF matched with controls with history of AF. From the matched study groups, associated rates of outcomes were assessed. Second, the associated rate of ischaemic stroke was analysed in stroke-naive patients. Third, to ensure that estimates were stable across calendar periods, since guideline alterations regarding OAC in AF was sharpened in 2010,[12] rates of ischaemic stroke were examined for a population restricted to admissions in 2010–18. Fourth, incidence and adjusted rates of ischaemic stroke and mortality were examined in a study population narrowed down to include only patients admitted with MI (i.e. excluding patients with UAP). Fifth, the in-hospital

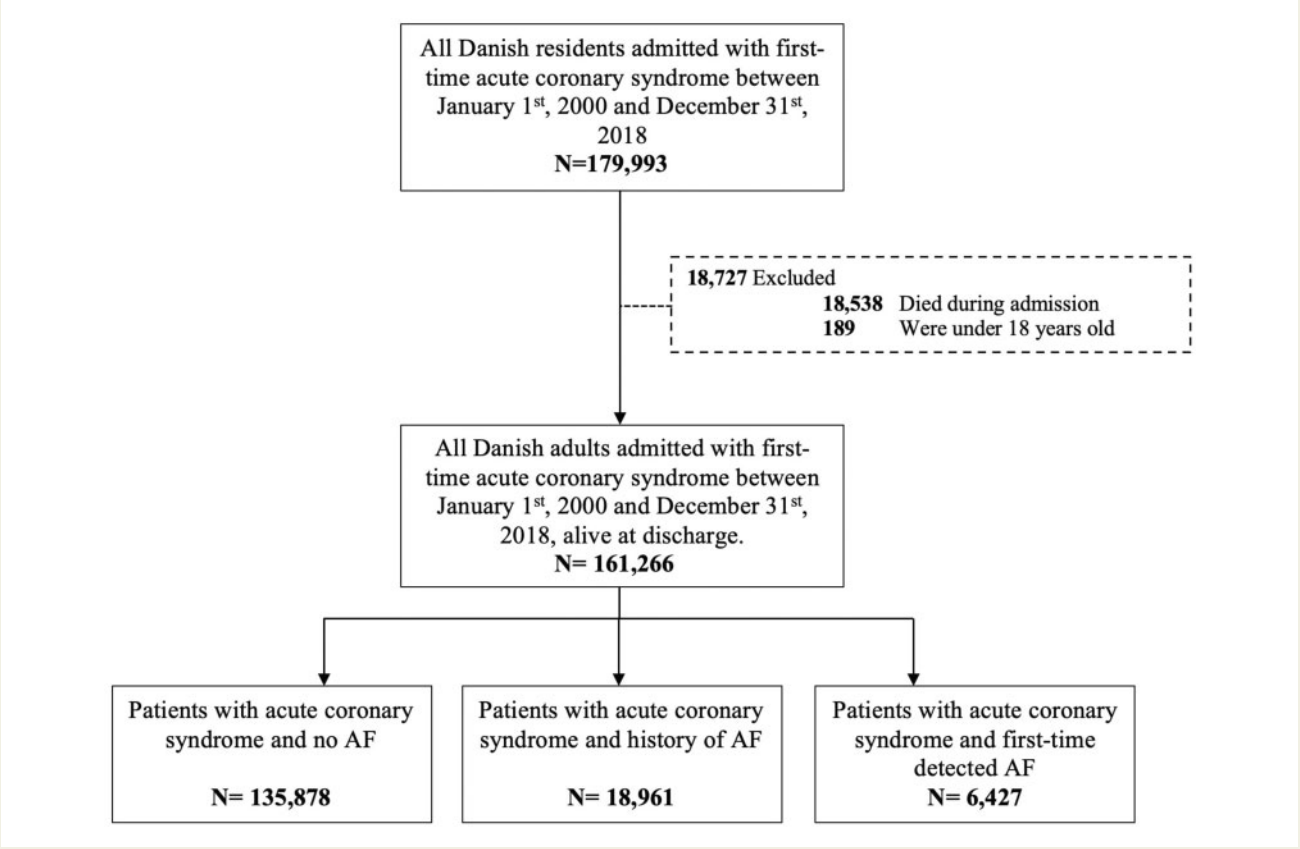


Figure 1 Flow chart of the study population.

mortality was examined in all patients admitted with ACS and the adjusted likelihood of in-hospital mortality was examined with multivariable logistic regression model including the previously mentioned variables. Sixth, to test differences between patients with first-time detected AF and history of AF, we changed the reference group when examining rates of ischaemic stroke and mortality.

Ethics

This project was approved by the Danish Data Agency with the project number P-2019-348. In Denmark, registry-based studies in which individuals cannot be identified do not require ethics committee approval.

Results

Study population and baseline characteristics

From 1 January 2000 to 31 December 2018, 161 266 patients were admitted with ACS and survived until discharge (*Figure 1*). Among these, 135 878 (84.2%) patients had no AF previous to or during their admission with ACS (64.0% male, median age 66.0 years, IQR 56.0–76.0), 18 961 (11.8%) patients had a history of AF (56.1% male, median age 78.0 years, IQR 70.0–84.0), and 6427 (4.0%) patients presented with first-time detected AF (55.8% male, median age 76.0 years, IQR 68.0–82.0). The patient group without AF presented with the least comorbidities, while the group with history of AF presented with a larger proportion of all comorbidities compared with the other study groups (*Table 1*).

Incidence of ischaemic stroke

The crude cumulative 1-year incidence of ischaemic stroke was 0.9%, 2.2%, and 1.9% for patients without AF, patients with history of AF, and patients with first-time detected AF, respectively ($P < 0.0001$) (*Graphical Abstract*) (*Figure 2*). Compared with patients without AF, adjusted analysis yielded an increased associated rate of ischaemic stroke in patients with history of AF [HR 1.38 (95% CI 1.22–1.56)] and in patients with first-time detected AF [HR 1.67 (95% CI 1.38–2.01)].

Incidence of all-cause mortality

The crude cumulative 1-year incidence of all-cause mortality was 7.9%, 21.8%, and 18.0% for patients without AF, patients with history of AF, and patients with first-time detected AF, respectively ($P < 0.0001$) (*Figure 3*). Compared with patients without AF, adjusted analysis yielded an increased associated rate of mortality in patients with history of AF [HR 1.25 (95% CI 1.21–1.31)] and in patients with first-time detected AF [HR 1.52 (95% CI 1.43–1.62)].

Table 1 Baseline characteristics

	No AF (n = 135 878)		History of AF (n = 18 961)		First-time detected AF (n = 6427)	
Male sex, *n* (%)	86 897	(64.0)	10 633	(56.1)	3586	(55.8)
Age (years), median [IQR]	66.0	[56.0–76.0]	78.0	[70.0–84.0]	76.0	[68.0–82.0]
Calendar period, *n* (%)						
2000–05	47 236	(34.8)	6633	(35.0)	2181	(33.9)
2006–11	42 430	(31.2)	5806	(30.6)	2116	(32.9)
2012–18	46 212	(34.0)	6522	(34.4)	2130	(33.1)
During admission with ACS, *n* (%)						
UAP diagnosis (DI200)	24 820	(18.3)	3932	(20.7)	644	(10.0)
MI diagnosis (DI21)	111 058	(81.7)	15 029	(79.3)	5783	(90.0)
CABG	7564	(5.6)	671	(3.5)	888	(13.8)
PCI	60 626	(44.6)	4327	(22.8)	1691	(26.3)
CAG	86 399	(63.6)	6968	(36.7)	3545	(55.2)
Cardiogenic shock[a]	4710	(3.5)	642	(3.4)	637	(9.9)
Medical history prior to ACS, *n* (%)						
HAS-BLED, median [IQR]	1	[0–1]	2	[1–2]	1	[0–2]
CHA_2DS_2-VASc, median [IQR]	2	[0–4]	4	[3–6]	3	[2–5]
Hypertension	39 818	(29.3)	11 792	(62.2)	2539	(39.5)
Chronic ischaemic heart disease	12 781	(9.4)	5624	(29.7)	574	(8.9)
Chronic heart failure	5226	(3.8)	5219	(27.5)	350	(5.4)
CIED	1001	(0.7)	1140	(6.0)	35	(0.4)
Stroke	9190	(6.8)	3099	(16.3)	611	(9.5)
Transient ischaemic attack	4608	(3.4)	1566	(8.3)	280	(4.4)
Diabetes	13 207	(9.7)	3514	(18.5)	657	(10.2)
Peripheral vascular disease	6817	(5.0)	2128	(11.2)	427	(6.6)
Bleeding	13 572	(10.0)	4043	(21.3)	753	(11.7)
COPD	9178	(6.8)	3188	(16.8)	590	(9.2)
Malignancy	14 404	(10.6)	3439	(18.1)	926	(14.4)
Chronic renal disease	4722	(3.5)	1595	(8.4)	278	(4.3)
Liver disease	2371	(1.7)	457	(2.4)	99	(1.5)
Pharmacotherapy 6 months prior to ACS, *n* (%)						
Statins	27 662	(20.4)	5923	(31.2)	1340	(20.8)
Beta blockers	23 148	(17.0)	8655	(45.6)	1480	(23.0)
Calcium channel blockers	24 883	(18.3)	5825	(30.7)	1500	(23.3)
RAS inhibitors	36 182	(26.6)	8363	(44.1)	2087	(32.5)
Diuretics	10 783	(7.9)	1561	(8.2)	616	(9.6)
Aspirin	31 746	(23.4)	7723	(40.7)	2038	(31.7)
$P2Y_{12}$ inhibitors	4463	(3.3)	925	(4.9)	235	(3.7)
OAC	174	(0.1)	8046	(42.4)	6	(0.1)

ACS, acute coronary syndrome; AF, atrial fibrillation; CABG, coronary artery bypass graft; CAG, coronary angiography; CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; ICD, International Classification of Diseases; IQR, interquartile range; MI, myocardial infarction; OAC, oral anticoagulant therapy; PCI, percutaneous coronary intervention; RAS, renin–angiotensin system; UAP, unstable angina pectoris.
[a]Defined by ICD-10 diagnosis code and/or treatment with inotropes or vasopressors (Supplementary material online, *Tables S1 and S2*).

Incidence of recurrent myocardial infarction

The crude cumulative 1-year incidence of recurrent MI was 9.0%, 10.1%, and 9.3% for patients without AF, patients with history of AF, and patients with first-time detected AF, respectively ($P < 0.0001$) (*Figure 4*). Compared with patients without AF, adjusted multivariable analysis yielded a lower associated rate of recurrent MI in patients with history of AF [HR 0.90 (95% CI 0.85–0.95)], while no significant difference was found in patients with first-time detected AF [HR 0.99 (95% CI 0.91–1.07)]. In the landmark analysis, examining MI rates from 0 to 14 days of follow-up, we found an associated lower rate of MI for patients with history of AF [HR 0.84 (95% CI 0.77–0.92)] and for patients with first-time detected AF [HR 0.79 (95% CI 0.68–0.92)]. Examining follow-up from 14 to 365 days, the MI rates were HR 0.92 (95% CI 0.87–0.98) and HR 1.12 (95% CI 1.01–1.23) for patients with a history of AF and for patients with first-time detected

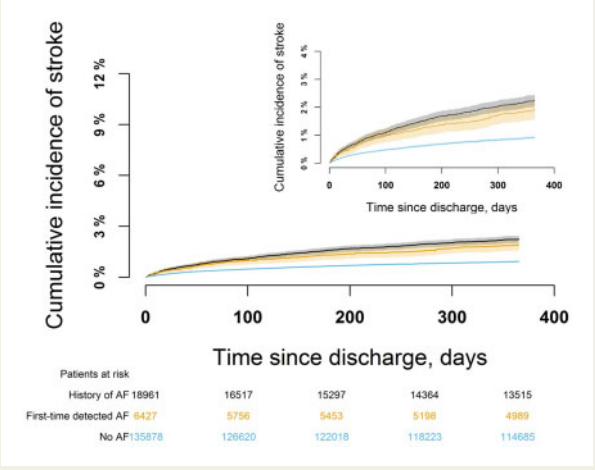


Figure 2 One-year cumulative incidence of ischaemic stroke. This figure shows the 1-year cumulative incidence of hospitalization for ischaemic stroke in patients with acute coronary syndrome and no atrial fibrillation, history of atrial fibrillation, and first-time detected atrial fibrillation.

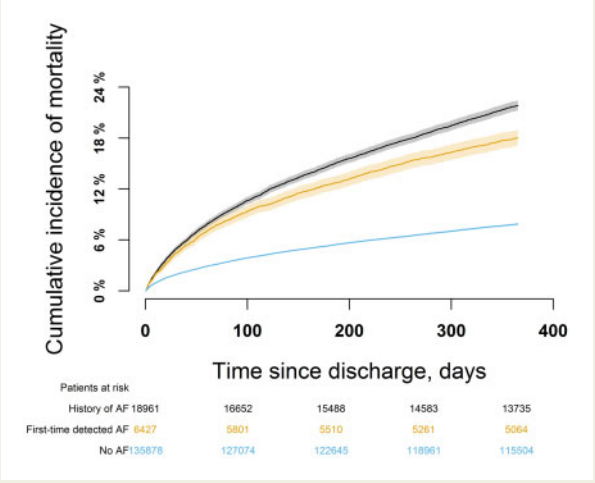


Figure 3 One-year cumulative incidence of mortality. This figure shows the 1-year cumulative risk of all-cause mortality in patients with acute coronary syndrome and no atrial fibrillation, history of atrial fibrillation, and first-time detected atrial fibrillation.

AF, respectively (Supplementary material online, *Figure S1*). In 30- and 60-day landmark analyses, similar results were observed, as compared with the 14-day landmark analysis (Supplementary material online, *Figure S2*).

Incidence of bleeding

The crude cumulative 1-year incidence of bleeding was 3.6%, 6.9%, and 5.7% for patients without AF, patients with history of AF, and patients with first-time detected AF, respectively ($P < 0.0001$) (*Figure 5*). Compared with patients without AF, adjusted analysis yielded an increased associated rate of bleeding in patients with history of AF [HR 1.22 (95% CI 1.14–1.30)] and in patients with first-time detected AF [HR 1.28 (95% CI 1.15–1.43)].

Antithrombotic therapy and associated outcomes

We identified 151 332 patients surviving 90 days after ACS discharge of which 86 367 were not treated with PCI, while 64 965 were treated with PCI during admission. Patients with first-time detected AF, who were not treated with PCI during admission ($n = 4359$), were mostly prescribed with aspirin only (24.9%) or OAC only (14.4%) and overall, 36.0% initiated OAC treatment with or without combination therapy (*Table 2*). Patients with first-time detected AF, who were treated with PCI during admission ($n = 1650$), were mostly prescribed with DAPT (35.6%) or triple therapy (27.6%) and overall, 46.3% initiated OAC treatment with or without combination therapy (*Graphical Abstract*) (*Table 2*). A similar pattern of prescriptions of antithrombotic therapy in patients with a history of AF was seen and overall, 40.7% and 44.2% received OAC treatment in those treated without PCI and with PCI, respectively (*Graphical Abstract*) (*Table 2*). For the examination of prescribed antithrombotic therapy and incidence of ischaemic stroke, patients treated with OAC showed the lowest cumulative incidence of ischaemic stroke in patients with history of AF and first-time detected AF (Supplementary material online, *Figure S3*). In adjusted analysis with antiplatelet therapy as reference, OAC showed decreased associated rates of ischaemic stroke in patients with history of AF [HR 0.87 (95% CI 0.63–1.20)] and first-time detected AF [HR 0.78 (95% CI 0.41–1.47)], although the difference was not statistically significant (Supplementary material online, *Table S3*). Furthermore, a significantly decreased associated rate of mortality and a non-significantly increased associated rate of bleeding were observed for patients in both AF groups receiving OAC (Supplementary material online, *Table S3*).

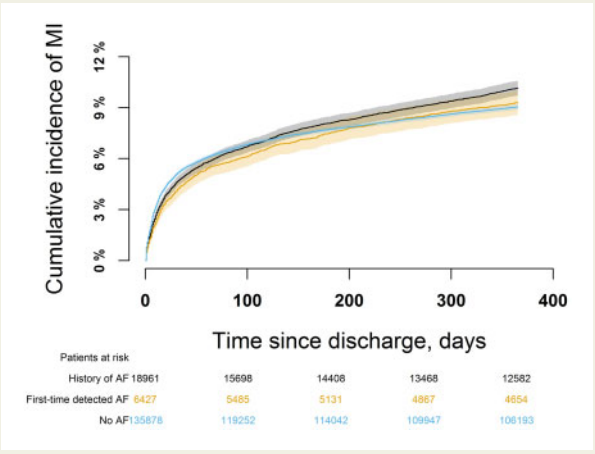


Figure 4 One-year cumulative incidence of recurrent myocardial infarction. This figure shows the 1-year cumulative incidence of hospitalization for recurrent myocardial infarction in patients with acute coronary syndrome and no atrial fibrillation, history of atrial fibrillation, and first-time detected atrial fibrillation.

Sensitivity analyses

Six additional analyses were conducted to test the robustness of our results. First, for the sex- and age-matched analysis, baseline characteristics are shown in Supplementary material online, *Table S4*. The crude and adjusted rates of outcomes in the matched study groups corresponded to the previously reported outcomes (i.e. increased rates of adverse outcomes in patients with AF, except for the rate of recurrent MI) (Supplementary material online, *Table S5*). Furthermore, compared to controls with history of AF, similar associated rates of bleeding and ischaemic stroke, and increased associated rates of mortality, and recurrent MI were observed for patients with first-time detected AF. Second, in stroke-naive patients with ACS (148 366 patients included), we identified no differences in the associated rate of ischaemic stroke as compared to the main results. Third, when restricting data to include patients from 2010 to 2018, 71 608 patients were enrolled with ACS (60 287 without AF; 8461 with history of AF; and 2860 with first-time detected AF). In adjusted analyses, the associated rates of ischaemic stroke were HR 1.24 (95% CI 1.16–1.32) for those with history of AF and HR 1.62 (95% CI 1.47–1.79) for those with first-time detected AF, as compared with those without AF. In the period from 2000 to 2009, the proportion of patients treated with OAC on admission was 32.3% for patients with history of AF. This proportion was 55.0% for the period 2010–18. Forth, when the study population was narrowed down to include patients with MI only (UAP excluded), results yielded similar findings to the main result (Supplementary material online, *Figure S4*). Fifth, 179 993 patients were admitted with ACS (149 635 without AF; 22 933 with history of AF; and 7425 with first-time detected AF). The in-hospital mortality was 9.5%, 15.9%, and 13.5% for patients without AF, history of AF, and first-time detected AF, respectively. In adjusted analysis, this corresponded to an odds ratio (OR) of 1.12 (95% CI 1.07–1.17) for patients with history of AF and OR 1.02 (95% CI 0.90–1.10) for patients with first-time detected AF. Finally, when patients with history of AF were considered the reference group, we found an associated higher rate of ischaemic stroke, though not statistically significant [HR 1.21 (95% CI 0.98–1.49)], for patients with first-time detected AF. Regarding mortality, first-time detected AF was associated with higher mortality [HR 1.22 (95% CI 1.14–1.30)] as compared with history of AF.

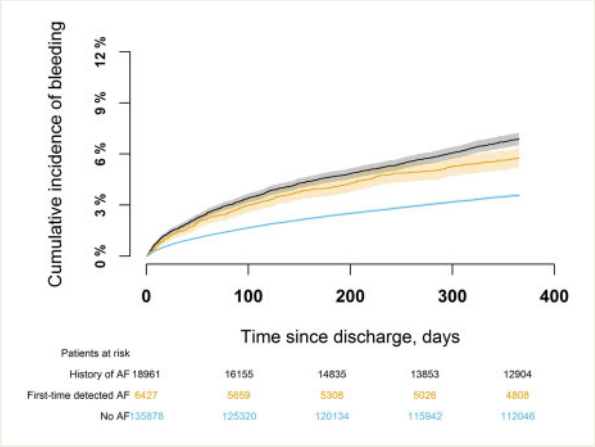


Figure 5 One-year cumulative incidence of bleeding. This figure shows the 1-year cumulative incidence of hospitalization for bleeding in patients with acute coronary syndrome and no atrial fibrillation, history of atrial fibrillation, and first-time detected atrial fibrillation.

Discussion

This nationwide observational study examined the association of ischaemic stroke and other adverse outcomes in patients presenting with first-time detected AF at ACS admission. First, our study showed that in patients with ACS, first-time detected AF appeared to be at least as strongly, or even higher, associated with the 1-year rates of ischaemic stroke, mortality, and bleeding as compared with patients with a history of AF. Second, similar practice patterns for prescription of antithrombotic therapy following ACS discharge were found in patients with history of AF and first-time detected AF, while <50% were treated with OAC therapy.

Table 2 Antithrombotic therapy following acute coronary syndrome in patients surviving 90 days post-discharge

	Patients with ACS not treated with PCI (n = 86 367)			Patients with ACS treated with PCI (n = 64 965)		
	No AF (n = 70 129)	History of AF (n = 11 879)	First-time detected AF (n = 4359)	No AF (n = 59 367)	History of AF (n = 3948)	First-time detected AF (n = 1650)
No antithrombotic therapy, n (%)	18 743 (26.7)	2081 (17.5)	762 (17.5)	3905 (6.6)	173 (4.4)	94 (5.8)
Aspirin only, n (%)	22 173 (31.6)	2648 (22.3)	1083 (24.9)	2502 (4.2)	127 (3.2)	71 (4.3)
$P2Y_{12}$-i only, n (%)	6863 (9.8)	738 (6.2)	238 (5.5)	8975 (15.2)	442 (11.2)	133 (8.1)
DAPT, n (%)	20 182 (28.8)	1569 (13.2)	709 (16.3)	42 652 (71.8)	1370 (34.7)	588 (35.6)
OAC only, n (%)	753 (1.1)	2143 (18.0)	638 (14.4)	117 (0.2)	177 (4.3)	69 (4.2)
OAC and aspirin/$P2Y_{12}$-i, n (%)	1051 (1.5)	1982 (16.7)	722 (16.6)	400 (0.7)	636 (15.3)	239 (14.5)
DAPT and OAC, n (%)	364 (0.5)	718 (6.0)	217 (5.0)	816 (1.4)	1023 (24.6)	456 (27.6)

ACS, acute coronary syndrome; AF, atrial fibrillation; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant therapy; PCI, percutaneous coronary intervention; $P2Y_{12}$-i, $P2Y_{12}$ inhibitors.

The relation between MI, new-onset AF, and stroke was evaluated in the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) from 2005.[3] In this randomized trial, new-onset AF carried an adjusted HR of 14.6 (95% CI 5.87–36.3) and 2.29 (95% CI 1.43–3.68) for stroke during the first 30 days after randomization and the whole duration of follow-up, respectively. Since the OPTIMAAL trial, other retrospective studies have investigated the prognostic impact of new AF in the setting of a MI.[1,2,5,9–11] Most studies, however, have been based on selected patient cohorts or extracted from data prior to the introduction of NOACs in standard AF management.[12] Recently, Fauchier *et al.*[11] published a French nationwide study on patients admitted with MI, demonstrating increased associated 1-year rates of ischaemic stroke in patients with new AF as compared with patients with history of AF. These results may partially be carried by the inclusion of in-hospital mortality, as patients in the French study were followed from the date of MI admission. Furthermore, Fauchier *et al.* did not examine antithrombotic treatment patterns, which may have varied between the two groups and affected the results. In adjusted analysis, we found that first-time detected AF was associated with a higher rate of stroke than history of AF, although this was non-significant. With contemporary data, from a nationwide cohort, our study is the first to describe similarly increased rates of ischaemic stroke in patients with history of and first-time detected AF following ACS discharge.

A multitude of studies has shown increased rates of mortality in patients with ACS and history of or first-time detected AF.[1,2,5–11] In line with these observations, our study suggests that first-time detected AF in ACS is at least as strongly associated with mortality as compared with patients with previously known AF.

The present study found mixed results regarding recurrent MI rates in the study groups. Initially, within 14 days of discharge, the AF groups showed lower MI rates compared to patients without AF. For the remaining follow-up, only including those surviving the acute phase of 14 days post-discharge, patients with first-time detected AF yielded an increased associated rate of MI, which is concurrent with previous studies.[1,9] Speculations on this finding include triple therapy for patients with AF; however, a higher burden of cardiovascular risk factors is also possible.

Some studies have investigated the incidence of bleeding in ACS survivors with concomitant first-time detected AF, which is of significant interest in relation to the antithrombotic treatment needed in this patient group. An American randomized controlled trial was conducted on patients with AF (paroxysmal, persistent, or permanent) who had successfully undergone PCI.[37] This trial showed increased rates of bleeding in patients treated with post-operative triple therapy compared with DAPT (26.9% vs. 15.4%). This study, however, did not differentiate between history of AF or first-time detected AF. In a Spanish cohort study enrolling 1361 patients with AF, Rivera-Caravaca *et al.*[38] found that initiation of warfarin in OAC-naive patients, as are those who typically develop AF in relation to ACS, was associated with the increased risk of bleeding, which can result in the cessation of antithrombotic medication and thus in the increased risk of new thromboembolic events. Our study found that the cumulative incidence of bleeding was 3.6%, 6.9%, and 5.7% for patients without AF and history of AF and first-time detected AF, respectively. These nationwide data thus present novel knowledge on this common complication to antithrombotic therapy in a relatively rare subgroup of patient.

In patients with first-time detected AF, 36.0% and 46.3% received OAC treatment within 90 days post-discharge in those treated without PCI and with PCI, while a similar antithrombotic treatment strategy was observed in patients with a history of AF, as 40.7% and 44.2% received OAC treatment in those without PCI and with PCI, respectively. This corresponds with previous findings in similar patient populations, taking into account that our study period went back to 2000 when treatment rates were lower than today, as also observed in our sensitivity analysis.[5,8–10] When determining the most appropriate antithrombotic therapy in patients with ACS and concomitant AF, it can be difficult to balance the risk of bleeding with the prevention of thrombosis.[20–22] This challenge is further reinforced by the lack of evidence on thromboembolic events and bleeding in patients with first-time detected AF. Our study yielded a somewhat similar practice pattern of antithrombotic treatment between patients with first-time detected AF and patients with history of AF. As the choice of antithrombotic treatment strategies are highly dependent on a series of patient's comorbid and clinical conditions, it is to be expected that the two AF groups, presenting with relatively similar baseline characteristics, are treated likewise. However, the apparent OAC undertreatment is still observed in both AF groups, which is consistent with previous studies from the Danish administrative registries.[39]

Furthermore, for patients treated with OAC across AF groups, we found no significant differences in the associated rate of ischaemic stroke and bleeding while we found a decreased associated rate of mortality, as compared with patients treated with antiplatelet therapy. However, the non-significant results for stroke and bleeding may be due to low power carried by few events. The results should be interpreted with caution in a clinical setting, as type II errors and confounding in observational studies cannot be excluded. Thus, the causal effect of antithrombotic therapy in patients with ACS and first-time detected AF warrants further investigation, and randomized trials examining the effects of antithrombotic therapy and management should be designed and performed.

Strengths and limitations

The main strength of this study is the completeness of data extracted from a nationwide cohort of patients with ACS. The registries have been extensively validated providing a valid source of data with minimal demographic sampling bias.[24,29,30] Furthermore, studies have validated the diagnosis codes of ACS, ischaemic stroke, AF, and bleeding with high PPV.[29,33,35]

Our study has some limitations. First, this is an observational study and, therefore, precludes that any causal inference can be made; thus, only associative conclusions can be drawn. This challenge is especially present when assessing outcomes associated with prescribed antithrombotic therapy, as the risk of residual confounding cannot be excluded. It further poses a challenge, as study groups present with significant differences in baseline characteristics, which is sought minimized by multivariable adjusted analyses. Second, data on critical clinical parameters such as electrocardiogram, echocardiography including data on atrial size (to help distinguish onset of AF), blood pressure, smoking, international normalized ratio, possible carotid stenosis, estimated glomerular filtration rate, smoking, and body mass index were not available. Likewise, data on type and duration of AF

(paroxysmal or chronic AF) and the accurate timing of AF onset (i.e. AF secondary to ACS or existing, undiagnosed AF) could not be determined. Third, bleeding could not be classified according to the International Society on Thrombosis and Hemostasis criteria nor the Thrombolysis in Myocardial Infarction bleeding criteria; however, the bleeding was of an admission-requiring magnitude. Finally, our study included patients hospitalized from 2000 to 2018, and while guidelines for treatment regimens for AF were drastically changed in 2010,[12] supplementary results yielded similar findings to the main analysis.

Conclusions

In ACS survivors, first-time detected AF appeared to be at least as strongly, or even higher, associated with the 1-year rates of ischaemic stroke, mortality, and bleeding as compared with patients with a history of AF. Practice patterns of antithrombotic therapy in patients with first-time detected AF were similar to patients with history of AF, while <50% were treated with OAC therapy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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