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Title page

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Abstract

Background: Many patients with atrial fibrillation have concomitant coronary artery disease with or without acute coronary syndromes and are in the need of additional antithrombotic therapy. There are few data on the long-term clinical outcome of atrial fibrillation patients with a history of acute coronary syndrome. This is a 2-year study of atrial fibrillation patients with or without a history of acute coronary syndromes.

Methods: Adults with newly diagnosed atrial fibrillation and ≥1 investigator-defined stroke risk factor were enrolled in GARFIELD-AF between Mar-2010 and Sep-2015. The association between prior acute coronary syndromes and long-term outcomes was determined using a Cox proportional hazards model, adjusting for baseline risk factors, OAC (oral anticoagulation) ± AP (antiplatelet therapy) and usual care.

Results: 10.5% of 39,679 patients had a history of acute coronary syndromes. At 2-year follow-up, patients with prior acute coronary syndromes had a higher adjusted risks of stroke/systemic embolism (hazard ratio: 1.39, 95% confidence interval: 1.08-1.78), major bleeding (1.30, 0.95 - 1.79), all-cause mortality (1.34, 1.21 -1.49), cardiovascular mortality (1.85, 1.51 -2.26) and new acute coronary syndromes (3.42, 2.62 -4.45). Comparing antithrombotic therapy in the acute coronary syndromes vs no acute coronary syndromes groups, most patients received OAC ± AP: 60.8% vs 66.1%, but AP therapy was more likely in the acute coronary syndromes group (68.1% vs 32.9%), either alone (34.9% vs 20.8%) or with OAC (33.2% vs 12.1%). Overall, 22.2% in the acute coronary syndromes group received dual AP therapy with (7.5%) or without OAC (14.7%). Among patients with moderate/high risk for stroke/systemic embolism, fewer in the acute coronary syndromes group received OAC with or without AP therapy (CHA_2DS_2-VASc 2: 52.1%

vs 64.7%; CHA_2DS_2-VASc ≥3: 62.0% vs 70.8%) and the majority with a HAS-BLED score ≥3 were on AP therapy (83.8% vs 65.6%).

Conclusions: In GARFIELD-AF, previous acute coronary syndromes are associated with worse 2-year outcomes and a greater likelihood of under-treatment with OAC, while two-thirds of patients receive AP therapy. Major bleeding was more common with previous acute coronary syndromes, even after adjusting for all risk factors.

Keywords

Anticoagulation; antiplatelet therapy; bleeding; mortality; stroke

Abbreviations

AC = anticoagulant, AP = antiplatelet, DAPT = dual antiplatelet therapy, OAC = oral anticoagulation, PCI = percutaneous coronary intervention, VKA = vitamin K antagonist

Introduction

Many patients with atrial fibrillation have concomitant coronary artery disease. Oral anticoagulation (OAC) is advised for prevention of stroke or systemic embolism[1, 2]. Coronary artery disease patients with atrial fibrillation also need antiplatelet (AP) therapy, either single AP therapy for stable coronary artery disease [3] or dual therapy (DAPT) with aspirin and a platelet P2Y12 blocker for previous acute coronary syndromes [4]. DAPT has become the standard of care for patients with acute coronary syndromes with or without coronary revascularization [5, 6]. In patients on DAPT and warfarin, the risk of bleeding increases two- to three-fold compared with warfarin alone [7-10].

In this report, we analysed primarily the outcomes over 2 years follow-up in patients with newly diagnosed atrial fibrillation with a moderate or high risk of stroke (according to CHA_2DS_2-VASc) who had acute coronary syndromes versus those without previous acute coronary syndromes. Secondly, we report on the choice of antithrombotic regimen and differences in outcomes between these regimens. The report is based on the data from Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF), a prospective non-interventional global registry of consecutive patients with newly diagnosed atrial fibrillation and ≥1 investigator-determined stroke risk factor [1].

Methods

Study design and participants

Men and women aged ≥18 years with atrial fibrillation diagnosed according to standard local procedures within the previous 6 weeks, and with ≥1 investigator-determined risk factor for stroke, were eligible for inclusion [2]. Risk factors were not pre-specified in the protocol nor were they limited to the components of existing risk stratification schemes. Patients with a transient reversible cause of atrial fibrillation and those for whom follow-up is not foreseen or possible were excluded. To minimize recruitment bias, investigator sites were selected randomly (except 18 sites, out of >1,000) and represent the different care settings in each participating country [1, 2]. Consecutive patients were enrolled prospectively and followed up at 4-month intervals up to 24 months.

The current analysis was conducted on patients enrolled prospectively between March 2010 and September 2015, in 35 countries, over 2-years follow-up. The data were extracted from the study database on 18th October 2017.

Ethics statement

Independent ethics committee and hospital-based institutional review board approvals were obtained, as necessary, for the registry protocol. Additional approvals were obtained from individual study sites. The registry is being conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation Good Pharmacoepidemiological and Clinical Practice Guidelines. Written

informed consent was obtained from all study participants. Confidentiality and anonymity of all enrolled patients are maintained.

Data collection and quality control

Patient demographics, medical history, and antithrombotic treatment were recorded at baseline; clinical outcomes were recorded during follow-up [2]. Baseline data on components of the CHA_2DS_2-VASc [11] and HAS-BLED [12] risk stratification schemes were collected to evaluate stroke and bleeding risks retrospectively. HAS-BLED scores were calculated excluding fluctuations in international normalized ratio.

GARFIELD-AF data are captured using an electronic case report form designed by Dendrite Clinical Systems Ltd (Henley-on-Thames, UK). Oversight of operations and data management are performed by the coordinating center Thrombosis Research Institute TRI (London, UK), with support from Quintiles (Durham, NC, USA), The University of Birmingham, Department of Primary Care Clinical Sciences (Birmingham, UK), Thrombosis Research Group – Brigham and Women's Hospital (Boston, MA, USA), and AIXIAL (Paris, France). Data management and quality assurance processes have been described previously [13].

Study outcomes and definitions

The acute coronary syndromes group included those patients with a history and/or current myocardial infarction or unstable angina. Patients without acute coronary syndromes included patients with stable angina as well as some who may have had a vascular stent for coronary or peripheral vascular disease.

Clinical endpoints of the study were: i) stroke/systemic embolism, ii) major bleeding, iii) all-cause mortality, iv) cardiovascular mortality, v) non-cardiovascular mortality, vi) new acute coronary syndromes, and vii) new or worsening heart failure at 2-year follow-up.

Oral anticoagulants (OAC) included vitamin K antagonists (VKAs), direct factor Xa inhibitors, and direct thrombin inhibitors. Antiplatelet (AP) therapy included: aspirin, adenosine diphosphate receptor antagonists (P2Y12 inhibitors) or both.

Vascular disease included peripheral artery disease or coronary artery disease with acute coronary syndromes. Chronic kidney disease was classified according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines (NKF KDOQI) [14] into moderate-to-severe (NKF KDOQI stages 3–5) and mild or none (none, NKF KDOQI stages 1 and 2).

Statistical analysis

Baseline patient characteristics and clinical outcomes were compared between patients with or without a history of acute coronary syndromes. Continuous variables are expressed as median (interquartile range, IQR), and categorical variables as frequency and percentage. Patients with missing values were not removed. Occurrence of adverse clinical outcomes is described using the number (%) of events, person-time event rate (per 100 person-years), and 95% confidence interval (CI). We estimated person-year rates using a Poisson model, with the number of events as the dependent variable and the log of person-time as an offset. Only the first occurrence of each event was taken into account.

Multiple imputation was employed to account for missing information, by using logistic and the chained equations method, which assumes an arbitrary missing pattern and joint distributions within the data [15]. The variables included in the imputation were: cohort, region, age, sex, race, hypertension, baseline measures of diastolic blood pressure, systolic blood pressure and pulse, heavy alcohol use, hypercholesterolaemia, diabetes, dementia, hyperthyroidism, hypothyroidism, acute coronary syndromes, cirrhosis, carotid occlusive disease, coronary artery bypass graft, stent, pulmonary embolism or deep vein thrombosis, stroke or transient ischemic attack or systemic embolism, moderate-severe chronic kidney disease, history of bleeding, type of atrial fibrillation, vascular disease, coronary artery disease, peripheral artery disease, heart failure, OAC use and a history of usual care (with statins, calcium channel blocker, beta blockers, ACE inhibitors, angiotensin receptor blockers).

Five completed data sets were created. These five data sets were used for a Cox proportional hazards model to assess the effects of acute coronary syndromes on clinical outcomes at 2 years after atrial fibrillation diagnosis. Hazard ratios (HRs) and 95% CIs for clinical outcomes were adjusted for the following risk factors at baseline: age (using a spline at three points), gender, race, smoking (history or current), alcohol consumption (heavy or not heavy), diabetes, hypertension, previous stroke/transient ischemic attack/systemic embolism, history of bleeding, type of atrial fibrillation, heart failure, moderate-to-severe chronic kidney disease, stroke prophylaxis with VKA, non-VKA OACs (NOACs), AP or no treatment and a history of usual care (with statins, calcium channel blocker, beta blockers, ACE inhibitors, angiotensin receptor blockers). Proportional hazards for acute coronary syndromes were

evaluated with the interaction of acute coronary syndromes by time and showed no evidence that acute coronary syndromes deviated from the proportional hazards assumption.

Data analysis was performed with SAS Enterprise guide version 7.15 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline patient characteristics

Of the 39,871 enrolled patients, 4,152 (10.5%) had a positive history and 35,527 (89.1%) had a negative history of acute coronary syndromes; 192 (0.5%) with missing data for this variable were excluded. Baseline characteristics of patients stratified by acute coronary syndromes are shown in Table 1. Differences between patients with the acute coronary syndromes and those without were statistically significant for all variables, except for use of angiotensin receptor blockers. Patients with a history of acute coronary syndromes were older and were predominantly male. The acute coronary syndromes group had a higher prevalence of heart failure coronary artery bypass graft, hypercholesterolemia, stenting, kidney disease and diabetes. Furthermore, acute coronary syndromes patients were more likely to be ex-smokers. The acute coronary syndromes group had higher risks of stroke and bleeding than the group without acute coronary syndromes.. The difference in prevalence of the factors likely to impact the risk of bleeding in both groups are outlined in Supplementary Table S1.

Antithrombotic treatment at baseline

Most patients received OAC with or without AP therapy for stroke prevention at enrolment, including 60.8% with a history of acute coronary syndromes and 66.1% of patients without . AP therapy was more likely in the acute coronary syndromes group (68.1% vs 32.9%), either alone AP without OAC (34.9% vs 20.8%) or in combination with OAC (33.2% vs 12.1%). Overall, 17.8% in the acute coronary syndromes group [and 1.9% in the group without acute coronary syndrome] received DAPT with (5.3% [0.6%]) or without OAC (12.5% [1.3%]) (Supplementary Table S2).

Among patients with moderate or high risk for stroke/systemic embolism, fewer patients in the acute coronary syndromes group than the group without acute coronary syndromes group received OAC with or without AP therapy (CHA_2DS_2-VASc score 2: 52.1% vs 64.7%; CHA_2DS_2-VASc score ≥3: 62.0% vs 70.8%) (Fig 1a).

Fig 1b shows the antithrombotics prescribed among patients with a CHA_2DS_2-VASc ≥2 (i.e. n = 2966 [61.0%] acute coronary syndromes and n = 20,471 [56.6%] without acute coronary syndromes), stratified by bleeding risk. As the HAS-BLED increased from a score of 0/1 to a score of ≥3, the proportion of patients on any AP therapy rose (from 44.4% to 83.8% [for acute coronary syndromes] and 10.5% to 65.6% [for those without acute coronary syndromes]). With this increase in HAS-BLED score, the number of patients on combined OAC + AP therapy also rose from 20.8% to 34.2% [for acute coronary syndromes] and 3.9% to 28.4% [without acute coronary syndromes], respectively.

Common reasons for not giving OAC to patients with a CHA_2DS_2-VASc score of ≥2 and a history of acute coronary syndromes included: i) the patient was taking AP therapy and ii) bleeding risk and iii) patient's refusal. For patients without a history of acute coronary syndromes and a CHA_2DS_2-VASc score of ≥2, the main reason provided by physicians was perceived low risk of stroke; (Table 2).

Clinical outcomes over 2-year follow-up and the impact of acute coronary syndromes

Over the 2-years of follow-up, the incidence of adverse clinical outcomes is given in Table 3 and Supplementary Table S3. In table 4 the breakdown of stroke (not systemic embolism), bleeding and mortality are given.

After adjustment for baseline risk factors, antithrombotics at enrolment and history of usual care (with statins, calcium channel blocker, beta blockers, ACE inhibitors, angiotensin receptor blockers), prior acute coronary syndromes was associated with higher risk of stroke/systemic embolism (hazard ratio [HR]: 1.39, 95% confidence interval: 1.08 to 1.78), major bleeding (1.30, 0.95 to 1.79), all-cause mortality (1.34, 1.21 to 1.49), cardiovascular mortality (1.85, 1.51 to 2.26), new acute coronary syndromes (3.42, 2.62 to 4.45), and new or worsening heart failure (1.39, 1.12 to 1.71)(Fig 2). There were no statistically significant differences in non-cardiovascular mortality (HR: 0.99, 0.77 to 1.28), between patients with or without a history of acute coronary syndromes (Fig 2).

Outcomes stratified by antithrombotic regimen

A secondary analysis evaluating the unadjusted rates of outcomes in patients stratified by antithrombotic regimens is presented in Supplementary Table S4 and figure S1. Overall, mortality was highest in acute coronary syndromes patients off OAC and nearly double than with OAC. These figures are much lower in the group without acute coronary syndromes. Strokes were highest in acute coronary syndromes patients off OAC, where there were no differences without acute coronary syndromes. Major bleeding rates were low in almost all subgroups, irrespective of acute coronary syndromes or not.

Discussion

This analysis of long-term outcomes shows that patients with newly diagnosed atrial fibrillation and a history of acute coronary syndromes had worse long-term outcomes: higher all-cause mortality, cardiovascular mortality, stroke/systemic embolism, recurrent acute coronary syndromes and heart failure, as opposed to those without a history of acute coronary syndromes. They were less likely to receive OAC despite their higher stroke-risk profile, and were more often treated with AP alone, which is against current atrial fibrillation guideline recommendations [16]. There was more major bleeding in acute coronary syndromes patients and this could be related to the higher median HAS-BLED score in these patients relative to those without acute coronary syndromes.

Clinical implications

Concomitant coronary artery disease is seen in up to 30% of patients with atrial fibrillation [17]. Since lifelong AP therapy is mandated in chronic coronary disease [3], most of the

patients with atrial fibrillation and comorbid coronary disease are on both AP and OAC, which is associated with increased bleeding risk [7-10]. Acute coronary syndromes patients presented with a higher bleeding risk and patients with a higher bleeding risk have factors that also increase their stroke and mortality risk. Overall, OAC was low in our acute coronary syndromes patients (61%), which may also have contributed to their increased stroke and death risk. Similar results on underuse of OAC have been observed in Swedish patients with atrial fibrillation and comorbid heart failure [18].

Other atrial fibrillation registries have seen a much higher use of OAC, but did not correct for prior acute coronary syndromes [19]. A reason for OAC under-treatment may be the perceived benefit of AP alone in stroke prevention in atrial fibrillation, which may seem appropriate for a patient with coronary artery disease and atrial fibrillation. However, trial evidence suggests that AP therapy alone is not effective for stroke prevention in atrial fibrillation and does not lead to a reduction in bleeding [20], as suggested also in the current analysis. Combining OAC and AP therapies after acute coronary syndromes in atrial fibrillation is only mandated for a maximum period of 1 year by current atrial fibrillation guidelines and recommendations. Patients with a very high risk for stent thrombosis such as those with multiple stents in multiple vessels would be excluded from this recommendation [16, 21, 22]. Several randomized trials have addressed the issue of DAPT in anticoagulated atrial fibrillation patients undergoing PCI (with or without acute coronary syndromes) and showed can be diminished by dropping aspirin from triple therapy in the WOEST trial[23] or dropping aspirin, and changing warfarin to a non-VKA anticoagulation (NOAC) in the PIONEER AF-PCI, RE-DUAL PCI and AUGUSTUS studies.[24-26] The findings from these studies support also current recommendations

to omit any AP one year after the onset of acute coronary syndromes in patients with atrial fibrillation.

Limitations

Firstly, only patients with newly diagnosed atrial fibrillation (less than 6 weeks' duration) and a perceived increased risk of stroke were included. These restrictions may have skewed the results on the use of AP alone without OAC. Secondly, although outcomes were adjusted for many baseline differences between patients with or without an acute coronary syndromes history, there may have been unknown factors that we have not accounted for. Thirdly, the acute coronary syndromes population represents a mix of patients receiving various treatment strategies for acute coronary syndromes, including 39.5% patients who received a stent; however, we did not collect information on the timing of acute coronary syndromes prior to inclusion in the GARFIELD-AF registry. In this study, patient numbers were too small to analyse the differences in outcomes between patients on AP monotherapy and DAPT.

Conclusion

In this large, global, prospective GARFIELD-AF registry, patients with a history of acute coronary syndromes had higher rates of mortality, stroke/systemic embolism, recurrent acute coronary syndromes, and major bleeding and a greater likelihood of under-treatment with OAC. Overall, patients received more often received AP alone in comparison to patients without a history of acute coronary syndromes. Whether the increased risk of bleeding in acute coronary syndromes patients is causally related to the high use of AP, or is a reflection of the predominance of other factors in acute coronary syndromes patients (including increasing age and moderate-to-severe chronic kidney disease), remains unclear.

Perspectives

To diminish the risk of unfavorable outcomes in patients with atrial fibrillation and previous acute coronary syndromes, NOAC use seems favorable, given their better safety profile and similarly, if not better, efficacy in prevention of stroke and possibly mortality. However, this should be tested in a prospective trial. Furthermore, physicians should be more convinced to avoid AP monotherapy for stroke prevention in atrial fibrillation in general, and in patients with prior acute coronary syndromes in particular.. Finally, another option could be to omit aspirin in stented atrial fibrillation patients, which has led to a substantial reduction in bleeding without an increase in ischemic events.

Contributors

FWAV, GA, JPB, AJC, DAF, SZG, SG, SH, GK, AGGT and AKK contributed to the study design. DA, JPC, PJ and JS contributed to data acquisition and contributed to data interpretation. LI analyzed the data. FWAV drafted the report. All authors critically reviewed the report and approved the final manuscript.

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Figure Legends:

Fig 1. Antithrombotic therapy received at baseline by patients with or without a history of acute coronary syndromes, according to: (a) CHA_2DS_2-VASc score and (b) HAS-BLED score in patients with a CHA_2DS_2-VASc score ≥ 2. (Color)

AP, antiplatelet; DTI, direct thrombin inhibitor; FXaI, factor Xa inhibitor; VKA, vitamin K antagonist.

Fig 2. Adjusted hazard ratios for outcomes over 2-year follow-up for patients with versus without a history of acute coronary syndromes (Color)

ACS, acute coronary syndromes; SE, systemic embolism; HF, Heart failure; CAB, Calcium (Ca) channel blockers; BB, Beta blocker; ACE, Ace inhibitor; ARB, Angiotensin receptor blocker

Table 1. Demographics, clinical characteristics, and care settings of patients with or without a history of acute coronary syndromes

Variable	Acute coronary syndromes * (N=4,152)	No Acute coronary syndromes (N=35,527)
Male, n/n (%)	2,789 (67.2)	19,332 (54.4)
Age at atrial fibrillation diagnosis (years), median (IQR)	73 (65 to 79)	71 (62 to 78)
Race, n/n (%)		
Afro-Caribbean	10 (0.2)	115 (0.3)
Asian (not Chinese)	543 (13.1)	8,159 (23.0)
Caucasian	2,839 (68.4)	21,718 (61.1)
Chinese	411 (9.9)	1,690 (4.8)
Hispanic/Latino	221 (5.3)	2,421 (6.8)
Mixed/other	60 (1.4)	519 (1.5)
Unwilling to declare/not recorded	68 (1.6)	905 (2.5)
BMI (kg/m²)		
Median (IQR)	27 (24 to 31)[a]	27 (24 to 31)[b]
Medical history, n/n (%)		
Heart failure	1,451 (34.9)	7,500 (21.1)
Carotid occlusive disease	266 (6.5)	932 (2.7)
Coronary artery bypass graft	747 (19.3)[c]	419 (1.2)[d]
History of hypertension	3,400 (82.0)[e]	26,958 (76.1)[f]
Hypercholesterolemia	2,647 (65.3)[g]	13,288 (38.5)[h]
Vascular disease	4,126 (99.4)[i]	1,685 (4.7)

Stroke/transient ischemic attack	633 (15.2)[j]	4022 (11.3)[k]
History of bleeding	171 (4.1)[l]	870 (2.5)[m]
Moderate-to-severe chronic kidney disease	695 (16.7)	3,386 (9.5)
Diabetes mellitus	1,330 (32.0)	7,312 (20.6)
Smoking, n/n (%)		
Non-smoker	2,067 (53.9)[p]	21,593 (66.7)[q]
Ex-smoker	1,337 (34.9)	7,288 (22.5)
Current smoker	428 (11.2)	3,497 (10.8)
CHA_2DS_2-VASc score, median (IQR)	4.0 (3.0 to 5.0)[r]	3.0 (2.0 to 4.0)[s]
HAS-BLED score, median (IQR)	2.0 (1.0 to 2.0)[t]	1.0 (1.0 to 2.0)[u]
Stenting	1,628 (39.5)[n]	946 (2.7)[o]
Type of stent (not mutually exclusive)		
Bare metal coronary stent	533 (32.2)	253 (23.8)
Drug eluting coronary stent	655 (39.5)	324 (30.5)
Carotid stent	13 (0.8)	39 (3.7)
Unknown	414 (25.0)	295 (27.7)
Usual care		
Statin	3,169 (76.3)	12,222 (34.4)
Calcium channel blockers	1,036 (25.0)	8,276 (23.3)
Beta blockers	2,363 (56.9)	15006 (42.2)
ACE inhibitor	1,947 (46.9)	10,652 (30.0)
Angiotensin receptor blocker	993 (23.9)	8,455 (23.8)

Specialty at diagnosis of atrial fibrillation, n/n (%)		
Cardiology	2,986 (71.9)	22,706 (63.9)
Geriatrics	8 (0.2)	146 (0.4)
Internal medicine	648 (15.6)	6,619 (18.6)
Neurology	43 (1.0)	672 (1.9)
Primary care/general practice	467 (11.2)	5,384 (15.2)
Care setting at diagnosis of atrial fibrillation, n (%)		
Hospital	2,620 (63.1)	20,631 (58.1)
Office	1,026 (24.7)	10,567 (29.7)
Anticoagulation clinic	39 (0.9)	267 (0.8)
Emergency room	467 (11.2)	4,062 (11.4)

; IQR, interquartile range; LVEF, left ventricular ejection fraction;

Percentages in the table refer to complete data only. Missing data: a = 832; b = 7,778; c = 278; d = 318; e = 5; f = 83; g = 98; h = 975; i = 2; j = 11; k = 90; l = 21; m = 107; n = 30; o = 118; p = 320; q = 3,149; r = 63; s = 822; t = 1,149; u = 10,463

* P value < 0.001 (acute coronary syndromes vs non acute coronary syndromes) for all patient characteristic and medical history variables except for body mass index (p=0.005), use of beta-blockers (p=0.02) and angiotensin receptor blockers (p=0.9)

Table 2. Main reasons why patients with a CHA_2DS_2-VASc score of ≥2 with or without a history of acute coronary syndromes were not on anticoagulants at baseline

Reason	Acute coronary syndromes (n=1,026) n (%)	No Acute coronary syndromes (n=6,209) n (%)
Taking AP therapy for another medical condition	211 (20.6)	316 (5.1)
Patient refusal	122 (11.9)	653 (10.5)
Previous bleeding event	21 (2.0)	146 (2.4)
Contraindicated or cautioned for use with VKA or AC	21 (2.0)	39 (0.6)
Other	167 (16.3)	1336 (21.5)
Unknown	191 (18.6)	1605 (25.8)
Physician's choice*	293 (28.6)	2114 (28.9)
Bleeding risk	130 (12.7)	541 (8.7)
Concern over patient compliance	52 (5.1)	310 (5.0)
Guideline recommendation	18 (1.8)	224 (3.6)
Fall risk	33 (3.2)	305 (4.9)
Low risk of stroke	60 (5.8)	734 (11.8)

*Percentages in each category under physician's choice are calculated with the available (non-missing) data of the variable as denominator. AC, anticoagulant; VKA, vitamin K antagonist.

Table 3. Rates of adverse clinical outcomes over 2-year follow-up in patients with or without a history of acute coronary syndromes

	Acute Coronary Syndrome (n=4,152)		No Acute Coronary Syndrome (n=35,527)	
	n (%)	**Rate (95% CI) per 100 person-years**	**n (%)**	**Rate (95% CI), per 100 person-years**
Stroke/systemic embolism	141 (3.4)	1.93 (1.64 to 2.28)	709 (2.0)	1.11 (1.03 to 1.19)
Major bleeding	85 (2.1)	1.16 (0.94 to 1.43)	421 (1.2)	0.66 (0.60 to 0.72)
All-cause mortality	472 (11.4)	6.38 (5.83 to 6.98)	2269 (6.4)	3.52 (3.38 to 3.67)
Cardiovascular mortality	232 (5.6)	3.13 (2.76 to 3.56)	773 (2.2)	1.20 (1.12 to 1.29)
Non-cardiovascular mortality	138 (3.3)	1.86 (1.58 to 2.20)	896 (2.5)	1.39 (1.30 to 1.48)
Undetermined cause of mortality	102 (2.5)	1.38 (1.14 to 1.67)	600 (1.7)	0.93 (0.86 to 1.01)
New acute coronary syndrome	161 (3.9)	2.22 (1.90 to 2.59)	314 (0.9)	0.49 (0.44 to 0.55)
New or worsening heart failure	124 (3.0)	1.72 (1.44 to 2.05)	618 (1.7)	0.97 (0.90 to 1.05)

Table 4. Clinical outcomes over 2-year follow-up in patients with or without a history of acute coronary syndromes

	Acute coronary syndromes (n=4,152)	**No Acute coronary syndromes (n=35,527)**
Stroke (not including systemic embolism)*	124	638
Primary ischemic stroke	89 (71.8)	440 (69.0)
Secondary hemorrhagic ischemic	6 (4.8)	25 (3.9)
Primary intracerebral hemorrhage	13 (10.5)	78 (12.2)
Intracerebral	7 (5.7)	53 (8.3)
Subarachnoid	2 (1.6)	12 (1.9)
Intraventricular	3 (2.4)	9 (1.4)
Subdural hematoma	1 (0.8)	2 (0.3)
Epidural hematoma		1 (0.2)
Undetermined	22 (17.7)	120 (18.8)
Bleeding events (not including minor bleeds)*	147	837
Severity of bleed		
Non-major clinically relevant	62 (42.2)	416 (49.7)
Major	85 (57.8)	421 (50.3)
Fatal†	6 (4.1)	56 (6.7)
All-cause death	472	2269
Cardiovascular causes	232 (49.2)	773 (34.1)

Congestive heart failure	74 (31.9)	253 (32.7)
Sudden/unwitnessed death	45 (19.4)	125 (16.2)
Acute coronary syndromes	36 (15.5)	78 (10.1)
Ischemic stroke	19 (8.2)	98 (12.7)
Other‡	58 (25.0)	219 (28.3)
Non-cardiovascular causes	138 (29.2)	896 (39.5)
Malignancy	41 (29.7)	274 (30.6)
Respiratory failure	23 (16.7)	174 (19.4)
Infection/sepsis	30 (21.7)	179 (20.0)
Suicide	3 (0.2)	0
Other§	41 (29.7)	269 (30.2)
Undetermined causes	92 (21.9)	611 (26.3)

*Only the first occurrence was taken into account.

†Fatal bleed is defined as major bleed with occurrence of death

‡Includes deaths due to intracranial hemorrhage, atherosclerotic vascular disease, dysrhythmia, pulmonary embolism, and hemorrhagic stroke.

§Includes deaths due to accidents/trauma, renal disease, and liver disease.

Clinical Significance

- The GARFIELD-AF registry shows that patients with newly diagnosed AF and a history of ACS had a worse long-term outcomes and were less likely to receive oral anticoagulation.

- ACS patients presented with a higher bleeding risk and factors that also increase stroke and mortality risk.

- These data support the current recommendations to omit any antiplatelet therapy one year after the onset of ACS in patients with AF.

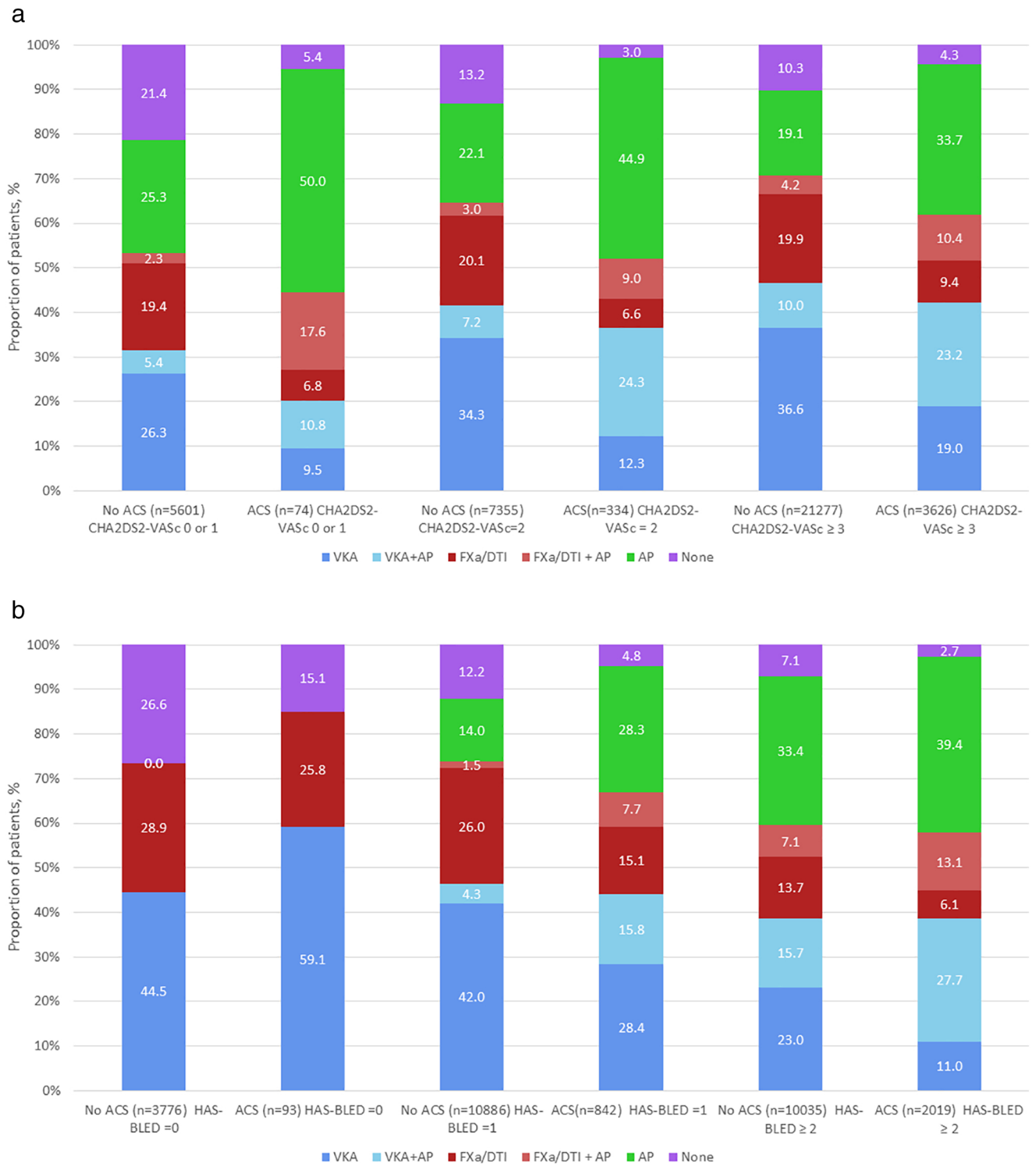
a
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Proportion of patients, %
21.4
25.3
2.3
19.4
5.4
26.3
5.4
50.0
17.6
6.8
10.8
9.5
13.2
22.1
3.0
20.1
7.2
34.3
3.0
44.9
9.0
6.6
24.3
12.3
10.3
19.1
4.2
19.9
10.0
36.6
4.3
33.7
10.4
9.4
23.2
19.0
No ACS (n=5601) CHA2DS2-VASc 0 or 1
ACS (n=74) CHA2DS2-VASc 0 or 1
No ACS (n=7355) CHA2DS2-VASc=2
ACS(n=334) CHA2DS2-VASc = 2
No ACS (n=21277) CHA2DS2-VASc ≥ 3
ACS (n=3626) CHA2DS2-VASc ≥ 3
VKA
VKA+AP
FXa/DTI
FXa/DTI + AP
AP
None
b
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Proportion of patients, %
26.6
0.0
28.9
44.5
15.1
25.8
59.1
12.2
14.0
1.5
26.0
4.3
42.0
4.8
28.3
7.7
15.1
15.8
28.4
7.1
33.4
7.1
13.7
15.7
23.0
2.7
39.4
13.1
6.1
27.7
11.0
No ACS (n=3776) HAS-BLED =0
ACS (n=93) HAS-BLED =0
No ACS (n=10886) HAS-BLED =1
ACS(n=842) HAS-BLED =1
No ACS (n=10035) HAS-BLED ≥ 2
ACS (n=2019) HAS-BLED ≥ 2
VKA
VKA+AP
FXa/DTI
FXa/DTI + AP
AP
None

Figure 1

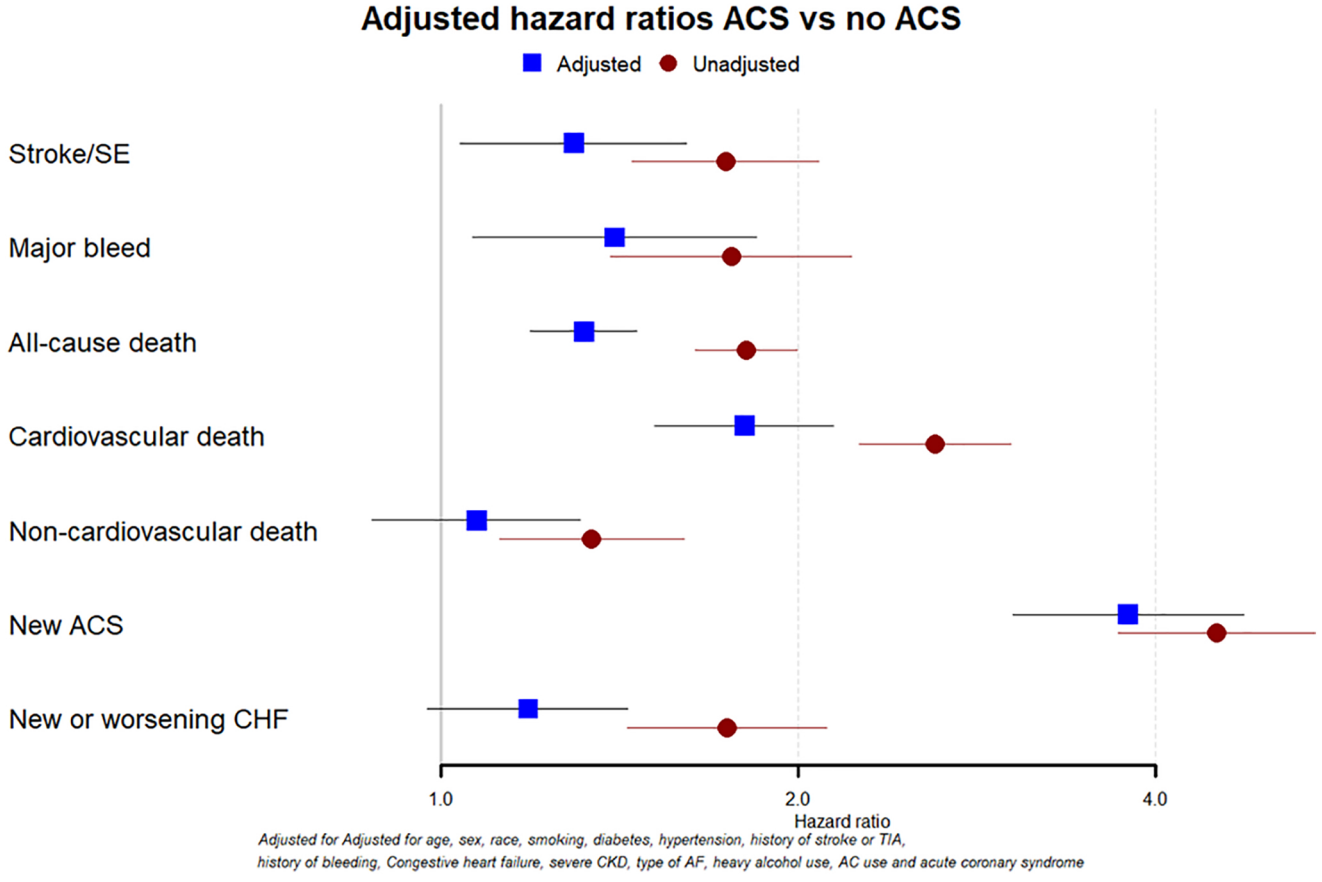
Adjusted hazard ratios ACS vs no ACS
Adjusted
Unadjusted
Stroke/SE
Major bleed
All-cause death
Cardiovascular death
Non-cardiovascular death
New ACS
New or worsening CHF
1.0
2.0
4.0
Hazard ratio
Adjusted for Adjusted for age, sex, race, smoking, diabetes, hypertension, history of stroke or TIA,
history of bleeding, Congestive heart failure, severe CKD, type of AF, heavy alcohol use, AC use and acute coronary syndrome

Figure 2