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Impact of known or new-onset atrial fibrillation on 2-year cardiovascular event rate in patients with acute coronary syndromes: results from the prospective EPICOR Registry

--Manuscript Draft--

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Abstract:	Background: Atrial fibrillation (AF) is associated with increased morbidity in acute coronary syndromes (ACS) patients, but impact on outcomes beyond 1-year is unclear. Methods: This was a post-hoc analysis from the long-tErm follow-uP of antithrombotic management patterns In acute CORonary syndrome patients (EPICOR) registry (NCT01171404), a prospective, observational study conducted in Europe and Latin America, which enrolled ACS survivors at discharge. Antithrombotic management patterns, mortality, a composite endpoint of death/new non-fatal myocardial infarction/stroke, and bleeding events were assessed after 2-years of follow-up in patients ±AF. Results: Of 10,568 patients enrolled, 397 (4.7%) had prior AF and 382 (3.6%) new-onset AF during index hospitalization. Fewer patients with AF underwent PCI (52.1% vs. 66.6%, p < 0.0001). At discharge, fewer AF patients received DAPT (71.6% vs. 89.5%, p < 0.0001); oral anticoagulant (OAC) use was higher in AF patients but still infrequent (35.0% vs. 2.5%, p < 0.0001). Use of DAPT and OAC declined over follow-up with >50% of all AF/no-AF patients remaining on DAPT (55.6% vs. 60.6%), and 23.3% (new-onset AF) to 42.1% (prior AF) on OAC at 2-years. At 2-years, mortality, composite endpoint and bleeding rates were higher in AF patients (all p < 0.0001) as compared to patients without AF. On multivariable analysis, risk of mortality or composite endpoint was significant for prior AF (p = 0.003, p = 0.001) but not new-onset AF (p = 0.88, p = 0.92).

	Conclusions: ACS patients with AF represent a high-risk group with increased event rates during long-term follow-up. Prior AF is an independent predictor of mortality and/or ischaemic events at 2-years. Use of anticoagulants in AF after ACS is still suboptimal.

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Dear Dr Vrints / Editor-in-Chief
European Heart Journal: Acute Cardiovascular Care

On behalf of all authors, and in response to your invitation of February 12, 2018, I am pleased to submit this revised article entitled, '**Impact of known or new-onset atrial fibrillation on 2-year cardiovascular event rate in patients with acute coronary syndromes: results from the prospective EPICOR Registry**', to be considered for publication in *European Heart Journal: Acute Cardiovascular Care*. We have found the Editor's and Reviewers comments very helpful and our detailed responses to each specific point are shown in bold below.

Reviewer's Comments

Reviewer #2

Reviewer #2: After the revision, the manuscript has improved.

There are still some parts that needs language editing [eg. in the abstract: At 2-years, mortality, composite endpoint and bleeding rates were higher in AF patients (all p < 0.0001)] should be followed by "as compared with patients without AF.

Response: done

Finally, a composite endpoint is not the sum of the components but rather the first occurrence of any of the components. This is why the correct wording logic is OR, not AND. A simple demonstration is exactly in Figure 2: the composite rate is always lower than the sum of the individual components (eg. prior AF composite rate at 2 yrs is 18.7% but the sum of the components is 15.1 +3.2 + 1.0= 19.3). Another hint is that in every RCT that used this composite endpoint reported in the NEJM trial (CURE, TRITON, PEGASUS, PLATO, TRACER, TRA2P, all CHAMPION trials, etc) the wording logic in the abstract is always death, MI, OR stroke. Therefore I invite the author to reconsider their disagreement.

Resonse: We agree and have changed the wording accordingly to or throughout the manuscript.

The authors again thank the reviewers for their thorough review. I can confirm all listed authors have contributed and approved this revised version.

We look forward to hearing from you.

Yours Sincerely

Uwe Zeymer

Impact of known or new-onset atrial fibrillation on 2-year cardiovascular event rate in patients with acute coronary syndromes: results from the prospective EPICOR Registry

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[II]This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Total word count: 3316 excluding references and tables/figures

Abstract

Background: Atrial fibrillation (AF) is associated with increased morbidity in acute coronary syndromes (ACS) patients, but impact on outcomes beyond 1-year is unclear.

Methods: This was a post-hoc analysis from the long-tErm follow-uP of antithrombotic management patterns In acute CORonary syndrome patients (EPICOR) registry (NCT01171404), a prospective, observational study conducted in Europe and Latin America, which enrolled ACS survivors at discharge. Antithrombotic management patterns, mortality, a composite endpoint of death/new non-fatal myocardial infarction/stroke, and bleeding events were assessed after 2-years of follow-up in patients ±AF.

Results: Of 10,568 patients enrolled, 397 (4.7%) had prior AF and 382 (3.6%) new-onset AF during index hospitalization. Fewer patients with AF underwent PCI (52.1% vs. 66.6%, $p < 0.0001$). At discharge, fewer AF patients received DAPT (71.6% vs. 89.5%, $p < 0.0001$); oral anticoagulant (OAC) use was higher in AF patients but still infrequent (35.0% vs. 2.5%, $p < 0.0001$). Use of DAPT and OAC declined over follow-up with >50% of all AF/no-AF patients remaining on DAPT (55.6% vs. 60.6%), and 23.3% (new-onset AF) to 42.1% (prior AF) on OAC at 2-years. At 2-years, mortality, composite endpoint and bleeding rates were higher in AF patients (all $p < 0.0001$) as compared to patients without AF. On multivariable analysis, risk of mortality or composite endpoint was significant for prior AF ($p = 0.003$, $p = 0.001$) but not new-onset AF ($p = 0.88$, $p = 0.92$).

Conclusions: ACS patients with AF represent a high-risk group with increased event rates during long-term follow-up. Prior AF is an independent predictor of

mortality and/or ischaemic events at 2-years. Use of anticoagulants in AF after ACS is still suboptimal.

Keywords: acute coronary syndromes, antithrombotic therapy, atrial fibrillation, registry

Introduction

Known or new-onset atrial fibrillation (AF) is a relatively common comorbid condition or complication in patients with acute coronary syndromes (ACS), and is observed in 4–12% of ACS patients.[1, 2] The existence of prior AF is associated with increased morbidity and mortality on top of the risk incurred by ACS, both in hospital and up to 1-year post-discharge,[2-4] but any impact on outcomes beyond 1-year has not yet been prospectively elucidated.[1]

It should perhaps be noted that this study was performed before many of the newer and more effective antithrombotic agents became available e.g., ticagrelor. In 2006, ESC guidelines recommended antithrombotic therapy to prevent thromboembolism for most patients with AF, specifically, anticoagulation with a vitamin K antagonist was recommended for patients with more than 1 moderate risk factor, combined with low-dose aspirin and/or clopidogrel following percutaneous coronary intervention (PCI).[5] In contrast, recent guidelines recommend revascularization therapies and use of intensive antithrombotic therapies in AF patients, including triple therapy with a combination of dual antiplatelet therapy (DAPT) and an oral anticoagulant, particularly those with a CHA_2DS_2-VASc (Cardiac failure, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled] – VAScular disease, Age 65–74 and Sex category [female]) score of ≥2, with the key aim of stroke prevention.[6-9] However, the risk of bleeding is increased considerably with triple therapy compared with DAPT.[10, 11] Since both ischaemic and bleeding complications are associated with impaired prognosis, the difficulty lies in achieving a balance between reducing the risk of cardiovascular events and increasing the risk

of bleeding, with consideration given to multiple factors, including individual patient characteristics, choice and duration of therapy and, where relevant, choice of stent.

The long-tErm follow-uP of antithrombotic management patterns In acute CORonary syndrome patients (EPICOR) registry (NCT01171404) was primarily designed to describe the frequency of different antithrombotic management patterns (AMPs) in a real-life setting in patients surviving hospitalization for an ACS, with a 2-year follow-up period.[12] The aim of this post-hoc analysis was to determine AMPs and long-term (2-year) post-discharge mortality and cardiovascular event rates in ACS patients with or without AF, including known prior AF or new-onset, in-hospital AF, in a real-life setting.

Methods

Study design

EPICOR was a multinational, observational, prospective cohort study conducted in 555 hospitals in 20 countries across four regions of the world: Eastern, Northern and Southern Europe, and Latin America. Full details of the EPICOR rationale and study design, definitions, in-hospital and long-term results have been published previously.[12-14] Briefly, patients aged at least 18 years who survived hospitalization for confirmed ST-elevation myocardial infarction (STEMI), or non-ST-segment elevation-ACS (NSTE-ACS, including NSTEMI and unstable angina) were enrolled at discharge from hospital and followed up for 2 years. Exclusion criteria included 'secondary' ACS (precipitated by or occurring as a complication of surgery, trauma, PCI, or other reasons), any serious comorbidities considered likely to limit life expectancy to less than 6 months, and prior enrolment in EPICOR.

Events were adjudicated by the local investigators. Data were collected using electronic case report forms, including details of acute-phase (from symptom onset to discharge) and long-term management and outcomes, the latter by telephone follow-up every 3 months by trained interviewers. All patients were required to have been hospitalized within 24-h of symptom onset, and to provide written informed consent. The final protocol was approved by the ethics committees of participating centres in accordance with each country's local regulations.

Objectives

The primary objective of the EPICOR registry was to evaluate acute and long-term AMPs in ACS patients in a real-life setting. A full list of secondary endpoints has been reported previously, and included evaluation of in-hospital and post-discharge

clinical outcomes (ischaemic and bleeding events).[12] The objectives of this post-hoc analysis were to compare patient characteristics, in-hospital and discharge AMPs, and clinical outcomes (mortality, cardiovascular events and bleeding events) at 2-years according to the presence or absence of AF, including known prior AF and new-onset AF Figure S1 (supplementary material). Known prior AF included all AF diagnosed before admission for the index event, even if it was no longer present, and AF that was ongoing at admission. New-onset AF included only AF that started during the index hospitalization; patients with prior AF (no longer ongoing) that re-emerged during the index hospitalization were included in the prior AF group rather than the new-onset AF group.

Statistical analysis

Comparisons of patient characteristics, in-hospital and discharge antithrombotic management and ischaemic and bleeding events between patients with and without AF were performed with Pearson's chi-squared test.

Multivariable logistic regression analysis was performed to assess the effect of baseline patient characteristics on in-hospital intervention, antithrombotic medication and cardiac complications. Univariable and multivariable Cox proportional hazards models were used to assess the effect of prior, new-onset or any AF on either 2-year mortality or a composite endpoint of death, non-fatal myocardial infarction (MI), or non-fatal stroke within 2 years. For each model, the assumption of proportional hazards was tested using Schoenfeld residuals. The baseline variables adjusted for in the multivariable models are those previously found to be predictive of mortality when the EPICOR dataset was used to create a risk score[15]: age (per 10 years), left ventricular ejection fraction (LVEF) <40% and

<30%, EuroQol 5 dimensions (EQ-5D) score (per unit), serum creatinine (per unit ≥1.2 mg/dL), other cardiac complications in hospital (MI/recurrent ischemia, cardiogenic shock, heart failure, or any other arrhythmia), blood glucose ≥160 mg/dL, chronic obstructive pulmonary disease, male gender, diagnosis (STEMI vs. NSTE-ACS), PCI or coronary artery bypass graft (CABG), haemoglobin <13 g/dL, peripheral vascular disease, on diuretics at discharge, and region (Eastern Europe, Latin America, Northern Europe, Southern Europe).

Results

Patients

A total of 10,568 ACS patients were enrolled in EPICOR between 1 September 2010 and 31 March 2011, of whom 497 (4.7%) had known prior AF at baseline and 382 (3.6%) had new-onset AF during the index event Figure S1 (supplementary material), (Table 1). Data were missing for 134 patients (117 for prior AF and 21 for new-onset AF, including four patients with missing data for both categories of AF). Patients with any AF were more likely than those without to have a diagnosis of NSTE-ACS (64.3% vs. 35.7%), were older (mean 70.5% vs. 60.9 years; age ≥65 years 70.9% vs. 37.3%), were less often men (66.9% vs. 75.8%), had higher proportions of LVEF <30% (5.5% vs. 2.2%), serum creatinine ≥1.2 mg/dL (34.8% vs. 20.3%), and blood glucose ≥160 mg/dL (28.8% vs. 22.6%), and a higher mean CHA_2DS_2-VASc score (3.0 vs. 1.7) (all $p < 0.001$) (Table 1). Patients with AF were also more likely to have comorbidities, such as peripheral vascular disease (10.2% vs. 4.6%), and chronic obstructive pulmonary disease (11.4% vs. 6.1%) (both $p < 0.001$) (Table 1), and a poorer quality of life, as indicated by higher EQ-5D scores ($p < 0.001$).

Management

Despite an apparently higher cardiovascular risk level than patients without AF, those with AF significantly less frequently underwent coronary angiography ($p < 0.05$) (Table 1), or were treated with PCI ($p < 0.001$) Figure S2 (supplementary material). In contrast, patients with new-onset AF were more likely to undergo CABG ($p < 0.001$) Figure S2 (supplementary material). The overall revascularization rate (PCI and CABG combined) for patients with versus without AF was 58.6% versus

68.7%. The differences for AF versus no-AF patients undergoing PCI or CABG remained significant ($p < 0.001$) after adjustment for baseline variables Table S1 (supplementary material).

The overall in-hospital use of antiplatelet agents was high, but patients with AF were less likely than those without to receive most of them, including aspirin (90.9% vs. 94.4%), prasugrel (3.2% vs. 8.0%), and glycoprotein IIb/IIIa inhibitors (12.4% vs. 17.1%) (all $p < 0.001$). There was no significant difference in the use of clopidogrel in patients with or without any AF (85.0% vs. 87.1%, $p = 0.082$), but both DAPT and triple antiplatelet therapy (TAPT) were used less frequently in AF patients (82.3% vs. 89.9%, $p < 0.001$; and 11.7% vs. 16.2%, respectively; $p = 0.001$) (Table 1). In most cases, the differences derived mainly from the population with prior AF. Conversely, patients with AF were more likely to receive low molecular weight heparin (LMWH) (51.1% vs. 46.9%, $p = 0.017$) as due to greater use in patients with new-onset AF (60.2%), and more were treated with oral anticoagulants (warfarin/acenocoumarol in most cases: 27.3% vs. 2.0%; $p < 0.001$). The use of fibrinolysis was low, particularly in AF patients (5.6% vs. 8.6%; $p < 0.001$). After adjustment for baseline characteristics, significance disappeared for many of the AF versus no-AF differences, but remained for prasugrel ($p = 0.002$), DAPT ($p = 0.006$), LMWH ($p = 0.028$) and oral anticoagulants ($p < 0.001$) Table S1 (supplementary material). It should be noted that the results for some parameters (e.g. use of aspirin for management of the index event) were significant but in opposite directions for prior and new-onset AF, effectively cancelling out the effect for any AF.

A similar pattern was observed for discharge medication, with fewer AF than non-AF patients receiving DAPT (71.6% vs. 89.5%, $p < 0.0001$) Figure S3A

(supplementary material), and more AF patients discharged on oral anticoagulants, albeit only one-third of them (35.0% vs. 2.5%, $p < 0.0001$), most of whom were on warfarin/acenocoumarol. Among AF patients, oral anticoagulant use at discharge was low despite many (~90% of prior AF patients) having a CHADs2VASc score ≥2, but was higher in those with prior AF than new-onset AF (42.9% vs. 24.9%). These included a relatively small percentage of AF patients who were discharged on an oral anticoagulant plus a single antiplatelet (13.5% vs. 0.8% for any vs. no AF), most of which was in patients with prior AF (17.3%). Therapy consisting of DAPT plus an oral anticoagulant, was more frequently given at discharge in AF versus no-AF patients, including prior AF (19.9% vs. 2.0%), new-onset AF (14.1% vs. 2.4%) and any AF (17.0% vs. 1.5%). By the end of follow-up, the differences in management pattern persisted, with over half of all AF and no-AF patients remaining on DAPT at 2-years (55.6% vs. 60.6%), and 17.2% of any AF patients on TAPT (Figure 1) and Figure S3B (supplementary material). Use of any oral anticoagulant in AF patients declined over time; to 42.1% of prior AF patients, and 23.3% of those with new-onset AF, at 2-years.

Cardiovascular and bleeding complications in-hospital

Patients with any AF were significantly more likely to have other in-hospital cardiovascular or bleeding complications than those without AF (31.2% vs. 16.1%, $p < 0.001$), including MI/recurrent ischaemia (7.7% vs. 5.5%), cardiogenic shock (2.3% vs. 0.9%), heart failure (16.0% vs. 4.8%), any other arrhythmia (8.9% vs. 4.7%), stroke (0.7% vs. 0.2%) and bleeding (5.8% vs. 3.0%) (Table 2). The overall rate of these complications was significantly different for prior versus no prior AF (26.8% vs. 16.9%) and new-onset versus no new-onset AF (37.0% vs. 16.7%) (both $p < 0.001$). However, the higher in-hospital complication rates in AF patients derived

from those with new-onset rather than prior AF. After adjustment for baseline variables, the differences remained significant but marginally less so for prior versus no prior AF (p = 0.034) Table S2 (supplementary material).

Two-year clinical outcomes

At 2-years of follow-up post-discharge, the proportion of patients who had died was significantly higher among ACS patients with prior AF versus no prior AF (15.1% vs. 5.2%), new-onset AF (9.9% vs. 5.6%), or any AF (12.9% vs. 5.0%) (all $p < 0.0001$) (Figure 2) and Figure S4 (supplementary material). Significant differences in the same direction were also observed for the composite endpoint of death, non-fatal MI or non-fatal stroke, and for bleeding events (all $p < 0.0001$ except new-onset vs. no new-onset AF bleeding events, p = 0.0001). The number of patients with the individual components of non-fatal MI and non-fatal stroke was small, and no statistical comparisons were performed, but non-fatal MI was numerically less frequent in patients with than without new-onset AF (1.0% vs. 1.9%), whereas non-fatal stroke was more frequent in all categories of patients with AF.

Univariable and multivariable analysis

Uni- and multivariable analysis provided significance for many variables, including for mortality and the composite endpoint:

Mortality

On univariable analysis, the hazard ratio (HR [95% confidence interval (CI)]) for risk of death was significantly higher in patients with prior AF, new-onset AF or any AF (3.15 [2.48, 4.02], 1.89 [1.36, 2.63] and 2.77 [2.25, 3.40], respectively; $p \leq 0.0001$ in each case). On multivariable analysis, after adjusting for other variables known to be

predictive of mortality, the HR (95% CI) for risk of death decreased in each case but remained significant for prior AF and any AF, but not for new-onset AF, 1.48 (1.14, 1.90), $p = 0.003$; 1.32 (1.06, 1.64), $p = 0.013$; and 1.03 (0.73, 1.44), $p = 0.88$, respectively Tables S3–S5 (supplementary material).

Among the multiple variables analysed, it was found that patients with prior AF were significantly less likely to receive PCI or CABG during index hospitalization (relative risk, RR [95% CI], 0.74 [0.68, 0.81], $p < 0.001$) Table S1 (supplementary material), and removal of adjustment for PCI/CABG increased the overall HR estimate from 1.48 to 1.54 (95% CI 1.19, 1.99; $p = 0.001$). This suggests that the risk of death in patients with prior AF is further increased by the reduced likelihood of invasive intervention during the index hospitalization.

Composite of death, non-fatal MI or non-fatal stroke

Prior AF, new-onset AF and any AF were also associated with significantly higher rates of the composite endpoint of death, non-fatal MI and non-fatal stroke on univariable analysis, HR (95% CI); 2.90 (2.34, 3.60), $p < 0.0001$; 1.67 (1.24, 2.24), $p = 0.0008$; and 2.48 (2.05, 2.99), $p < 0.0001$, respectively. As for the endpoint of death alone, the HR (95% CI) for the composite endpoint remained significant on multivariable analysis for prior AF (1.46 [1.16, 1.83], $p = 0.001$) and any AF (1.28 [1.06, 1.56], $p = 0.012$), but not for new-onset AF (0.98 [0.73, 1.33], $p = 0.92$) Tables S6–S8 (supplementary material). Again, removal of PCI/CABG from the adjustment for prior AF increased the estimated HR (95% CI) to 1.51 (1.21, 1.90); $p = 0.0004$.

Discussion

The results of this analysis of 2-year follow-up data from the EPICOR registry demonstrate that AF, particularly prior AF, is a major contributor to in-hospital cardiac complications, and increased risk of mortality and cardiovascular events in the long term. Furthermore, despite guideline recommendations,[6, 8, 10] fewer AF patients underwent PCI (52% compared with 67% of non-AF patients), only 72% were discharged on DAPT (compared with 90% of non-AF patients), and only 35% were discharged on oral anticoagulant therapy (43% with prior AF and 25% with new-onset AF) even though the majority had a CHADs2VASc score ≥2. At the end of follow-up, use of any oral anticoagulant in AF patients had declined to 34%. While triple therapy was used in 17% of AF patients at discharge, combination therapy with an oral anticoagulant and a single antiplatelet was used in 14%.

Consistent findings were reported in a recent European Heart Rhythm Association (EHRA) survey, an internet questionnaire-based study, in which only 15 (41%) of 37 centres routinely administered triple therapy to all AF patients following PCI, and 22 (59%) centres used them in AF patients with moderate-to-high thromboembolic risk.[11] Over 90% of centres surveyed used a combination of aspirin, clopidogrel and warfarin.

Despite the relatively low use of oral anticoagulants (OACs) at discharge in EPICOR, there was a significantly greater long-term risk of bleeding events in AF patients, both prior and new-onset. Stroke was reported infrequently during follow-up, but was numerically more likely to occur in patients with any category of AF. The majority were discharged on warfarin/acenocoumarol, whereas evidence indicates that the newer, non-vitamin K oral anticoagulants (NOACs) have a more favourable

risk profile.[16] However, given recent reports of lower bleeding rates with NOACs compared with vitamin K antagonists, when used in combination with antiplatelet agents after an ACS and/or PCI, it can be speculated that current OAC use will be higher.[17, 18]

Additionally, multivariable analysis of the data from EPICOR showed that adjustment for other variables resulted in important changes in terms of the cardiovascular risk associated with AF. Multivariable analysis reconfirmed the increased risk of events in ACS patients with AF; that is, after adjustment for other baseline predictor variables, prior AF remained associated with worse outcomes of both death (HR 1.48, 95% CI 1.14, 1.90; *p* = 0.003), and the composite endpoint of death, non-fatal MI or non-fatal stroke (HR 1.46, 95% CI 1.16, 1.83; *p* = 0.001). These results suggest that prior AF, but not new-onset AF, is an independent predictor of increased risk of both mortality and the composite endpoint of death, non-fatal MI or non-fatal stroke. The lower risk of clinical events associated with new-onset AF might be related not only to the lower risk profile but in addition to the fact that some patients may have had AF only in the acute phase related to the ischemia, and maintained thereafter in sinus rhythm.

Limitations of this study include being a sub-study, potential bias or inaccuracy in reporting of the follow-up data due to the 3-month interval between telephone calls, ~~and~~ changes in availability of antithrombotic drugs over the study duration, and investigator-led adjudication of clinical events. Also, as the population included only hospital survivors, there is no means of determining whether AF is associated with early, in-hospital, mortality. Finally, the analysis did not account for cardiac rhythm at hospital discharge. It may well be that, in patients with new-onset

AF, outcomes differ in those with AF persisting at discharge versus those in sinus rhythm at discharge.

In conclusion, in clinical practice, patients with ACS and AF (known prior and new-onset) are treated less frequently with revascularization therapies, and more than half do not receive oral anticoagulation at discharge, with a decline in use over time. They also experience a high event rate during long-term follow-up, with increased mortality, and cardiovascular and bleeding events compared with ACS patients without AF. Multivariable analysis indicates that prior AF is an independent predictor of both mortality and the composite endpoint of death, non-fatal MI or non-fatal stroke during the first 2 years after discharge, whereas new-onset AF is not. Every effort should be made to increase the rate of guideline-adherent therapies in these high-risk patients after ACS. The adoption of a more personalized management approach, addressing individual patient risk factors, as well as closer follow-up may also help to improve long-term outcomes in patients with AF.

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Conflict of interest

U.Z. has received research grants from Daiichi-Sankyo, Eli Lilly, Novartis, and Sanofi; and honoraria from AstraZeneca, Bayer Healthcare, Boehringer-Ingelheim, Daiichi-Sankyo, Eli Lilly, MSD, Novartis, Sanofi, and The Medicines Company. L.A. has received consulting and lecture fees from AstraZeneca. N.D. has received consulting or speaking fees from Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, GSK, MSD-Schering Plough, Novartis, Pierre Fabre, Pfizer, Roche, Sanofi-Aventis, Servier, Takeda, and The Medicines Company. S.P. has received research funding from AstraZeneca. S.N. has received research funding from AstraZeneca. F.V.d.W. has received consulting fees and research grants from Boehringer-Ingelheim, and Merck, and consulting fees from Roche, Sanofi-Aventis, AstraZeneca, and The Medicines Company. J.M. is an employee of AstraZeneca. H.B. has received consulting fees from AstraZeneca, Bayer, BMS-Pfizer, Ferrer, Novartis, Servier, and MEDSCAPE-the heart.org; and fees for research activities from AstraZeneca, BMS, Janssen, and Novartis.

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Table 1. Patient demographics, disease parameters and management; AF versus no AF, prior or new-onset.

	Prior AF Y / N (*n* = 497 / 9954)	**RR[c]; *p*-value**	**New-onset AF Y / N (*n* = 382 / 10,165)**	**RR[c]; *p*-value**	**Any AF Y / N (*n* = 879 / 9565)**	**RR[c]; *p*-value**
Demographics and disease parameters						
Diagnosis						
STEMI	129 (26.0) / 4762 (47.8)	< 0.001	185 (48.4) / 4748 (46.7)	0.51	314 (35.7) / 4572 (47.8)	< 0.001
NSTE-ACS	368 (74.0) / 5192 (52.2)		197 (51.6) / 5417 (53.3)		565 (64.3) / 4993 (52.2)	
Age, years; mean (SD)	72.5 (9.9) / 61.2 (12.1)	< 0.001	67.9 (11.5) / 61.5 (12.2)	< 0.001	70.5 (10.9) / 60.9 (12.1)	< 0.001
Age group						
<65	113 (22.7) / 6146 (61.8)	< 0.001	143 (37.4) / 6166 (60.7)	< 0.001	256 (29.1) / 5997 (62.7)	< 0.001
65–74	149(30.0) / 2229 (22.4)		115 (30.1) / 2285 (22.5)		264 (30.0) / 2111 (22.1)	
>74	235 (47.3) / 1578 (15.9)		124 (32.5) / 1713 (16.9)		359 (40.8) / 1456 (15.2)	
Sex						
Men	301 (60.6) / 7541 (75.8)	< 0.001	287 (75.1) / 7619 (75.0)	0.94	588 (66.9) / 7250 (75.8)	0.001
Women	196 (39.4) / 2413 (24.2)		95 (24.9) / 2546 (25.0)		291 (33.1) / 2315 (24.2)	
LVEF						
≥40%	375 (83.7) / 8238 (89.8)	< 0.001	283 (80.6) / 8379 (89.7)	<0.001	658 (82.4) / 7946 (90.1)	< 0.001
<40%	52 (11.6) / 725 (7.9)		45 (12.8) / 743 (8.0)		97 (12.1) / 681 (7.7)	

<30%	21 (4.7) / 212 (2.2)		23 (6.6) / 216 (2.3)		44 (5.5) / 191 (2.2)	
COPD	59 (12.0) / 616 (6.2)	< 0.001	40 (10.6) / 642 (6.4)	0.001	99 (11.4) / 575 (6.1)	< 0.001
PVD	57 (11.8) / 470 (4.8)	< 0.001	30 (8.1) / 498 (5.0)	0.007	87 (10.2) / 439 (4.6)	< 0.001
On diuretics[a]	219 (44.5) / 1713 (17.3)	< 0.001	136 (35.8) / 1826 (18.0)	< 0.001	355 (40.7) / 1578 (16.7)	< 0.001
CHA_2DS_2-VASc score; mean (SD)	3.4 (1.6) / 1.7 (1.5)	< 0.001	2.4 (1.6) / 1.8 (1.6)	< 0.001	3.0 (1.7) / 1.7 (1.5)	< 0.001
CHA_2DS_2-VASc score						
0	12 (2.5) / 2249 (23.2)	< 0.001	39 (10.7) / 2219 (22.6)	< 0.001	51 (6.0) / 2207 (23.7)	< 0.001
1	47 (9.8) / 2796 (28.8)		86 (23.6) / 2759 (28.1)		133 (15.8) / 2709 (29.0)	
2	80 (16.7) / 1984 (20.4)		76 (20.9) / 1983 (20.2)		156 (18.5) / 1902 (20.4)	
3	110 (23.0) / 1354 (14.0)		72 (19.8) / 1388 (14.1)		182 (21.6) / 1277 (13.7)	
4	111 (23.2) / 822 (8.5)		53 (14.6) / 881 (9.0)		164 (19.5) / 768 (8.2)	
5–9	119 (24.8) / 500 (5.2)		38 (10.4) / 584 (6.0)		157 (18.6) / 463 (5.0)	
In-hospital management						
Fibrinolysis	16 (1.7) / 931 (9.4)	0.35; < 0.001	33 (8.6) / 921 (9.1)	0.95; 0.77	49 (5.6) / 896 (9.4)	0.60; < 0.001
Antiplatelets						
Aspirin	434 (87.3) / 9404 (94.5)	0.92; < 0.001	365 (95.5) / 9557 (94.0)	1.02; 0.15	799 (90.9) / 9032 (94.4)	0.96; 0.001
Clopidogrel	410 (82.5) / 8667 (87.1)	0.95; 0.010	337 (88.2) / 8820 (86.8)	1.02; 0.39	747 (85.0) / 8327 (87.1)	0.98; 0.10
Prasugrel	13 (2.6) / 783 (7.9)	0.33; < 0.001	15 (3.9) / 787 (7.7)	0.51; 0.008	28 (3.2) / 765 (8.0)	0.40; < 0.001

GP IIb/IIIa inhibitor	42 (8.5) / 1705 (17.1)	0.49; < 0.001	67 (17.5) / 1691 (16.6)	1.05; 0.64	109 (12.4) / 1638 (17.1)	0.72; < 0.001
DAPT	383 (77.1) / 8950 (89.9)	0.86; < 0.001	340 (89.0) / 9067 (89.2)	1.00; 0.91	723 (82.3) / 8603 (89.9)	0.91; < 0.001
Aspirin+clopidogrel	372 (74.8) / 8385 (84.2)	0.89; < 0.001	327 (85.6) / 8501 (83.6)	1.02; 0.28	699 (79.5) / 8054 (84.2)	0.94; 0.001
TAPT[b]	39 (7.8) / 1612 (16.2)	0.48; < 0.001	64 (16.8) / 1598 (15.7)	1.07; 0.58	103 (11.7) / 1548 (16.2)	0.72; 0.001
Anticoagulants						
UFH	143 (28.8) / 3527 (35.4)	0.81; 0.004	124 (32.5) / 3567 (35.1)	0.93; 0.30	267 (30.4) / 3400 (35.5)	0.85; 0.003
LMWH	219 (44.1) / 4713 (47.3)	0.93; 0.16	230 (60.2) / 4744 (46.7)	1.29; < 0.001	449 (51.1) / 4483 (46.9)	1.09; 0.013
Fondaparinux	45 (9.1) / 1051 (10.6)	0.86; 0.29	53 (13.9) / 1049 (10.3)	1.34; 0.024	98 (11.1) / 998 (10.4)	1.07; 0.51
Bivalirudin	2 (0.4) / 162 (1.6)	0.25; 0.049	3 (0.8) / 162 (1.6)	0.49; 0.22	5 (0.6) / 159 (1.7)	0.34; 0.018
Oral anticoagulants	167 (33.6) / 257 (2.6)	13.01; < 0.001	73 (19.1) / 358 (3.5)	5.42; < 0.001	240 (27.3) / 189 (2.0)	13.82; < 0.001
Warfarin/ acenocoumarol	166 (33.4) / 255 (2.6)	13.04; < 0.001	73 (19.1) / 355 (3.5)	5.47; < 0.001	239 (27.2) / 187 (2.0)	13.91; < 0.001
Dabigatran	1 (0.2) / 2 (0.02)	10.01; 0.060	0 (0.0) / 3 (0.03)	– ; –	1 (0.1) / 2 (0.02)	5.44; 0.17
Intervention						
Coronary angiography	356 (71.8) / 8202 (82.6)	0.87; <0.001	297 (77.7) / 8339 (82.3)	0.95; 0.042	653 (74.4) / 7896 (82.8)	0.90; <0.001
PCI	245 (49.3) / 6586 (66.2)	0.75; < 0.001	213 (55.8) / 6674 (65.7)	0.85; < 0.001	458 (52.1) / 6367 (66.6)	0.78; < 0.001
CABG	8 (1.6) / 256 (2.6)	0.63; 0.19	49 (12.8) / 217 (2.1)	6.01; < 0.001	57 (6.5) / 205 (2.1)	3.03; 0.001
Medication at discharge		<0.001		<0.001		<0.001
No antiplatelet	5 (1.0) / 41 (0.4)		4 (1.0) / 42 (0.4)		9 (1.0) / 37 (0.4)	

SAPT	30 (6.0) / 901 (9.1)		49 (12.8) / 900 (8.9)		79 (9.0) / 851 (8.9)	
DAPT	248 (49.9) / 8657 (87.0)		233 (61.0) / 8743 (86.0)		481 (54.7) / 8416 (88.0)	
Oral anticoagulants	214 (43.1) / 353 (3.5)		96 (25.1) / 478 (4.7)		310 (35.3) / 260 (2.7)	

All data are for evaluable patients only, and values are *n* (%) of patients unless otherwise indicated.

AF: atrial fibrillation; CHA_2DS_2-VASc: Cardiac failure, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled] – VAScular disease, Age 65–74 and Sex category [female]; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; DAPT: dual antiplatelet therapy; GP: glycoprotein; LMWH: low molecular weight heparin; LVEF: left ventricular ejection fraction; NSTE-ACS: non-ST-segment elevation-acute coronary syndrome; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; RR: relative risk; STEMI: ST-segment elevation myocardial infarction; TAPT: triple antiplatelet therapy; UFH: unfractionated heparin; Y / N: yes / no.

p-values are for difference between patients with or without AF in each case.

[a]At discharge.

[b]Aspirin plus either clopidogrel or prasugrel, and a GP IIb/IIIa inhibitor.

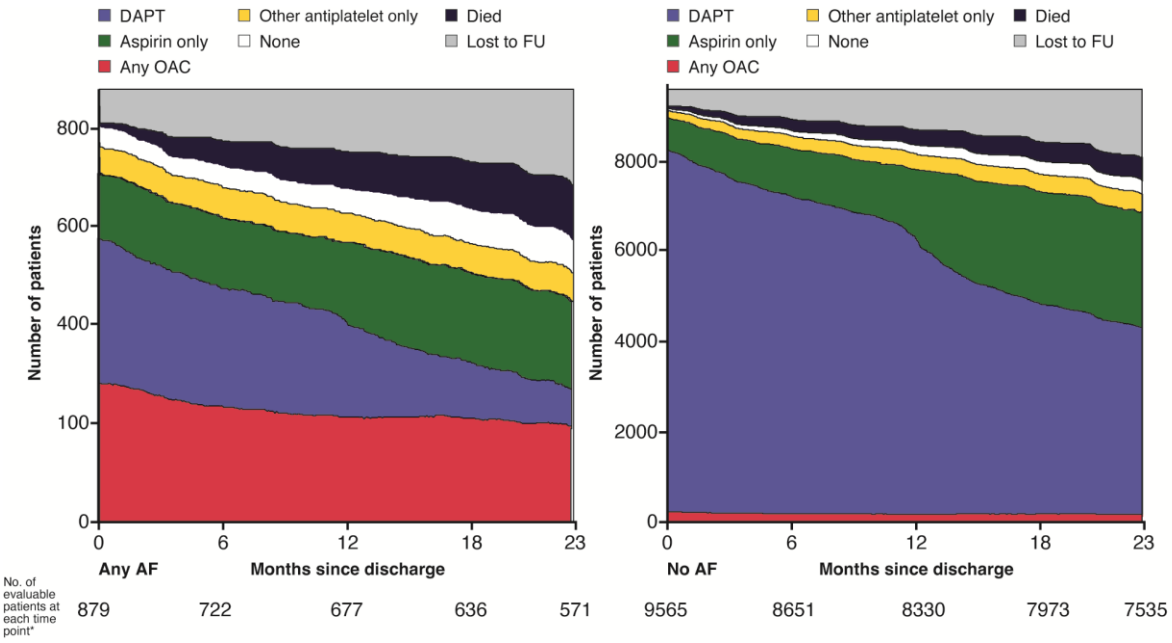
[c]Applies to in-hospital management only.

Table 2. Other in-hospital cardiovascular and bleeding complications.

	Prior AF Y (*n* = 497) / N (*n* = 9954)	***RR***	***p***	**New-onset AF Y (*n* = 382) / N (*n* = 10 165)**	***RR***	***p***	**Any AF Y (*n* = 879) / N (*n* = 9565)**	***RR***	***p***
None	358 (73.2) / 8195 (83.1)	1.59	< 0.001	235 (63.0) / 8390 (83.3)	2.21	< 0.001	593 (68.8) / 7964 (83.9)	1.94	< 0.001
Any of the following	131 (26.8) / 1666 (16.9)			138 (37.0) / 1688 (16.7)			269 (31.2) / 1527 (16.1)		
MI/recurrent ischaemia	33 (6.7) / 554 (5.6)	1.19	0.31	34 (9.1) / 565 (5.6)	1.63	0.004	67 (7.7) / 519 (5.5)	1.41	0.005
Cardiogenic shock	5 (1.0) / 99 (1.0)	1.01	0.97	15 (3.9) / 93 (0.9)	4.29	< 0.001	20 (2.3) / 83 (0.9)	2.63	< 0.001
Heart failure	71 (14.4) / 528 (5.3)	2.70	< 0.001	69 (18.1) / 547 (5.4)	3.35	< 0.001	140 (16.0) / 460 (4.8)	3.32	< 0.001
Any other arrhythmia	28 (5.7) / 500 (5.0)	1.13	0.53	50 (13.2) / 486 (4.8)	2.76	< 0.001	78 (8.9) / 450 (4.7)	1.90	< 0.001
Stroke	1 (0.2) / 26 (0.3)	0.77	0.80	5 (1.3) / 22 (0.2)	6.04	< 0.001	6 (0.7) / 21 (0.2)	3.11	0.014
Bleeding	22 (4.4) / 321 (3.2)	1.37	0.14	29 (7.6) / 313 (3.1)	2.46	< 0.001	51 (5.8) / 291 (3.0)	1.91	< 0.001

AF: atrial fibrillation; MI: myocardial infarction; RR: relative risk.

Figure 1. Change in antithrombotic medication over time; any AF and no AF.

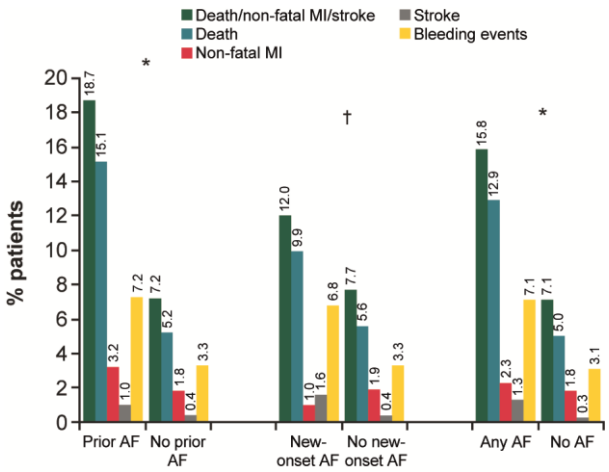


Differences in management pattern persisted during follow-up, with over half of all AF and no-AF patients remaining on DAPT at 2-years.

AF: atrial fibrillation; DAPT: dual antiplatelet therapy; FU: follow up; OAC: oral anticoagulant.

*Excluding patients who died or were lost to follow-up at each time point.

Figure 2. Clinical outcomes at 2-years: composite of death/non-fatal MI/stroke, the three individual components, and bleeding events.



At 2-years, rates of mortality, composite endpoint, and bleeding events were significantly higher among acute coronary syndrome patients with AF versus no AF, whether prior, new-onset, or any AF.

AF: atrial fibrillation; MI: myocardial infarction.

*$p < 0.0001$ AF versus no AF for death, death/non-fatal MI/stroke, and bleeding events.

†$p < 0.0001$ AF versus no AF for death, death/non-fatal MI/non-fatal stroke, and $p = 0.0001$ for bleeding events.

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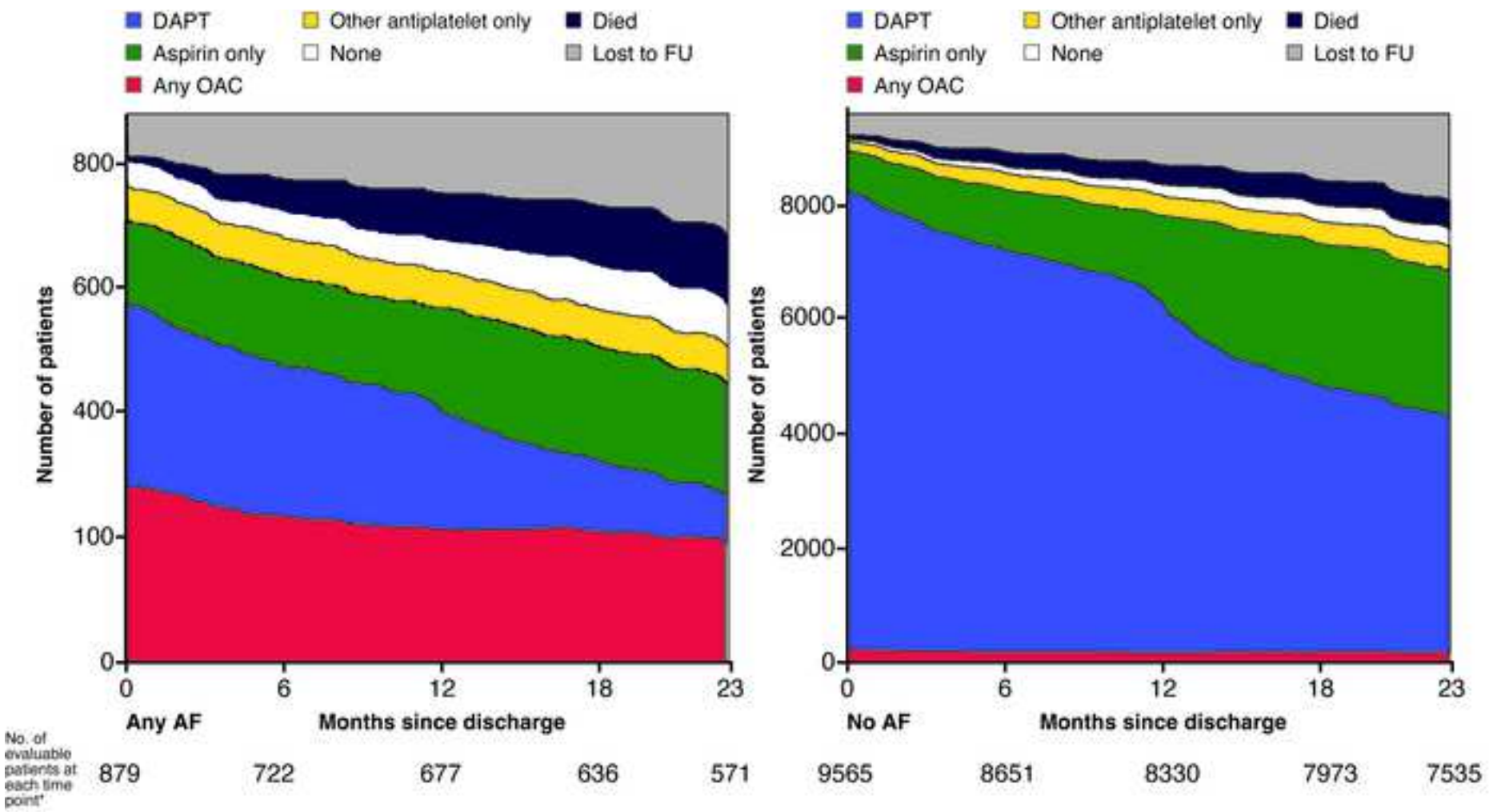

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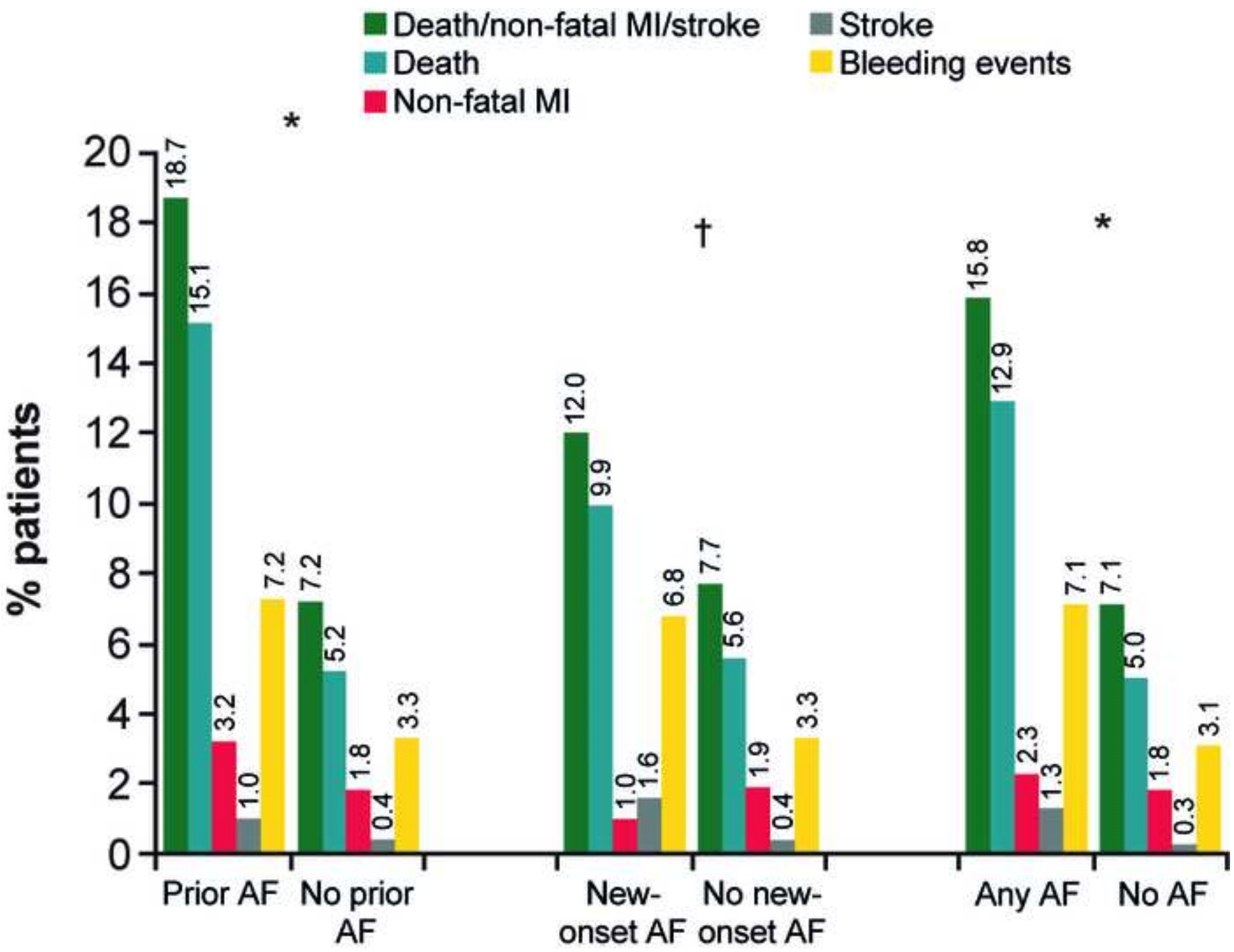

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No amendment or modification of any provision of this Agreement shall be valid or binding unless made in writing and signed by all parties.

This Agreement constitutes the entire agreement between the parties with respect to its subject matter, and supersedes all prior and contemporaneous agreements, understandings and representations. The invalidity or unenforceability of any particular provision of this Agreement shall not affect the other provisions, and this Agreement shall be construed in all respects as if any invalid or unenforceable provision were omitted.

If any difference shall arise between you and the Proprietor touching the meaning of this Agreement or the rights and liabilities of the parties thereto, the same shall be referred to the arbitration of two persons (one to be named by each party) or their mutually agreed umpire, in accordance with the provision of the England Arbitration Act 1996 or any amending or substituted statute for the time being in force.

Consent for Commercial Electronic Messages.
You hereby provide your express consent for the Proprietor, its affiliates and licensees (expressly including SAGE, where SAGE is not the Proprietor), and their respective designees to contact you in connection with any business communication or other correspondence. The parties agree that such consent may be withdrawn by you at a later time by providing written notice (including by email) to the Proprietor (and/or SAGE if different than the Proprietor). This clause shall survive expiration or earlier termination of this Agreement.

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