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Prognostic role of atrial fibrillation in acute coronary syndromes: a real-life, contemporary analysis

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Summary

OBJECTIVES: To analyse the impact of atrial fibrillation (AF) on in-hospital mortality and the role of antithrombotic regimens on 1-year outcomes in patients presenting acute coronary syndrome (ACS) and AF over a 4-year period in a Swiss tertiary referral centre.

METHODS: Between 2011 and 2014, in-hospital mortality of ACS patients in AF was compared to that observed for ACS patients in sinus rhythm. Major adverse cardiovascular events (MACE) and major bleeding were analysed at 1 year according to the antithrombotic regimen at discharge.

RESULTS: Out of the 2234 ACS patients, 187 (8.4%) presented with AF, either at admission (54%) or during the hospital stay (46%). In-hospital mortality was higher in ACS-AF cohort than in ACS patients in sinus rhythm (7.5 vs 4.1%; odds ratio [OR] 1.89, 95% confidence interval [CI] 1.06–3.38; p = 0.039). After adjustment for age and ACS presentation, AF did not appear to represent an independent risk factor for in-hospital mortality in ACS patients (OR 1.44, 95% CI 0.78–2.65; p = 0.25). Through combination of the type of ACS and presence of AF, in-hospital mortality was stratified into four risk categories: low (non-ST-segment elevation myocardial infarction [NSTEMI] without AF); intermediate (NSTEMI with AF; OR 3.25, 95% CI 1.017–9.09]); high (ST-segment-elevation myocardial infarction [STEMI] without AF; OR 5.12, 95% CI 2.93–8.95) and very high risk (STEMI with AF; OR 8.62, 95% CI 3.63–20.48). MACE or major bleedings did not differ according to antithrombotic regimens at discharge.

CONCLUSION: AF is common in the ACS setting and associated with increased risk of in-hospital mortality. Although AF did not represent an independent prognosticator in ACS, a progressive increase on in-hospital death was observed when combining type of ACS and presence/absence of AF.

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Introduction

The increasing incidence of atrial fibrillation (AF) in western countries represents a medical, social and economic challenge owing to its impact on prognosis, quality of life and healthcare costs. The clinical relevance of AF becomes even more crucial when it is associated with acute coronary syndromes (ACS). In fact, up to 10% of patients with ACS may present with concomitant AF either evident at admission or occurring during the hospitalisation.

Whether AF *per se* adversely affects prognosis in ACS or is merely a marker of comorbidities that effectively drive the outcome is still widely debated; nonetheless the poor outcome of patients presenting both conditions is well established [1–6].

The onset of AF in ACS patients is associated with higher mortality rates [7–9] and represents a therapeutic concern because of need to manage the thrombotic and ischaemic risk (by means of anticoagulants and platelet inhibitors) and to avoid haemorrhagic complications.

Despite being a common clinical situation with substantial impacts on outcome and clinical management, little is known about different management strategies and their related impact on outcomes in AF-ACS patients. Available data derive from *post hoc* analyses of randomised trials (neither focused nor powered to answer this issue) or from international registries [8–12]. As a result of this lack of medical evidence, current guidelines recommend an empirical approach aiming at individualising medical management. Recent expert consensus documents by the European Society for Cardiology (ESC) and guidelines by Canadian Society of Cardiology support this approach in clinical practice [13–17].

In the light of the complexity associated with the management of this clinical scenario, we aimed at analysing the

impact of AF on in-hospital mortality of ACS patients and the impact of antithrombotic regimens on 1-year outcomes in patients admitted for an ACS associated with AF over a 4-year period in a tertiary referral centre in Switzerland.

Methods

Study population

Clinical and administrative records including survival data at discharge of all patients admitted at our institution for ACS [18] between January 2011 and December 2014 were reviewed. Medical data from patients presenting with AF [19] either at admission (without further differentiation into paroxysmal, persistent, permanent) or at discharge were analysed with respect to clinical and angiographic characteristics. According to a twelve-lead ECG, clinical symptoms and sensitive troponin I, patients were divided into two groups: (1) patients presenting with typical symptoms and ST-segment elevation (STEMI) and/or left bundle branch block and treated by urgent/emergency percutaneous coronary intervention (PCI) and (2) patients with ACS classified as non-ST-segment elevation myocardial infarction (NSTEMI) and scheduled for an invasive approach within 48–72 hours. Preloading regimens and periprocedural antithrombotic treatments were administered according to local guidelines and to the clinical context. Survival status, occurrence of cardiac death, myocardial infarction, definite stent thrombosis, target vessel revascularisation, ischaemic stroke and clinically relevant major bleeding were determined at discharge and 1 year. Moreover, the 1-year outcome according to the antithrombotic and antiplatelet regimen prescribed at discharge was also analysed. In order to evaluate the relationship between medical management and outcome, the entire population was split into three subgroups: (1) patients discharged on dual antiplatelet therapy (DAPT); (2) patients discharged on single antiplatelet therapy + oral anticoagulation (SAPT + OAC); and (3) patients discharged on a triple antithrombotic regimen (DAPT + OAC).

Endpoints

In-hospital mortality was determined and compared with that observed in the cohort of ACS patients without AF admitted in the same time span (between January 2011 and December 2014). Major adverse cardiovascular event (MACE) at 1 year was a composite endpoint including cardiac death, myocardial infarction, definite stent thrombosis, target vessel revascularisation and ischaemic stroke [20]. Clinically relevant major bleedings at 1 year were defined according to the Bleeding Academic Research Consortium (BARC) definition [21]. Life status and clinical events were ascertained at 12 months by telephone contact in all patients.

Statistical analysis

Data are described as mean ± standard deviation (SD) when continuous and count and percentage (%) when categorical. Comparisons between treatment groups were performed with the Kruskall-Wallis test and the Fisher exact test, as appropriate. Logistic regression was used to assess the association of AF and in-hospital death, while adjusting for a series of predefined risk factors (age, gender and ACS presentation). Odds ratios (ORs) and 95% confidence intervals (CIs) were also reported. The interaction of AF and ACS presentation was tested and, given the clinical relevance, the effect of AF was presented separately for ACS-STEMI and ACS-NSTEMI. Median follow-up (25th–75th percentiles) was computed with the inverse Kaplan-Meier method. Kaplan-Meier event-free survival curves were plotted. The log-rank test was used to compare event-free survival between treatment groups. The hazard ratio (HR) and 95% CI was computed from a Cox model. To account for confounding, inverse probability weight when fitting the model was used. This weight was computed as the inverse of the probability of being treated with triple therapy and was derived from a logistic model including 16 demographic and clinical characteristics. The p-score command in Stata was used, with the common support option and the logit link. Stata 14.1 (Stata Corp, College Station, TX, USA) was used for computation. A two-sided p-value <0.05 was considered statistically significant. For *post-hoc* comparisons between treatment groups, significance was set at 0.017 (according to the Bonferroni correction).

Results

ACS-AF patients' characteristics

Between January 2011 and December 2014, 2234 consecutive patients were admitted for ACS (fig. 1): 1097 (49.1%) with STEMI and 1137 (50.9%) with NSTEMI. Of these, 187 (8.4%) presented with concomitant AF either evident at admission (n = 101, 54%) or occurring during the hospital stay (n = 86, 46%). Table 1 reports the clinical characteristics and acute management strategies in the ACS-AF cohort. In this group, 121 (64.5%) were treated by PCI/stenting, 14 (7.5%) underwent surgical revascularisation and 52 (28%) were medically managed.

In-hospital mortality and its predictors

The rate of in-hospital mortality was higher in ACS-AF cohort (14/187) as compared with ACS patients in sinus rhythm (SR) (84/2047) and this difference was statistically significant (7.5 vs 4.1%; OR 1.89, 95% CI 1.06–3.38; p = 0.039). The highest in hospital mortality was observed in the AF-STEMI group (11.4 vs 7.1% for STEMI patients in sinus rhythm [SR]; p 0.17), whereas the lowest was detected in the NSTEMI-SR group (1.7 vs 4.6% for NSTEMI-AF, p = 0.034) (fig. 2); no interaction between AF and ACS presentation was observed (p = 0.28). After adjustment for age and ACS presentation, AF did not appear to represent an independent prognostic risk factor for in hospital mortality in ACS patients (OR 1.44, 95% CI 0.78–2.65; p = 0.25) (Table 2).

Through combination of the type of ACS (STEMI vs NSTEMI) and the presence of AF, in-hospital mortality was stratified into four risk categories: low risk (OR 1, reference: NSTEMI without AF); intermediate risk (OR 3.25, 95% CI 1.017–9.09; p = 0.0171: NSTEMI with AF); high risk (OR 5.12, 95% CI 2.93–8.95: STEMI without AF) and very high risk (OR 8.62, 95% CI 3.63–20.48, p <0.00001: STEMI with AF) (fig. 3).

One-year Follow up

One hundred and seventy-three patients were discharged alive after an ACS with concomitant AF. Of these, 17 (9.83%) were discharged on SAPT or only OAC and were therefore excluded from our analysis. The remaining 156 patients were divided according to their medical treatment into three regimen groups: (1) patients on DAPT (n = 88, 56.4%); (2) patients on SAPT + OAC (n = 23, 14.7%); and (3) patients on a triple antithrombotic regimen DAPT + OAC (n = 45, 28.9%).

No differences in clinical presentation were observed between the groups (table 3) except for age (with a progressive decrease from triple to SAPT+OAC and DAPT, p = 0.037) and treatment with PCI (highest in patients receiving DAPT, lowest in SAPT+OAC; p = 0.039) as well as referral for surgical revascularisation (highest in SAPT+OAC; p <0.001).

Ten deaths occurred over a median follow-up of 15 months (25th–75th percentiles 12–27), corresponding to a mortality rate of 4.0 per 100 person-years (95% CI 2.1–7.4). Among this population of ACS with concomitant AF, 118

Figure 1: Acute coronary syndrome (ACS) undergoing percutaneous intervention (PCI) between 2011 and 2014 in Canton Ticino. 8.4% (n = 187) of ACS patients presented with concomitant atrial fibrillation (AF). In a subgroup of patients (n = 156) three antithrombotic regimens (triple therapy; SAPT + OAC; DAPT) were compared with respect to the predefined endpoints.

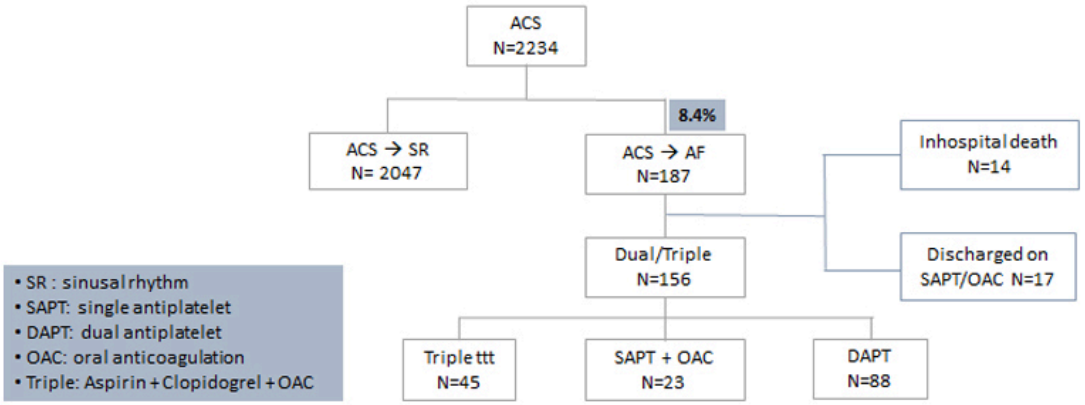


Table 1: Characteristics of the entire cohort of ACS patients presenting concomitant atrial fibrillation.

	ACS-AF cohort
Number	187
Age (years)	74 ± 11
Female (%)	31
ACS STEMI (%)	43.8
ACS NSTEMI (%)	56.2
Cardiogenic shock (%)	10.7
New onset AF (%)	46
CHADS2-VASC score	4.1 ± 1.5
HAS-BLED score	3 ± 1.2
LVEF (%)	46 ± 12.5
Radial access (%)	19.5
Acute treatment	
– PCI (%)	64.5
– CABG (%)	7.5
– Medical (%)	28

ACS = acute coronary syndrome; AF = atrial fibrillation; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction

Table 2: Predictors of in-hospital mortality in ACS patients; logistic regression model with atrial fibrillation and confounding factors such as ACS presentation (ST+/ST–), sex (female or male), age. After adjustment for age and ACS presentation AF do not appear as an independent prognostic factor of mortality in ACS patients.

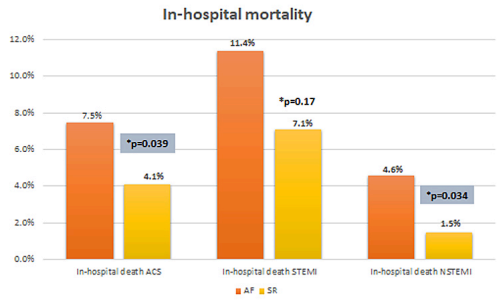
Mortality	OR	95% CI	p-value
AF– AF+	1.00 (base) 1.44	– (0.78–2.65)	– 0.246
ST– ST+	1.00 (base) 5.56	– (3.38–9.15)	– 0.0001
Sex female Sex male	1.00 (base) 1.03	– (0.65–1.64)	– 0.887
Age, per year	1.06	(1.04–1.08)	0.0001

ACS = acute coronary syndrome; AF = atrial fibrillation; CI = confidence interval; OR = odds ratio; ST = ST-segment elevation

patients (75.6%) were discharged in sinus rhythm and 38 (24.4%) remained in AF. One-year survival did not differ among patients discharged in sinus rhythm or AF (p = 0.65). Mortality among the three groups was comparable (p = 0.31; table 4).

MACE occurred more frequently in the group on the triple therapy regimen (n = 7/45; 15.6%) with a HR of 1.93 (95% CI 0.68–5.51) than the group discharged on SAPT + OAC (HR = 1.83, 95% CI 0.47–7.10). However, no statistically significant differences were observed between the three group (p = 0.41; table 4).

Figure 2: In-hospital mortality in the population with acute coronary syndrome according to the rhythm at presentation (AF = atrial fibrillation, SR = sinus rhythm). * Fisher exact test. NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

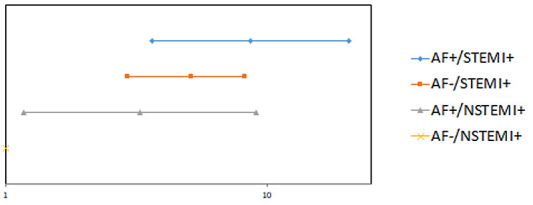


Major Bleeding

Major bleeding occurred more frequently in the triple therapy group (n = 5/45, 11.1%) as compared with the SAPT+OAC group (none observed) and DAPT group (n = 6/88, 6.8%). However, no statistically significant difference were observed between the groups (HR 1.68 for triple therapy, 95% CI 0.51–5.50; p = 0.27).

Univariable analysis and adjustment using propensity score inverse weighting for event prediction at 12 months (death, MACE, major bleeding) did not reveal any statisti-

Figure 3: Forrest plot demonstrating stratification of in-hospital mortality in 4 categories: low risk (yellow), intermediate risk (grey), high risk (orange), very high risk (blue). *odds ratio, **confidence interval, *** Fisher exact test. AF = atrial fibrillation; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction



AF/ACS	OR*	95% CI**	p***
AF+ / STEMI	8.62	(3.63 - 20.48)	p <0.00001
AF - / STEMI	5.12	(2.93 - 8.95)	p <0.00001
AF+ / NSTEMI	3.25	(1.17 - 9.09)	p <0.0171
AF - / NSTEMI	1	-	-

Table 3: Clinical characteristics of the three groups of patients defined according to the antithrombotic regimen.

	Triple therapy	SAPT + OAC	DAPT	p-value
Number	45	23	88	-
Age (years)	77 ± 7	76 ± 11	71 ± 12	0.04
Gender female (%)	31.3	21.7	32.7	0.65
STEMI/NSTEMI (%)	33.3/66.7	39.1/60.9	50/50	0.14
Cardiogenic shock (%)	6.3	13	13.3	0.42
New onset AF (%)	41.7	60.9	42.9	0.27
CHADS2-VASC score	4± 1.5	4.7± 1.9	4.1± 1.6	0.24
HAS-BLED score	3 ± 1.3	3.1 ± 1	2.9 ± 1.3	0.64
LVEF (%)	47 ± 12.3	43 ± 9.8	46 ± 13.1	0.35
Radial access (%)	20.8	8.7	21.4	0.41
Acute treatment				
– PCI, n (%)	34 (75.6)	11 (47.8)	62 (70.5)	0.04
– CABG, n (%)	0 (0)	6 (26.1)	2 (2.2)	0.001
– Medical, n (%)	11 (24.4)	6 (26.1)	24 (27.3)	0.94

AF = atrial fibrillation; CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; SAPT = single antiplatelet therapy; STEMI = ST-segment elevation myocardial infarction; triple therapy = OAC + aspirin + clopidogrel Age and scores were represented as mean value ± standard deviation. The others parameters were represented in percentages.

Table 4: One-year outcomes (death, MACE and major bleeding events) according to the antithrombotic regimen.

1-year outcomes	Triple therapy n = 45	AOC + SAPT n = 23	DAPT n = 88	p-value*
Death n; HR; 95% CI	n = 3 HR = 1.48 95% CI 0.33–6.63	n = 3 HR = 3.06 95% CI [0.68 -13.67]	n = 4 HR = 1 (base)	0.31
MACE n; HR; 95% CI	n = 7 HR = 1.95 95% CI 0.68–5.51	n = 3 HR = 1.83 95% CI [0.47 -7.10]	n = 7 HR = 1 (base)	0.41
Major bleeding n; HR; 95% CI	n = 5 HR = 1.68 95% CI 0.51–5.50	n = 0 – –	n = 6 HR = 1 (base)	0.27

CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; MACE = major adverse cardiovascular event; OAC = oral anticoagulant (oral vitamin K antagonist); SAPT = single antiplatelet therapy; triple therapy = OAC + aspirin 100 mg + clopidogrel 75 mg * p-value estimated with log-rank test.

cally significant difference between the groups. The results are reported in table 5.

Discussion

The present analysis represents a real life snapshot of the clinical characteristics and outcomes of contemporary patients admitted with ACS associated with AF in a tertiary western PCI centre.

Some important considerations may be drawn out from our data:

- The presence of atrial fibrillation in the clinical context of an ACS should be regarded as a red flag identifying those patients at higher risk of in-hospital mortality.
- An interplay between presence/absence of AF and ACS clinical presentation (NSTEMI vs STEMI) was clearly evident from a prognostic perspective.
- Owing to the lack of significance after multivariable analysis (adjustment for ACS type and age), the role of AF as an independent prognosticator in ACS remains elusive.

In our study, the cumulative prevalence of AF in the clinical context of ACS was 8.4%. This result is in line with those of other large registries [16, 22, 23], as well as to those reported by the AMIS plus (Swiss national registry of myocardial infarction). In the international Global Registry of Acute Coronary Events Study (GRACE registry) including 59,032 ACS patients between 2000 and 2007, authors reported a history of AF in 7.6% of the cohort and a rate of new-onset of the arrhythmia (deemed related to the ACS) in 5.3% of patients. This represent a cumulative prevalence of 12.9% [22]. In the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) registry including 69,255 patients with ACS, the prevalence of previous AF weeks before the index ACS event was 7.1% [23].

The presence of AF is known to be associated with increased mortality [24], but its real impact in ACS is subject to debate. Whether AF *per se* adversely affects prognosis in ACS or should be considered as a marker of comorbidities, the latter effectively driving the outcome, is still largely unclear [1–6].

In line with previous studies and with current clinical knowledge, our data show that in-hospital mortality is significantly higher for AF patients. Moreover, we confirmed that an interaction exists between the clinical presentation as STEMI vs NSTEMI and the arrhythmia, which is in line with results reported by Angeli et al. in a previous meta-analysis [25] and those derived from the GRACE registry by Mehta et al. In this sub-analysis of GRACE registry, authors concluded that previous and new-onset AF are associated with increased hospital morbidity and mortality [26]. We were able to stratify in-hospital mortality into four categories of risk: low risk (NSTEMI without AF); intermediate risk (NSTEMI with AF); high risk (STEMI without AF) and very high risk (STEMI with AF). Our data complete the results of Poçi et al., which showed that AF in patients with ACS should be regarded as an important risk factor irrespective of its presentation because there was no difference on long-term mortality (10 years) between the groups according to the type of AF [27]. A recent analysis derived from the nationwide Swiss AMIS plus registry further supported this finding [28]. However, in our study AF did not appear to be a supplementary independent prognostic risk factor of in-hospital mortality in ACS, indicating to the elusive role of AF in this setting.

In real life, STEMI patients benefit from an aggressive and urgent approach to management. Our data are hypothesis-generating and we speculate whether an analogous approach should be used in NSTEMI patients with previous or new-onset AF, on the basis of the detrimental effect of the arrhythmia on in-hospital mortality. Different risk scores are available to predict death or myocardial infarction following an initial ACS (GRACE 2.0 score, AMIS risk score), but none of them mention AF as a risk marker in the prediction of in-hospital death [28, 29]. Although larger prospective studies are needed to confirm our data, it seems necessary, from a clinical standpoint, to include AF as an essential variable in estimates of in-hospital mortality in ACS patients.

Several limitations should be mentioned to put our data in context. Our study was observational, retrospective, longitudinal and single-centre, and therefore has the intrinsic limitations of this study design. Despite the long time span of 4 years, the number of patients included in our analysis was small and data on several comorbidities (chronic obstructive pulmonary disease, hypertension, kidney failure, heart failure) were not available. Consequently, the number of events at follow up are few and do not allow any definite conclusion when outcome data are compared especially because our analysis was carried out before the results of the four major trials comparing dual antiplatelet plus a direct acting oral anticoagulant vs triple antithrombotic treatment in patients with AF (PIONEER-AF-PCI, RE-DUAL PCI, AUGUSTUS and ENTRUST-AF-PCI) were available [30–34]. We also note that 75.6% of patients with

Table 5: One-year outcomes (survival, MACE and major bleeding events) according to the antithrombotic regimen after adjustment for confounding factors (ACS presentation ST+/ST−; sex; age).

1 year outcomes	Triple therapy n = 45	OAC + SAPT n = 23	DAPT n = 88	p-value*
Deaths HR; 95% CI	HR = 2.68 95% CI 0.39–18.51	HR = 3.66 95% CI 0.44–30.26	HR = 1 (base)	0.44
MACE HR; 95% CI	HR = 3.41 95% CI 0.93–12.45	HR = 1.52 95% CI 0.25–9.20	HR = 1 (base)	0.17
Major bleeding HR; 95% CI	HR = 2.33 95% CI 0.64–8.52	– –	HR = 1 (base)	0.13

ACS = acute coronary syndrome; CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; MACE = major adverse cardiovascular event; OAC = oral anticoagulant (oral vitamin K antagonist); SAPT = single antiplatelet therapy; ST = ST-segment elevation; triple therapy = OAC + aspirin 100 mg + clopidogrel 75 mg * p-value estimated with weighting propensity score.

AF were discharged in sinus rhythm. Unfortunately, as a result of the missing data, we were not able to ascertain whether a spontaneous conversion occurred or an intervention (pharmacological or electrical) was performed in order to restore the rhythm control. No patient was treated with catheter ablation.

Conclusion

AF is common in the setting of ACS and is associated with an increased risk of in-hospital mortality. Although it seems not to have a supplementary independent prognostic effect in ACS after adjustment for confounding factors, AF should nonetheless be added as a parameter for scoring in-hospital mortality in the acute setting of ACS due to a gradual increase of in-hospital mortality with the combination of AF and any ACS presentation.

Disclosure statement
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