Comparison of Outcomes of Patients With Acute Coronary Syndromes With and Without Atrial Fibrillation

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Preexisting or new-onset atrial fibrillation (AF) commonly occurs in patients with an acute coronary syndrome (ACS). However, it is currently unknown if previous or new-onset AF confers different risks in these patients. To determine the prognostic significance of new-onset and previous AF in patients with ACS, we evaluated all patients with ACS enrolled in the multinational Global Registry of Acute Coronary Events (GRACE) between April 1999 and September 2001. We compared clinical characteristics, management, and hospital outcomes in patients with ACS and new-onset and previous AF with those without AF. Of a total of 21,785 patients with ACS enrolled in GRACE, 1,700 (7.9%) had previous AF and 1,221 (6.2%) had new-onset AF. Patients with any AF were older, more likely to be women, had more co-morbid conditions, and worse hemodynamic status. Most in-hospital adverse events (reinfarction, shock, pulmonary edema, bleeding, stroke, and mortality) were significantly higher in patients with any AF than those without AF. Only new-onset AF (not previous AF) was an independent predictor of all adverse in-hospital outcomes. We conclude that compared with patients with ACS without any AF, previous and new-onset AF are associated with increased hospital morbidity and mortality. However, only new-onset AF is an independent predictor of in-hospital adverse events in patients with ACS.
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Using data from patients with an acute coronary syndrome (ACS) enrolled in the Global Registry of Acute Coronary Events (GRACE),[1–3] we examined differences in the clinical features, management, and hospital outcomes of patients with previous and new-onset atrial fibrillation (AF) compared with those without any AF.

METHODS

Full details of the GRACE rationale and methods have been previsouly published.[1–3] GRACE is designed to reflect an unbiased population of patients with ACS, irrespective of geographic region. Currently, 94 hospitals located in 14 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, United Kingdom, and the United States) are participating in this observational study.

Study population: For purposes of this analysis, we restricted our study sample to patients who were enrolled in GRACE between April 1999 and September 2001 and who had ACS (ST-segment elevation acute myocardial infarction [AMI], non–ST-segment elevation AMI, and unstable angina pectoris). We defined ST-segment elevation AMI according to the following criteria: ST-segment elevation of $\geq$1 mm in $\geq$1 location or presumed new left bundle branch block on presenting electrocardiogram. Non–ST-segment elevation AMI was defined by elevation of cardiac enzymes to more than the upper limit of normal in patients with ischemic symptoms, but without ST-segment elevation or left bundle branch block. Unstable angina was defined as presence of new or accelerated ischemic symptoms with or without electrocardiographic changes, but without elevation of cardiac enzymes. AF was defined as the presence of either AF or flutter on the electrocardiogram. Patients were classified into those with previous AF and those with new-onset AF based on the presence (or absence) of a medical history of AF. Stroke was defined as the occurrence of a neurologic deficit caused by an ischemic event with residual symptoms. Major bleeding was defined as significant blood loss (from any site), not caused by trauma, that required blood transfusion. Cardiogenic shock was defined as pulmonary edema and organ hypoperfusion with systolic blood pressure of $<$80 mm Hg. Diagnosis of a recurrent AMI was established by new electrocardiographic changes and/or elevation of cardiac enzymes using the following criteria: (1) reelevation of creatine kinase-MB

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TABLE 1 Demographics and History of Patients With Acute Coronary Syndromes Who Have New-onset or Previous Atrial Fibrillation (AF) Compared With Those Without Any AF

Characteristics	No AF (n = 18,454)	New AF (n = 1,221)	p Value*	Previous AF (n = 1,700)	p Value†
ST-segment elevation AMI	6,323 (34%)	526 (43%)	<0.001	361 (21%)	<0.001
Non–ST-segment elevation AMI	5,471 (30%)	471 (39%)	<0.001	630 (37%)	<0.001
Unstable angina	6,660 (36%)	224 (18%)	<0.001	709 (42%)	<0.001
United States patients	3,986 (22%)	342 (28%)	<0.001	542 (32%)	<0.001
Age (mean, yrs)	64.2 (12.8)	71.9 (11.3)	<0.001	74.4 (10.0)	<0.001
Women	5,947 (32%)	429 (35%)	0.031	679 (40%)	<0.001
Medical history					
Prior angina	11,656 (63.4%)	699 (57.3%)	<0.001	1,228 (72.9%)	<0.001
Prior AMI	5,530 (30.0%)	337 (27.7%)	0.089	702 (41.5%)	<0.001
Prior stroke or transient ischemic attack	1,352 (7.4%)	129 (10.6%)	<0.001	288 (17.0%)	<0.001
Prior congestive heart failure	1,603 (8.7%)	156 (12.9%)	<0.001	568 (33.6%)	<0.001
Prior percutaneous coronary interventions	2,675 (14.5%)	117 (9.6%)	<0.001	275 (16.3%)	<0.001
Prior coronary artery bypass surgery	2,169 (11.8%)	94 (7.7%)	<0.001	365 (21.6%)	<0.001
Current smoker	5,162 (29.0%)	232 (19.8%)	<0.0001	199 (12.2%)	<0.001
Systemic hypertension	10,530 (57.2%)	778 (63.9%)	<0.001	1,179 (69.7%)	<0.001
Diabetes mellitus	4,365 (23.7%)	308 (25.3%)	0.210	503 (29.8%)	<0.001
Hyperlipidemia	8,302 (45.1%)	452 (37.2%)	<0.001	701 (41.9%)	0.032

*p Value for comparison between patients without AF and new-onset AF.
†p Value for comparison between patients without AF and previous AF.

concentrations to above the upper limit of normal and increased by ≥50% over the previous value; (2) if creatine kinase-MB was not available, then reelevation of total creatine kinase to >2 times the upper limit of normal and increased by 25% over the previous value; (3) after percutaneous coronary intervention: creatine kinase-MB (or creatine kinase) elevation to >3 times the upper limit of normal and increased by ≥50% over the previous value; and (4) after coronary artery bypass surgery: creatine kinase-MB (or creatine kinase) elevation to >3 times the upper limit of normal and increased by ≥50% over the previous value. Patients with ACS were divided into 3 groups according to the presence of AF and the time of its occurrence in relation to the acute event. These included patients with new-onset AF, those with a history of AF, and those who did not have a history of AF and did not develop AF during hospitalization for ACS. Patients were considered "ideal" for treatment if they had an indication and no contraindication to such therapy.[4]

Statistical analysis: Summary statistics are presented as frequencies and percentages or as medians and interquartile ranges. Comparisons between groups were made using the 2-tailed Wilcoxon's rank-sum test for continuous variables and the chi-square or Fisher's exact tests for categorical variables. Stepwise multivariable logistic regression was utilized to identify clinical predictors of new-onset AF using variables that showed marginal associations with AF on univariate testing ($p < 0.20$). Variables used to develop this model included age, gender, type of ACS, medical history variables (angina, AMI, stroke, congestive heart failure, coronary bypass surgery, history of current smoking, diabetes, hypertension, and hyperlipidemia), presentation variables (pulse, systolic and diastolic blood pressure, cardiac arrest, Killip class, initial cardiac enzymes, and serum creatinine), electrocardiographic findings (ST-segment deviation, location of ST-segment deviation, any significant Q wave, left bundle branch block), and previous medications.

Logistic regression models were constructed to compare the significance of differences between patients with new-onset AF and those without any AF (as well as between those with previous AF and those without any previous AF) with regard to 5 in-hospital outcomes (death, reinfarction, cardiogenic shock, major bleeding, and stroke) while controlling for potentially confounding variables. Crude odds ratios (OR) and accompanying 95% confidence intervals (CI) were computed to evaluate the effects of AF compared with patients without any AF on the risk of each of these outcomes. Stepwise multivariate logistic models (backward elimination) were used to adjust for age, gender, and differences in baseline characteristics between groups. Only variables with a significant ($p < 0.05$) association with the outcome under study were included in the final regression models. All regression models were evaluated for goodness of fit using the Hosmer and Lemeshow goodness-of-fit test. The discriminative power of the final models was determined using the area under the receiver-operating characteristic curve (c-statistic). SAS 8.2 (SAS Institute, Cary, North Carolina) was utilized for all analyses.

RESULTS

Patient demographics, history, and clinical presentation: Of 21,785 patients enrolled in GRACE during the study period, 1,221 (6.2%) had new-onset AF and 1,700 (7.9%) had a history of AF. Compared with patients with ACS and no AF, those with any AF were more likely to be older and have non–ST-segment elevation AMI at presentation (Table 1). Patients with any AF were more likely to have a history of transient ischemic attack and/or stroke, congestive heart failure, hypertension and diabetes, higher heart

TABLE 2 Medications on Admission, Presenting Clinical Features and Electrocardiographic Findings of Patients With ACS Having New-onset and Previous AF Compared With Those Without Any AF

Characteristics	No AF (n = 18,454)	New AF (n = 1,221)	p Value*	Prior AF (n = 1,700)	p Value†
Medications					
β blockers	5,327 (29.0%)	319 (26.3%)	0.041	606 (35.9%)	<0.001
Calcium channel blockers	3,498 (19.3%)	255 (21.1%)	0.116	464 (27.6%)	<0.001
Digoxin	561 (3.1%)	74 (6.2%)	<0.001	550 (32.9%)	<0.001
Warfarin	422 (2.3%)	32 (2.7%)	0.461	457 (27.3%)	<0.001
Presenting features					
Pulse (mean) (beats/min)	78.3 (19.6)	89.4 (29.3)	<0.001	88.0 (28.4)	<0.001
Systolic blood pressure (mean) (mm Hg)	142.2 (29.7)	136.8 (32.2)	<0.001	139.9 (32.1)	0.034
Diastolic blood pressure (mean) (mm Hg)	81.2 (17.8)	78.3 (21.0)	<0.001	78.7 (19.6)	<0.001
Serum creatinine (mean) (mg/dl)	1.2 (0.8)	1.3 (1.0)	<0.001	1.4 (1.1)	<0.001
Cardiac arrest	317 (1.8%)	51 (4.3%)	<0.001	36 (2.2%)	0.520
Killip class III	602 (3.4%)	102 (8.6%)	<0.001	140 (8.5%)	<0.001
Killip class IV	193 (1.1%)	36 (3.0%)	<0.001	21 (1.3%)	<0.001
Electrocardiographic findings					
Anterior ST-segment elevation	3,351 (18.2%)	245 (20.1%)	0.095	228 (13.4%)	<0.001
ST-segment depression	2,963 (16.1%)	291 (23.8%)	<0.001	304 (17.9%)	0.160
Significant Q waves	4,583 (24.8%)	344 (28.2%)	0.009	369 (21.7%)	0.002
Left bundle branch block	838 (4.5%)	79 (6.5%)	0.002	159 (9.4%)	<0.001

*p Value for comparison between patients without AF and new-onset AF.
†p Value for comparison between patients without AF and previous AF.

rates, lower blood pressure, higher admission serum creatinine, Killip class III or IV and ST-segment depression, left bundle branch block, and Q waves on the presenting electrocardiogram. In contrast, history of smoking and hyperlipidemia were significantly less frequent among patients with any AF compared with those without AF.

A number of clinical features differed between patients with previous AF and new-onset AF (Table 2). Compared with patients with ACS who did not have AF, those with new-onset AF were more likely to have had an anterior or any ST-segment elevation AMI and cardiac arrest on arrival, characteristics that were either similar or less frequent among those with previous AF. In contrast, patients with previous AF were more likely to be women and have a history of angina, AMI, or coronary revascularization. These features were less frequent or similar in patients with new AF compared with those without any AF.

In-hospital management: Patients with any AF were less likely to undergo percutaneous coronary intervention and were more likely to receive a temporary pacemaker or be on a ventilator compared with those without any AF (Table 3). The utilization of cardiac catheterization, coronary artery bypass surgery, and pulmonary artery catheterization was less frequent in patients with previous AF. These procedures were more frequently performed or similarly utilized in patients with new-onset AF compared with those without any AF.

Medical management also varied in our 3 primary comparison groups, both at the time of admission and during their hospital stay. Patients with previous AF were more likely to be on drugs that slowed atrioventricular conduction (β blockers, calcium channel blockers, and digoxin) as well as warfarin before admission. Compared with patients without AF, patients with any AF were less likely to receive reperfusion therapy, β blockers, or statins, and more frequently received angiotensin-converting enzyme inhibitor therapy or warfarin if they were appropriate candidates for such therapies. The use of aspirin and heparin was less frequent in patients with previous AF than in those with no AF. Compared with patients with previous AF who did not receive coumadin before hospital admission, those with previous AF on coumadin at presentation were less likely to receive aspirin (91% vs 78%, $p < 0.001$) and heparin (83% vs 64%, $p < 0.0001$). In contrast, these treatments were utilized in similar or higher proportions of patients with new-onset AF.

In-hospital outcomes: Most in-hospital complications were higher in patients with ACS with any AF than in those without any AF, including higher mortality (Tables 4 and 5). When stratified by the time of onset, all complications were higher in patients with ACS with new-onset AF than in those with previous AF. New-onset AF remained an important independent association of most in-hospital outcomes after adjustment for baseline differences in clinical characteristics (Table 5 and Figure 1). In contrast, a multivariate adjustment markedly attenuated the association of previous AF with any in-hospital outcomes (Table 5 and Figure 1).

Predictors of new-onset atrial fibrillation: Multivariate logistic regression analysis identified older age (per 10-year increase, OR 1.58, 95% CI 1.49 to 1.67), female gender (OR 1.24, 95% CI 1.07 to 1.45), ST-segment (OR 2.08, 95% CI 1.74 to 2.49) or non–ST-segment (OR 1.85, 95% CI 1.55 to 2.22) elevation AMI, history of hypertension (OR 1.34, 95% CI 1.17 to 1.53), higher heart rate (per 30 beats/min increase, OR 1.65, 95% CI 1.53 to 1.79), lower blood pressure (per 20 mm Hg decrease OR 1.16, 95% CI 1.12 to 1.21), cardiac arrest on presentation (OR 1.65, 95% CI 1.17 to 2.34), Killip class II or higher (OR 1.36, 95%

TABLE 3 In-hospital Management of Patients With ACS Who Have New-onset and Previous AF Compared With Those Without Any AF

Characteristics	No AF (n = 18,454)	New AF (n = 1,221)	p Value*	Prior AF (n = 1,700)	p Value†
Procedure use					
Cardiac catheterization	9,778 (53.5%)	627 (51.6%)	0.192	651 (38.9%)	<0.001
Percutaneous coronary interventions	5,832 (32.0%)	303 (25.0%)	<0.001	320 (19.1%)	<0.001
Coronary artery bypass surgery	1,052 (5.8%)	261 (21.6%)	<0.001	71 (4.2%)	<0.001
Pulmonary artery catheter	855 (4.7%)	265 (21.9%)	<0.001	69 (4.1%)	0.004
Ventilator	1,300 (7.1%)	360 (29.7%)	<0.001	141 (8.4%)	0.746
Intra-aortic balloon pump	420 (2.3%)	127 (10.6%)	<0.001	27 (1.6%)	0.003
Temporary pacemaker	628 (3.5%)	152 (12.7%)	<0.001	101 (6.1%)	<0.001
Medical management					
Aspirin‡	16,178 (95.0%)	999 (94.5%)	0.522	1,286 (87.7%)	<0.001
Ticlopidine/clopidogrel	6,612 (36.5%)	344 (28.7%)	<0.001	435 (26.1%)	<0.001
Any heparin‡	14,833 (85.5%)	974 (90.9%)	<0.001	1,216 (78.1%)	<0.001
Thrombolytics‡	2,326 (54.6%)	190 (50.1%)	0.095	66 (28.0%)	<0.001
Primary percutaneous coronary interventions‡	1,311 (20.7%)	84 (16.0%)	<0.001	64 (17.7%)	0.005
Warfarin	716 (4.0%)	208 (17.4%)	<0.001	506 (30.3%)	<0.001
β blocker†	10,714 (87.6%)	359 (82.5%)	0.002	614 (78.0%)	<0.001
Angiotensin-converting enzyme inhibitor‡	9,132 (59.1%)	590 (69.4%)	<0.001	784 (64.5%)	0.001
Statins‡	2,174 (67.1%)	111 (55.5%)	<0.001	110 (49.1%)	<0.001

*p Value for comparison between patients without AF and new-onset AF.
†p for comparison between patients without AF and previous AF.
‡In patients with an indication and no contraindications.

TABLE 4 In-hospital Outcomes of Patients With ACS Who Have New-onset and Previous AF Compared With Those Without Any AF

Characteristics	No AF (n = 18,454)	New AF (n = 1,221)	p Value*	Prior AF (n = 1,700)	p Value†
In-hospital outcomes					
Death	836 (4.6%)	181 (14.9%)	<0.001	153 (9.1%)	<0.001
Reinfarction	275 (1.5%)	44 (3.6%)	<0.001	24 (1.4%)	0.499
Angina pectoris	3,267 (17.8%)	223 (18.4%)	0.615	304 (18.0%)	0.854
Cardiogenic shock	708 (3.8%)	181 (14.9%)	<0.001	87 (5.1%)	0.275
Pulmonary edema	953 (5.2%)	260 (21.4%)	<0.001	168 (9.9%)	<0.001
Cardiac arrest	809 (4.4%)	169 (13.9%)	<0.001	123 (7.3%)	<0.001
Major bleeding	616 (3.4%)	103 (8.6%)	<0.001	76 (4.5%)	0.102
Stroke	178 (1.0%)	33 (2.7%)	<0.001	27 (1.6%)	0.061
Length of stay (mean) (d)	7.8 (7.5)	12.5 (10.7)	<0.001	8.3 (7.5)	0.133

*p Value for comparison between patients without AF and new-onset AF.
†p Value for comparison between patients without AF and previous AF.

CI 1.17 to 1.57), and initial serum creatinine (OR 1.07, 95% CI 1.01 to 1.15) to be significant predictors of new-onset AF. In contrast, previous coronary artery bypass surgery (OR 0.71, 95% CI 0.56 to 0.90) and previous AMI (OR 0.85, 95% CI 0.74 to 0.99) were found to have protective effects on the occurrence of new-onset AF. The c-index for the model was 0.74, suggesting a good model discrimination (chi-square 9.19, degrees of freedom 8, p = 0.33).

DISCUSSION

Our study in unselected patients in the community at large indicates that a history of AF was not uncommon in patients with ACS. Furthermore, our data demonstrate that new-onset AF frequently complicated an acute coronary event. Thus, AF was present in approximately 1 of every 7 patients presenting with ACS. Both previous AF and new-onset AF were associated with clinical characteristics that are known to be related to poor outcomes in patients with ACS. These included advanced age, diabetes mellitus, previous congestive heart failure, previous stroke, and variables suggesting hemodynamic compromise (low blood pressure, higher heart rates, New York Heart Association functional class, admission serum creatinine, and ST-segment or non–ST-segment elevation AMI). As a result, patients with ACS and any AF had worse in-hospital outcomes than those without any AF. Our results extend the findings from previous reports of the common occurrence and poor in-hospital outcomes of AF complicating AMI in patients with ACS.[5–12]

Patients with ACS and any AF were more likely to have a complicated in-hospital course than those without this arrhythmia. This was particularly true of patients with new-onset AF in whom there was a 2.5- to 4-fold increase in the adverse events of reinfarction, cardiogenic shock, pulmonary edema, cardiac arrest,

TABLE 5 In-hospital Outcomes of Patients With ACS Who Have New-onset and Previous AF Compared With Those Without Any AF

Outcome	New AF Odds Ratio*	New AF 95% Confidence Interval*	Prior AF Odds Ratio*	Prior AF 95% Confidence Interval*
Death (unadjusted)	3.67	3.09–4.37	1.96	1.41–2.73
Death (adjusted)	1.65	1.30–2.09	1.01	0.78–1.30
Reinfarction (unadjusted)	2.48	1.79–3.42	1.37	0.77–2.45
Reinfarction (adjusted)	2.00	1.37–2.93	0.92	0.55–1.54
Cardiogenic shock (unadjusted)	4.38	3.67–5.21	2.69	1.91–3.78
Cardiogenic shock (adjusted)	2.40	1.88–3.06	0.64	0.46–0.89
Pulmonary edema (unadjusted)	4.98	4.28–5.80	3.25	2.41–4.38
Pulmonary edema (adjusted)	2.83	2.27–3.52	0.83	0.64–1.08
Cardiac arrest (unadjusted)	3.53	2.96–4.21	2.53	1.86–3.45
Cardiac arrest (adjusted)	1.97	1.56–2.50	1.07	0.81–1.41
Stroke (unadjusted)	2.86	1.97–4.17	1.49	0.74–3.03
Stroke (adjusted)	1.33	0.80–2.20	1.19	0.70–2.02
Major bleed (unadjusted)	2.69	2.16–3.34	1.42	0.98–2.06
Major bleed (adjusted)	1.64	1.25–2.14	0.79	0.57–1.08

*Referrent = no AF.

major bleeding, and stroke. As a result, in-hospital death rates were increased nearly threefold in patients with new-onset AF. Importantly, almost all complications remained higher in patients with new-onset AF compared with no AF, even after adjustment for baseline differences in clinical characteristics. In contrast, although in-hospital mortality was increased twofold in patients with previous AF compared with those without any AF, the independent effect of previous AF on in-hospital mortality was not upheld when a variety of potentially confounding prognostic factors were controlled for in a multivariate regression analysis. These data imply that while any AF is an important marker of a subset of patients with ACS who are more critically ill, only new-onset AF is an independent predictor of in-hospital adverse outcomes. In contrast, previous AF may be an indicator of increased co-morbid conditions that account for most of the risk associated with this arrhythmia. This is not surprising as previous AF would not necessarily be expected to have a strong relation to the ischemic burden or its consequence, factors that are important in the pathogenesis of new-onset AF.

Because of the potentially serious consequences of new-onset AF in patients with ACS, we sought to identify patient characteristics that were associated with high risk for developing new-onset AF. Several previous studies have established predictive tools for this purpose in patients with AMI.[7–10] Our study expands the paradigm of predictive models for AF to patients with all ACSs. Older age, female gender, and a history of hypertension, clinical characteristics shown to increase the risk of AF in general and in patients with AMI, were significantly linked to the occurrence of new-onset AF in patients with ACS. Similarly, a compromised hemodynamic state (low blood pressure, high heart rate, Killip class higher than II, cardiac arrest on presentation, and myocardial necrosis) was also predictive of new-onset AF, suggesting that this mechanism may play a dominant role in the pathophysiology of this arrhythmia. Adverse hemodynamics or increased co-morbid conditions are both common in patients with high initial creatinine and new-onset AF, partially explaining why creatinine on admission is predictive of this arrhythmia. Finally, ACS syndromes in patients with previous coronary artery bypass surgery or AMI are more likely to be unstable angina or non–ST-segment elevation AMI than ST-segment elevation AMI,[13–15] explaining why new-onset AF occurs less frequently in these patient populations. Alternatively, it is also possible that these patients are already on effective cardiac therapies for the secondary prevention of ACS, such as β blockers and angiotensin-converting enzyme (ACE) inhibitors that might decrease the risk for the development of AF. Like any other analytic model, our predictive tool may be used to identify high-risk patients with ACS so that appropriate therapies can be targeted to this high-risk cohort to improve their hospital and potentially long-term outcomes.

Study limitations: Our study was observational with data collected retrospectively, therefore, it has an inherent bias resulting from incomplete or missing information. We were unable to provide information on AF and atrial flutter separately as these 2 atrial arrhythmias were collected as a single variable in GRACE. We were unable to establish a temporal relation between new-onset AF and the occurrence of in-hospital complications being studied. As such, only the association between AF and these complications, rather than cause and effect relation, should be inferred from our study. Finally, we could not discriminate between the proportion of patients with new-onset AF who remained in AF at the time of hospital discharge and those who later reverted to normal sinus rhythm (paroxysmal AF). As such, we were unable to distinguish differences in hospital outcomes between these 2 groups of patients with new-onset AF.

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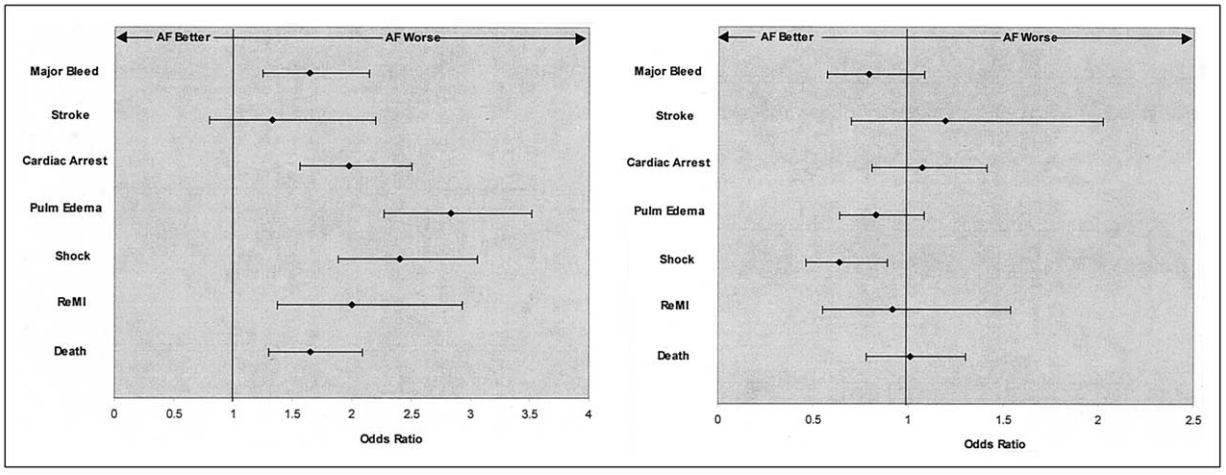

FIGURE 1. Adjusted ORs for in-hospital adverse events in patients with ACS and new-onset AF (referent no AF; *left panel*) and previous AF (referent no AF; *right panel*).

APPENDIX

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