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Antithrombotic Strategies and Outcomes in Acute Coronary Syndrome with Atrial Fibrillation

Alanna M. Chamberlain, PhD, MPH^a, Bernard J. Gersh, MB, ChB, DPhil^b, Roger M. Mills, MD^c, Winslow Klaskala, MS, PhD^c, Alvaro Alonso, MD, PhD^d, Susan A. Weston, MS^a, and Véronique L. Roger, MD, MP^{a,b}

^aDepartment of Health Sciences Research, Mayo Clinic, 200 First Street, Rochester, MN, 55905

^bDivision of Cardiovascular Diseases, Mayo Clinic, 200 First Street, Rochester, MN, 55905

^cJanssen Research and Development, LLC, 920 Rt 202, Raritan, NJ, 08869

^dDivision of Epidemiology and Community Health, School of Public Health, University of MN, 1300 S. 2nd Street, Suite 300, Minneapolis, MN, 55455

Abstract

Atrial fibrillation (AF) frequently occurs with acute coronary syndromes (ACS) and adds complexity to the selection of an appropriate antithrombotic strategy. We determined whether associations of antithrombotic treatment with bleeding, stroke, and death differ between ACS patients with and without AF. Olmsted County, MN residents hospitalized with incident ACS during 2005–2010 were classified according to the presence or absence of AF either prior to or during the index ACS hospitalization. Antithrombotic strategy at discharge was categorized as double/triple agents vs. no/single agent. Patients were followed through 2012 and propensity scores were used to estimate associations of treatment with bleeding, ischemic stroke, and mortality. Of 1159 incident ACS patients, 252 (21.7%) had concomitant AF (ACS+AF). Over a median follow-up of 4.3 years, 312 bleeds, 67 ischemic strokes, and 268 deaths occurred. The overall risks of bleeding, stroke, and death were similar between treatment strategies. Although limited by the small number of events, a suggestion of a lower risk of ischemic stroke for ACS+AF patients on double/triple therapy was observed; the hazard ratios for stroke with double/triple vs. no/single therapy were 0.30 (0.07–1.26) and 1.10 (0.52–2.33) among those with and without AF, respectively (p-value for interaction=0.10). In conclusion, the choice of antithrombotic strategy is not associated with the risk of ischemic stroke, bleeding, or death in ACS patients overall. ACS+AF patients on double/triple therapy may experience reduced risks of stroke, although future studies are needed to confirm this finding.

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Corresponding author: Véronique L. Roger, MD, MPH, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Telephone: 507-538-6768, Fax: 507-284-1516, roger.veronique@mayo.edu.

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Conflict of Interest

Dr. Klaskala, deceased, was an employee of Janssen Research and Development, LLC. Dr. Mills is a full-time employee of Janssen Research and Development, LLC. All authors have no conflict of interest to disclose.

Keywords

acute coronary syndrome; myocardial infarction; unstable angina; atrial fibrillation; antithrombotic therapy; outcomes

Introduction

Atrial fibrillation (AF) often complicates acute coronary syndromes (ACS), with at least 1 in 8 patients with ACS having AF.^{1–3} Selection of an optimal antithrombotic regimen for these patients is complex. Yet to date, no clinical trials have been undertaken to study the impact of antithrombotic treatment on adverse outcomes in ACS focusing specifically on differences between those with and without AF. Accordingly, we undertook this study to describe, in a well-defined community setting, the spectrum of antithrombotic treatment in ACS patients with and without AF, and the association of antithrombotic strategies with subsequent risk of bleeding, stroke, and all-cause mortality.

Methods

This study was conducted in Olmsted County, MN utilizing the resources of the Rochester Epidemiology Project (REP).⁴ Virtually complete capture of healthcare utilization and outcomes in Olmsted County is possible because only a few providers deliver most health care to local residents and each provider uses comprehensive medical records, which are indexed through the REP. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Olmsted County, MN residents with hospital discharge diagnoses of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 410–411 between January 1, 2005 and December 31, 2010 were identified. The presence of cardiac chest pain was used to validate UA using the Braunwald classification.⁵ Epidemiologic criteria incorporating cardiac pain, biomarker levels, and Minnesota coding of the electrocardiogram (ECG) were used to validate MI.^{6–8} According to guidelines using Troponin T in the algorithm,⁹ the presence or absence of a change between any 2 troponin measurements is defined by a difference of 0.05 ng/mL. As troponin can remain elevated for 2 weeks after events causing its rise, the biomarkers were downgraded from abnormal to equivocal when these conditions occurred 2 weeks before the MI.¹⁰

AF events occurring prior to ACS or during the index ACS hospitalization were identified using ECGs and ICD-9-CM codes 427.31 or 427.32 assigned during inpatient or outpatient visits. The ECGs were electronically interpreted, and as part of routine clinical practice, all ECGs were subsequently verified by a cardiologist. When no ECG was present or when inconsistencies between the dates of the ECG and diagnostic code precluded the ability to determine whether or not AF was present at or prior to index, manual review of the medical record was used to validate the AF event.

Patient demographics, cigarette smoking status, procedures and discharge medications were obtained from review of patient medical records. Antithrombotic prophylaxis therapies

included warfarin, aspirin, and other antiplatelets (clopidogrel, ticlopidine, and dipyridamole). Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Clinicians' diagnoses were used to identify history of hyperlipidemia, hypertension, heart failure (HF), chronic obstructive pulmonary disease (COPD), cancer, or stroke or transient ischemic attack prior to ACS. The American Diabetes Association criteria was used to define diabetes.¹¹ Glomerular filtration rate (eGFR) was estimated using the closest serum creatinine within 1 year of index using the Modification of Diet in Renal Disease Study equation.¹² The CHADS₂ risk score for future stroke risk prediction¹³ and the ATRIA bleeding risk score¹⁴ were calculated.

Participants were followed through December 31, 2012 for bleeding, strokes, and deaths from any cause. Bleeding events after discharge were ascertained using ICD-9-CM codes identified by Fosbol, et al as a guideline.¹⁵ For strokes, we excluded from our analyses individuals who had a prior history of ischemic stroke (N=41), and in the remaining individuals, ICD-9-CM codes 433.x1, 434.x1 and 436 were used to identify incident ischemic strokes. Deaths were obtained from inpatient and outpatient medical records, death certificates from the state of Minnesota, and obituaries and notices of death in the local newspapers.

Statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC). Baseline participant characteristics by presence of AF were compared using chi-square tests for categorical variables and t-tests for continuous variables. Patients were categorized based on the number of antithrombotic agents (none, single, double, triple). Logistic regression was used to determine predictors of double/triple vs. no/single antithrombotic therapy after adjustment for age and sex.

A propensity score for double/triple vs. no/single antithrombotic therapy was estimated using the following variables at index ACS: age, sex, marital status, highest level of education attained, BMI, smoking status, eGFR, family history of coronary artery disease, hypertension, hyperlipidemia, diabetes, COPD, HF, stroke or transient ischemic attack, malignancy, presence of AF, type of ACS (UA or MI), reperfusion/revascularization, peak troponin, statins, beta blockers, and angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACE-I/ARBs). Inverse probability of treatment weights were assigned using a weight of 1/P for those on double/triple therapy and 1/(1-P) for no/single therapy, where P is the propensity score for double/triple therapy. To assess the associations of double/triple vs. no/single antithrombotic therapy with bleeding, ischemic stroke, and all-cause mortality, Cox proportional hazard regression, using inverse probability of treatment weighting of the propensity score and adjusting for age and sex, were modeled.^{16,17} In ancillary analyses, a propensity score for warfarin vs. no warfarin was created and the Cox regression analyses were repeated for warfarin vs. no warfarin.

Results

Between 2005 and 2010, 1244 incident ACS were identified, of which 23 did not grant complete research authorization and 62 died in hospital, leaving 1159 incident ACS patients (mean age 66.5 ± 14.5 years, 60% male, 93% White) for our study. Of these, 729 (63%) had

MI and 430 (37%) had UA. In addition, 252 (22%) had concomitant AF. Those with AF presented with a similar proportion of UA and MI as those without AF. However, those with ACS+AF were older, more likely to be female, less likely to be a current smoker, and had more comorbidities (Table 1).

Nearly 80% of all ACS patients underwent coronary angiography, but differences were observed between those with and without AF. Those with AF were less likely to have angiography (153 (63%) for those with AF and 742 (82%) for those without AF). However, of those who underwent angiography, a higher proportion of the ACS+AF patients had 2 vessels with >75% stenosis as compared to ACS patients without AF (40% vs. 27%, respectively).

More ACS+AF patients were managed non-invasively than those without AF (58% vs. 36%, respectively). Only 106 (42%) ACS+AF patients received reperfusion/revascularization during the hospitalization compared to 583 (64%) of ACS patients without AF. Of those who received reperfusion/revascularization, 67 (63%) and 512 (88%) had percutaneous coronary intervention (PCI) with stent placement in the ACS+AF and no AF categories, respectively (Figure 1). Most patients were prescribed beta blockers (86%) and ACE-I/ARBs (58%), which did not differ by AF. However, ACS+AF patients were less likely to be prescribed statins (72% vs. 87% among those without AF).

AF status substantially impacted the choice of antithrombotic strategy at discharge (Table 2). Fewer than half (48%) of the ACS+AF patients were discharged on 2 or 3 antithrombotic agents and 33% received warfarin, usually in combination with a single antiplatelet agent, and only 10% received warfarin with 2 antiplatelet agents. In contrast, among ACS patients without AF, 63% were discharged on either 2 or 3 agents, the majority on dual antiplatelets, with only 4% on warfarin and 1% on warfarin with 2 antiplatelets.

After adjustment for age and sex, the predictors of double/triple antithrombotic treatment strategies in ACS+AF patients included younger age, non-smoking status, overweight and obesity, hypertension, no history of COPD, higher CHADS₂ score, higher peak troponin, and reperfusion/revascularization; a trend for increased use of double/triple therapy was observed for those with lower eGFR (Figure 2A). In those without AF, the predictors of double/triple therapy included younger age, male gender, higher education, higher eGFR, no history of HF or cancer, MI as the index ACS event, higher peak troponin, and reperfusion/revascularization (Figure 2B).

Over a median follow-up of 4.3 years for all ACS patients, 312 patients experienced a bleed, 67 incident strokes occurred, and 268 patients died. Overall, the risk of subsequent bleeding, strokes, and all-cause mortality were similar for patients discharged on double/triple and no/single antithrombotic therapy (Table 3). However, a trend suggesting a lower risk for ischemic stroke was observed for ACS+AF patients on double/triple therapy.

Due to the small number of outcome events and limited number of individuals on warfarin plus dual antiplatelets ('triple therapy'), we are unable to provide estimates for those receiving triple therapy. Those on warfarin (alone or in any combination with antiplatelet agents) experienced higher rates of bleeding compared to those not on warfarin overall (HR

1.98, 95% CI 1.12–3.48); however, the increased risk was nonsignificant among ACS+AF patients (HR 1.47, 95% CI 0.89–2.44). Overall, the risk of all-cause mortality did not differ between those on warfarin vs. no warfarin (HR 1.17, 95% CI 0.63–2.16), but there was an indication of a decreased risk of death among ACS+AF patients who received warfarin (HR 0.48, 95% CI 0.30–0.77).

Discussion

ACS+AF patients are older, have more extensive coronary artery disease, and have a higher burden of comorbidities than ACS patients without AF. As compared to ACS patients without AF, ACS+AF patients are less likely to undergo diagnostic coronary angiography and subsequent reperfusion/revascularization. We did not detect an impact of antithrombotic strategy on overall risk of stroke, bleed, or death in the full study cohort. However, ACS patients with AF showed trends for reduction in ischemic stroke with double/triple antithrombotics.

The use of invasive management in ACS has been documented to decrease with increasing age^{18–20} and is lower in patients who have more comorbidities.^{19,20} Among 1001 patients presenting to a German hospital with ACS, older patients with comorbidities were less likely to undergo invasive management (PCI or CABG), even though an invasive strategy was associated with significantly lower in-hospital and long-term mortality.¹⁹ In the TACTICS-TIMI 18 trial, an early (< 48 hours) invasive management strategy was associated with a reduced risk of MI and rehospitalization for ACS within 30 days and MI within 6 months for elderly (> 65 years) but not younger patients with NSTEMI and UA. Despite this potential benefit of invasive management for elderly patients, an increased risk of major bleeding was apparent among those over 75 who were treated invasively.²¹ These findings highlight the complexity of choice for invasive or conservative management of ACS, which may be further complicated in patients with concomitant AF.

The choice of dual antiplatelet therapy versus triple therapy for ACS+AF patients is complicated due to the increased risk of bleeding with triple therapy²² and the difficulties of managing warfarin. Furthermore, ACS patients with either pre-existing or new-onset AF who undergo PCI are at an increased risk of both stroke and stent thrombosis;²³ however, most patients with AF undergoing PCI are also at a high risk for bleeding.²⁴ Thus, while these patients generally meet accepted indications for oral anticoagulation for stroke prevention in addition to dual-antiplatelet therapy, physicians may avoid triple therapy due to the high risk of bleeding.

In our community-based study, only 10% of ACS+AF patients were discharged on triple therapy. This low rate of triple therapy has been consistently reported in other studies, ranging from 5.7% to 10.0% among NSTEMI patients with AF from the EARLY ACS randomized clinical trial²⁵ and CRUSADE registry,¹⁵ respectively, 13.7% among STEMI patients with AF enrolled in the APEX-AMI clinical trial,²⁶ 7.2% among AF patients with coronary artery disease in the Duke Databank for Cardiovascular Disease,²⁷ and between 13.0% and 15.6% among AF patients with MI or PCI in a national registry in Denmark.^{28,29}

Studies including AF patients with ACS or who underwent PCI have overwhelmingly shown an increased risk of bleeding for those on triple therapy.^{15,24,28,29} Despite this increased risk, some evidence indicates that patients who receive triple therapy benefit from a reduced risk of major adverse cardiac events (death, MI, and/or target lesion revascularization)²⁴ and all-cause mortality.^{24,28} While our study was limited by sample size, we found an increased risk of bleeding overall for individuals on warfarin, which remained elevated but became nonsignificant in patients with AF. In contrast, strategies that included warfarin appeared to decrease the risk of mortality in ACS+AF patients. These results are consistent with previous clinical trials, where warfarin was associated with a reduction in stroke or death within 90 days,²⁶ and death or MI within 6 months.³⁰

Some limitations deserve mention. First, these data, largely from a single practice, may not be fully representative of other practices. Second, we relied on the medical record for antithrombotic medications prescribed at discharge, and thus, we cannot confirm whether the medications were taken or if they were stopped. Third, we relied on billing codes for the capture of stroke and bleeding outcomes, which may have resulted in some misclassification of the outcomes. Fourth, the sample size did not enable the assessment of the association of each combination of treatment separately with bleeding, strokes, and all-cause mortality. Finally, although we used propensity scores to control for confounding by indication, residual confounding may still be present.

Despite these limitations, our study has many strengths. First, our cohort is community-based and captures the full spectrum of ACS, including incident MI and UA patients. Second, the long follow-up of the cohort enables assessment of long-term outcomes, which is generally not feasible with clinical trials. Finally, unlike a clinical trial where strict inclusion criteria result in the inclusion of only a subgroup of patients and where treatment is randomized, we have provided estimates of the effect of antithrombotic treatment strategy with adverse outcomes in a 'real-world' setting.

These population-based data reflect the comprehensive experience of a community and suggest that, overall, clinical judgment results in satisfactory selection of antithrombotic strategies for ACS patients. Nonetheless, our data also suggest some important hypotheses for further consideration. First, the presence of AF and the presumed necessity for more complex antithrombotic management may, in part, account for lower rates of acute revascularization in ACS+AF. Second, cardio-embolic strokes are only one of multiple competing adverse outcomes in this elderly population with substantial comorbidity burden, and the stroke rate attributable to AF is relatively low compared to the overall mortality rate. A two-agent antithrombotic regimen that includes an anticoagulant and a single antiplatelet agent, such as clopidogrel, is likely to provide satisfactory outcomes. Third, ACS+AF patients seem likely to derive greater benefit from intensified (double/triple) antithrombotic strategies, as shown by a trend toward lower risk of stroke. Finally, the effect of intensified antithrombotic strategies on stroke risk may be impacted by the adoption of novel oral anticoagulants in AF patients. Future research specifically focusing on ACS patients with AF is warranted.

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Figure 1.

Reperfusion/revascularization treatments for acute coronary syndrome patients by atrial fibrillation status for (A) all acute coronary syndrome patients, (B) myocardial infarction patients, and (C) unstable angina patients.

ACS, acute coronary syndrome; AF, atrial fibrillation; CABG, coronary artery bypass graft; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; UA, unstable angina.

Figure 2.

A. Age- and sex-adjusted predictors of double/triple versus no/single antithrombotic therapy in acute coronary syndrome patients with atrial fibrillation.

B. Age- and sex-adjusted predictors of double/triple versus no/single antithrombotic therapy in acute coronary syndrome patients without atrial fibrillation.

Table 1

Baseline characteristics of acute coronary syndrome patients overall and by atrial fibrillation status

Variable	Atrial Fibrillation			P-value
	Total (N=1159)	Yes (N=252)	No (N=907)	
Age (years)	66.5 (14.5)	76.2 (11.8)	63.8 (14.1)	<0.001
Male	694 (59.9%)	130 (51.6%)	564 (62.2%)	0.002
Married	718 (61.9%)	132 (52.4%)	586 (64.6%)	<0.001
High school or greater education	1020 (88.5%)	216 (86.1%)	804 (89.2%)	0.162
Body mass index (kg/m ²)	29.4 (6.5)	29.0 (6.4)	29.5 (6.5)	0.137
Smoking status				
Never	456 (39.3%)	108 (42.9%)	348 (38.4%)	<0.001
Former	450 (38.8%)	112 (44.4%)	338 (37.3%)	
Current	253 (21.8%)	32 (12.7%)	221 (24.4%)	
Hypertension	821 (70.8%)	217 (86.1%)	604 (66.6%)	<0.001
Hyperlipidemia	801 (69.1%)	189 (75.0%)	612 (67.5%)	0.022
Diabetes mellitus	252 (21.7%)	56 (22.2%)	196 (21.6%)	0.835
Family history of CAD	258 (22.3%)	39 (15.5%)	219 (24.1%)	0.003
Heart failure	142 (12.3%)	72 (28.6%)	70 (7.7%)	<0.001
Stroke/transient ischemic attack	120 (10.4%)	44 (17.5%)	76 (8.4%)	<0.001
Cancer	208 (17.9%)	73 (29.0%)	135 (14.9%)	<0.001
Chronic obstructive pulmonary disease	164 (14.2%)	57 (22.6%)	107 (11.8%)	<0.001
eGFR (mL/min per 1.73 m ²)	69.4 (25.0)	61.0 (24.7)	71.8 (24.6)	<0.001
Type of ACS				
Unstable angina pectoris	430 (37.1)	101 (40.1)	329 (36.3)	0.253
STEMI	168 (14.5)	29 (11.5)	139 (15.3)	
NSTEMI	561(48.4)	122 (48.4)	439 (48.4)	
Peak troponin (ng/mL)	1.3 (2.8)	1.0 (2.5)	1.3 (2.9)	0.083

Values are expressed as mean (SD) for continuous variables and N (%) for categorical variables.

CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction

Family history of coronary artery disease is defined as myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention in first-line relatives under the age of 55 for males and 65 for females.

Table 2

Antithrombotic treatment strategy at hospital dismissal in patients with acute coronary syndrome by presence or absence of atrial fibrillation

Variable	Overall (N=1159)	Atrial Fibrillation	
		Yes (N=252)	No (N=907)
Individual Therapy Combinations			
None	67 (5.8%)	14 (5.6%)	53 (5.8%)
Aspirin alone	360 (31.1%)	99 (39.3%)	261 (28.8%)
Other antiplatelet alone	20 (1.7%)	5 (2.0%)	15 (1.7%)
Warfarin alone	18 (1.6%)	12 (4.8%)	6 (0.7%)
Aspirin + other antiplatelet	593 (51.2%)	50 (19.8%)	543 (59.9%)
Aspirin + warfarin	64 (5.5%)	46 (18.3%)	18 (2.0%)
Warfarin + other antiplatelet	2 (0.2%)	2 (0.8%)	0 (0.0%)
All 3 treatments	35 (3.0%)	24 (9.5%)	11 (1.2%)
Number of Treatments			
None	67 (5.8%)	14 (5.6%)	53 (5.8%)
Single	398 (34.3%)	116 (46.0%)	282 (31.1%)
Double	659 (56.9%)	98 (38.9%)	561 (61.9%)
Triple	35 (3.0%)	24 (9.5%)	11 (1.2%)

Table 3

Rates and hazard ratios for bleeding, ischemic stroke, and all-cause mortality in acute coronary syndrome patients for double/triple therapy versus no/single therapy

		Bleeding		Ischemic Stroke		All-Cause Mortality	
		No/Single	Double/Triple	No/Single	Double/Triple	No/Single	Double/Triple
Overall	N events	132	180	31	36	159	109
	Rate (95% CI) ^a	87.78 (73.44–104.1)	72.05 (61.90–83.37)	17.30 (11.75–24.55)	12.12 (8.49–16.78)	85.82 (73.00–100.2)	35.70 (29.32–43.07)
	HR (95% CI) ^b	1.00 (ref)	1.00 (0.74–1.36)	1.00 (ref)	0.82 (0.43–1.54)	1.00 (ref)	0.97 (0.71–1.35)
By AF Status							
AF	N events	44	47	10	4	73	40
	Rate (95% CI) ^a	139.4 (101.3–187.2)	125.3 (92.05–166.6)	24.71 (11.85–45.45)	8.33 (2.27–21.33)	171.2 (134.2–215.2)	82.13 (58.67–111.8)
	HR (95% CI) ^b	1.00 (ref)	1.07 (0.60–1.91) ^d	1.00 (ref)	0.30 (0.07–1.26) ^e	1.00 (ref)	0.80 (0.48–1.35) ^c
No AF	N events	88	133	21	32	86	69
	Rate (95% CI) ^a	74.06 (59.40–91.25)	62.64 (52.45–74.24)	15.13 (9.37–23.14)	12.85 (8.79–18.14)	60.30 (48.23–74.47)	26.89 (20.92–34.03)
	HR (95% CI) ^b	1.00 (ref)	0.99 (0.69–1.42) ^d	1.00 (ref)	1.10 (0.52–2.33) ^e	1.00 (ref)	1.14 (0.76–1.71) ^c

CI, confidence interval; HR, hazard ratio; AF, atrial fibrillation

^aUnadjusted rate per 1,000 person-years.

^bHazard ratios are adjusted for age and sex, and are weighted for the inverse probability of the propensity score for double/triple therapy.

^cP-value for therapy*atrial fibrillation interaction = 0.37.

^dP-value for therapy*atrial fibrillation interaction = 0.91.

^eP-value for therapy*atrial fibrillation interaction = 0.10.