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†RDN arm reduction from baseline.

**ANCOVA adjusted; secondary efficacy analysis.

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Dual Antiplatelet Therapy and Outcomes in Patients With Atrial Fibrillation and Acute Coronary Syndromes Managed Medically Without Revascularization: Insights From the TRILOGY ACS Trial

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ABSTRACT

Associations between atrial fibrillation (AF), outcomes, and response to antiplatelet therapies in patients with acute coronary syndrome (ACS) managed medically without revascularization remain uncertain. We examined these associations for medically managed ACS patients randomized to dual antiplatelet therapy (DAPT) using patient data from the TRILOGY ACS trial. DAPT included aspirin plus clopidogrel 75 mg/d or prasugrel 10 mg/d (5 mg/d for those <60 kg or age ≥75 years). Patients receiving oral anticoagulants were excluded. Cox proportional hazards regression modeling was used to characterize associations between patients with AF (AF+) vs those without (AF−) and risk of ischemic and bleeding events, and to explore effects of randomized treatment on outcomes. Among 9101 patients with baseline AF status, 710 (7.8%) had AF. AF+ patients were older and had more comorbidities. Unadjusted associations of the composite of cardiovascular death/myocardial infarction/stroke were significantly higher among AF patients at 30 months (31.1% vs 18.4%; HR: 1.61, 95% CI: 1.35-1.92, $P < 0.001$), but differences did not persist after adjustment (HR: 1.16, 95% CI: 0.97-1.39, $P = 0.11$). When individual components of the composite endpoint were evaluated, 30-month risk of events in AF+ patients was significantly higher. Thirty-month risk of all-cause death was significantly higher in AF+ patients: 18.1% vs 11.1% (HR: 1.62, 95% CI: 1.30-2.02, $P < 0.001$). There was no significant interaction with randomized treatment and AF for the primary endpoint. Among medically managed high-risk ACS patients receiving DAPT, AF was associated with higher unadjusted risks of ischemic and bleeding outcomes that were similar by treatment group.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is a risk factor for ischemic stroke and cardiovascular mortality.[1] In patients with stable coronary artery disease, the prevalence of AF is 12.5%[2-4] and is associated with a higher risk of cardiovascular outcomes.[5] Dual antiplatelet therapy (DAPT), comprising aspirin and a $P2Y_{12}$ receptor inhibitor, is standard of care following percutaneous coronary intervention (PCI) for patients with acute coronary syndromes (ACS). However, a substantial proportion of these patients have AF, for which oral anticoagulants (OACs) provide superior prevention of stroke compared with antiplatelet agents; but, when combined with DAPT, they may significantly increase the risk of bleeding, specifically when prescribed with a newer $P2Y_{12}$ receptor inhibitor such as prasugrel or ticagrelor.[6-11]

Patients with both AF and ACS present a clinical conundrum, given uncertainty regarding the optimal antithrombotic strategy, as well as for those undergoing PCI (A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention [PIONEER AF-PCI; http://www.ClinicalTrials.gov NCT01830543] and Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting [REDUAL-PCI; NCT02164864]). Currently, controversy exists regarding the prognostic role of AF in patients with ACS,[12,13] and to date there are no studies analyzing the association between AF and outcomes among ACS patients at highest risk—specifically, elderly patients managed medically without coronary revascularization. The randomized Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS; NCT00699998) trial included a prospective analysis plan to evaluate the prognostic role of AF in elderly patients with ACS. Accordingly, using the TRILOGY ACS study, we sought to (1) determine the risk of ischemic and bleeding outcomes in high-risk patients with both AF and ACS who were medically managed with DAPT and without planned invasive revascularization; (2) evaluate the safety and efficacy of DAPT with prasugrel or clopidogrel among high-risk elderly patients with AF and ACS; and (3) evaluate the magnitude of platelet aggregation in AF patients with recent ACS using platelet reactivity units (PRUs) obtained from the substudy of the TRILOGY ACS trial.

Methods

Trial Design

The design, methods, and primary results of TRILOGY ACS have been previously described.[14,15] Briefly, TRILOGY ACS was an international, randomized, active-controlled, double-blinded, double-dummy trial that enrolled 9326 intention-to-treat (ITT) patients who were planned to undergo medical management without invasive revascularization for unstable angina (UA) or non–ST-segment elevation myocardial infarction (NSTEMI). Study participants were randomly assigned in a 1:1 fashion to receive prasugrel 10 mg/d (5 mg/d in patients <60 kg body weight or age ≥75 years) or clopidogrel (75 mg/d), plus background low-dose aspirin therapy.[15] Participants for whom AF status at baseline was missing (n = 225, 2.4%) were excluded from the present analysis. A final cohort of 9101 participants was assessed for ischemic outcomes; for the analysis of

safety outcomes, patients were assessed during the "at-risk" interval of actual study-drug treatment through 7 days after study-drug discontinuation (n = 9022).

All appropriate national regulatory agencies and institutional review boards at each participating center approved the TRILOGY ACS study and all participants gave informed consent. An international multidisciplinary executive committee designed the study and takes responsibility for the accuracy and completeness of all data and subsequent analyses.

Clinical Outcomes

The primary efficacy endpoint was the composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. An independent cardiovascular adjudication committee whose members were blinded to study-group assignments evaluated suspected ischemic and bleeding endpoints. Key bleeding and safety endpoints included Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria for severe or life-threatening bleeding unrelated to coronary artery bypass grafting and Thrombolysis in Myocardial Infarction (TIMI) criteria for major bleeding unrelated to coronary artery bypass grafting.[16,17]

Platelet Function Substudy

A total of 2564 TRILOGY ACS subjects from participating sites were enrolled in a prospective platelet function substudy that evaluated differences in platelet reactivity over time for patients receiving prasugrel vs clopidogrel.[18] Briefly, substudy participants underwent serial platelet reactivity assessments (as measured in $P2Y_{12}$ PRUs) with the VerifyNow system (Accriva Diagnostics, San Diego, CA). The PRU measurements were performed at baseline, at 2 hours, and at 1, 3, 6, 12, 18, 24, and 30 months following randomization. Participants receiving prasugrel 10 mg/d exhibited significantly lower platelet reactivity vs those receiving clopidogrel, but no significant independent associations with ischemic endpoints were seen after adjustment.[18]

Atrial Fibrillation

Patients included in this secondary analysis had a history of AF prior to or during the index hospitalization and were not taking an OAC. In addition to identifying a history of prior or current AF, additional characteristics were collected, including duration of AF, a history of prior thromboembolic events associated with AF prior to randomization, the use of OACs prior to randomization, antiarrhythmic drug use within the previous 12 months prior to randomization, and discontinuation of OAC due to a bleeding complication. Site investigators were not queried as to the overall use of OAC in patients with AF and why patients were not treated with OAC prior to an ACS event.

Statistical Analysis

Baseline characteristics have been summarized according to AF status at baseline. This analysis analyzed patients with history of current or prior AF (AF+) vs those without history of AF (AF−). Continuous variables are presented as median (interquartile range [IQR]), and differences are compared using the Wilcoxon rank-sum test. Categorical variables are presented as counts (percentages), and differences are compared using the Pearson χ^2 test when cell frequencies are sufficient; otherwise, an exact test is used.

For patients with a history of AF (current or prior), the duration of AF (in months), stoppage of an OAC due to a bleeding event, and treatments received within the last 12 months are summarized according to treatment and for the entire ITT population. For continuous variables, descriptive statistics (ie, mean, SD, median, minimum, and maximum) are reported, and differences between treatments are compared using the Wilcoxon rank-sum test. Categorical variables are presented as counts (percentages), and differences are compared using the Pearson χ^2 test if cell frequencies are sufficient; otherwise, an exact test is used.

For each ischemic and bleeding endpoint, the total number of events and Kaplan-Meier event rate estimate (95% confidence interval [CI]) through 30 months after randomization are shown separately for AF+ vs AF− patients. Events across the follow-up period are compared by AF status using the log-rank test. To examine the relationship between AF and clinical outcomes, unadjusted and adjusted Cox proportional hazards regression models were developed that tested the univariate and multivariate association of AF (AF+ vs AF−) and each clinical outcome. The TRILOGY ACS adjustment models have been built for each ischemic and bleeding outcome and control for baseline characteristics and risk factors.[19] When fitting the adjustment model, the proportional hazards assumption was checked for each variable and the linearity assumption was checked for each continuous variable. If the proportional hazard assumption was violated, an interaction of the variable with log-transformed time was included in the model. If the linearity assumption was violated, a restricted cubic spline was used to approximate the nonlinear relationship of the variable with the outcome. For a full description of the TRILOGY ACS adjustment models used in this analysis, see Supporting Information in the online version of this article.

Only patients enrolled in the platelet function substudy (n = 2564) were considered for the analysis comparing platelet function of medically managed ACS patients with/without a history of AF and treated with prasugrel or clopidogrel. For each treatment group, the Wilcoxon rank-sum test was used to test whether the distribution of 30-day PRU was different between patients with vs without AF. Results are presented as medians (IQR). To test for a difference across the 4 groups, the Kruskal-Wallis test was used.

All statistical tests are 2-sided, and a P value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC) and R version 3.0.3 (R Foundation, Vienna, Austria) by independent statisticians at the Duke Clinical Research Institute in Durham, North Carolina.

Results

A total of 9326 TRILOGY ACS participants underwent randomization according to the ITT definition. As previously noted, 225 (2.4%) participants who lacked data regarding

Table 1. Baseline Characteristics of the Study Population

Characteristic	History of Prior or Current AF		P Value
	Yes, n = 710[a]	No, n = 8391[b]	
Demographics			
Sex			<0.001
F	323 (45.5)	3237 (38.6)	
M	387 (54.5)	5154 (61.4)	
Median age, y	72.0 (66.0–78.0)	65.0 (58.0–73.0)	<0.001
Age ≥75 y	282 (39.7)	1718 (20.5)	<0.001
Median weight, kg	77.0 (66.1–88.0)	75.0 (65.0–86.0)	0.008
Weight <60 kg	87/709 (12.3)	1287/8385 (15.3)	0.028
Region			<0.001
Central/Eastern Europe	341 (48.0)	2681 (32.0)	
East Asia	57 (8.0)	684 (8.2)	
Indian subcontinent	17 (2.4)	1114 (13.3)	
Latin America	68 (9.6)	1190 (14.2)	
Mediterranean basin	33 (4.6)	594 (7.1)	
North America	104 (14.6)	1129 (13.5)	
Western Europe/Scandinavia	77 (10.8)	876 (10.4)	
Rest of world	13 (1.8)	123 (1.5)	
Randomized treatment			0.538
Prasugrel	347 (48.9)	4202 (50.1)	
Clopidogrel	363 (51.1)	4189 (49.9)	
Prasugrel dose			<0.001
5 mg	153/347 (44.1)	1317/4202 (31.3)	
10 mg	194/347 (55.9)	2885/4202 (68.7)	
Presentation characteristics			
Median time from presentation until start of study drug, h	117.3 (71.8–167.4)	107.3 (61.5–158.9)	<0.001
Killip class II–IV on presentation	137/709 (19.3)	965/8387 (11.5)	<0.001
Disease classification			0.881
UA/unknown	217 (30.6)	2542 (30.3)	
NSTEMI	493 (69.4)	5849 (69.7)	
Cardiovascular risk factors			
Family history of CAD	186/595 (31.3)	2269/7544 (30.1)	0.545
HTN	636 (89.6)	6802/8370 (81.3)	<0.001
Hyperlipidemia	428/671 (63.8)	4672/7993 (58.5)	0.007
DM	228 (32.1)	3217/8374 (38.4)	<0.001
Current/recent smoking[c]	94/703 (13.4)	1718/8312 (20.7)	<0.001
CVD history			
Prior MI	292/706 (41.4)	3582/8333 (43.0)	0.402
Prior PCI	194/707 (27.4)	2167/8351 (25.9)	0.386

Table 1. Continued

| Characteristic | History of Prior or Current AF | | P Value |
	Yes, n = 710[a]	No, n = 8391[b]	
Prior CABG	134 (18.9)	1265/8373 (15.1)	0.008
Prior PAD	67/690 (9.7)	592/8270 (7.2)	0.014
Prior HF	238/707 (33.7)	1348/8350 (16.1)	<0.001
Baseline risk assessment			
Median GRACE risk score	138.0 (120.0–155.0)	120.0 (104.0–138.0)	<0.001
CHA$_2$DS$_2$-VASc risk of stroke			
Mean score	3.7 ± 1.4	2.9 ± 1.4	<0.001
Score			<0.001
1	30 (4.2)	1022 (12.2)	
2	91 (12.8)	2155 (25.7)	
3	196 (27.6)	2287 (27.3)	
4	200 (28.2)	1623 (19.3)	
5	122 (17.2)	784 (9.3)	
6	49 (6.9)	248 (3.0)	
7	14 (2.0)	62 (0.7)	
8	3 (0.4)	4 (0.0)	
9	1 (0.1)	2 (0.0)	
Baseline laboratory values			
Median SBP, mm Hg	130.0 (120.0–140.0)	129.0 (119.0–139.0)	0.054
Median heart rate, bpm	68.0 (61.0–76.0)	69.0 (62.0–76.0)	0.412
Median Hgb, g/dL	13.4 (12.4–14.5)	13.6 (12.4–14.7)	0.108
Median CrCl, mL/min	64.4 (46.5–84.2)	73.8 (55.1–97.0)	<0.001
Prerandomization procedures			
Angiography performed	263 (37.0)	3464 (41.3)	0.027
Concomitant medications at randomization			
ASA			
Daily dose <100 mg	246 (34.6)	2808 (33.5)	0.521
Daily dose 100–250 mg	369 (52.0)	4460 (53.2)	0.545
Daily dose >250 mg	54 (7.6)	583 (6.9)	0.510
β-Blocker	551 (77.6)	6530 (77.8)	0.894
ACEI/ARB	577 (81.3)	6284 (74.9)	<0.001
Statin	563 (79.3)	7033 (83.8)	0.002
PPI	185 (26.1)	2099 (25.0)	0.539

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid (aspirin); CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHA$_2$DS$_2$-VASc, congestive heart failure, HTN, age ≥75 y, DM, stroke/TIA, vascular disease, age 65–74 y, sex category (women); CrCl, creatinine clearance; CVD, cardiovascular disease; DM, diabetes mellitus; F, female; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; Hgb, hemoglobin; HTN, hypertension; IQR, interquartile range; M, male; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischemic attack; UA, unstable angina.
Data are presented as n (%), mean ± SD, or median (IQR).
[a]Total no. of patients is 710 unless otherwise noted. [b] Total no. of patients is 8391 unless otherwise noted. [c] Smoking within 30 days of randomization.

baseline AF status were excluded from this analysis. Key clinical characteristics of AF+ patients are shown in Table 1. In this medically managed population, AF+ patients were older and more likely to have an increased number of medical comorbidities, as well as higher CHA_2DS_2-VASc scores (congestive heart failure, hypertension, age $\geq$75 y, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 y, sex category [women]) and higher Global Registry of Acute Coronary Events (GRACE) risk scores.

Within the ITT population, 4549 (50.0%) participants were randomly assigned to receive prasugrel and 4552 (50.0%) were randomly assigned to clopidogrel. The proportion of AF+ within the ITT population (n = 710, 7.8%) was balanced between treatment groups (7.6% vs 8.0%; $P = 0.54$). The median duration of AF for both treatment groups was 1 month ($P = 0.81$), with 64.5% (453/702) of AF+ patients reporting duration of AF $\leq$1 month. There was no significant difference between treatment groups in the proportion of AF+ patients who were treated with antiarrhythmic drug therapy in the previous 12 months (38.0% vs 37.7%; $P = 0.97$). Groups were balanced with respect to previous treatment with OACs (19.9% vs 22.3%; $P = 0.72$). There was no difference in previous thromboembolic events associated with AF between treatment groups (2.0% vs 2.2%; $P = 0.41$).

Ischemic Outcomes

The unadjusted association of the primary composite endpoint of cardiovascular death, MI, or stroke occurred with increased risk in AF+ patients at 30 months: 31.1% vs 18.4% (hazard ratio [HR]: 1.61, 95% CI: 1.35-1.92, $P < 0.001$; Table 2/Figure 1). When all secondary outcomes were evaluated, there was a significantly increased risk of events, particularly stroke, in AF+ patients at 30 months, although the overall incidence of stroke was low (Table 2, Figure 2). The rate of all-cause death was significantly higher in AF+ patients at 30 months: 18.1% vs 11.1% (HR: 1.62, 95% CI: 1.30-2.02, $P < 0.001$). After adjustment, there was no difference in rates of the composite endpoint of cardiovascular death, MI, or stroke (HR: 1.16, 95% CI: 0.97-1.39, $P = 0.11$). Rates of all-cause death were also similar between AF+ and AF− patients (HR: 1.10, 95% CI: 0.87-1.39, $P = 0.42$).

Although no significant treatment interactions were found for either the primary composite endpoint or secondary component endpoints, a significant interaction was observed for AF+ patients treated with prasugrel and an increased risk of MI (P for interaction = 0.01).

Bleeding Outcomes

Rates of major bleeding (GUSTO severe or life-threatening bleeding; GUSTO severe, life-threatening, or moderate bleeding; TIMI major bleeding) at 30 months were similar between both AF groups. The TIMI major or minor bleeding was higher in patients with AF: 8.3% vs 3.0% (HR: 1.76, 95% CI: 1.10-2.81, $P = 0.016$; Table 2). This effect, however, was attenuated after adjustment (HR: 1.46, 95% CI: 0.90-2.36, $P = 0.124$). There was no significant interaction for AF by treatment for any bleeding endpoint.

Study-Drug Discontinuation

Rates of study-drug discontinuation were highest among AF+ patients. The primary indications for study-drug discontinuation among AF+ patients include patient decision and adverse events (Table 3). Among AF+ patients, the rate of study-drug discontinuation for the initiation of OAC therapy was low but significantly higher than in non-AF patients. In addition, there were no significant differences in loss to follow-up for either AF+ or AF− study participants (0.3% vs 0.2%; $P = 0.34$).

Atrial Fibrillation and Platelet Function

Among patients randomized to clopidogrel, there was no statistically significant difference in the median PRU values between AF+ patients (212 PRU [IQR, 140–246]) and AF− patients (206 PRU [IQR, 143–263]; $P = 0.63$). However, among those randomized to prasugrel, AF+ patients had significantly higher median PRU values (131 PRU [IQR, 76–197]) than AF− patients (85 PRU [IQR, 42–154]); $P < 0.001$. In addition, AF+ patients receiving prasugrel had lower median PRU values than did those receiving clopidogrel.

Discussion

This study, which examined the association of AF with ischemic and bleeding outcomes in ACS patients treated medically with DAPT but without oral anticoagulation, yields several important findings. First, AF is accompanied by older age, an increased burden of comorbidities, as well as an increased risk of stroke/systemic embolism and death or death/MI, as evidenced by higher CHA_2DS_2-VASc and GRACE risk scores, respectively. Second, the presence of AF is associated with significantly higher median PRU measurement values at 30 days among AF patients treated with the 5-mg dose of prasugrel and with an increased risk of MI in this subgroup. Third, the presence of AF in study participants with UA/NSTEMI who were treated with DAPT was not associated with worse ischemic or bleeding outcomes after adjustment when compared with patients without AF.

Atrial fibrillation has been assumed to be a causal factor associated with increased morbidity and mortality in patients with MI. Potential mechanistic explanations include loss of atrial contraction, decreased atrioventricular synchrony, elevated filling pressures with enhanced remodeling and worsening left ventricular systolic dysfunction, and increased rates of ventricular arrhythmias and sudden cardiac death.[20−22] Previous studies have shown an increased risk of major adverse cardiovascular events and all-cause mortality in AF patients with ACS.[23−29] However, controversy still exists as to whether AF plays a prognostic role in poor outcomes or is merely a marker of worsening risk due to an increased number of confounding comorbidities.

In our analysis from a large, randomized trial of medically managed patients with UA/NSTEMI, we demonstrated that patients with AF do not have an increased risk of ischemic or bleeding outcomes after covariate adjustment. This suggests that patients with AF and ACS within the TRILOGY ACS cohort who undergo medical management without

Table 2. Association of AF on the Risk of Ischemic and Bleeding Outcomes

Efficacy and Safety[a] Outcomes	AF+, N = 710	AF−, N = 8391	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Interaction P Value[b]
Cardiovascular death, MI, or stroke			1.61 (1.35-1.92)	1.16 (0.97-1.39)	0.067
No. of events	138	1085			
Event rate at 30 months (95% CI)	31.1 (25.1-37.2)	18.4 (17.1-19.6)			
Cardiovascular death			1.69 (1.32-2.16)	1.15 (0.89-1.49)	0.549
No. of events	73	537			
Event rate at 30 months (95% CI)	16.7 (11.6-21.7)	9.3 (8.4-10.2)			
MI			1.48 (1.16-1.88)	1.09 (0.85-1.40)	0.013
No. of events	75	640			
Event rate at 30 months (95% CI)	16.3 (12.3-20.3)	11.1 (10.0-12.2)			
Stroke			2.23 (1.37-3.63)	1.59 (0.96-2.65)	0.401
No. of events	19	107			
Event rate at 30 months (95% CI)	6.6 (2.2-11.0)	2.0 (1.5-2.4)			
All-cause death			1.62 (1.30-2.02)	1.10 (0.87-1.39)	0.373
No. of events	88	672			
Event rate at 30 months (95% CI)	18.1 (13.5-22.7)	11.1 (10.2-12.1)			
GUSTO severe/life-threatening bleeding			1.89 (0.80-4.45)	1.40 (0.58-3.37)	0.685
No. of events	6	42			
Event rate at 30 months (95% CI)	3.4 (0.0-7.3)	0.9 (0.6-1.2)			
GUSTO severe/life-threatening/moderate bleeding			1.33 (0.77-2.30)	1.01 (0.58-1.78)	0.310
No. of events	14	139			
Event rate at 30 months (95% CI)	6.8 (2.0-11.7)	2.8 (2.3-3.3)			
TIMI major bleeding			0.96 (0.44-2.06)	0.76 (0.35-1.65)	0.716
No. of events	7	97			
Event rate at 30 months (95% CI)	3.9 (0.0-7.9)	2.0 (1.5-2.4)			
TIMI major or minor bleeding			1.76 (1.10-2.81)	1.46 (0.90-2.36)	0.189
No. of events	20	150			
Event rate at 30 months (95% CI)	8.3 (3.4-13.2)	3.0 (2.5-3.6)			

Abbreviations: AF, atrial fibrillation; CI, confidence interval; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; HR, hazard ratio; MI, myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.
[a]Safety outcomes computed on the population of patients who received study treatment (AF+: n = 702; AF−: n = 8320). [b]AF-by-treatment interaction P values are from the adjusted models.

oral anticoagulation or planned invasive revascularization represent a high-risk, older population with a greater burden of confounding comorbid conditions that accompany AF.

To date, few randomized studies have examined outcomes from patients with AF and ACS by treatment strategy. Ruiz-Nodar and colleagues have described the largest randomized cohort of patients with AF and ACS undergoing revascularization with PCI and subsequent outcomes based on antithrombotic therapy.[30] In this 2-center cohort of patients with AF and ACS who were treated with medical therapy and revascularization, those discharged on DAPT comprising aspirin and clopidogrel (n = 174, 40.8%) had increased mortality compared with patients receiving triple oral antithrombotic therapy (n = 213, 50%): 38.7% vs 26.5% (HR: 4.9, 95% CI: 1.61-7.54, $P = 0.002$), as well as higher rates of major adverse cardiovascular events: 27.8% vs 17.8% (HR: 3.43, 95% CI: 2.17-11.1, $P < 0.01$), but no differences in major or minor bleeding.[30]

In comparison, observational studies have demonstrated conflicting results with regard to outcomes for patients

Cardiovascular death, MI, or Stroke

No. at Risk:

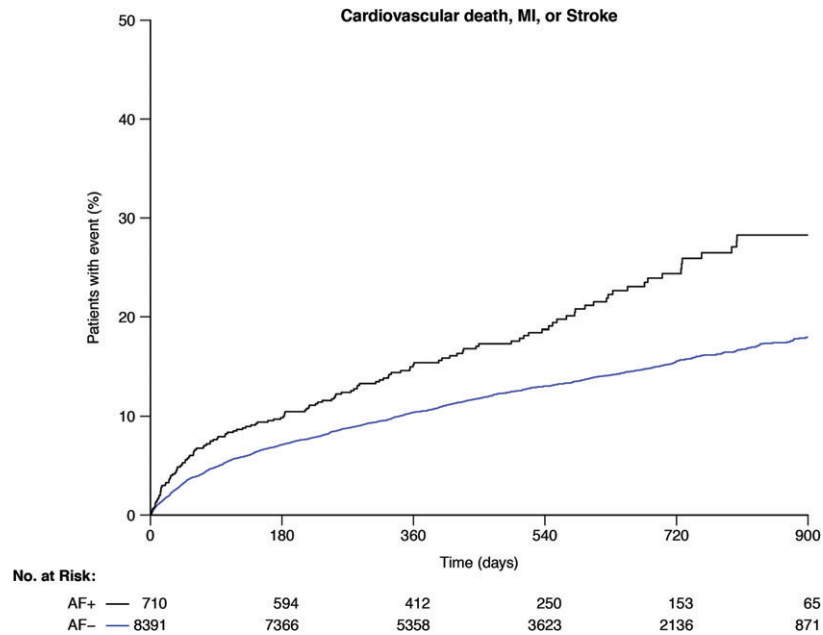|	0	180	360	540	720	900
AF+	710	594	412	250	153	65
AF−	8391	7366	5358	3623	2136	871

Figure 1. Kaplan-Meier estimates of the composite of cardiovascular death, MI, or stroke through 30 months in patients with AF (black line) and without AF (blue line). Abbreviations: AF, atrial fibrillation; MI, myocardial infarction.
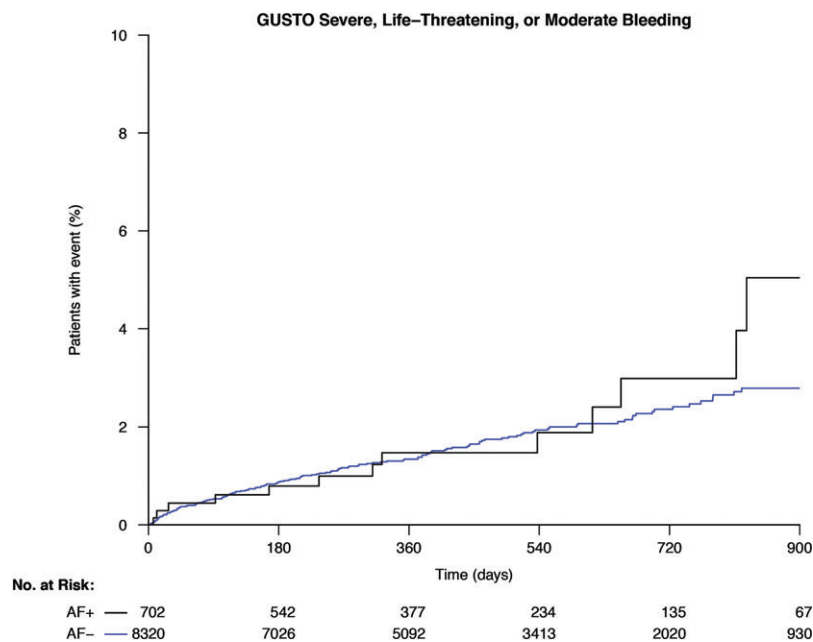
GUSTO Severe, Life–Threatening, or Moderate Bleeding

No. at Risk:

	0	180	360	540	720	900
AF+	702	542	377	234	135	67
AF−	8320	7026	5092	3413	2020	930

Figure 2. Kaplan-Meier estimates of GUSTO severe/life-threatening/moderate bleeding through 30 months in patients with AF (black line) and without AF (blue line). Abbreviations: AF, atrial fibrillation; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries.

with AF and ACS based on antithrombotic drug regimens. Hansen et al showed that combination therapy with OACs and DAPT is associated with a significantly higher risk of bleeding compared with monotherapy.[9] Conversely, Goa et al showed that combination therapy with warfarin and DAPT did not decrease the rates of MI or mortality but did increase major bleeding.[31]

Our analysis cohort is derived from a randomized population of elderly participants, who are at greater risk for developing AF. In addition, patients were balanced with respect to study-drug treatment with a $P2Y_{12}$ receptor inhibitor (prasugrel: n = 347, 48.9%; clopidogrel: n = 363, 51.1%) and were not treated with OACs. In this study, we observed significant increases in the incidence of primary-endpoint events in participants with both ACS and AF. However, after adjusting for possible confounders such as age, sex, hypertension, history of diabetes mellitus, systolic blood pressure, heart rate, Killip class at presentation, and

Table 3. Primary Reason for Permanent Study-Drug Discontinuation

Disposition, n (%)	All Patients, N = 9022	AF+, n = 702	AF−, n = 8320	P Value[a]
Permanent study-drug discontinuation	2076 (23.0)	221 (31.5)	1855 (22.3)	<0.001
Subject had a procedure	21 (0.2)	1 (0.1)	20 (0.2)	1.00
Adverse event	793 (8.8)	91 (13.0)	702 (8.4)	<0.001
Hemorrhagic	261 (2.9)	24 (3.4)	237 (2.8)	0.39
Nonhemorrhagic	532 (5.9)	67 (9.5)	465 (5.6)	<0.001
Need for OAC	102 (1.1)	25 (3.6)	77 (0.9)	<0.001
Investigator decision	97 (1.1)	7 (1.0)	90 (1.1)	0.84
Subject decision	981 (10.9)	88 (12.5)	893 (10.7)	0.14
Study drug unblinded	3 (0.0)	0 (0.0)	3 (0.0)	1.00
Entry criteria not met	62 (0.7)	7 (1.0)	55 (0.7)	0.33
Lost to follow-up	16 (0.2)	2 (0.3)	14 (0.2)	0.34

Abbreviations: AF, atrial fibrillation; OAC, oral anticoagulation.
[a] P value based on Fisher exact test.

history of MI, the rates of primary-endpoint events were not significantly different between study participants with vs without AF. These findings suggest that comorbidities and not AF play an increased prognostic role in outcomes for ACS patients treated primarily with medical therapy, and that AF is merely one marker of overall increased risk.

Although OAC has been proven to be superior to DAPT in reducing stroke, DAPT offers a reasonable option for reducing ischemic outcomes including both all-cause and cardiac mortality. In our analysis, DAPT was chosen by treating physicians and was not an exclusion criterion in the trial. The results from our analysis are important given the documented suboptimal utilization of oral anticoagulation in patients with AF.[32,33] Dual antiplatelet therapy has been demonstrated to reduce the risk of ischemic endpoints including stroke and systemic embolism (the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events [ACTIVE W] trial, NCT00243178).[34] Additionally, long-term use of DAPT with a $P2Y_{12}$ receptor inhibitor has been shown to reduce the risk ischemic endpoints including stroke (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin [PEGASUS-TIMI 54], NCT01225562).[35]

Atrial fibrillation is known to cause increased platelet activation. However, the effect of specific $P2Y_{12}$ receptor inhibitors on PRU values in the setting of AF is unknown. In our study, the 5-mg/d dose of prasugrel was used more frequently among elderly AF+ patients to decrease the risk of bleeding, which explains the difference in observed PRU values among patients taking prasugrel. In addition, among AF+ patients, the PRU value associated with prasugrel is lower than the PRU value associated with clopidogrel. This suggests that prasugrel did reduce platelet reactivity to a greater extent than clopidogrel for patients with and without AF. However, in patients with AF+ vs AF−

on prasugrel, median PRU values were higher for those AF+ patients receiving prasugrel, suggesting that full suppression of platelets was not achieved. It is unclear from this study whether multiple factors including prasugrel dosing, comorbidities, higher percentage of elderly patients in the AF+ group, or AF type led to such a finding and whether the inability to fully suppress platelet aggregation for AF+ patients on prasugrel led to increased risk of MI in the prasugrel group.

Study Limitations

Our study has several limitations. First, the present investigation is a post hoc analysis of prospectively collected clinical trial data, and the findings are only hypothesis-generating. Second, AF+ patients were defined as those with either current or prior AF as a clinical variable only, without detailed information or a confirmatory electrocardiogram regarding timing or type of AF or proof of AF, respectively. Third, patients receiving OAC therapy were excluded from this study, and the reasons for not using an OAC were not collected on the baseline case-report form. In addition, patients were only initiated on OAC therapy after study-drug discontinuation. Finally, there may be unmeasured confounders associated with AF that potentially could have influenced comparisons.

Conclusion

Among a randomized population of high-risk elderly patients with ACS managed medically with DAPT and without OAC therapy or invasive revascularization, current or prior AF was not associated with higher adjusted risks of ischemic and bleeding outcomes. Further studies are needed to elucidate both the contribution of AF to the constellation of comorbid conditions affecting prognosis in this patient population as well as optimal therapeutic strategies for patients with both ACS and AF.

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