JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.
VOL. 66, NO. 6, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.05.062

Use and Outcomes of Triple Therapy Among Older Patients With Acute Myocardial Infarction and Atrial Fibrillation

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ABSTRACT

BACKGROUND Antithrombotic therapy for acute myocardial infarction (MI) with atrial fibrillation (AF) among higher risk older patients treated with percutaneous coronary intervention (PCI) remains unclear.

OBJECTIVES This study sought to determine appropriate antithrombotic therapy for acute MI patients with AF treated with PCI.

METHODS We examined 4,959 patients ≥65 years of age with acute MI and AF who underwent coronary stenting (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines). The primary effectiveness outcome was 2-year major adverse cardiac events (MACE) comprising death, readmission for MI, or stroke; the primary safety outcome was bleeding readmission. Outcomes with dual antiplatelet therapy (DAPT) or triple therapy (DAPT plus warfarin) were compared using Cox proportional hazard modeling with inverse probability-weighted propensity adjustment.

RESULTS Among 4,959 patients, 27.6% (n = 1,370) were discharged on triple therapy. Relative to DAPT, patients on triple therapy had a similar risk of MACE (adjusted hazard ratio [HR]: 0.99 [95% confidence interval (CI): 0.86 to 1.16]) but significantly greater risk of bleeding requiring hospitalization (adjusted HR: 1.61 [95% CI: 1.31 to 1.97]) and greater risk of intracranial hemorrhage (adjusted HR: 2.04 [95% CI: 1.25 to 3.34]). Of 1,591 Medicare Part D patients, 90-day post-discharge warfarin persistence among patients discharged on warfarin was 93.2% (n = 412). Results of 90-day landmark analyses comparing triple therapy versus DAPT in patients persistently on warfarin versus those not discharged on warfarin who had not filled a warfarin prescription were similar to our primary findings.

CONCLUSIONS Approximately 1 in 4 older AF patients undergoing PCI for MI were discharged on triple therapy. Those receiving triple therapy versus DAPT had higher rates of major bleeding without a measurable difference in composite MI, death, or stroke. (J Am Coll Cardiol 2015;66:616–27) © 2015 by the American College of Cardiology Foundation.

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Selection of the optimal antithrombotic regimen for patients with acute myocardial infarction (MI) who have concomitant atrial fibrillation (AF) and are treated with percutaneous coronary intervention (PCI) presents a therapeutic challenge. Current guidelines for the management of AF recommend anticoagulation for thromboembolic prophylaxis in AF patients who are at average or higher risk for stroke but not at prohibitive risk for bleeding (1). Guidelines for the management of acute MI and

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PCI patients recommend treatment with dual antiplatelet therapy (DAPT) to reduce the risks of major adverse cardiac events (MACE) and stent thrombosis (2); however, clinicians may be reluctant to treat AF patients with concurrent indications for DAPT by using the combination of warfarin, aspirin, and clopidogrel (triple therapy) due to the high bleeding risk associated with this regimen (3,4).

Although previous studies have found that bleeding risk is higher among patients receiving triple therapy (4–6), some data also suggest a lower risk of MACE among patients treated with triple therapy relative to DAPT (7,8). Given the paucity of randomized data, studies have shown variability in anticoagulant agent use according to the predicted risks of stroke and bleeding in this patient population (8–11). Therapeutic decisions for older patients with AF and coronary artery disease may be especially challenging. Older patients in particular are at greater risk for AF-related stroke and recurrent events after acute MI but also have a higher risk for bleeding events (12). Importantly, the older population has been excluded from or underrepresented in clinical trials and, therefore, remains understudied.

By linking data from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines (ACTION Registry-GWTG) with Medicare administrative claims, we had a unique opportunity to examine a large group of older MI patients with AF undergoing PCI. We sought to: 1) describe the patterns of use of discharge triple therapy versus DAPT in older MI patients with AF treated by using PCI; 2) characterize warfarin use patterns post-discharge; and 3) compare the safety and effectiveness of triple therapy versus DAPT.

METHODS

DATA SOURCES. Clinical and procedural data for our study were obtained from the ACTION Registry-GWTG, a national quality improvement registry capturing data on consecutive MI patients treated at >500 hospitals in the United States; this registry has been described previously (13). Because patient information was collected without unique patient identifiers, we used indirect identifiers in combination (date of birth, sex, hospital identification, date of admission, and date of discharge) to link patients ≥65 years of age in the ACTION Registry-GWTG with Medicare claims data (methods previously described) (14). The linked data for our analysis were available from January 1, 2007, through December 31, 2010. We examined longitudinal outcomes by using Medicare Part A inpatient administrative data, and information regarding post-discharge warfarin and $P2Y_{12}$ receptor inhibitor use was obtained from Medicare Part D data. Warfarin was the only anticoagulant agent available for clinical use in the United States during this time period.

STUDY POPULATION. Among 123,349 patients ≥65 years of age at 683 sites identified in the ACTION Registry-GWTG during our study period, 64.7% (79,750 patients from 502 sites) were linked to Centers for Medicare & Medicaid Services data (**Figure 1**). In this linked database, there were 6,098 patients with acute MI who were eligible for Medicare

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CABG = coronary artery bypass grafting

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke/transient ischemic attack

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

MACE = major adverse cardiac event(s)

MI = myocardial infarction

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), WebMD (Continuing Medical Education steering committees), *Clinical Cardiology* (Deputy Editor); has received research funding from Amarin, AstraZeneca, Biotronik, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi, St. Jude Medical, and The Medicines Company; has served as a trustee for the American College of Cardiology; and has performed unfunded research for FlowCo, PLx Pharma, and Takeda. Dr. Saucedo is a member of the advisory board of Janssen Pharmaceuticals and Eli Lilly. Dr. Wang has received institutional research grant support from AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, Gilead Sciences, GlaxoSmithKline, and Regeneron; and honoraria from AstraZeneca, Eli Lilly, and PREMIER Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Jonathan Tobis, MD, served as Guest Editor for this paper.

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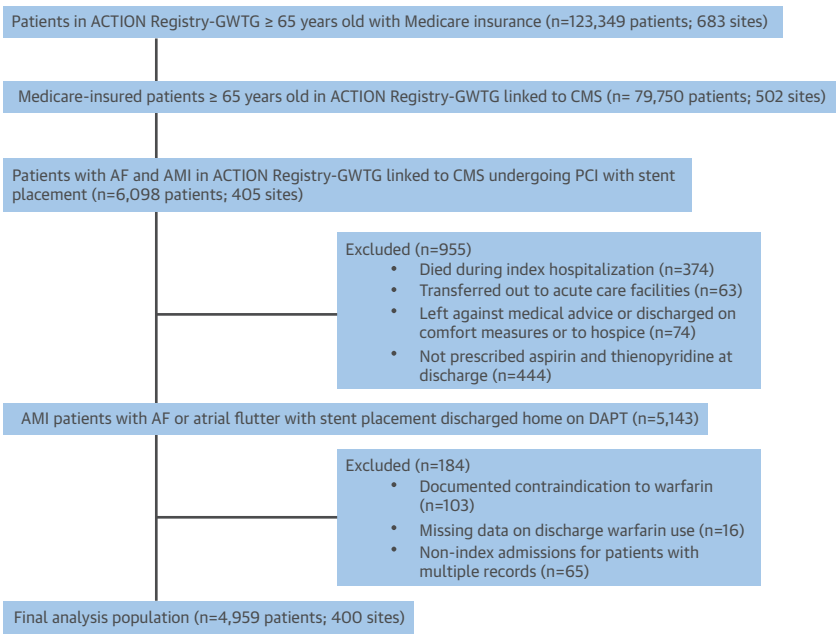
Manuscript received November 21, 2014; revised manuscript received May 28, 2015, accepted May 29, 2015.

FIGURE 1 Study Population



Flow diagram of the study cohort, from initial study population through exclusions. ACTION Registry-GWTG = Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines; AF = atrial fibrillation; AMI = acute myocardial infarction; CMS = Centers for Medicare & Medicaid Services; DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention.

fee-for-service during the index discharge month, who had a history of AF or atrial flutter, and who underwent in-hospital PCI with stent placement at 1 of 405 hospitals in the ACTION Registry-GWTG during this study period. History of AF or atrial flutter was considered to be present if indicated as occurring during the 2 weeks before the MI admission on the ACTION Registry-GWTG data collection form or if the International Classification of Diseases-Ninth Revision code 427.3x appeared in any inpatient or outpatient encounter billing record within the year before the index MI hospitalization. In-hospital PCI and stent use were determined from the ACTION Registry-GWTG data collection form. We excluded patients who died during the index hospitalization (n = 374), were transferred out to another acute care hospital (n = 63), and who left against medical advice or were discharged on comfort measures or to hospice (n = 74). Also excluded were patients who were not discharged on both aspirin and a $P2Y_{12}$ antagonist (clopidogrel, prasugrel, or ticlopidine; n = 444), patients with a documented contraindication to warfarin (n = 103), patients with missing data on discharge warfarin use (n = 16), and nonindex admissions for patients with multiple records (n = 65). Our final analysis population consisted of 4,959 patients treated at 400 sites. A breakdown of the data source used to identify AF patients is shown in the Online Appendix.

OUTCOMES AND DEFINITIONS. The primary effectiveness outcome for our study was MACE at 2 years, defined as death or readmission for MI or stroke (ischemic and hemorrhagic). Secondary effectiveness outcomes included individual components of the composite MACE outcome, as well as ischemic stroke alone. We also examined bleeding readmission within 2 years after the index hospitalization as our primary safety endpoint, as well as readmissions involving intracranial hemorrhage. Outcomes were identified by using International Classification of Diseases-Ninth Revision codes (Online Appendix) from Medicare inpatient claims data.

Patients were classified according to stroke risk by using the $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke or transient ischemic attack) risk score (15). $CHADS_2$ scores were calculated by assigning 1 point each for history of congestive heart failure, hypertension, age ≥75 years, or diabetes mellitus, and 2 points for history of stroke or transient ischemic attack. To determine patient risk for bleeding, we calculated the ATRIA (Anticoagulation and Risk Factors in

Atrial Fibrillation) risk score (16). ATRIA scores were summed by assigning 3 points each for anemia (hemoglobin <13 g/dl in men, <12 g/dl in women) or severe renal disease (glomerular filtration rate <30 ml/min or dialysis dependent), 2 points for age ≥75 years, and 1 point each for hypertension or prior bleeding. An ATRIA score >3 was considered high bleeding risk.

As a sensitivity analysis, post-discharge warfarin and $P2Y_{12}$ inhibitor prescription fill information was obtained from a Medicare Part D prescription claims database (n = 1,591). We then examined medication persistence at 90 days after discharge from the index MI hospitalization, defined as continuation of the medication prescribed at discharge without a gap in filling >60 days (17). We also examined warfarin initiation post-discharge by determining time to first warfarin prescription fill post-discharge.

STATISTICAL ANALYSIS. Baseline clinical and procedural characteristics were described according to discharge on DAPT versus triple therapy. Continuous and categorical variables were presented by using medians with interquartile ranges and proportions, respectively, and compared by using respective Wilcoxon rank-sum and chi-square tests. Kaplan-Meier estimates of all-cause mortality and MACE outcomes were reported, and readmission outcomes were reported by using the cumulative incidence function to account for the competing risk of death. Follow-up for all outcomes was started at the time of discharge from the index hospitalization. Inverse probability weighting was used to account for confounding by observed covariates, and the relationship between discharge therapy and outcomes was assessed as intention-to-treat. Propensity scores were estimated by using logistic regression with triple therapy versus DAPT as the outcome to determine the probability of each patient undergoing the treatment he or she received conditional on observed covariates. The inverse of this probability was then assigned as each patient's "weight." Unadjusted and adjusted Cox proportional hazard models were fit for each outcome of interest: unadjusted models included discharge therapy as the sole variable, and weights were then applied in adjusted models. The proportional hazards assumption was met for all models, and covariates were adequately balanced after propensity score weighting (Online Appendix). Hazard ratios (HRs) for triple therapy versus DAPT and corresponding 95% confidence intervals (CIs) were reported.

The following variables were used in the propensity models (these covariates were selected on the basis of clinical judgment, as well as significant differences observed in univariate comparisons): age, sex, body mass index, hypertension, dyslipidemia, diabetes, peripheral artery disease, prior MI, prior PCI, prior coronary artery bypass grafting (CABG), prior heart failure, prior stroke, prior bleeding within 1 year, home medications (i.e., aspirin, beta-blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, statin), MI type (ST-segment elevation myocardial infarction [STEMI] vs. non-ST-segment elevation myocardial infarction [NSTEMI]), signs and symptoms of heart failure at presentation or in-hospital, left ventricular ejection fraction (i.e., >40%, ≤40%, not evaluated), baseline hemoglobin, baseline creatinine, arrival-to-cardiac catheterization time ≤48 h, multivessel disease, drug-eluting stent (DES) versus bare-metal stent use, discharge medications (i.e., angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, statin), hospital region and teaching status, and in-hospital major bleeding. In-hospital major bleeding is defined by the ACTION Registry-GWTG as an absolute hemoglobin decrease of ≥4 g/dl, intracranial hemorrhage, documented or suspected retroperitoneal bleed, any red blood cell transfusion with baseline hemoglobin ≥9 g/dl, or transfusion with baseline hemoglobin <9 g/dl with a suspected bleeding event. Only preoperative bleeding events in CABG patients were included. All variables had a missing rate <1%. For all modeling, missing categorical variables were imputed to the most frequent level, and missing continuous variables were imputed to the median.

Several secondary analyses were conducted. First, we assessed for differences in the relationship between discharge therapy and outcomes in the following subgroups of interest: age ≥75 years versus <75 years, female versus male patients, high versus low $CHADS_2$ risk score, high versus low ATRIA bleeding risk score, DES versus bare-metal stent use, and MI type (NSTEMI versus STEMI). For each subgroup, the propensity score model was allowed to include interactions with the subgroup of interest, such that balance would be preserved within each subgroup. The subgroup variable and interaction term were then added into the Cox models. As a sensitivity study, a landmark analysis was performed examining the associations between 90-day treatment status and subsequent MACE and bleeding outcomes among patients enrolled in Medicare Part D at 90 days post-discharge. We compared outcomes among patients discharged on warfarin who were persistently on warfarin therapy at 90 days post-discharge versus those not discharged on warfarin who did not fill a warfarin prescription within 90 days post-discharge.

The Duke University Medical Center Institutional Review Board granted a waiver of the informed

TABLE 1 Patient, In-Hospital, and Discharge Treatment Characteristics According to Discharge Warfarin Use

	DAPT (n = 3,589)	Triple Therapy* (n = 1,370)	p Value
Patient features			
Age, yrs	78.0 (72.0–84.0)	77.0 (72.0–82.0)	<0.01
Female	1,602 (44.6)	505 (36.9)	<0.01
Body mass index, kg/m^2	26.6 (23.6–30.5)	27.7 (24.6–31.6)	<0.01
Hypertension	2,911 (81.1)	1,145 (83.6)	0.04
Dyslipidemia	2,226 (62.0)	922 (67.3)	<0.01
Diabetes	1,075 (30.0)	486 (35.5)	<0.01
Prior MI	991 (27.6)	431 (31.5)	<0.01
Prior HF	606 (16.9)	337 (24.6)	<0.01
Prior CABG	730 (20.3)	362 (26.4)	<0.01
Prior PCI	1,014 (28.3)	424 (31.0)	<0.01
AF/flutter in previous 2 weeks	1,014 (39.7)	586 (60.8)	<0.01
Prior stroke	369 (10.3)	175 (12.8)	0.01
Peripheral arterial disease	466 (13.0)	211 (15.4)	0.03
$CHADS_2$ score			<0.01
0	186 (5.2)	39 (2.9)	
1	733 (20.4)	244 (17.8)	
2	1,201 (33.5)	444 (32.4)	
3	899 (25.1)	362 (26.4)	
4	372 (10.4)	189 (13.8)	
5	112 (3.1)	66 (4.8)	
6	52 (1.5)	22 (1.6)	
ATRIA score >3	1,286 (35.8)	457 (33.4)	0.10
Bleeding admission in prior year	127 (3.5)	41 (3.0)	0.34
Home antithrombotic therapy			
Aspirin	1,948 (54.3)	664 (48.4)	<0.01
Clopidogrel	686 (19.1)	173 (12.6)	<0.01
Prasugrel	3 (0.1)	3 (0.3)	0.21
Warfarin	276 (7.7)	851 (62.1)	<0.01
In-hospital features			
NSTEMI (vs. STEMI)	2,014 (56.1)	862 (62.9)	<0.01
Baseline hemoglobin, g/dl	13.4 (12.1–14.6)	13.5 (12.3–14.7)	<0.01
Baseline creatinine, mg/dl	1.1 (0.9–1.4)	1.2 (0.9–1.4)	0.05
LVEF >40%	2482 (74.3)	839 (65.6)	<0.01
Time to catheterization, h	5.8 (1.0–32.0)	14.9 (1.1–46.1)	<0.01
Multivessel disease	2,483 (69.7)	953 (70.03)	0.92
DES use (STEMI)	640 (47.8)	202 (46.4)	0.62
DES use (NSTEMI)	1,233 (61.2)	458 (53.1)	<0.01
Procedural antithrombotic therapy			
Unfractionated heparin	2,484 (69.6)	923 (68.5)	0.47
Low-molecular-weight heparin	1,068 (29.9)	364 (27.0)	0.05
Glycoprotein IIb/IIIa inhibitor	1,727 (49.9)	528 (40.2)	<0.01
Bivalirudin	1,214 (34.0)	513 (38.1)	<0.01
CABG	35 (1.0)	4 (0.3)	0.02
Major bleeding event	569 (15.9)	174 (12.7)	<0.01
Discharge $P2Y_{12}$ inhibitor			
Clopidogrel	3,490 (97.7)	1,346 (98.8)	0.01
Prasugrel	89 (3.5)	19 (2.0)	0.02
Ticlopidine	10 (0.5)	5 (0.5)	0.86

Categorical variables presented as n (%) and continuous variables presented as median (25th to 75th percentiles).
*Triple therapy indicates warfarin, aspirin, and $P2Y_{12}$ inhibitor.

AF = atrial fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; CABG = coronary artery bypass grafting; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke/transient ischemic attack; DAPT = dual antiplatelet therapy; DES = drug-eluting stent(s); HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RBC = red blood cell; STEMI = ST-segment elevation myocardial infarction.

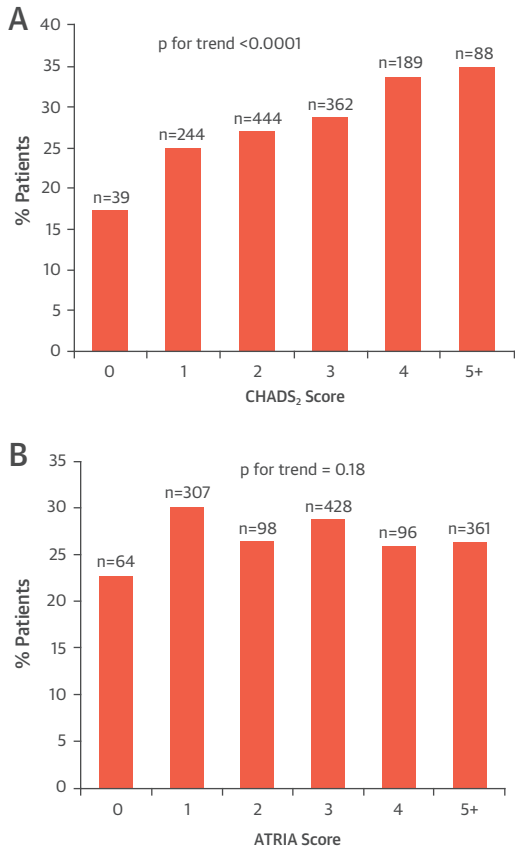
consent and authorization for this study, and all analyses were conducted by the Duke Clinical Research Institute.

RESULTS

PATIENT AND IN-HOSPITAL CHARACTERISTICS AMONG DAPT VERSUS TRIPLE THERAPY GROUPS. Among 4,959 MI patients presenting with a history of AF who were treated with PCI, 27.6% (n = 1,370) were discharged on triple therapy, and 72.4% (n = 3,589) were discharged on DAPT (Table 1). Compared with patients prescribed DAPT at discharge, those receiving triple therapy were more often male and more frequently had a history of PCI or CABG, prior stroke, and recent AF or atrial flutter. Patients discharged on triple therapy were frequently already on warfarin before admission, whereas those discharged on DAPT were more likely to have had an in-hospital major bleeding event. Use of triple therapy increased with higher predicted stroke risk (p for trend < 0.0001) but was not associated with predicted bleeding risk (p for trend = 0.18) (Figure 2). Patients in the triple therapy group also more often presented with NSTEMI than STEMI and more often had a left ventricular ejection fraction ≤40%. There was greater use of glycoprotein IIb/IIIa inhibitors among patients discharged on DAPT, whereas patients in the triple therapy group more often received bivalirudin during their PCI. Patients prescribed triple therapy who underwent PCI for NSTEMI were less likely to undergo DES implantation, whereas DES use for primary PCI among STEMI patients was similar between the DAPT and triple therapy groups.

CLINICAL OUTCOMES ACCORDING TO DISCHARGE ANTITHROMBOTIC REGIMEN. Clinical outcomes were examined according to discharge prescription of triple therapy versus DAPT (Figure 3). Unadjusted cumulative incidence rates of 2-year post-discharge MACE between triple therapy and DAPT groups were similar (32.6% vs. 32.7%; p = 0.99). Unadjusted cumulative incidence rates of the individual MACE component endpoints were also similar between patients discharged on triple therapy versus DAPT: all-cause mortality (23.8% vs. 24.8%; p = 0.70), MI readmission (8.5% vs. 8.1%; p = 0.54), and stroke readmission (4.7% vs. 5.3%; p = 0.23). The unadjusted cumulative incidence of ischemic stroke was lower for patients discharged on triple therapy versus DAPT (3.2% vs. 4.7%; p = 0.02). After adjustment for patient, treatment, and hospital characteristics, there was no association of triple therapy with 2-year MACE (adjusted HR: 0.99 [95% CI: 0.86 to 1.16]; p = 0.94), all-cause mortality (adjusted HR: 0.98 [95% CI: 0.83

FIGURE 2 Warfarin Use According to Risk of Stroke and Bleeding



Use of triple therapy according to: **(A)** stroke risk assessed by using the $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke or transient ischemic attack) score; and **(B)** bleeding risk assessed by using the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) score.

to 1.16]; p = 0.82), MI readmission (adjusted HR: 1.03 [95% CI: 0.79 to 1.33]; p = 0.83), or stroke readmission (adjusted HR: 0.85 [95% CI: 0.58 to 1.23]; p = 0.38). The adjusted HR for ischemic stroke was lower at 0.66 with triple therapy compared with DAPT; however, this comparison remained nonstatistically significant (95% CI: 0.41 to 1.06; p = 0.09).

The cumulative incidence of bleeding requiring hospitalization within 2 years post-discharge was significantly higher for patients discharged on triple therapy compared with DAPT (17.6% vs. 11.0%; p < 0.0001), with curves diverging early after discharge (Figure 4A). This association persisted after adjustment for case-mix, treatment, and hospital features (adjusted HR: 1.61 [95% CI: 1.31 to 1.97]; p < 0.0001). Unadjusted cumulative incidence of intracranial hemorrhage was higher for patients treated with triple therapy versus DAPT (3.4% vs. 1.5%; p < 0.001) (Figure 4B). After adjustment, triple therapy remained significantly associated with intracranial hemorrhage (adjusted HR: 2.04 [95% CI: 1.25 to 3.34]; p < 0.01).

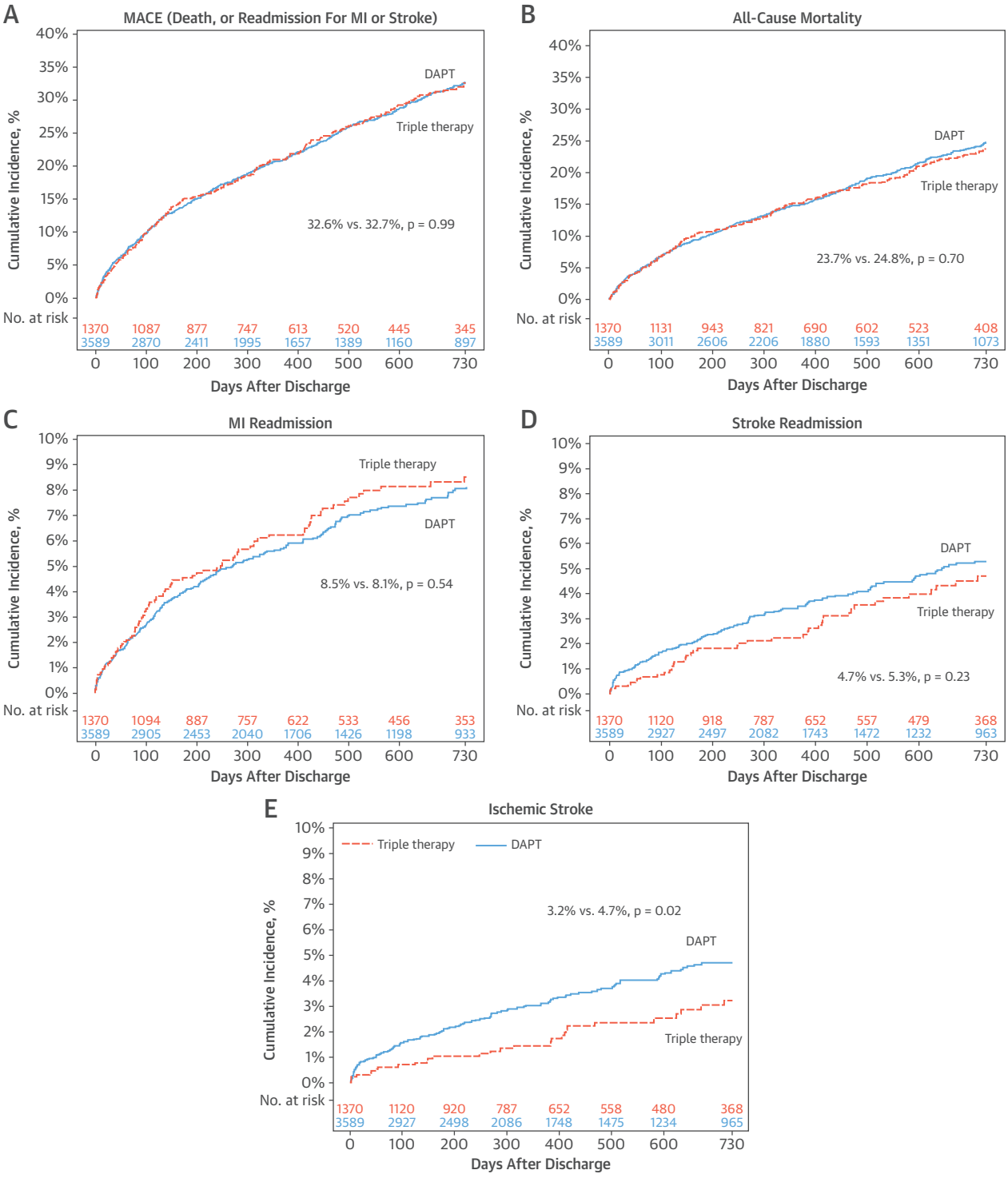
SECONDARY ANALYSES. Several subgroup analyses were performed. After adjustment, the association of triple therapy with risk of 2-year MACE was similar between older (≥75 years) versus younger patients, men versus women, patients with high ($CHADS_2$ score cutoffs of >2 and ≥4) versus low predicted stroke risk, patients with shorter versus longer duration of AF, patients treated with DES versus bare-metal stent, and patients presenting with NSTEMI versus STEMI (p for interaction >0.05 for all) (Figure 5A). Among these same subgroups, results were also consistent when examining triple therapy and risk of 2-year bleeding readmissions (adjusted p for interaction >0.05) (Figure 5B).

A total of 1,591 patients in our study had Medicare Part D prescription coverage before discharge. Among this cohort, 27.8% (n = 442) were discharged on warfarin, and 72.2% (n = 1,149) were discharged on DAPT only. Post-discharge antithrombotic therapy use was examined (Table 2). Within 90 days post-discharge, the rates of warfarin persistence among patients discharged on warfarin was 93.2% (n = 412), and $P2Y_{12}$ inhibitor persistence among patients discharged on DAPT was 94.7% (n = 1,088). Among patients not discharged on warfarin, 11.4% (n = 232) had filled a warfarin prescription within 90 days of discharge. Of the 425 patients with a $CHADS_2$ score >2 who were not discharged on warfarin, 12.7% had filled a warfarin prescription within 90 days of discharge. In a landmark analysis starting 90 days post-discharge, we found that patients discharged on warfarin who were persistently taking warfarin at that time had a similar 2-year risk of MACE (adjusted HR: 0.96 [95% CI: 0.67 to 1.36]; p = 0.81) and a trend for higher risk of bleeding (adjusted HR: 1.50 [95% CI: 0.92 to 2.46]; p = 0.10) compared with patients not discharged on warfarin who had not filled a warfarin prescription during that time.

DISCUSSION

This is one of the largest studies of antithrombotic treatment and outcomes of older acute MI patients with history of AF who were treated with PCI. Overall, we found that about one-fourth of patients were discharged on triple therapy. Use of triple therapy versus DAPT increased with predicted stroke risk but not with bleeding risk. Compared with DAPT, the use of triple therapy was not associated with a lower

FIGURE 3 MACE Outcomes According to Use of Triple Therapy Versus DAPT



Cumulative incidence curves for triple therapy versus DAPT for: **(A)** major adverse cardiac events (MACE); **(B)** all-cause mortality; **(C)** myocardial infarction (MI); **(D)** stroke (ischemic and hemorrhagic); and **(E)** ischemic stroke. Abbreviations as in Figure 1.

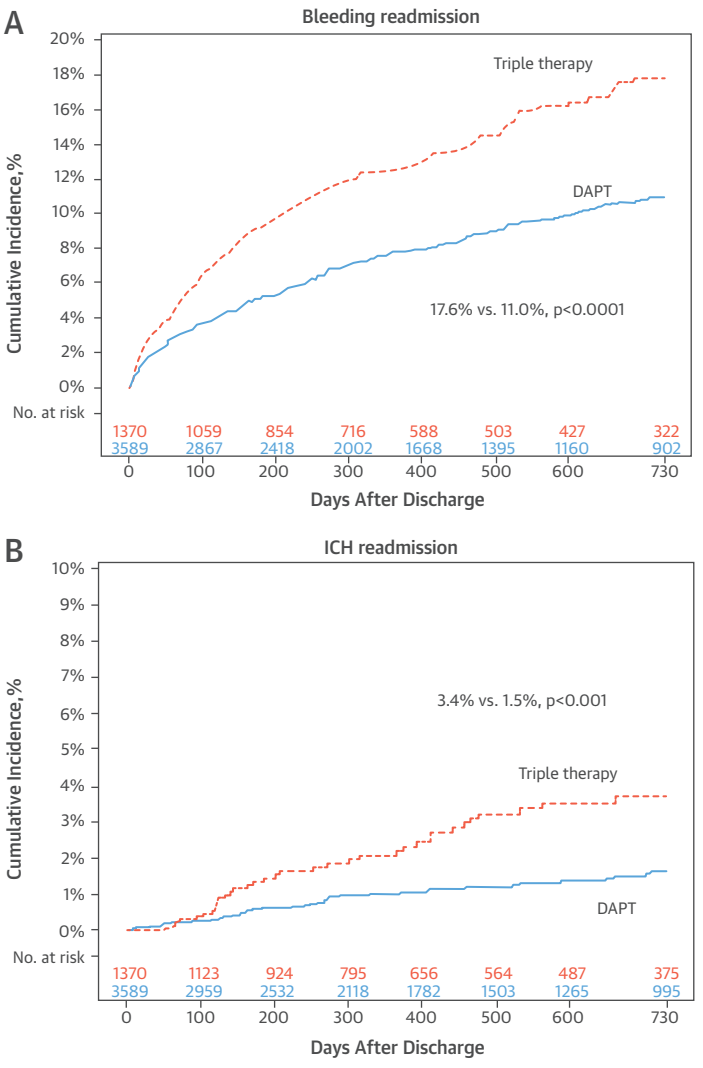
2-year risk of mortality or MACE but was associated with a significantly higher early and long-term risk of bleeding, including intracranial hemorrhage (**Central Illustration**). These associations were robust among various patient subgroups assessed according to age, sex, predicted stroke and bleeding risk groups, stent type, and MI type.

Defining the optimal antithrombotic treatment strategy for MI patients with history of AF who have been treated with PCI has been a conundrum given the limited randomized trial evidence and the safety concerns observed with triple therapy in this patient population. To date, however, much of the available data have come from observational single-center studies and have had conflicting findings with regard to any benefit of triple therapy on MACE (6,7,18–22). For example, a recent report investigating 1,648 patients with AF undergoing stenting for NSTEMI found that triple therapy was not associated with a risk of stroke or bleeding (22). In a Danish study of 12,165 AF patients with either MI or PCI, DAPT and individual combinations of oral anticoagulation plus clopidogrel or aspirin were not associated with increased coronary events compared with triple therapy; nevertheless, DAPT was associated with increased all-cause mortality and higher risk of ischemic stroke. Bleeding rates with oral anticoagulation plus clopidogrel were similar to those with triple therapy but lower for oral anticoagulation plus aspirin or DAPT (20).

Our study adds to the existing literature in several ways. First, we used national registry data from 2007 to 2010 from >400 U.S. hospitals to identify a large cohort of MI patients with a history of AF who underwent stent implantation; therefore, our study population had clinical indications for both dual antiplatelet and anticoagulant therapy. Second, we focused on a growing population of older patients who are at highest risk of thrombotic events (and consequently might benefit the most from triple therapy) but who are also at high risk for bleeding. This combination of a larger sample size and a higher risk population permitted the statistical power to assess the relationship between antithrombotic therapy selection and post-discharge outcomes. Third, we had access to detailed clinical information, as well as in-hospital treatments and events captured in the ACTION Registry-GWTG, and we were able to include these variables in robustly risk-adjusted models. Finally, the use of Medicare Part D data to examine post-discharge warfarin persistence or initiation added insight when explaining our findings.

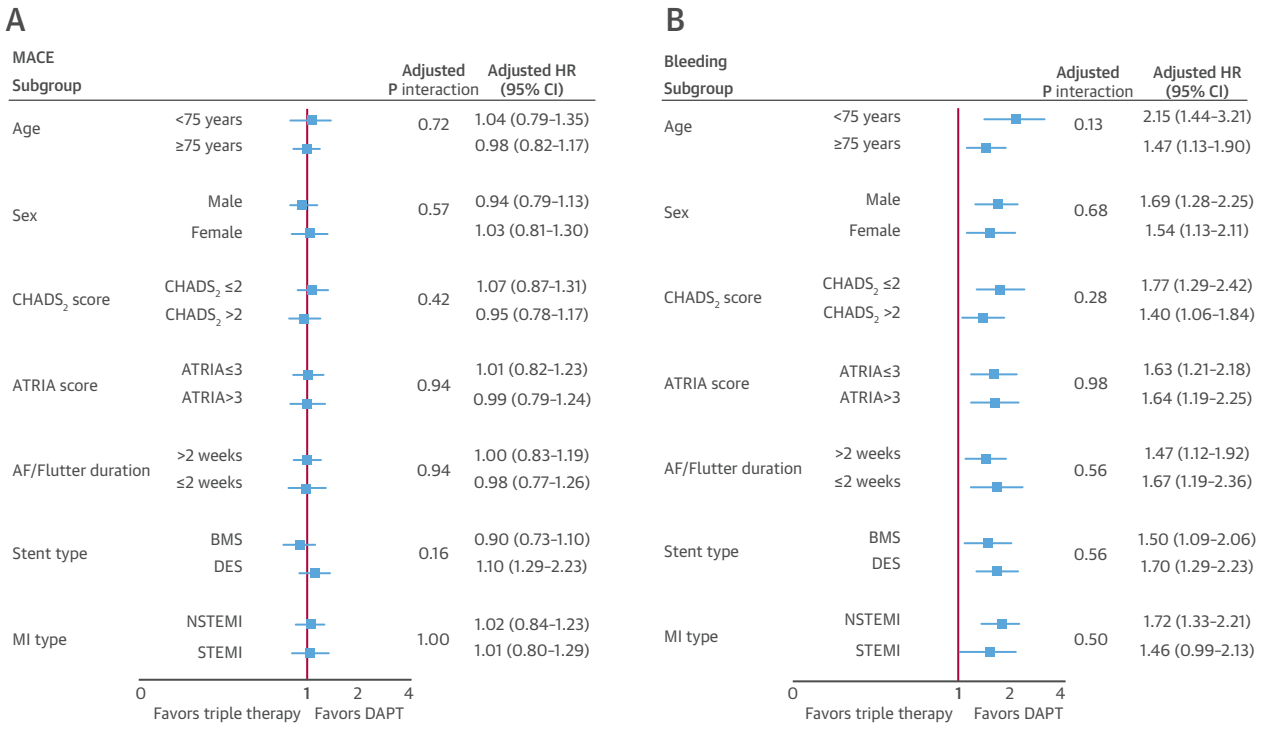
In patients with an indication for anticoagulation undergoing PCI with stenting or presenting with MI, current practice guidelines recommend use of triple therapy for as short a time as possible (Level of Evidence: C) but also advocate careful consideration of stroke, thrombosis, and bleeding risk when making treatment decisions (12,23). We found that 27.6% of older MI patients with a history of AF treated with PCI were discharged on triple therapy. This proportion increased with the estimated stroke risk and did not vary with the predicted bleeding risk, lending insight into how U.S. providers decide between triple therapy versus DAPT for these patients. In addition, we observed high rates of warfarin persistence at 3 months post-MI among patients discharged on triple therapy. Conversely, ~1 in 9 patients not

FIGURE 4 Bleeding Outcomes According to Triple Therapy Versus DAPT



Cumulative incidence curves for triple therapy versus DAPT for: **(A)** bleeding readmission and **(B)** intracranial hemorrhage. Abbreviation as in **Figure 1**.

FIGURE 5 MACE and Bleeding Outcomes Among Selected Subgroups



Shown in the forest plot are outcomes for: **(A)** MACE; and **(B)** bleeding readmission comparing triple therapy versus DAPT among patients according to age, sex, $CHADS_2$ score, ATRIA score, atrial fibrillation/flutter duration, stent type, and MI type. BMS = bare-metal stent(s); CI = confidence interval; DES = drug-eluting stent(s); HR = hazard ratio; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Figures 1 to 4.

discharged on warfarin were started on warfarin in the next 3 months. Some of these delayed initiations may be due to completion of the $P2Y_{12}$ inhibitor treatment course, resolution of in-hospital bleeding events, recurrence of AF events, or perhaps deferral of treatment decisions to an outpatient care provider. Further investigation may help to clarify the benefits and risk of upfront versus delayed anticoagulation in these PCI-treated patients with AF.

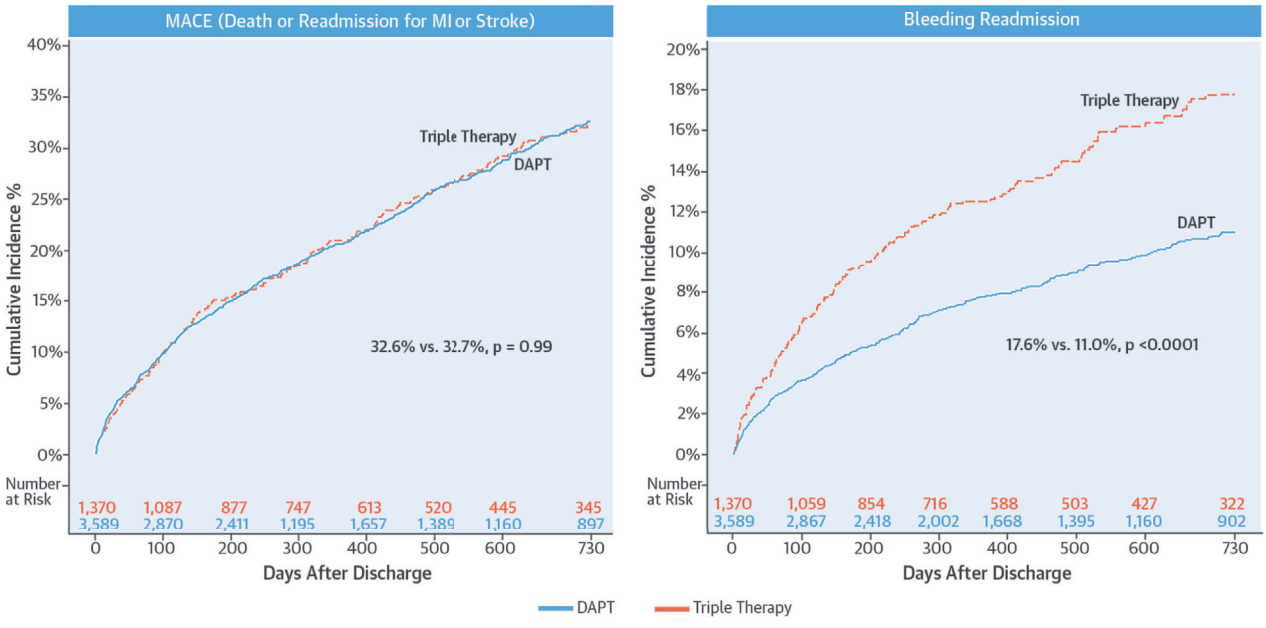
Our study suggests that, compared with DAPT, triple therapy use is not associated with lower MACE risk among older acute MI patients with a history of AF undergoing coronary stenting. The 90-day landmark analysis confirms these findings among patients who remain on warfarin therapy for at least 90 days versus those who were not anticoagulated. Furthermore, we tested for interactions among multiple subgroups and found no evidence of any association of triple therapy with outcomes. There was, however, a nonsignificant trend for lower risk of ischemic stroke associated with triple therapy, an endpoint for which warfarin might be expected to have the greatest potential benefit. These findings differ from a previous report of increased mortality among

TABLE 2 Post-Discharge Antithrombotic Medication Persistence

	DAPT		Triple Therapy		
	Evaluable (n)	% (n) Remaining on $P2Y_{12}$ Inhibitor	No. Evaluable	% (No.) Remaining on $P2Y_{12}$ Inhibitor	% (n) Remaining on Warfarin
3 months	1,149	94.7% (1,088)	442	95.9% (424)	93.4% (412)
6 months	1,013	94.4% (956)	368	94.6% (348)	91.8% (338)
12 months	722	73.4% (530)	270	63.7% (172)	57.4% (155)

Abbreviation as in Table 1.

CENTRAL ILLUSTRATION **Outcomes According to Triple Therapy Versus DAPT**



Hess, C.N. et al. J Am Coll Cardiol. 2015; 66(6):616–27.

The Kaplan-Meier curves demonstrate major adverse cardiac events (MACE); and bleeding readmission for patients on triple therapy versus dual antiplatelet therapy (DAPT). MI = myocardial infarction.

patients taking DAPT versus triple therapy (20). In another study by the same investigators, the authors found an immediate risk of bleeding after MI/PCI that was highest with triple therapy compared with other antithrombotic regimens (4). They also found that the higher risk of triple therapy-associated bleeding persisted over the next year. We observed similar early divergence of our bleeding curves with continued separation over the study period, indicating persistently increased bleeding risk with triple therapy versus DAPT. In addition, we found that triple therapy compared with DAPT was associated with a significantly increased risk of intracranial hemorrhage. Taken together, these studies suggest that we need to carefully consider the risk/benefit ratio of immediate triple therapy use among older patients with AF and acute MI treated with PCI.

Several lines of investigation may help to assess alternatives to triple therapy for these types of patients. The MUSICA-2 (Anticoagulation in Stent Intervention; NCT01141153) trial is currently randomizing lower risk AF patients undergoing stenting to triple therapy or DAPT, and the ongoing ISAR-Triple (Triple Therapy in Patients on Oral Anticoagulation after Drug-Eluting Stent Implantation; NCT00776633) trial is studying AF patients undergoing DES placement treated with triple therapy for 6 weeks versus 6 months. The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial randomized patients taking oral anticoagulant agents undergoing PCI to receive additional clopidogrel or clopidogrel plus aspirin (24). The investigators found that compared with triple therapy, clopidogrel plus warfarin reduced bleeding complications but did not increase thrombotic events. Although we examined triple therapy versus DAPT, the WOEST results suggest that use of warfarin plus clopidogrel as an alternative to triple therapy could be further investigated in our study population. Finally, how novel oral anticoagulant agents used for thromboprophylaxis in AF patients (e.g., dabigatran, rivaroxaban, apixiban) interact with antiplatelet therapy is of great interest. Available data thus far demonstrate increased bleeding with these drugs when used in combination with antiplatelet therapy after MI (25,26), but these agents may provide an advantage when combined with a single antiplatelet agent, potentially including an antiplatelet more potent than clopidogrel (e.g., prasugrel, ticagrelor). An

ongoing randomized trial studying combinations of rivaroxaban, warfarin, and DAPT in AF patients undergoing PCI will add important insight to the field (PIONEER AF-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]; NCT01830543); a similar trial with dabigatran (REDUAL PCI [Evaluation of Dual Therapy with Dabigatran vs. Triple Therapy with Warfarin in Patients with AF That Undergo a PCI with Stenting]; NCT02164864) is planned.

STUDY LIMITATIONS. First, although the method of AF identification by using Medicare and registry data has been previously used (5,27), it has not been validated; therefore, differences in the data source for AF diagnosis between the triple therapy and DAPT groups could result in bias. For example, the greater proportion of AF patients identified by using ACTION Registry-GWTG data in the triple group might reflect more permanent AF and, hence, provider decisions for oral anticoagulation in addition to DAPT. This approach, using a 1-year period to identify prior AF diagnoses, may also miss patients with more remote AF diagnoses. Second, our study was observational and subject to unmeasured confounders. We had no data regarding provider rationale for treatment choices (e.g., timing, type, or duration of AF; patient bleeding risk; upcoming invasive procedures); as a result, selection bias may persist despite propensity adjustment. Third, our primary analysis was on the basis of intention-to-treat. We observed significant post-discharge treatment crossover in the subcohort of Medicare Part D enrollees, with a large drop in the proportion of patients taking warfarin between 6 and 12 months. Multiple factors, such as uncaptured bleeding events, reassessment of fall risk in this older population, medication discontinuation for procedures, and difficulty with international normalized ratio monitoring, might account for this decrease. Such treatment crossover may mask potential associations between warfarin use and outcomes. Fourth, although we included bleeding events involving rehospitalization, we were unable to assess bleeding of lesser severity that may have required outpatient evaluation and treatment or may have affected quality of life or medication adherence. Fifth, the study was likely underpowered to detect differences in stroke and did not have adequate sample size to compare combinations of antithrombotic therapies other than triple therapy versus DAPT (e.g., warfarin plus clopidogrel or aspirin). Sixth, we could not assess novel oral anticoagulant agents given the timing of this dataset. Seventh, we could not use the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history/predisposition, labile international normalized ratio, and elderly) bleeding risk score (28), which is currently cited in the European guidelines, or the HEMORR$_2$HAGES (hepatic or renal disease, ethanol abuse, malignancy, older, reduced platelet count/function, hypertension, anemia, genetic factors, excessive fall risk, and stroke) score (29), because we did not have all the data necessary to calculate these scores. Finally, our analysis focused on older patients, and our results may not apply to younger, healthier populations.

CONCLUSIONS

Balancing the risks of thrombosis and bleeding for acute MI patients with concurrent indications for antiplatelet and anticoagulant therapy remains a therapeutic challenge, especially for older patients. We observed that approximately one-fourth of older MI patients with a history of AF who are treated with coronary stenting in the United States are discharged on triple therapy. Use of triple therapy was associated with predicted risk of stroke but not bleeding. With regard to downstream outcomes, triple and DAPT therapy had similar MACE rates, but those treated with triple therapy had significantly higher early and long-term risk of bleeding, including intracranial hemorrhage, even after risk adjustment.

ACKNOWLEDGMENTS The authors thank Erin Hanley, MS, for her editorial contributions to the manuscript. Ms. Hanley did not receive compensation for her contributions, apart from her employment at the institution where this study was conducted.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Approximately one-fourth of older patients with AF who undergo coronary stenting after acute MI in the United States are discharged on DAPT plus an anticoagulant agent (triple therapy). Compared with those taking DAPT alone, patients on triple therapy had similar rates of MACE but experienced significantly greater risk of bleeding.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to compare the risks and benefits of various combinations of antithrombotic therapy, including target-specific oral anticoagulant agents, in patients with AF undergoing coronary stenting after acute MI.

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KEY WORDS antithrombotic therapy, atrial fibrillation, myocardial infarction, percutaneous coronary intervention

APPENDIX For supplemental materials, please see the online version of this article.