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ORIGINAL ARTICLE

Atrial Fibrillation and Coronary Artery Disease: A Long-Term Perspective on the Need for Combined Antithrombotic Therapy

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BACKGROUND: Older adults with atrial fibrillation (AF) are often treated with the shortest possible duration of antiplatelet/anticoagulant therapy after myocardial infarction (MI) or percutaneous coronary intervention (PCI) due to concern for bleeding. However, the risk of recurrent MI or PCI prompting antiplatelet therapy extension is unknown in this population.

METHODS: Using the National Cardiovascular Data Registry linked to Medicare claims, we described the cumulative incidence of recurrent MI or PCI over a median of 7-year follow-up for patients ≥65 years old with AF discharged alive after acute MI between 2008 and 2017. We used pharmacy fill data to describe the proportion of patients filling prescriptions for both oral anticoagulants and $P2Y_{12}$ inhibitors for ≥50% of the indicated duration after MI or PCI.

RESULTS: Of 187 622 older patients discharged alive after MI, 50 539 (26.9%) had AF. Over a median of 7-year follow-up in patients with AF, the cumulative incidence was 14.5% for recurrent MI, 12.1% for PCI, 7.9% for stroke, and 9.5% for bleeding hospitalization. Among 7998 patients with AF and recurrent MI or PCI, 1668 (20.9%) had >1 MI or PCI during follow-up. Assuming each MI or PCI should be followed by 6 months of $P2Y_{12}$ inhibitor therapy, patients with AF who had a recurrent MI/PCI had a median estimated indication for antiplatelet/anticoagulant treatment of 287 days (194, 358), but filled both $P2Y_{12}$ inhibitor and oral anticoagulant for a median of 0 days (0, 21). In this cohort, 12.2% of patients filled prescriptions for both a $P2Y_{12}$ inhibitor and oral anticoagulant for ≥50% of the indicated duration.

CONCLUSIONS: Older adults with AF and MI have high incidences of downstream recurrent MI or PCI requiring extended antiplatelet/anticoagulant therapy durations, yet many appear to be under-treated. These results highlight the need for better thrombosis prevention strategies in this group of patients.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: anticoagulants ■ atrial fibrillation ■ myocardial infarction ■ percutaneous coronary intervention ■ thrombosis

See Editorial by Brener

Older adults are at higher risk of both atrial fibrillation (AF) and coronary artery disease.[1] The antithrombotic management after myocardial infarction (MI) for a patient with AF is challenging: Long-term treatment with an oral anticoagulant (OAC) is necessary to prevent stroke and systemic embolization related to AF, but dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor represents the standard of care in patients with MI to reduce recurrent ischemic events or prevent stent thrombosis in those treated with percutaneous coronary intervention (PCI).[2,3] The rate of major bleeding in patients treated with triple antithrombotic therapy (OAC plus aspirin plus

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WHAT IS KNOWN

- Patients with atrial fibrillation who have a myocardial infarction or undergo percutaneous coronary intervention should be treated with a non-vitamin K oral anticoagulant plus $P2Y_{12}$ inhibitor for 6 to 12 months.

WHAT THE STUDY ADDS

- Among patients ≥65 years old with fee-for-service Medicare admitted with myocardial infarction to a hospital participating in a nationwide quality improvement registry, 26% have concomitant atrial fibrillation.
- Over median 7-year follow-up, 14.5% will have a recurrent myocardial infarction, 12.1% will undergo percutaneous coronary intervention (with 21% of these having more than 1 coronary event) that might extend the duration of dual antiplatelet/anticoagulant treatment, yet 10% will be hospitalized for bleeding.
- Prescription fill data show that many older patients with atrial fibrillation and myocardial infarction are not treated or received shorter durations of anticoagulant and $P2Y_{12}$ inhibitor treatment than what is recommended by clinical guidelines.
- These results highlight the need for better thrombosis prevention strategies for these patients who are at high risk for both bleeding and recurrent ischemic events.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
CPMI	Chest Pain–Myocardial Infarction
DCF	data collection form
HR	hazard ratio
ICD	International Classification of Diseases
MI	myocardial infarction
OAC	oral anticoagulant
PCI	percutaneous coronary intervention

a $P2Y_{12}$ inhibitor) approaches 10% per year, a rate 2- to 3-fold higher than that of patients treated with OAC alone.[4] As such, consensus guidelines for the treatment of these patients, based on pivotal clinical trials, recommend 6 to 12 months of treatment with OAC plus a $P2Y_{12}$ inhibitor, with or without the short-term addition of aspirin, followed by a return to OAC alone.[5–7] Though these regimens reduce the rate of major bleeding compared with triple antithrombotic therapy (OAC plus $P2Y_{12}$ inhibitor plus aspirin), the bleeding risk remains higher than with dual antiplatelet therapy or OAC alone,[8–12] and often presents a clinical dilemma in older patients.[13,14]

Moreover, pivotal clinical trials to date have focused only on treatment strategies for the early time period (typically no longer than 12 months) following MI. Coronary artery disease is a chronic illness, and patients with one MI are at substantial risk of a second ischemic event.[15] If the risk of recurrent ischemic events and attendant need for extended $P2Y_{12}$ inhibitor therapy is high over long-term follow-up, it may change the risk-benefit ratio of nonpharmacological strategies for stroke prevention at the time of the index event. Furthermore, roughly 75% of patients with concomitant AF and MI are not prescribed OAC upon hospital discharge, reflecting patient and clinician concerns regarding the risk of bleeding on combined antithrombotic therapy.[16] Understanding real-world practices with respect to use of combined antithrombotic therapy over long-term follow-up in patients with concomitant AF and coronary artery disease may also inform decision-making with respect to earlier use of nonpharmacological strategies for stroke prophylaxis.

We, therefore, used data from a nationwide US registry to (1) describe the incidence of recurrent ischemic events among older patients with concomitant AF and MI over long-term follow-up, including the incidence of multiple recurrent events; (2) identify factors associated with recurrent MI or PCI and need for prolonged antiplatelet/anticoagulant therapy; and (3) describe long-term antithrombotic therapy treatment patterns after recurrent ischemic events in these patients.

METHODS

The data, analytic methods, and study materials used in this manuscript will not be made available to other researchers.

Patient Population

The National Cardiovascular Data Registry's Chest Pain–Myocardial Infarction (CPMI) Registry captures consecutive patients admitted to participating hospitals with ST-segment–elevation myocardial infarction and non–ST-segment–elevation myocardial infarction.[17,18] Trained data abstractors at each hospital collect detailed information on medical history, clinical presentation, and in-hospital treatment via retrospective chart review. Real-time data quality feedback and annual audits ensure data accuracy. Definitions of abstracted National Cardiovascular Data Registry data variables are available online at https://www.ncdr.com/webncdr/action/home/datacollection. Patients ≥65 years old in this registry with fee-for-service Medicare have previously been linked to their Medicare claims data using 5 indirect identifiers (date of birth, sex, hospital identifier, date of admission, and date of discharge).[19–21] We used this linked data source to identify a cohort of older adult patients with MI who had AF before admission or developed it during their MI admission and to capture long-term outcomes and antithrombotic therapy.

Between October 2008 and December 2017, 226 331 patients ≥65 years old were admitted to 864 hospitals with MI (with or without ST-segment elevation) and were included in the linked database. Because we were interested in understanding long-term postdischarge patterns of mortality and readmission, we excluded patients who died while hospitalized (n=14 747), patients who were transferred to a hospital that did not participate in the CPMI Registry before discharge (n=9017) and patients discharged to hospice (n=1827). To avoid double-counting,

we included only a patients' first MI admission during the study period and excluded all nonindex admissions (n=13 118). Our final study population thus included 187 622 patients with MI treated at 854 hospitals (Figure 1). For analyses of antithrombotic therapy usage patterns, we included only patients with AF and Part D Medicare prescription coverage (n=30 221). Patients were only included in these analyses for the span of time that they were alive and continuously enrolled in Medicare Part D.

Definitions and Outcomes

The CPMI Registry captures preadmission history of AF or atrial flutter on the data collection form (DCF). Since 2015, the CPMI Registry DCF has also captured new-onset AF developing during the index MI admission. Because this variable was not captured for the entirety of our study period, we also identified patients with *International Classification of Diseases Ninth or Tenth Edition* (ICD-9 or -10) codes consistent with AF or atrial flutter (ICD-9: 427.31, 427.32; ICD-10: I48.0, I48.1, I48.2, I48.3, I48.4, I48.9x) during the index admission. Patients were considered to have AF if they had prior AF or new-onset AF captured on the CPMI DCF, or AF identified in diagnosis codes during the index admission. For patients with and without AF, we report Acute Coronary Treatment and Intervention Outcomes Network in-hospital mortality and bleeding risk scores at the time of index MI as a short-term indicators of risk,[22,23] and CHA_2DS_2-VASc and Outcomes Registry for Better Informed Treatment of Atrial Fibrillation scores at the time of index MI as indicators of long-term stroke and bleeding risk.[24,25]

Outcomes of interest included all-cause death, readmission for MI, readmission for stroke, readmission for bleeding, and repeat PCI (inpatient or outpatient). Mortality was identified using Medicare denominator files. Readmissions were identified based on the first diagnostic code for any subsequent inpatient hospitalization using ICD-9 or -10 codes (Table S1). PCIs were identified by ICD-9 and -10 codes in any position, as well as Current Procedural Terminology and Healthcare Common Procedure Coding System codes for outpatient procedures.

Statistical Analysis

We compared baseline characteristics of patients with and without AF at the time of their index MI. Categorical variables were reported as frequencies with percentages and compared using χ^2 tests, and continuous variables were reported as medians with 25th and 75th percentiles and compared using Wilcoxon rank-sum tests. To compare outcomes in patients with and without AF at baseline from hospital discharge through 7-year follow-up, we produced cumulative incidence curves using the Kaplan-Meier estimator to describe long-term all-cause mortality, and nonparametric cumulative incidence estimates considering competing risk with all-cause mortality to describe nonfatal outcomes, which were readmission for MI, readmission for stroke, readmission for bleeding, and recurrent PCI. We compared these curves using the log-rank test for all-cause mortality and nonparametric Gray test for nonfatal outcomes. To further understand the long-term association between AF and these outcomes, we performed a landmark analysis from 6 months after hospital discharge through 7 years among those patients who survived free of each outcome, respectively, a 6 months after discharge.

As cumulative incidence curves above were generated considering only time to first event and patients may have multiple recurrent ischemic events, we described the total number of readmissions for MI and recurrent PCI episodes among patients with AF over long-term follow-up.

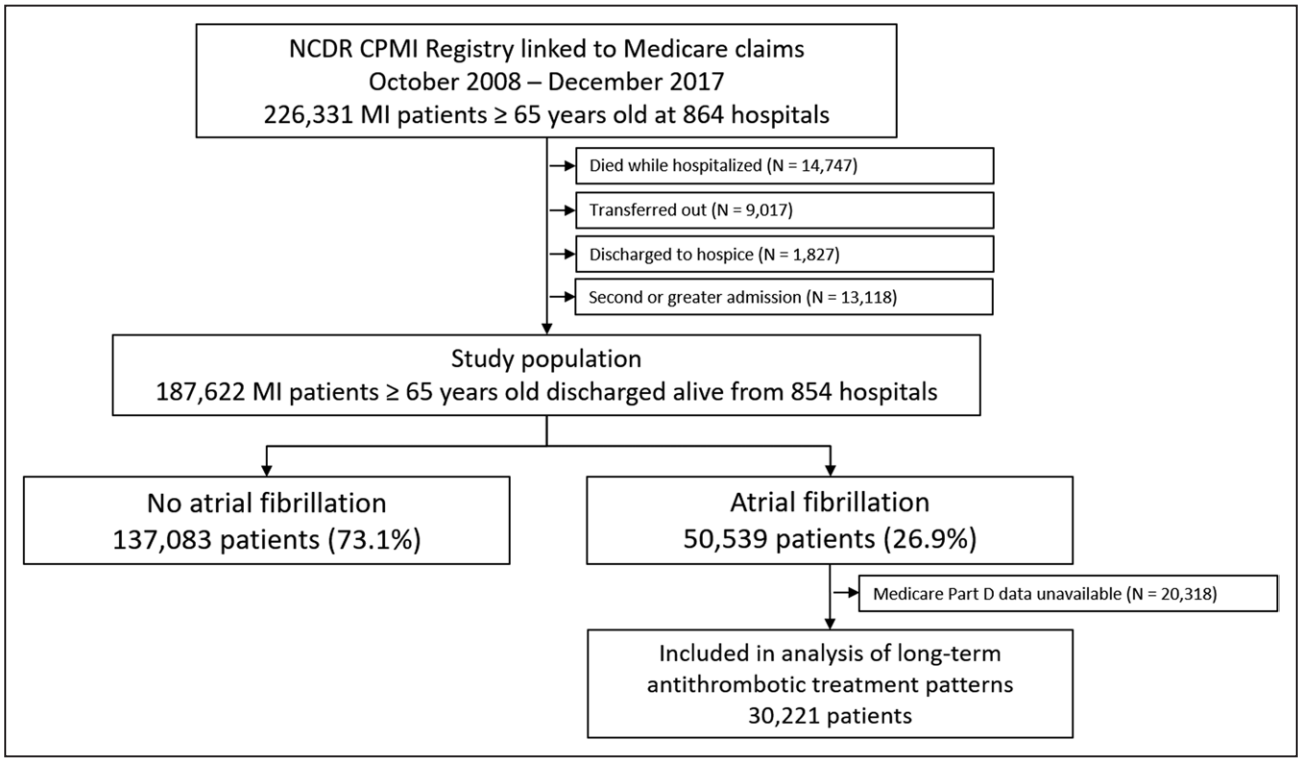

Figure 1. Study flow.
NCDR CPMI indicates National Cardiovascular Data Registry's Chest Pain–Myocardial Infarction; and MI, myocardial infarction.

We then used a multivariable cause-specific hazard model adjusting for the competing risk of long-term death to identify variables known at the time of discharge from the index MI hospitalization associated with having an MI or PCI (and a recurrent indication for antiplatelet/anticoagulant therapy) during long-term follow-up among patients with AF at the time of their index MI. Variables entered into the multivariable model were selected based on clinical relevance and included demographic variables, comorbidities/past medical history, and details of the index MI admission (Table S2). For continuous variables, linearity of relationship with the outcome was assessed in the multivariable hazard model by the use of restricted cubic splines.[26] When Wald χ^2 testing showed that the association between the variable and outcome was nonlinear, associations were plotted and spline terms with knots were assigned based on visual inspection. When variables were missing, we used multiple imputation. Fully conditional specification method regression was specified for continuous variables, fully conditional specification logistic regression was specified for binary/ordinal categorical variables, and fully conditional specification discriminant function was specified for nominal categorical variables in the multiple imputation. Five imputed data sets were created, and the results from the logistic regression models were combined to derive estimates. Adjusted hazard ratios (HR) and 95% CIs are presented.

We subsequently used Medicare Part D data to describe actual antithrombotic treatment patterns over long-term follow-up. Using prescription fill data, we determined the number of days each patient had a supply of both OAC and $P2Y_{12}$ inhibitor. $P2Y_{12}$ inhibitors included ticlopidine, clopidogrel, ticagrelor, and prasugrel; OACs included warfarin, dabigatran, apixaban, rivaroxaban, and edoxaban. We also calculated the number of days antiplatelet/anticoagulant therapy was indicated for each patient, assuming 6 months (180 days) of antiplatelet/anticoagulant therapy after any MI or PCI event, based on current guidelines. Guidelines for management of patients with ACS or undergoing PCI in force during the study period did not make specific recommendations for patients with AF, and combining recommendations from these guidelines and AF guidelines would lead to a recommendation for 12 months of triple antithrombotic therapy with OAC, $P2Y_{12}$ inhibitor, and aspirin.[2,3] As such, a 6 month duration of antiplatelet/anticoagulant therapy was chosen to be conservative. We described the proportion of patients who had a supply of both OAC and $P2Y_{12}$ inhibitor for 0%, >0 to <50%, 50% to <100%, and 100% of days for which these treatments were indicated, as well as the proportion of patients who had a supply of $P2Y_{12}$ inhibitor alone, OAC alone, and neither medication. We repeated this process for the cohort of patients who had a recurrent MI or PCI event during long-term follow-up. As a sensitivity analysis, we repeated this analysis in patients with AF noted on the CP-MI Registry DCF, to capture only patients with long-standing, well-documented AF before their index MI. To elucidate potential reasons for stopping antithrombotic therapy, among patients who filled a prescription for both a $P2Y_{12}$ inhibitor and OAC for >0 but <100% of the indicated duration (ie, those who prematurely stopped therapy), we described the proportion of patients who were hospitalized for bleeding during the time that both antithrombotic medications were indicated.

All analyses were conducted by faculty and staff statisticians and the Duke Clinical Research Institute using SAS version 9.4 software (SAS Institute, Cary, NC). The Duke University Medical Center Institutional Review Board granted a waiver of informed consent and authorization for this study.

RESULTS

Of 187 622 patients over age 65 years admitted with acute MI to 854 hospitals in the United States between October 1, 2008, and December 31, 2017, 50 539 (26.9%) had AF. Of these, 98.7% (n=49 889) had a diagnosis of AF before admission and 1.3% (n=650) developed new-onset AF while hospitalized. In patients with AF, the median CHA_2DS_2-VASc score was 5 (25th, 75th percentiles 4, 6) and the median Outcomes Registry for Better Informed Treatment of Atrial Fibrillation bleeding risk score was 4 (25th, 75th percentiles 3, 5), suggesting high estimated thromboembolic and bleeding risks. Compared with patients without AF, patients with AF were older (median age 78 versus 74) and were more likely to have cardiovascular comorbidities, including prior MI, prior heart failure, hypertension, hyperlipidemia, diabetes, cerebrovascular and peripheral artery disease, and end-stage renal disease on dialysis (Table 1). They more often presented with non–ST-segment–elevation MI and more often had moderate or severe left ventricular systolic dysfunction. They less often underwent diagnostic cardiac catheterization and PCI, but more often had multivessel coronary artery disease on coronary angiography.

Incidence of Long-Term Adverse Outcomes After MI

Over a median of 7-year follow-up in patients with AF, the cumulative incidence was 68.8% for all-cause mortality, 14.5% for recurrent MI, 12.1% for PCI, 7.9% for stroke, and 9.5% for hospitalization for major bleeding. Mortality rates were higher for patient with than without AF and mortality curves diverged early (Figure 2A, $P<0.001$). Similarly, patients with AF were at higher risk of stroke and rehospitalization for major bleeding than patients without AF (Figure 2B and 2C, $P<0.001$ for both). By contrast, patients with AF had similar risk of recurrent MI and were less likely to receive downstream PCI (Figure 2D and 2E, $P=0.75$ and <0.001, respectively). Over 1- and 3-year follow-up, patients with AF had a higher cumulative incidence of death, readmission for stroke, and readmission for bleeding, but not higher rates of PCI or MI (Table S3).

Incidence rates remained high for these events for patients with AF who survived the first 6 months after the index MI and might be ready to transition off $P2Y_{12}$ inhibitor therapy: 65.4% for all-cause mortality, 12.2% for recurrent MI, 9.5% for PCI, 7.8% for stroke, and 8.5% for hospitalization for major bleeding (Figure S1).

Table 1. Baseline Characteristics of Patients With and Without Atrial Fibrillation at the Time of Index MI

	Atrial fibrillation (n=50 539)	No atrial fibrillation (n=137 083)	*P* value
Demographics			
Age	78 (72–84)	74 (69–81)	<0.001
Male	29 450 (58.3%)	80 211 (58.5%)	0.35
Weight, kg	79.9 (67.8–93.6)	80.0 (68.0–93.0)	0.10
Race			<0.001
White	45 557 (90.5%)	117 965 (86.4%)	
Black	2679 (5.3%)	10 798 (7.9%)	
Hispanic	1303 (2.6%)	5293 (3.9%)	
Asian	515 (1.0%)	1594 (1.2%)	
Other	263 (0.5%)	866 (0.6%)	
Comorbidities			
Hypertension	43 738 (86.6%)	111 073 (81.0%)	<0.001
Diabetes	19 389 (38.4%)	48 787 (35.6%)	<0.001
Cerebrovascular disease	11 382 (22.5%)	21 238 (15.5%)	<0.001
Peripheral arterial disease	7719 (15.3%)	15 926 (11.6%)	<0.001
Currently on dialysis	1937 (3.8%)	3127 (2.3%)	<0.001
Dyslipidemia	35 540 (70.4%)	92 164 (67.3%)	<0.001
Current/recent smoker	6244 (12.4%)	24 682 (18.0%)	<0.001
Prior MI	14 969 (29.6%)	33 159 (24.2%)	<0.001
Prior HF	13 724 (27.2%)	17 072 (12.5%)	<0.001
Prior PCI	14 862 (29.4%)	35 598 (26.0%)	<0.001
Prior CABG	11 435 (22.6%)	24 009 (17.5%)	<0.001
Details of index MI			
STEMI	12 213 (24.2%)	44 914 (32.8%)	<0.001
LV ejection fraction			<0.001
<25%	3144 (6.7%)	5208 (4.0%)	
25%–40%	9976 (21.3%)	21 118 (16.3%)	
40%–50%	10 074 (21.5%)	26 723 (20.7%)	
≥50%	23 721 (50.6%)	76 203 (59.0%)	
Cardiogenic shock	1670 (3.3%)	2950 (2.2%)	<0.001
Heart rate on admission, bpm	85 (70–105)	80 (68–94)	<0.001
Systolic BP on admission, mm Hg	142 (121–164)	149 (128–171)	<0.001
Diagnostic cardiac catheterization	39 520 (78.2%)	119 349 (87.1%)	<0.001
Number of diseased vessels			<0.001
3	16 395 (41.7%)	42 821 (36.0%)	
2	10 915 (27.8%)	36 650 (30.8%)	
1	9511 (24.2%)	33 345 (28.0%)	
None	2478 (6.3%)	6077 (5.1%)	
PCI	23 423 (46.4%)	87 309 (63.7%)	<0.001
CABG	6868 (13.6%)	10 049 (7.3%)	<0.001
ACTION in-hospital mortality risk score	40 (32–47)	35 (28–42)	<0.001
ACTION in-hospital major bleeding risk score	20 (13–26)	17 (11–23)	<0.001
CHA_2DS_2-VASc score	5 (4–6)	4 (3–5)	<0.001
ORBIT-AF bleeding risk score	4 (3–5)	3 (2–4)	<0.001

ACTION indicates Acute Coronary Treatment and Interventions Outcomes Network; BP, blood pressure; CABG, coronary artery bypass graft surgery; HF, heart failure; LV, left ventricular; MI, myocardial infarction; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

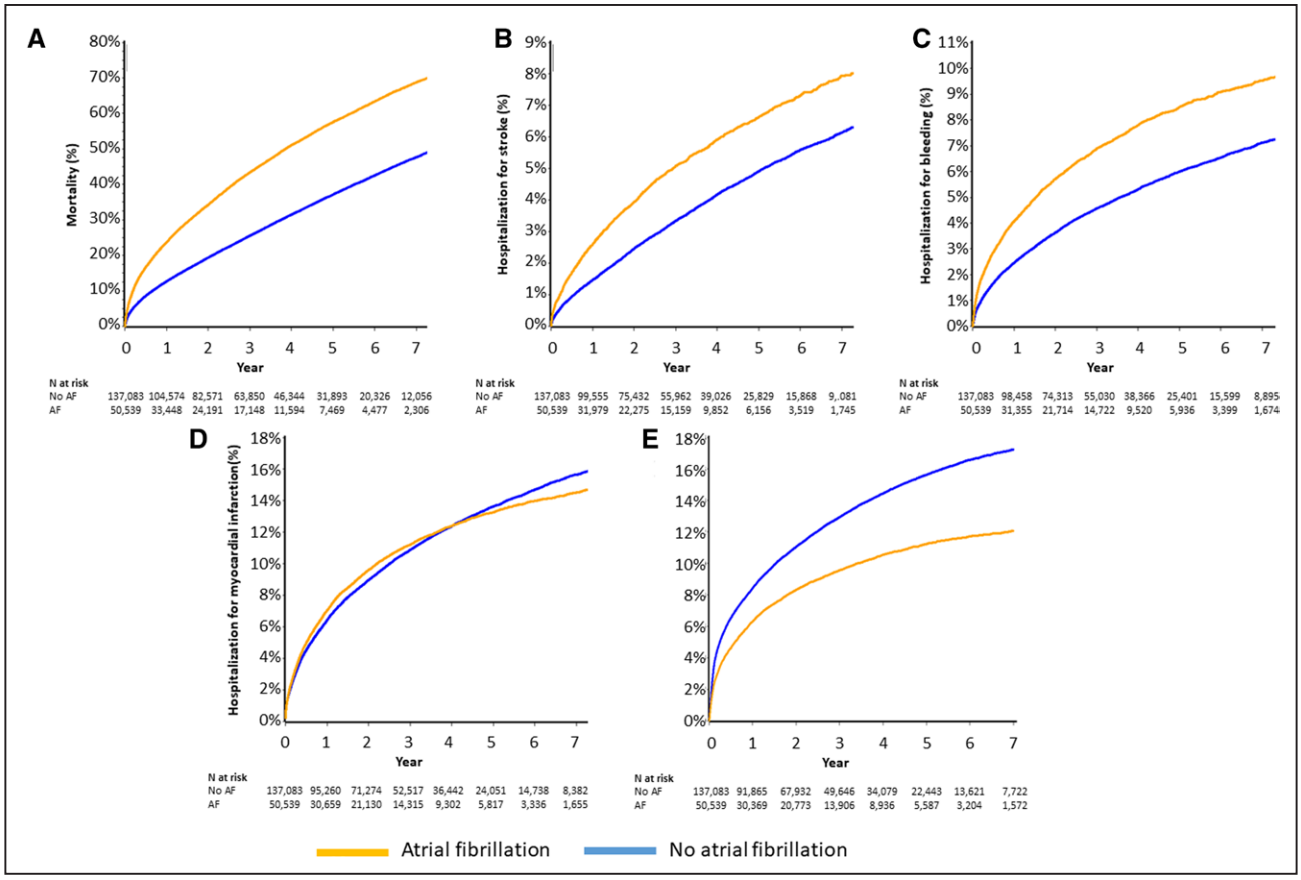

Figure 2. Outcomes by presence of atrial fibrillation (AF) at the time of index myocardial infarction (MI).
A, Depicts all-cause mortality; (**B**) hospitalization for stroke; (**C**) hospitalization for bleeding; (**D**) hospitalization for MI; (**E**) percutaneous coronary intervention. Patients with AF at the time of index MI had higher all-cause mortality and hospitalization for stroke and bleeding than those without (log-rank $P<0.0001$ for all comparisons); patients without AF had a higher risk of percutaneous coronary intervention ($P<0.0001$). There was no difference in risk of hospitalization for recurrent MI ($P=0.75$) by AF status.

Recurrent Ischemic Events With an Indication for Prolonged or Resumed $P2Y_{12}$ Inhibitor Therapy

Of the 5438 patients with AF who had at least 1 recurrent MI postdischarge, 742 (13.6%) had 2 and 263 (4.8%) had 3 or more recurrent events over the course of follow-up. Similarly, of 4697 patients with AF who had at least 1 postdischarge PCI event, 638 (13.6%) had 2 and 234 (5.0%) had 3 or more recurrent PCI events over the course of follow-up. Of 7998 patients AF with either a recurrent MI or PCI event, 6329 (79.1%) had 1 recurrent MI or PCI event after the index MI, 1305 (16.3%) had 2, and 364 (4.6%) had 3 or more.

On multivariable modeling, factors present at the time of discharge following index MI most strongly associated with having a recurrent MI or PCI (and prolongation or resumption of $P2Y_{12}$ inhibitor therapy) included 3-vessel coronary artery disease (HR, 2.45 [95% CI, 2.13–2.81]), prior PCI (HR, 1.30 [95% CI, 1.24–1.36]), prior coronary artery bypass graft surgery (HR, 1.20 [95% CI, 1.14–1.27]), and diabetes (HR, 1.23 [95% CI, 1.18–1.29]; Table 2). Coronary artery bypass graft surgery at the time of index admission (HR, 0.25 [95% CI, 0.23–0.28]) was associated with lower likelihood of developing a recurrent ischemic event, as were PCI and diagnostic angiography

Antithrombotic Therapy Treatment Patterns

Overall, 30221 of 50539 (59.8%) patients with AF were enrolled in Medicare Part D permitting examination of antithrombotic medication fills. Overall, 1.0% of patients filled prescriptions for $P2Y_{12}$ inhibitors and OAC for 100% of the indicated duration, and 10.3% for 50% to 100% of the indicated duration. The remainder (88.8%) of patients were under-treated, defined as being treated with shorter durations of antiplatelet/anticoagulant therapy or treated with either a $P2Y_{12}$ inhibitor or an anticoagulant alone; 76.4% of patients were not treated with both a $P2Y_{12}$ inhibitor and OAC for any of the follow-up days for which both treatments were indicated. Most patients were treated with either a $P2Y_{12}$ inhibitor or an OAC for at least some of follow-up, though 20.1% of patients filled a prescription for neither antithrombotic medication for the entirety of the indicated duration (Table S4). Overall, 61.9% of patients

Table 2. Factors Associated With Recurrent MI or PCI Among Patients With Atrial Fibrillation on Multivariable Modeling

Variable	Adjusted OR (95% CI)	*P* value	χ^2
Procedure performed during index MI		<0.001	707.1
Diagnostic cath only (vs no procedure)	0.70 (0.66–0.75)		
PCI (vs no procedure)	0.80 (0.75–0.86)		
CABG (vs no procedure)	0.25 (0.23–0.28)		
Number of diseased vessels		<0.001	536.9
One (vs no obstructive CAD)	1.30 (1.12–1.51)		
Two (vs no obstructive CAD)	1.97 (1.71–2.27)		
Three (vs no obstructive CAD)	2.45 (2.13–2.81)		
Prior PCI	1.30 (1.24–1.36)	<0.001	120.1
Glomerular filtration rate		<0.001	99.5
Every 5 unit increase if eGFR ≤45 mL/min	0.94 (0.93–0.95)	<0.001	
Every 5 unit increase if eGFR >45 mL/min	1.00 (1.00–1.01)	<0.001	
Diabetes	1.23 (1.18–1.29)	<0.001	75.3
Prior CABG	1.20 (1.14–1.27)	<0.001	42.9
Prior MI	1.11 (1.06–1.17)	<0.001	15.5
Left ventricular ejection fraction		0.004	11.1
Every 5 unit increase if LVEF ≤40%	1.04 (1.02–1.06)		
Every 5 unit increase if LVEF >40	1.00 (0.98–1.01)		
Prior heart failure	1.08 (1.03–1.14)	0.002	9.4
Race: White (vs other)	0.89 (0.82–0.96)	0.003	8.9
STEMI (vs NSTEMI)	0.92 (0.87–0.97)	0.003	8.8
Peripheral artery disease	1.09 (1.03–1.16)	0.003	8.6
Current/recent smoker	1.08 (1.00–1.15)	0.04	4.4

CABG indicates coronary artery bypass graft surgery; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

were treated with either a $P2Y_{12}$ inhibitor, OAC, or both for ≥50% of the indicated duration. Results were similar among the 14 991 patients who had long-standing AF, as denoted on the CP-MI DCF (Table S5). Among 6842 patients who filled prescriptions for both $P2Y_{12}$ inhibitor and OAC for >0% but <100% of the indicated duration (ie, patients who started double antithrombotic therapy and stopped prematurely), 303 (4.4%) were hospitalized for bleeding during the period during which OAC and $P2Y_{12}$ inhibitor therapy was indicated. Patients with AF who had a recurrent MI or PCI during follow-up (n=5007 with Medicare Part D) had an estimated indication for combined antiplatelet/anticoagulant therapy for a median of 283 days (190, 358), but had a median supply of both $P2Y_{12}$ inhibitor and OAC for 0 days (0, 21) of indicated days. Among these patients, 0.3% filled prescriptions for $P2Y_{12}$ inhibitors and OAC for 100% of the indicated duration and 11.9% for 50% to 100%, 24.6% for 0% to 50%, and 63.2% for 0% to 50%. Overall, 7.4% of patients with a recurrent MI or PCI during follow-up filled neither a $P2Y_{12}$ inhibitor or an OAC for 100% of the indicated duration.

DISCUSSION

In this older post-MI population, we found that a substantial proportion of patients had AF with high CHA_2DS_2-VASc score for which anticoagulation is indicated, on top of the $P2Y_{12}$ inhibitor therapy recommended by guidelines after MI or PCI. Over a median of 7-year follow-up, these patients with AF were at high-risk of recurrent MI or PCI, for which $P2Y_{12}$ inhibitor therapy needed to be extended or resumed, and many of these patients had multiple recurrent MI or PCI events. When examining pharmacy fill data, only 1 in 4 patients with an indication for both anticoagulant and $P2Y_{12}$ inhibitor therapy filled prescriptions for both therapies for at least 90 days; this pattern of under-treatment persisted among patients with recurrent MI or PCI.

Despite advances in treatment for patients with an acute MI,[15,27–30] long-term mortality and morbidity following MI remain poor, especially for older adults.[27] Our study shows that outcomes are worse for patients with MI with AF than those without AF. The older age and greater burden of comorbidities of patients with AF likely explain much of the difference in long-term mortality; however, the higher risk of stroke suggests a direct effect of AF. Patients with AF had similarly high risks of recurrent MI but a lower likelihood of downstream PCI than patients without AF, which may reflect clinician desire to avoid escalation of antithrombotic therapy with its attendant bleeding risk.[31]

Both AF and coronary artery disease carry a substantial risk of serious thrombotic complications, but these thrombotic complications are pathophysiologically distinct and require different treatment strategies. Randomized controlled trials have demonstrated the superiority of OAC over antiplatelet therapy for thromboprophylaxis in patients with AF,[32] and the superiority of dual antiplatelet therapy over OAC for prevention of ischemic events in patients with MI and undergoing PCI.[33,34] Patients with both AF and MI would thus benefit from the combination of OAC and dual antiplatelet therapy; however, risk of serious bleeding with this combination exceeds 10% annually, with even higher rates in older adults.[4] In recent clinical trials, the combination of a non-vitamin K antagonist OAC plus a $P2Y_{12}$ inhibitor reduced the risk of bleeding compared with triple antithrombotic therapy in patients with AF and either MI or PCI, without a significant increase in stroke, systemic embolization, or recurrent MI.[35] A prior study showed that ≈25% of patients with AF who had MI were discharged with prescriptions for both a $P2Y_{12}$ inhibitor and OAC.[16] Our study shows that over long-term follow-up, patients took this combination

therapy very infrequently, with fewer than 1 in 10 patients adherent to this regimen for the full duration that it was indicated and <15% adherent for half the duration. The low rate of adherence to combined antiplatelet/anticoagulant therapy may increase the real-world risk of thromboembolic stroke and recurrent MI compared with rates observed in clinical trials in this patient population.

Moreover, even though combined antiplatelet/anticoagulant therapy is likely to offer the best balance between protection from thromboembolic and coronary events and avoidance of bleeding events, it is not risk-free. In pivotal randomized controlled trials, roughly 3% of patients treated with a non-vitamin K antagonist OAC plus a $P2Y_{12}$ inhibitor suffered a major bleed and 10% suffered a clinically relevant bleeding event,[8,11,36,37] a rate >2-fold higher than with non-vitamin K antagonist OAC alone and 50% higher than with dual antiplatelet therapy alone.[12,38] Despite low use of combined antiplatelet/anticoagulant therapy in our real-world patient population, nearly 10% of patients were hospitalized for bleeding over long-term follow-up, including 4% over the first year following MI. Bleeding risk increases approximately linearly with increasing duration of antithrombotic therapy,[39] so with longer combined antiplatelet/anticoagulant treatment duration, bleeding risk is likely to be higher. Our study shows that recurrent ischemic events occur in a substantial minority of patients with AF and coronary heart disease over long-term follow-up, with a requirement for prolongation or a return to antiplatelet/anticoagulant therapy. In these patients, prolonged exposure to treatment with non-vitamin K antagonist OAC plus $P2Y_{12}$ inhibitor will increase the risk of bleeding, with attendant increased risk of mortality and reduction in quality of life.[13,14,40] Poor outcomes and low adherence to guideline-recommended antiplatelet/anticoagulant therapy suggest a need for the further development of strategies for prevention of coronary and cerebrovascular ischemic events in this high-risk cohort.

We found that several variables available at the time of discharge following the index MI were associated with a higher risk of recurrent MI or PCI, including younger age, multivessel coronary artery disease, prior coronary artery disease, and diabetes. Identification at the time of index MI of patients at high risk for prolonged exposure to combined antiplatelet/anticoagulant therapy due to multiple recurrent ischemic events may enable early consideration for nonpharmacological stroke prophylaxis therapies, including left atrial appendage exclusion, especially as this technology matures and complication rates decrease.[41]

Several limitations should be acknowledged. First, hospitalizations for stroke, bleeding, MI, and PCI were captured from administrative data and may be subject to bias; specifically, physicians caring for patients with AF or treated with anticoagulation may be more likely to attribute hospitalizations to stroke or bleeding. Second, the earliest cohort of patients included in our study population were enrolled in 2008, and outcomes for patients with MI with and without AF may have changed in the intervening years. Third, Medicare Part D data does not reliably capture whether patients were treated with aspirin, and it is, therefore, likely our analyses examining long-term use of antithrombotic agents undercount the proportion of time patients were treated with antiplatelet agents; however, the role of aspirin in managing patients with AF and PCI is uncertain. Fourth, our analysis of long-term antithrombotic treatment patterns is limited to patients enrolled in Medicare Part D. Patients with MI enrolled in Part D are more often women, more often non-White, more dual eligible for Medicaid, and have a greater prevalence of several comorbidities, including heart failure, stroke, and diabetes.[42] Despite these differences, in-hospital treatments are similar for patients with MI enrolled and not enrolled in Part D. Though our findings with respect to long-term antithrombotic treatment and adherence patterns may apply only to patients enrolled in Part D, this group comprises a majority of older patients with concomitant AF and MI. Lastly, this analysis reports treatment patterns and outcomes only in patients ≥65 years old. Though this group represents a large and growing proportion of patients with MI, especially those with AF, results from this study may not apply to patients <65 years old.

CONCLUSIONS

AF is common in older adults presenting with MI, and ≈1 in 10 older adults with AF and MI will have recurrent ischemic events necessitating prolongation or re-initiation of combined antiplatelet/anticoagulant therapy. Furthermore, only a minority of patients with MI with AF are treated with antiplatelet and anticoagulant therapy for the duration recommended by practice guidelines. Our data highlight the need for better strategies to improve outcomes in this high-risk group of patients.

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Supplemental Material

Tables S1–S5
Figure S1

REFERENCES

1. Fosbol EL, Wang TY, Li S, Piccini JP, Lopes RD, Shah B, Mills RM, Klaskala W, Alexander KP, Thomas L, Roe MT, Peterson ED. Safety and effectiveness of antithrombotic strategies in older adult patients with atrial fibrillation and non-ST elevation myocardial infarction. *Am Heart J*. 2012;163:720–728. doi: 10.1016/j.ahj.2012.01.017
2. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of cardiology/American Heart association task force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable Ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2016;134:e123–e155. doi: 10.1161/CIR.0000000000000404
3. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, et al; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:e199–e267. doi: 10.1161/CIR.0000000000000041
4. van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. *Circulation*. 2019;139:775–786. doi: 10.1161/CIRCULATIONAHA.118.036248
5. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. *Circulation*. 2019;140:e125–e151. doi: 10.1161/CIR.0000000000000665
6. Kumbhani DJ, Cannon CP, Beavers CJ, Bhatt DL, Cuker A, Gluckman TJ, Marine JE, Mehran R, Messe SR, Patel NS, et al. 2020 ACC expert consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease: a report of the American College of cardiology solution set oversight committee. *J Am Coll Cardiol*. 2021;77:629–658. doi: 10.1016/j.jacc.2020.09.011
7. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, et al; ESC Scientific Document Group. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373–498. doi: 10.1093/eurheartj/ehaa612
8. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, et al; RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377:1513–1524. doi: 10.1056/NEJMoa1708454
9. Gibson CM, Pinto DS, Chi G, Arbetter D, Yee M, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Recurrent hospitalization among patients with atrial fibrillation undergoing intracoronary stenting treated with 2 treatment strategies of rivaroxaban or a dose-adjusted oral vitamin K antagonist treatment strategy. *Circulation*. 2017;135:323–333. doi: 10.1161/CIRCULATIONAHA.116.025783
10. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, et al; TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med*. 2012;367:1297–1309. doi: 10.1056/NEJMoa1205512
11. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, et al; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380:1509–1524. doi: 10.1056/NEJMoa1817083
12. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–962. doi: 10.1016/S0140-6736(13)62343-0
13. Généreux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, et al. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coronary intervention. *J Am Coll Cardiol*. 2015;66:1036–1045. doi: 10.1016/j.jacc.2015.06.1323
14. Marquis-Gravel G, Dalgaard F, Jones AD, Lokhnygina Y, James SK, Harrington RA, Wallentin L, Steg PG, Lopes RD, Storey RF, et al. Post-discharge bleeding and mortality following acute coronary syndromes with or without PCI. *J Am Coll Cardiol*. 2020;76:162–171. doi: 10.1016/j.jacc.2020.05.031
15. Smolina K, Wright FL, Rayner M, Goldacre MJ. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. *Circ Cardiovasc Qual Outcomes*. 2012;5:532–540. doi: 10.1161/CIRCOUTCOMES.111.964700
16. Hess CN, Peterson ED, Peng SA, de Lemos JA, Fosbol EL, Thomas L, Bhatt DL, Saucedo JF, Wang TY. Use and outcomes of triple therapy among older patients with acute myocardial infarction and atrial fibrillation. *J Am Coll Cardiol*. 2015;66:616–627. doi: 10.1016/j.jacc.2015.05.062
17. Peterson ED, Roe MT, Chen AY, Fonarow GC, Lytle BL, Cannon CP, Rumsfeld JS. The NCDR ACTION Registry-GWTG: transforming contemporary acute myocardial infarction clinical care. *Heart*. 2010;96:1798–1802. doi: 10.1136/hrt.2010.200261
18. Peterson ED, Roe MT, Rumsfeld JS, Shaw RE, Brindis RG, Fonarow GC, Cannon CP. A call to ACTION (acute coronary treatment and intervention outcomes network): a national effort to promote timely clinical feedback and support continuous quality improvement for acute myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2009;2:491–499. doi: 10.1161/CIRCOUTCOMES.108.847145
19. Shah RU, de Lemos JA, Wang TY, Chen AY, Thomas L, Sutton NR, Fang JC, Scirica BM, Henry TD, Granger CB. Post-hospital outcomes of patients with acute myocardial infarction with cardiogenic shock: findings from the NCDR. *J Am Coll Cardiol*. 2016;67:739–747. doi: 10.1016/j.jacc.2015.11.048
20. Pokorney SD, Miller AL, Chen AY, Thomas L, Fonarow GC, de Lemos JA, Al-Khatib SM, Peterson ED, Wang TY. Implantable cardioverter defibrillator use among medicare patients with low ejection fraction after acute myocardial infarction. *JAMA*. 2015;313:2433–2440. doi: 10.1001/jama.2015.6409
21. Hammill BG, Hernandez AF, Peterson ED, Fonarow GC, Schulman KA, Curtis LH. Linking inpatient clinical registry data to Medicare claims data using indirect identifiers. *Am Heart J*. 2009;157:995–1000. doi: 10.1016/j.ahj.2009.04.002
22. McNamara RL, Kennedy KF, Cohen DJ, Diercks DB, Moscucci M, Ramee S, Wang TY, Connolly T, Spertus JA. Predicting in-hospital mortality in patients with acute myocardial infarction. *J Am Coll Cardiol*. 2016;68:626–635. doi: 10.1016/j.jacc.2016.05.049
23. Desai NR, Kennedy KF, Cohen DJ, Connolly T, Diercks DB, Moscucci M, Ramee S, Spertus J, Wang TY, McNamara RL. Contemporary risk model for inhospital major bleeding for patients with acute myocardial infarction: the acute coronary treatment and intervention outcomes network (ACTION) registry®-Get With The Guidelines (GWTG)®. *Am Heart J*. 2017;194:16–24. doi: 10.1016/j.ahj.2017.08.004

24. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272. doi: 10.1378/chest.09-1584
25. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P, Fonarow GC, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J*. 2015;36:3258–3264. doi: 10.1093/eurheartj/ehv476
26. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*. Springer; 2015.
27. Kochar A, Chen AY, Sharma PP, Pagidipati NJ, Fonarow GC, Cowper PA, Roe MT, Peterson ED, Wang TY. Long-term mortality of older patients with acute myocardial infarction treated in US clinical practice. *J Am Heart Assoc*. 2018;7:e007230. doi: 10.1161/JAHA.117.007230
28. Gulliksson M, Wedel H, Köster M, Svärdsudd K. Hazard function and secular trends in the risk of recurrent acute myocardial infarction: 30 years of follow-up of more than 775,000 incidents. *Circ Cardiovasc Qual Outcomes*. 2009;2:178–185. doi: 10.1161/CIRCOUTCOMES.108.802397
29. Leander K, Wiman B, Hallqvist J, Andersson T, Ahlbom A, de Faire U. Primary risk factors influence risk of recurrent myocardial infarction/death from coronary heart disease: results from the Stockholm Heart Epidemiology Program (SHEEP). *Eur J Cardiovasc Prev Rehabil*. 2007;14:532–537. doi: 10.1097/HJR.0b013e328012e3cc
30. Capewell S, Murphy NF, MacIntyre K, Frame S, Stewart S, Chalmers JW, Boyd J, Finlayson A, Redpath A, McMurray JJ. Short-term and long-term outcomes in 133,429 emergency patients admitted with angina or myocardial infarction in Scotland, 1990-2000: population-based cohort study. *Heart*. 2006;92:1563–1570. doi: 10.1136/hrt.2005.085399
31. Mohamed MO, Kirchhof P, Vidovich M, Savage M, Rashid M, Kwok CS, Thomas M, El Omar O, Al Ayoubi F, Fischman DL, et al. Effect of concomitant atrial fibrillation on in-hospital outcomes of non-ST-elevation-acute coronary syndrome-related hospitalizations in the United States. *Am J Cardiol*. 2019;124:465–475. doi: 10.1016/j.amjcard.2019.05.040
32. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903–1912. doi: 10.1016/S0140-6736(06)68845-4
33. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med*. 1998;339:1665–1671. doi: 10.1056/NEJM199812033392303
34. Schömig A, Neumann FJ, Kastrati A, Schühlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med*. 1996;334:1084–1089. doi: 10.1056/NEJM199604253341702
35. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, Granger CB, Verheugt FWA, Li J, Ten Berg JM, et al. Optimal antithrombotic regimens for patients with atrial fibrillation undergoing percutaneous coronary intervention: an updated network meta-analysis. *JAMA Cardiol*. 2020;5:582–589. doi: 10.1001/jamacardio.2019.6175
36. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375:2423–2434. doi: 10.1056/NEJMoa1611594
37. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, Batushkin V, Campo G, Lysak Z, Vakaliuk I, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet*. 2019;394:1335–1343. doi: 10.1016/S0140-6736(19)31872-0
38. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med*. 2019;381:2032–2042. doi: 10.1056/NEJMoa1908419
39. Alfredsson J, Neely B, Neely ML, Bhatt DL, Goodman SG, Tricoci P, Mahaffey KW, Cornel JH, White HD, Fox KA, et al; TRILOGY ACS Investigators. Predicting the risk of bleeding during dual antiplatelet therapy after acute coronary syndromes. *Heart*. 2017;103:1168–1176. doi: 10.1136/heartjnl-2016-310090
40. Amin AP, Wang TY, McCoy L, Bach RG, Effron MB, Peterson ED, Cohen DJ. Impact of bleeding on quality of life in patients on DAPT: insights from TRANSLATE-ACS. *J Am Coll Cardiol*. 2016;67:59–65. doi: 10.1016/j.jacc.2015.10.034
41. Freeman JV, Varosy P, Price MJ, Slotwiner D, Kusumoto FM, Rammohan C, Kavinsky CJ, Turi ZG, Akar J, Koutras C, et al. The NCDR left atrial appendage occlusion registry. *J Am Coll Cardiol*. 2020;75:1503–1518. doi: 10.1016/j.jacc.2019.12.040
42. Goyal A, de Lemos JA, Peng SA, Thomas L, Amsterdam EA, Hockenberry JM, Peterson ED, Wang TY. Association of patient enrollment in medicare part D with outcomes after acute myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2015;8:567–575. doi: 10.1161/CIRCOUTCOMES.115.001650