Usefulness of Antithrombotic Therapy in Patients With Atrial Fibrillation and Acute Myocardial Infarction

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To examine patterns of preadmission and discharge antithrombotic therapies in coronary artery disease (CAD) and atrial fibrillation (AF) patients admitted for acute myocardial infarction (AMI), we performed a retrospective analysis of the Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines (ACTION Registry-GWTG), which captures consecutive AMI patients treated at participating US hospitals. We included patients with CAD, AF, and CHA_2DS_2-VASc score ≥ 2 admitted for AMI (07/01/2013−09/30/2016). In the 15,034 AMI patients with previous AF and CAD, median age was 75; 32% were female. Preadmission, 32% of patients were on $P2Y_{12}$ inhibitors, 36% were anticoagulated, 72% were on aspirin, and 5% were on triple therapy. At discharge post-AMI, 73% were prescribed $P2Y_{12}$ inhibitors and 41% anticoagulation. Discharge anticoagulation use did not vary directly with CHA_2DS_2-VASc score; 16% of previously anticoagulated patients had discontinued anticoagulation at discharge. In patients receiving anticoagulants at discharge, 27% used nonvitamin K antagonist oral anticoagulants. Triple therapy was prescribed in 23% at discharge; 27% of these were with nonvitamin K antagonist oral anticoagulants and 14% with prasugrel or ticagrelor. $P2Y_{12}$ inhibitors and anticoagulants without aspirin were used in 2%. In conclusion, patients with previous CAD and AF are undertreated for both recurrent ischemic events and stroke prevention. After AMI hospitalization, $P2Y_{12}$ inhibition was preferentially selected over oral anticoagulation. **(Am J Cardiol 2019;123:12−18)**

Approximately 1/3 of patients with atrial fibrillation (AF) also have a coronary artery disease (CAD) history, such as previous acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG)[1]; these patients are at higher risk for cardiovascular morbidity and mortality.[2,3] Anticoagulation therapy is recommended for AF patients who are at increased risk for stroke,[4,5] whereas dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is indicated for secondary prevention post-AMI.[6-8] Nonvitamin K antagonist oral anticoagulants (NOACs) have become clinically available and have several advantages over warfarin.[9] Additionally, studies with higher potency $P2Y_{12}$ inhibitors have shown further reduction of cardiovascular events compared with clopidogrel.[10,11] We examined treatment patterns by studying Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines (ACTION Registry-GWTG) data. Many patients with co-existing AF and CAD are already on anticoagulants, antiplatelet drugs, or combinations thereof when admitted for AMI. We focused on patients with previous CAD and AF admitted for AMI to specifically examine changes in antithrombotic therapy between admission and discharge, as well as factors associated with starting either antiplatelet or anticoagulant therapy during hospitalization.

Methods

The ACTION Registry-GWTG is a voluntary registry that collects demographic and clinical data on consecutive AMI patients from participating United States hospitals.[12] Registry participation was approved by local institutional review boards, or was deemed essential to quality improvement and, therefore, not subject to institutional review board approval.

For this analysis, we included AMI patients with a previous history of CAD (i.e., previous AMI, PCI, or CABG); concomitant AF or flutter for the 2 weeks before AMI; and a CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, previous Stroke or TIA or thromboembolism, Vascular disease, Age 65−74 years, Sex category) score ≥ 2 (this CHA_2DS_2-VASc threshold was selected since guidelines recommend anticoagulant use in this population).[4,5] Data on type of AF (paroxysmal, persistent, or permanent) were not systematically collected in this registry. Our starting population included 488,370 consecutive patients treated for AMI captured in ACTION Registry-GWTG (07/01/2013−09/30/2016). Of these, 21,969 patients had AF and a previous history of CAD. Patients were excluded if they had a CHA_2DS_2-VASc score ≤ 1 (n = 117), died during the index hospitalization

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(n = 1,552), were transferred out to another hospital (n = 2,825), or if antithrombotic drug status at admission or discharge was missing (n = 2,441). After exclusions, our final population was comprised of 15,034 patients.

Antithrombotic use was described preadmission (i.e., home medication use at the time of AMI presentation) and at discharge (i.e., antithrombotics prescribed by the hospital at the time of AMI discharge). Patterns of preadmission and discharge antithrombotics are described overall and by drug. Patients without preadmission anticoagulation were divided into 2 groups: (1) remained off anticoagulation at discharge; and (2) anticoagulation started during admission. We also divided patients without preadmission $P2Y_{12}$ inhibitors into 2 groups: (1) remained off $P2Y_{12}$ inhibitors at discharge; and (2) $P2Y_{12}$ inhibitors started during admission. Continuous variables are presented as medians and 25th, 75th percentiles; categorical variables are presented as counts with associated percentages. We compared baseline characteristics of those who remained off treatment at discharge with those who had treatment started during admission (for anticoagulation and for $P2Y_{12}$ inhibitors) using Wilcoxon rank-sum test for continuous variables, and chi-square or Fisher's exact test for categorical variables. We performed secondary analyses to describe frequencies of discharge therapy use according to CHA_2DS_2-VASc score (predicted stroke risk in the setting of AF) and ACTION mortality risk score (predicted post-AMI mortality risk).

Logistic regression models were used to examine the association between patient characteristics and starting antithrombotics. In the first model, the primary outcome was anticoagulant use at discharge; patients without anticoagulation at discharge were the reference group. In the second model, the primary outcome was $P2Y_{12}$ inhibitor use at discharge; patients without $P2Y_{12}$ inhibitors at discharge were the reference group (see Supplementary Methods for adjustment variables). A hierarchical modeling approach was used, with patients clustered within hospitals and hospitals treated as a random effect. This approach considers that a patient's probability of receiving anticoagulants or antiplatelets at discharge may depend on the hospital at which they received care. A median odds ratio (OR) described hospital effect; a median OR >1 suggests that the treating hospital contributes to individual patient probability of being treated; the magnitude of hospital effect can be assessed by the magnitude of the median OR alongside the OR point estimates for other multivariable model factors.

Results are presented as ORs with 95% confidence intervals (CIs). For the hospital effect, the median OR with 95% CI is presented. Analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC). All tests were 2-sided and a p value <0.05 was considered statistically significant. No adjustment was made for multiple comparisons. All analyses were performed at the Duke Clinical Research Institute (Durham, NC).

Results

In 15,034 patients with previous CAD and AF with CHA_2DS_2-VASc score ≥ 2, the median age was 75 years (25th, 75th percentiles: 67, 82), 32% were female, 50% had diabetes, 17% had previous stroke, and 42% had previous heart failure. The median CHA_2DS_2-VASc score was 4 (25th, 75th percentiles: 3, 5). The median length of stay was 4 days (25th, 75th percentiles: 2, 6).

Patterns of antithrombotic treatments at the time of AMI hospitalization are shown in Table 1. In the 5,391 patients with preadmission anticoagulation, warfarin was the agent most frequently used (74%); 26% used NOACs (Table 2). Ticagrelor or prasugrel were used by 10% of those on preadmission $P2Y_{12}$ inhibitors. In the 9,643 patients who were not anticoagulated, 38% were on $P2Y_{12}$ inhibitor therapy preadmission.

At discharge, 41% of patients were prescribed anticoagulation and 73% were prescribed a $P2Y_{12}$ inhibitor

Table 1
Patterns of pre-admission and discharge antithrombotic treatment among patients with previous atrial fibrillation (CHA_2DS_2-VASc ≥ 2) and coronary artery disease admitted for acute myocardial infarction categorized by treatment type

	Preadmission	Discharge	Discharge among patients who underwent PCI
	(N = 15,034)	(N = 15,034)	(N = 7,917)
No therapy	1732 (12%)	70 (1%)	3 (0.04%)
Monotherapy			
Aspirin only	4260 (28%)	1576 (11%)	81 (1%)
$P2Y_{12}$ inhibitors only	584 (4%)	89 (1%)	41 (1%)
Anticoagulant only	1576 (11%)	168 (1%)	13 (0.2%)
Dual therapy			
Aspirin + $P2Y_{12}$ inhibitors	3067 (20%)	7123 (47%)	4831 (61%)
Aspirin + anticoagulant	2615 (17%)	2325 (16%)	129 (2%)
$P2Y_{12}$ inhibitors + anticoagulant	387 (3%)	219 (2%)	98 (1%)
Triple therapy	813 (5%)	3464 (23%)	2721 (34%)
Any therapy			
Any aspirin	10755 (72%)	14488 (96%)	7762 (98%)
Any $P2Y_{12}$ inhibitors	4851 (32%)	10895 (73%)	7691 (97%)
Any anticoagulant	5391 (36%)	6176 (41%)	2961 (37%)

Data are number (%).

CHA_2DS_2-VASc = Congestive heart failure; Hypertension; Age ≥ 75 years; Diabetes mellitus; prior Stroke or TIA or thromboembolism; Vascular disease; Age 65-74 years; Sex category; PCI=percutaneous coronary intervention.

Table 2
Patterns of preadmission and discharge antithrombotic treatment among patients with previous atrial fibrillation (CHA_2DS_2-VASc ≥ 2) and coronary artery disease admitted for acute myocardial infarction categorized by drug type

	Preadmission antithrombotic treatment	Discharge antithrombotic treatment	Discharge among patients who underwent PCI
	(N = 15,034)	(N = 15,034)	(N = 7917)
Anticoagulants	5391 (36%)	6176 (41%)	2961 (37%)
Warfarin	4012 (74%)	4536 (73%)	2139 (72%)
Dabigatran	232 (4%)	224 (4%)	127 (4%)
Rivaroxaban	555 (10%)	560 (9%)	276 (9%)
Apixaban	592 (11%)	856 (14%)	419 (14%)
$P2Y_{12}$ inhibitors	4851(32%)	10,895 (73%)	7691 (97%)
Clopidogrel	4371 (90%)	8775 (81%)	5818 (76%)
Ticagrelor	228 (5%)	1402 (13%)	1253 (16%)
Prasugrel	252 (5%)	718 (7%)	620 (8%)

Data are number (%).
CHA_2DS_2-VASc = Congestive heart failure; Hypertension; Age ≥ 75 years; Diabetes mellitus; prior Stroke or TIA or thromboembolism; Vascular disease; Age 65-74 years; Sex category; PCI=percutaneous coronary intervention.

(Table 1). In patients discharged without anticoagulation, 63.4% received clopidogrel, and 18% prasugrel or ticagrelor. In patients discharged without $P2Y_{12}$ inhibition, 45% received warfarin, and 15% a NOAC. In the subset of patients who underwent PCI during the AMI admission (n = 7,917, 53%), 97% received $P2Y_{12}$ inhibitors and 37% received anticoagulants at discharge.

NOACs were used in 27% of patients receiving anticoagulants at discharge (Table 2); in these, 47% received triple therapy with NOACs. In patients discharged on triple therapy, 63% received clopidogrel, warfarin, and aspirin; 22% clopidogrel, NOACs, and aspirin; 10% ticagrelor or prasugrel, warfarin, and aspirin; and 5% ticagrelor or prasugrel, NOACs, and aspirin.

In patients with previous CAD and AF with a CHA_2DS_2-VASc score ≥ 2 admitted for AMI without preadmission anticoagulation, 1,646 (17%) were discharged on anticoagulants (Figure 1). In patients started on an anticoagulant, 35% also newly started a $P2Y_{12}$ inhibitor. Patients started on anticoagulation were younger, more frequently male, had higher body weight, more likely to have diabetes, and less likely to be on dialysis or have peripheral artery disease (Supplementary Table 1). PCI for ST-segment elevation myocardial infarction (STEMI) and non−ST-segment elevation myocardial infarction rates were lower for patients started on anticoagulation at discharge (78% vs 87%; p < 0.0001, 38% vs 48%; p < 0.0001, respectively), whereas CABG rates were higher (8% vs 4%; p < 0.0001). Patients with anticoagulation at discharge had modestly, but significantly, higher rates of in-hospital stroke and cardiogenic shock than those without anticoagulation at discharge.

In multivariable modeling, in-hospital stroke was infrequent, but was most strongly associated with likelihood of starting anticoagulation (Figure 2). Increasing age was associated with a higher likelihood of starting anticoagulation until age 75, beyond which likelihood of anticoagulation decreased. Male sex, STEMI, higher body weight, higher peak creatinine levels, and lower ejection fraction were all associated with an increased likelihood of starting anticoagulation. Use of $P2Y_{12}$ inhibitors at discharge, presence of ≥ 2 diseased vessels on coronary angiogram, having in-hospital transfusion, lower nadir hemoglobin, preadmission aspirin use, and current and/or recent smoking were associated with a lower likelihood of starting anticoagulation. The treating hospital significantly contributed to individual patient probability of starting anticoagulation (median OR 1.53, 95% CI 1.40 to 1.67).

Starting anticoagulation did not vary directly with CHA_2DS_2-VASc score (Supplementary Tables 2 and 3). In patients with CHA_2DS_2-VASc score < 5, who were started on an anticoagulant, more than half were also newly started on a $P2Y_{12}$ inhibitor. Increasing CHA_2DS_2-VASc score was modestly associated with greater anticoagulation persistence (p for trend = 0.024), although 14.6% of patients with CHA_2DS_2-VASc score ≥ 6 who were previously anticoagulated had discontinued anticoagulation at discharge.

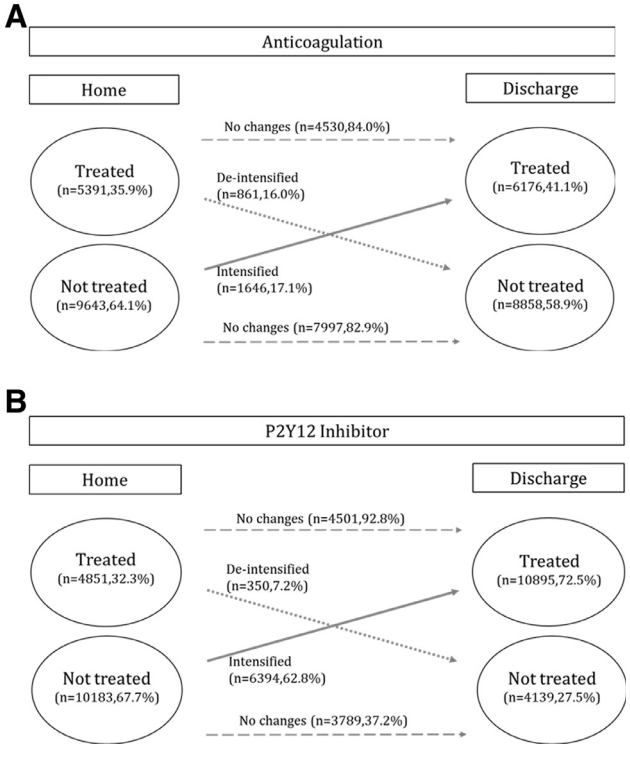

Figure 1. Changes between admission and discharge in (*A*) anticoagulation therapy and (*B*) $P2Y_{12}$ inhibitors.

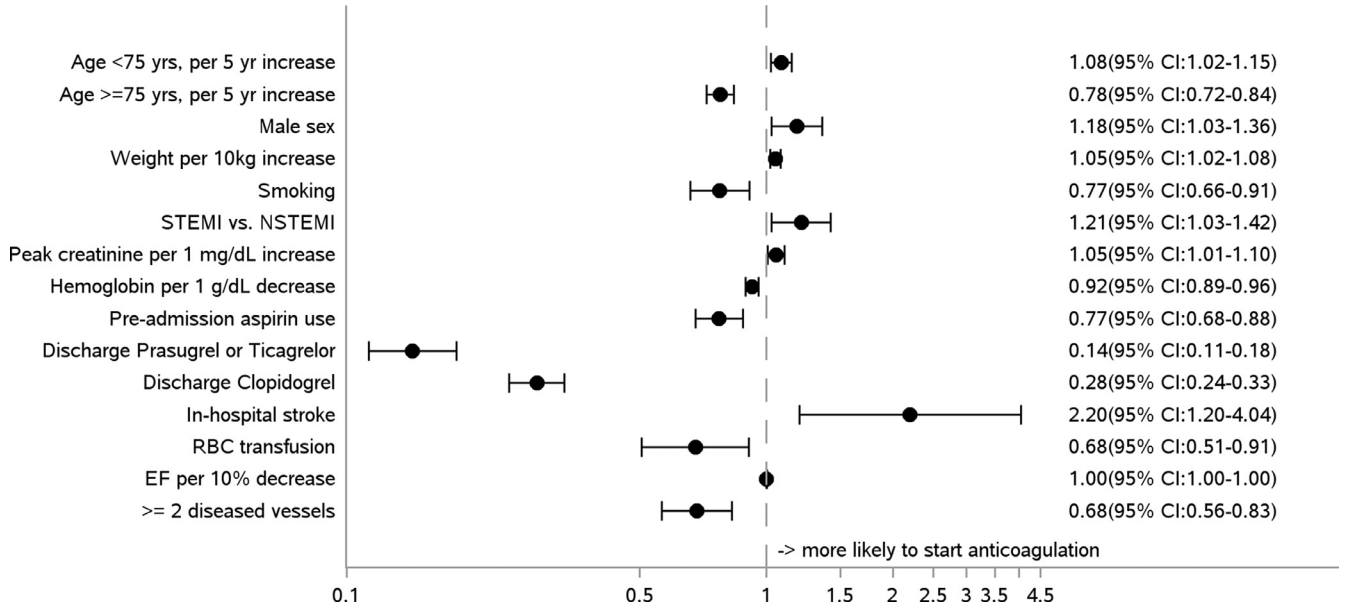

Figure 2. Association between clinical characteristics and starting anticoagulation at admission in the multivariable model. CABG = coronary artery bypass grafting; CI = confidence interval; EF = ejection fraction; NSTEMI = non−ST-segment elevation myocardial infarction; RBC = red blood cell; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Of these, 77.2% had their anticoagulant replaced with a $P2Y_{12}$ inhibitor.

In patients with CAD and AF admitted for AMI without pre-admission $P2Y_{12}$ inhibitor use, 6,394 (63%) were discharged on $P2Y_{12}$ inhibitors (Figure 1). Compared with patients without $P2Y_{12}$ inhibitors at discharge, those started on $P2Y_{12}$ inhibitors were more likely to be young, male, have higher body weight, smoke, and have had previous revascularization (Supplementary Table 4). Patients started on $P2Y_{12}$ inhibitors more frequently presented with STEMI (24% vs 6%; $p < 0.0001$) and were less likely to have heart failure (40% vs 51%; $p < 0.0001$) than those who remained off $P2Y_{12}$ inhibitors at discharge. PCI for STEMI rates were higher for patients started on $P2Y_{12}$ inhibitors at discharge (93% vs 32%; $p < 0.0001$), as well as for non-ST-segment elevation myocardial infarction (73% vs 3%; $p < 0.0001$), whereas CABG rates were lower (2% vs 10%; $p < 0.0001$). Patients started on $P2Y_{12}$ inhibitors were more likely to present with recurrent AMI, cardiac arrest, and major bleeding, and less likely to present with stroke and red blood cell transfusion than those without $P2Y_{12}$ at discharge.

In multivariable modeling, decreasing age until 75 years, male sex, previous revascularization, STEMI, higher peak troponin levels, higher nadir hemoglobin levels, and higher ejection fraction were all associated with an increased likelihood of starting $P2Y_{12}$ inhibitors (Figure 3). Use of preadmission aspirin or anticoagulants at discharge was associated with a lower likelihood of starting $P2Y_{12}$ inhibitors at hospitalization. In-hospital AMI, PCI with drug-eluting stents, and ≥ 2 diseased vessels on coronary angiogram were also associated with a higher likelihood of starting $P2Y_{12}$ inhibitors, whereas patients who underwent CABG or red blood cell transfusion had a lower likelihood. The patient's probability of starting $P2Y_{12}$ inhibitors was also significantly dependent on the hospital at which they were cared for (median OR 1.70, 95% CI 1.56 to 1.87). Patterns of $P2Y_{12}$ inhibitor initiation and discontinuation did not vary directly with ACTION mortality risk score (Supplementary Table 3).

Discussion

Our study provides a contemporary overview of changes in antithrombotic treatment for patients with previous CAD and AF with CHA_2DS_2-VASc score ≥ 2 admitted for AMI. We had 4 main findings. First, we observed that many patients indicated for anticoagulation were undertreated for stroke prevention before AMI, with little improvement post-AMI hospitalization, even in patients with very high CHA_2DS_2-VASc scores. Second, despite guideline recommendations, more than 1/4 of patients with previous CAD and recurrent AMI did not receive $P2Y_{12}$ inhibitors at discharge when there was a concurrent AF history. Third, in patients with CAD and AF, triple therapy was used in 23% of patients at discharge, and dual antithrombotic therapy without aspirin has been adopted in only 2%. Finally, new combinations of antithrombotics, including NOACs, prasugrel, and ticagrelor, were observed, despite lack of strong evidence supporting these treatment options.

Previous studies have shown underutilization of anticoagulation in eligible patients, especially in those with previous CAD.[13–18] With a median age of 73 years, almost half with diabetes, and >15% with previous stroke, our population had a high stroke risk, yet only 36% were on home anticoagulation preadmission. Although previous studies have suggested that the low anticoagulation rate in these patients is due to the concomitant indication for chronic antiplatelet therapy, we show here that, in patients who were not anticoagulated, only 38% were on $P2Y_{12}$ inhibitor therapy preadmission. Hospitalization for acute illnesses is an opportunity to identify AF patients with an indication for anticoagulation. In-hospital stroke was uncommon, but

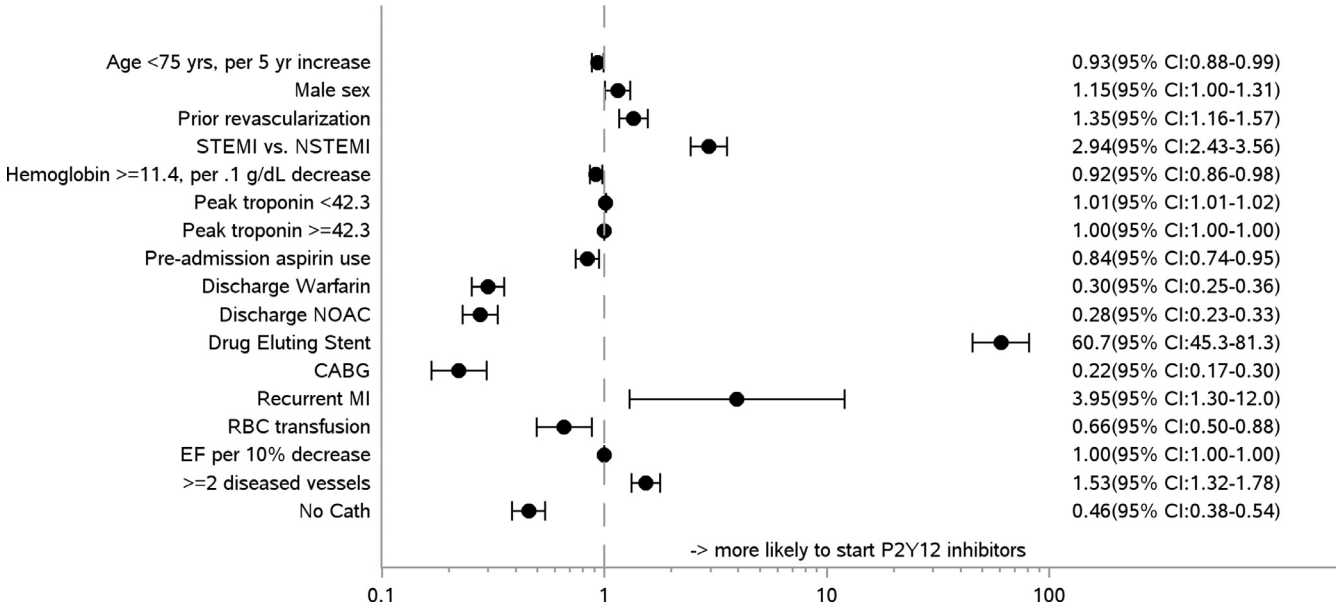

Figure 3. Association between clinical characteristics and starting $P2Y_{12}$ inhibitors at admission in the multivariable model. CABG = coronary artery bypass grafting; CI = confidence interval; EF = ejection fraction; MI = myocardial infarction; NOAC = non-vitamin K antagonists oral anticoagulants; NSTEMI = non−ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RBC = red blood cell; STEMI = ST-segment elevation myocardial infarction.

represented the strongest factor associated with anticoagulation initiation. However, more than half of patients in our study (57% of patients with CHA_2DS_2-VASc score ≥ 6) were not prescribed anticoagulation at discharge. Interhospital differences were significant drivers of the variability in both anticoagulant and $P2Y_{12}$ inhibitor use at discharge, which highlights the challenge of treating these patients in real practice. After an AMI, clinicians appear to more strongly favor the addition of $P2Y_{12}$ inhibitor therapy. Use of $P2Y_{12}$ inhibitor was the strongest predictor against discharge anticoagulation, as seen in other studies.[15,19]

Guidelines recommend the use of $P2Y_{12}$ inhibitors for all AMI patients with or without PCI. In patients with concomitant indication for anticoagulants, guidelines are less definitive, and the selection and duration of antithrombotics take into account the CHA_2DS_2-VASc score, the risk of bleeding, and the stent type in patients who underwent PCI with stenting.[20] Almost all stented patients received $P2Y_{12}$ inhibitors at discharge; therefore, the 27.5% of patients who did not were largely managed noninvasively. We did not observe a clear relation between starting $P2Y_{12}$ inhibitors during hospitalization and the ACTION mortality risk score.[21] Although guidelines provide a Class IIa recommendation for prasugrel and ticagrelor, their concomitant use with anticoagulants is largely unstudied. Nevertheless, we observed that 25% of patients discharged on prasugrel and/or ticagrelor were also prescribed an anticoagulant.

Triple antithrombotic therapy meets the needs for patients with both CAD and AF, but is associated with a high bleeding risk.[20,22,23] In our study, NOACs were prescribed in more than 1/4 of patients receiving anticoagulation at discharge, and half of these as part of a triple therapy regimen. Prasugrel and ticagrelor were also used concurrently with warfarin and NOACs. Our study showed that omitting aspirin at discharge has only occurred in a very small proportion of patients. Recently, a randomized trial showed that bleeding requiring medical attention was less frequent in patients who were treated with rivaroxaban-based regimens, compared with those on triple therapy with warfarin post-PCI.[24] Another trial showed that the risk of major or clinically relevant nonmajor bleeding was lower in the 2 dabigatran-based arms compared with the triple therapy group with warfarin. Importantly, none of these previous studies have been powered to assess efficacy. Ongoing randomized trials are testing different antithrombotic strategies with NOACs for patients with coexisting AF and CAD.[25−27]

Our findings should be interpreted in light of several limitations. First, when modeling factors associated with therapy selection, unmeasured confounders always remain. Second, the timing of previous AMI or last revascularization was unknown for patients with previous CAD. Preadmission $P2Y_{12}$ inhibitor therapy may not be indicated if the last ischemic event was remote. Third, we did not have data available on NOAC dosing or target international normalized ratio range for warfarin use, so we could not assess the use of low-dose strategies in this population. Furthermore, our study was unable to characterize the influence of recent trials, such as PIONEER-AF and RE-DUAL PCI on anticoagulation (and in particular NOAC selection) in patients with AF undergoing PCI. Fourth, the intended durations of antiplatelet and anticoagulant treatment postdischarge were not collected in this registry. Fifth, it was not possible to assess bleeding risk through risk scores, since data on international normalized ratio liability, history of bleeding, and use of alcohol are not systematically collected. Finally, patient adherence to therapies prescribed at discharge is unknown.

Our findings show that patients with CAD and AF are undertreated on both fronts, and remain at risk of recurrent

ischemic events and stroke after their AMI hospitalization. $P2Y_{12}$ inhibition is preferentially selected at discharge; only 1 in 4 patients are treated with triple antithrombotic therapy or dual antithrombotic therapy without aspirin. More robust evidence and clearer guideline recommendations are needed to improve the consistency of antiplatelet and antithrombotic therapy use in these patients.

Author Contributions

All authors have been involved in the study design, analysis, and manuscript preparation. All authors read and approved the final manuscript.

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Supplementary materials

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