Outcomes According to Cardiac Catheterization Referral and Clopidogrel Use Among Medicare Patients With Non–ST-Segment Elevation Myocardial Infarction Discharged Without In-hospital Revascularization

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Background—While use of P2Y12 receptor inhibitor is recommended by guidelines, few studies have examined its effectiveness among older non–ST-segment elevation myocardial infarction patients who did not undergo coronary revascularization.

Methods and Results—We included unrevascularized non–ST-segment elevation myocardial infarction patients ≥65 years discharged home from 463 ACTION Registry-GWTG hospitals from 2007 to 2010. Rates of discharge clopidogrel use were described for patients with no angiography, angiography without obstructive coronary artery disease (CAD; ≥50% stenosis in ≥1 vessel), and angiography with obstructive CAD. Two-year outcomes were ascertained from linked Medicare data and included composite major adverse cardiac events (defined as all-cause death, myocardial infarction readmission, or revascularization), and individual components. Outcomes associated with clopidogrel use were adjusted using inverse probability-weighted propensity modeling. Of 14 154 unrevascularized patients, 54.7% (n=7745) did not undergo angiography, 10.6% (n=1494) had angiography without CAD, and 34.7% (n=4915) had angiography with CAD. Discharge clopidogrel was prescribed for 42.2% of all unrevascularized patients: 37.8% without angiography, 34.1% without obstructive CAD at angiography, and 51.6% with obstructive CAD at angiography. Discharge clopidogrel use was not associated with major adverse cardiac events in any group: without angiography (adjusted hazard ratio [95% CI]: 0.99 [0.93–1.06]), angiography without CAD (1.04 [0.74–1.47]), and angiography with CAD (1.12 [1.00–1.25], $P_{interaction}$=0.20).

Conclusions—We found no association between discharge clopidogrel use and long-term risk of major adverse cardiac events among older, unrevascularized non–ST-segment elevation myocardial infarction patients. Clopidogrel use in this population requires further prospective evaluation. (*J Am Heart Assoc.* 2016;5:e002784 doi: 10.1161/JAHA.115.002784)

Key Words: effectiveness • P2Y12 receptor inhibitor • unrevascularized non–ST-segment elevation myocardial infarction patients

Older patients comprise an increasing proportion of the acute myocardial infarction (MI) population.[1] Coronary revascularization can improve outcomes for patients presenting with non–ST-segment elevation myocardial infarction (NSTEMI),[1] yet a substantial proportion of older NSTEMI patients do not undergo revascularization during the index

hospitalization.[2] Data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial showed that clopidogrel plus aspirin compared with aspirin alone reduces cardiac events in NSTEMI patients, regardless of in-hospital revascularization strategy.[3] Therefore, guidelines recommend 12 months of clopidogrel treatment for NSTEMI patients, including those who did not undergo coronary revascularization.[1] Yet prior data have shown that only half of medically managed NSTEMI patients receive clopidogrel at discharge.[4,5] Whether CURE data apply to a more contemporary NSTEMI population with higher rates of evidence-based secondary prevention use is unknown. Among older MI patients, the perceived increased risk of bleeding may reduce provider willingness to consider clopidogrel use.

Patients with NSTEMI who do not undergo in-hospital coronary revascularization represent a heterogeneous population which includes patients with NSTEMI events due to plaque rupture or erosion (type I MI), as well as those with MI from

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nonatherothrombotic mechanisms, including dynamic arterial occlusion and acute supply/demand mismatch (type II MI). Among patients undergoing diagnostic angiography, coronary revascularization may be deferred due to absence of significant coronary artery disease (CAD) or diseased coronary anatomy not suitable for percutaneous or surgical intervention. Other factors, such as active bleeding or high bleeding risk, renal insufficiency, or patient preference, may also deter providers from an invasive approach. The variation in pathophysiology, patient characteristics, and treatment among the unrevascularized NSTEMI population is most likely under-represented in clinical trials that have tested the efficacy of clopidogrel and other P2Y12 inhibitors. This heterogeneity may result in differences in cardiovascular prognosis and relative benefit of clopidogrel. Therefore, we sought to (1) describe the clinical characteristics and long-term outcomes of older NSTEMI patients not undergoing in-hospital revascularization according to use of angiography and presence of CAD; and (2) assess for an association between clopidogrel use and outcomes according to use of angiography and presence of CAD using data from the National Cardiovascular Data Registry® Acute Coronary Treatment and Intervention Outcomes Network Registry®-Get With the Guidelines™ (ACTION Registry-GWTG).

Methods

Data Sources

Clinical data for the index MI hospitalization was obtained from ACTION Registry-GWTG, a national quality improvement registry of acute MI patients. Details regarding ACTION Registry-GWTG have been previously published.[6] Briefly, in January 2007, hospitals participating in ACTION Registry-GWTG began submitting data for consecutive patients who had a primary diagnosis of acute MI presenting to the hospital within 24 hours of ischemic symptom onset. The registry collects detailed patient and procedure characteristics, as well as in-hospital treatments and outcomes, using common data standards and definitions described online at https://www.ncdr.com/web-ncdr/action/home/datacollection. Since patient information was collected without unique patient identifiers in ACTION Registry-GWTG, we used 5 indirect identifiers in combination (date of birth, sex, hospital identifier, date of admission, date of discharge) to link registry patients older than 65 years to their Medicare claims record (methods described previously).[7] Longitudinal postdischarge outcomes were identified from linked Medicare inpatient and denominator files.

Study Population

We started with all patients in ACTION Registry-GWTG from January 2007 through December 2010 who were ≥65 years of
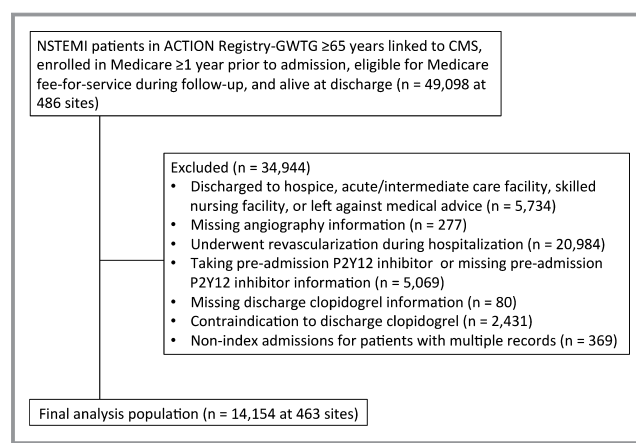
Figure 1. Flow diagram of patient selection, from the initial cohort, through exclusions, to the final study population. ACTION Registry-GWTG indicates Acute Coronary Treatment and Intervention Outcomes Network Registry®-Get With the Guidelines™; CMS, Centers for Medicare & Medicaid Services; NSTEMI, non–ST-segment elevation myocardial infarction.

age, linked to Medicare data, and eligible for Medicare fee-for-service during the follow-up period. To adjust for comorbidities not captured in ACTION Registry-GWTG but available from Medicare data, patients in our analysis were required to have at least 1 year of enrollment in Medicare Parts A and B prior to the index hospitalization, resulting in an initial population of 49 098 NSTEMI patients (Figure 1). We excluded patients who underwent coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) during the index hospitalization (n=20 984). We also excluded patients transferred to another acute care facility, those discharged to a hospital or to a skilled nursing facility, and patients who left against medical advice (n=5734). Patients discharged to another acute care hospital or against medical advice were excluded, since discharge medications are unknown for these patients. Compared with patients discharged to home, those discharged to hospice or a skilled nursing facility often have a higher risk of downstream adverse outcomes that introduce unmeasured bias when examining comparative outcomes. Patients for whom angiographic information was missing were also excluded (n=277). Due to a strong association between pre-admission and discharge use of clopidogrel resulting in extreme weights for propensity modeling, we excluded patients receiving P2Y12 receptor inhibitors prior to admission (n=4987) and those missing information regarding pre-admission P2Y12 receptor inhibitor use (n=82). Patients were also excluded if they had missing discharge clopidogrel status (n=80) or if clopidogrel was documented as contraindicated (n=2431). Finally, we excluded nonindex admissions for patients with multiple records in ACTION Registry-GWTG (n=369). Our final analysis population consisted of 14 154 patients discharged alive from 463 US hospitals.

Outcomes

Follow-up for all outcomes began at index hospitalization discharge. The primary effectiveness outcome for our study was the composite of major adverse cardiac events (MACE), defined as all-cause death, MI readmission, or revascularization within 2 years after discharge from the index hospitalization. Two-year secondary outcomes included the individual components of MACE: all-cause mortality, readmission for MI, or revascularization. Mortality was ascertained from the Medicare denominator file. Rehospitalizations for MI (410.x1) and revascularization (36.0x, 00.66, 36.x1, 36.2, 36.3x) were ascertained using the primary International Classification of Diseases, Ninth Revision, diagnosis code and all procedure codes for subsequent hospitalizations in the Medicare claims file. To avoid counting elective revascularizations planned early after discharge as an outcome, revascularizations within 60 days of index hospital discharge were excluded unless associated with at least one of the following diagnoses: acute MI, unstable angina, heart failure (HF), arrhythmia, and cardiac arrest.

Statistical Methods

Patients who did not undergo revascularization were divided into the following 3 groups: (1) those who did not undergo angiography (no angiography); (2) those who underwent angiography but had all vessels with <50% stenosis (angiography without obstructive CAD); and (3) those who underwent angiography and were found to have at least one vessel with ≥50% stenosis (angiography with obstructive CAD). We examined patient characteristics for each group and further categorized by use of discharge clopidogrel. Data were presented as frequencies and percentages for categorical variables, and medians with interquartile ranges for continuous variables. Comparisons among categorical and continuous variables were made using χ^2 and Kruskal–Wallis tests, respectively. We reported the unadjusted cumulative incidence of outcomes for each of the 3 groups (no angiography, angiography without obstructive CAD, angiography with obstructive CAD). Kaplan–Meier methodology was used to estimate the probability of mortality and MACE end points, and the 3 groups were compared with the log-rank test. For other outcomes, we used the cumulative incidence function to account for the competing risk of death and compared the 3 groups with the Gray test.

Within each of the 3 groups, we presented unadjusted cumulative incidences of outcomes according to the use of clopidogrel at discharge. We used inverse probability-weighting to evaluate the adjusted association between clopidogrel use and long-term outcomes. Propensity scores were estimated using logistic regression to fit a model for discharge clopidogrel use. The group variable (no angiography, angiography without disease, angiography with disease), potential covariates, and interactions between groups and potential covariates were entered into the propensity model. Covariates considered for the model included the group (no angiography, angiography without disease, angiography with disease); demographics (age, sex, race, body mass index); medical history (hypertension, diabetes, peripheral artery disease, recent smoker, dyslipidemia, prior myocardial infarction, prior PCI, prior CABG, prior HF, prior stroke, Charlson comorbidity index [defined as sum of the following medical history, 1 point each, based on Medicare Part A claims 1 year prior to and including index admission: congestive HF, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, renal disease, hypertension, PCI, CABG, dementia, paraplegia/hemiplegia, cancer, and atrial fibrillation], renal dysfunction [creatinine clearance ≤30 mL/min or use of dialysis]); medications prior to admission (aspirin, warfarin, β-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, aldosterone blocking agent, statin, nonstatin lipid-lowering agent); presentation features (cardiogenic shock, HF, heart rate, systolic blood pressure, ECG findings [ST-segment changes versus none], baseline hemoglobin [g/dL], baseline troponin ratio [times the upper limit of normal], left ventricular ejection fraction, multivessel disease at angiography, transfer-in status); and in-hospital events (stroke, red blood cell transfusion, major bleeding event, cardiac rehabilitation referral). Backward selection was adopted to keep only significant (*P*<0.05) variables in the propensity model. Covariates retained in the final propensity model included the group; age; heart rate; systolic blood pressure; ECG findings; diabetes; peripheral artery disease; dyslipidemia; prior MI; prior PCI; prior CABG; prior HF; prior stroke; baseline hemoglobin; baseline troponin ratio; home medication use (warfarin, β-blocker, statin, nonstatin lipid-lowering agent); in-hospital red blood cell transfusion; Charlson comorbidity index; and interactions between the group variable and diabetes, prior MI, prior PCI, prior CABG, prior congestive HF, and home β-blocker. For each outcome, Cox proportional hazards models with and without weights were fit, including fixed effects for discharge (to estimate the overall association) and then adding a fixed effect for group and the group by discharge clopidogrel interaction (to estimate group-specific associations). Hazard ratios (HRs) comparing discharge clopidogrel versus no discharge clopidogrel use are presented with associated 95% CIs. All continuous variables in the propensity model were checked for linearity; nonlinearity was detected for hemoglobin, troponin, and systolic blood pressure, and these variables were fit using restricted cubic splines. Examination of distributions of the inverse probability-weighted sample revealed no associations between variables and the use of discharge clopidogrel (Figure 2).
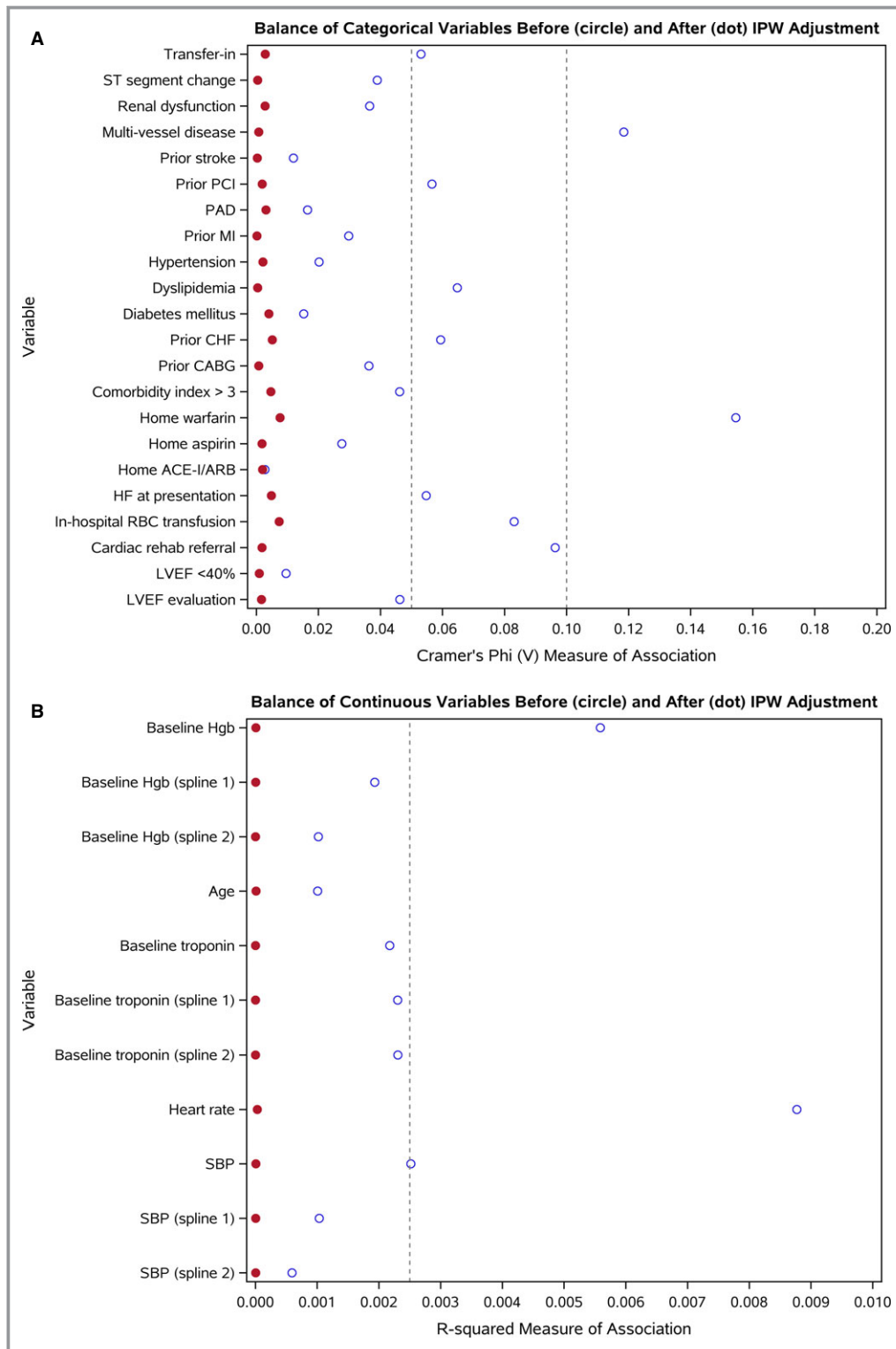
Figure 2. Association between covariates and discharge clopidogrel. Shown are graphs depicting the association of (A) categorical and (B) continuous variables before and after inverse probability-weighting adjustment showing no significant associations between covariates and use of discharge clopidogrel after adjustment. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CHF, congestive heart failure; Hgb, hemoglobin; HF, heart failure; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RBC, red blood cell; SBP, systolic blood pressure.

Most variables had very low (<1%) rates of missing data. For descriptive tables, only nonmissing variables were compared among groups. For modeling, missing categorical variables were imputed to the most frequent level, and missing continuous variables were imputed to the median value. A significance level of 0.05 and 2-sided tests were used for all analyses. Analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC). This study was approved by the Duke University Health System Institutional Review Board and was determined to meet requirements for waiver of informed consent.

Results

Characteristics of Unrevascularized NSTEMI Patients

Among the 14 154 NSTEMI patients in the ACTION Registry-GWTG who did not undergo coronary revascularization during the index hospitalization, 54.7% (n=7745) were not referred for angiography, 10.6% (n=1494) underwent angiography but had no significant obstructive epicardial CAD, and 34.7% (n=4915) underwent angiography and were found to have at least one stenosis ≥50%. Patient characteristics were examined according to use of angiography and presence of obstructive CAD (Table 1). Compared with patients referred for cardiac catheterization, patients managed with a noninvasive strategy were markedly older, had a greater burden of comorbidities, and more often had symptoms and signs of HF and renal insufficiency on admission. Among patients undergoing angiography, those with obstructive CAD more often had cardiovascular risk factors or evidence of prior vascular disease, including diabetes, peripheral artery disease, prior MI, and prior stroke; these patients were also more likely than those without obstructive CAD to have symptoms and signs of HF on admission.

Patients not referred for angiography were more likely to have in-hospital major bleeding events and red blood cell transfusions than patients referred for angiography. Compared with patients without obstructive CAD at angiography, patients with significant CAD were slightly more likely to receive antithrombotic therapies, including heparin (52.8% versus 47.5%) and glycoprotein IIb/IIIa inhibition (21.9% versus 18.1%) within 24 hours of hospitalization, as well as evidence-based therapies for MI (eg, aspirin, β-blocker, statin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) at discharge; these patients also more frequently had subsequent in-hospital bleeding events and packed red blood cell transfusions.

Clopidogrel Use Among Unrevascularized NSTEMI Patients

Overall, 42.2% (n=5969) of unrevascularized NSTEMI patients were discharged on clopidogrel. Rates of clopidogrel use were highest at 51.6% among patients found to have significant CAD at angiography. In comparison, 34.1% of patients without significant CAD at angiography and 37.8% of patients not undergoing angiography were discharged on clopidogrel. Among patients who were discharged on clopidogrel but were not sent for angiography, were referred for angiography but did not have significant CAD, and were referred for angiography and did have significant CAD, rates of clopidogrel use within the first 24 hours of hospitalization were 58.3%, 57.0%, and 52.8%, respectively.

We examined patient characteristics within each subgroup according to use of clopidogrel (Table 2). Among patients not referred for angiography, those discharged on clopidogrel were older and more often had diabetes, peripheral artery disease, prior MI, and prior PCI. Within the cohort of patients without obstructive CAD at angiography, patients receiving discharge clopidogrel were younger and more frequently had a history of prior MI and prior coronary revascularization, but less congestive HF at presentation. In contrast, patients with obstructive CAD on angiography who were discharged on clopidogrel were of similar age and had a similar burden of comorbid conditions, with the exception of a less frequent history of MI and congestive HF, than patients in this group not discharged on clopidogrel. In all subgroups, patients discharged on clopidogrel were also more often discharged on other evidence-based medicines, such as a β-blocker and a statin, and were less likely to have in-hospital major bleeding and packed red blood cell transfusions.

Clinical Outcomes

Clinical outcomes were assessed among the overall cohort according to use of angiography and the presence of obstructive CAD. As shown in Figure 3A, the observed cumulative incidence of MACE at 2 years was highest among patients not undergoing angiography (62.3%), followed by patients undergoing angiography and found to have significant CAD (37.3%), and lowest among patients without obstructive CAD at angiography (15.5%). Similar relationships were observed among groups for all-cause mortality and MI (Figure 3B and 3C). In contrast, rates of postdischarge revascularization were highest among patients found to have obstructive CAD on angiography during index hospitalization and lowest among patients without significant CAD on angiography (Figure 3D).

We examined relationships between the use of discharge clopidogrel and clinical outcomes (Figure 4). In the overall cohort, clopidogrel use at discharge was not significantly associated with MACE (adjusted HR 1.02; 95% CI 0.97–1.09; P=0.42). We found no relationship between discharge clopidogrel use and any of our secondary outcomes. We assessed whether the association between discharge clopidogrel use

Table 1. Patient Characteristics According to Use of Angiography and Presence of CAD

	Angiography Status		Extent of CAD at Angiography	
	No Angiography (n=7745)	Angiography (n=6409)	Without Obstructive CAD (n=1494)	With Obstructive CAD (n=4915)
Demographics				
Median age (IQR), y	85.0 (78.0, 89.0)	76.0 (71.0, 82.0)	75.0 (70.0, 81.0)	77.0 (71.0, 82.0)
Female sex, %	57.6	51.7	76.4	44.2
Median BMI (IQR), kg/m^2	25.6 (22.2, 29.6)	27.1 (23.8, 31.2)	26.7 (23.1, 31.2)	27.2 (23.9, 31.2)
Nonwhite race, %	13.2	11.9*	14.4	11.2
Medical history, %				
Hypertension	84.0	83.3*	80.5	84.1
Diabetes mellitus	37.3	34.9	24.6	38.0
Peripheral artery disease	16.7	14.0	6.8	16.2
Recent smoker	7.9	14.2	10.8	15.3
Prior MI	29.7	28.6*	13.5	33.2
Prior PCI	14.8	20.4	10.2	23.5
Prior CABG	21.8	28.4	6.0	35.2
Prior HF	34.1	18.7	12.6	20.6
Prior stroke	16.8	10.5	7.5	11.4
Charlson comorbidity index >3	33.6	19.3	14.6	20.8
Features on admission				
Cardiogenic shock, %	0.9	0.9*	0.9	0.9*
HF, %	40.8	22.5	16.9	24.1
Median heart rate (IQR), beats per minute	90 (75, 107)	84 (70, 100)	83 (70, 100)	84 (70, 100)*
Median SBP (IQR), mm Hg	140 (119, 161)	146 (126, 168)	145 (124, 168)	146 (126, 168)*
ECG findings (ST-segment changes vs none), %	34.5	35.6	31.5	36.9
Median baseline hemoglobin (IQR), g/dL	12.2 (10.9, 13.5)	13.2 (12.0, 14.4)	13.2 (12.2, 14.3)	13.2 (11.9, 14.4)
Renal dysfunction (CrCl ≤30 mL/min, or dialysis), %	34.8	11.7	10.0	12.3
LVEF >50%, %	50.0	55.6	64.5	52.9
Transfer in, %	14.5	32.3	29.5	33.2
In-hospital events				
Median peak troponin ratio (IQR), xULN	15.7 (4.5, 61.2)	20.0 (5.3, 71.7)	12.7 (3.8, 43.5)	22.5 (6.0, 82.7)
Recurrent MI, %	0.3	0.3*	0.2	0.4*
Stroke, %	0.5	0.5*	0.5	0.5*
Major bleeding,[†] %	10.2	8.5	5.5	9.4
PRBC transfusion, %	11.3	6.9	3.4	8.0
Discharge medications, %				
Aspirin	93.4	96.2	93.7	96.9
β-Blocker	93.3	94.8	91.2	95.9
Statin	73.1	84.6	76.0	87.2
ACEI/ARB	64.1	71.9	68.8	72.8
Warfarin	15.2	15.3*	16.0	15.1*
Clopidogrel	37.8	47.5	34.1	51.6

Table 1. Continued

	Angiography Status		Extent of CAD at Angiography	
	No Angiography (n=7745)	Angiography (n=6409)	Without Obstructive CAD (n=1494)	With Obstructive CAD (n=4915)
Hospital characteristics				
Academic, %	22.0	25.7	24.2	26.2
Region, %				
West	13.0	10.8	10.6	10.8
Northeast	10.9	8.1	8.8	7.8
Midwest	35.0	35.2	31.7	36.2
South	41.1	46.0	48.9	45.2

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI indicates body mass index; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CrCl, creatinine clearance; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PRBC, packed red blood cell; SBP, systolic blood pressure; xULN, times the upper limit of normal.

*P-values were calculated for pairwise comparisons of (1) no angiography vs angiography and (2) angiography without disease vs angiography with disease. All P-values <0.05 unless indicated by an asterisk.

†Major bleeding was defined according to the ACTION Registry-GWTG definition as an absolute hemoglobin drop of ≥4 g/dL, intracranial hemorrhage, document of suspected retroperitoneal bleed, any PRBC transfusion with baseline hemoglobin ≥9 g/dL, or any PRBC transfusion with baseline hemoglobin <9 g/dL and a suspected bleeding event. Bleeding events in CABG patients were included if they occurred prior to surgery.

and outcomes differed based on referral for coronary angiography and the presence of significant angiographic disease. Discharge clopidogrel use was not associated with lower MACE among any of the 3 groups: those without angiography (adjusted HR 0.99; 95% CI 0.93–1.06), angiography without obstructive CAD (adjusted HR 1.04; 95% CI 0.74–1.47), and angiography with obstructive CAD (adjusted HR 1.12; 95% CI 1.00–1.25; $P_{interaction}$=0.20). We also did not demonstrate any association between discharge clopidogrel and secondary outcomes for patient subgroups according to angiography status or presence of disease at angiography.

Discussion

In this large national registry, we examined a cohort of older NSTEMI patients who were discharged from 463 US hospitals without undergoing coronary revascularization during the index MI hospitalization. Our key findings were as follows: (1) more than 50% of these unrevascularized patients were treated upfront with a noninvasive strategy (ie, not referred for angiography), and of those referred for angiography, 1 in 5 patients had no significant CAD; (2) overall, patients treated noninvasively had worse clinical outcomes than those referred for angiography; (3) ≈40% of unrevascularized MI patients were discharged on clopidogrel; and (4) after multivariable adjustment, we found no association between discharge clopidogrel use and long-term ischemic outcomes overall, regardless of referral for angiography and/or presence of CAD at angiography.

For the management of moderate- or high-risk patients presenting with NSTEMI, current guidelines recommend an early invasive strategy, including angiography followed by revascularization.[1,8] Despite these recommendations, prior studies have reported that ≈30% of NSTEMI patients are not referred for coronary angiography, and ≈50% of patients with CAD do not undergo coronary revascularization during the initial hospitalization.[2,9–11] In our analysis of older unrevascularized NSTEMI patients, more than 50% were not referred for coronary angiography. Prior data have shown that conservatively treated NSTEMI patients have worse outcomes than those treated with invasive strategies.[2,11] Our study focused on patients older than 65 years and found similar associations between nonreferral to angiography and worse outcomes, including higher risks of mortality and readmission for MI. Furthermore, we observed worse outcomes in this group compared with patients who were found to have significant disease on angiography, but remained unrevascularized. Rates of postdischarge revascularization over the next 2 years were <10% in both groups, underscoring the prevalence of comorbidities and other unmeasured factors that likely drove the initial decision not to pursue revascularization in both of these patient populations. A selection bias is evident whereby patients not sent for angiography were markedly older and sicker and, therefore, were more likely to have worse outcomes postdischarge than those who underwent initial angiography. Patients without significant CAD at angiography had the best outcomes, perhaps because their NSTEMI events were not necessarily mediated by plaque rupture.

The use of P2Y12 receptor inhibitors for the treatment of unrevascularized NSTEMI patients remains an area of interest. In the CURE trial, clopidogrel plus aspirin compared with aspirin alone reduced recurrent ischemia in patients with non–ST-segment elevation acute coronary syndrome (NSTE

Table 2. Patient and In-Hospital Features Among Patients According to Angiography Status and Clopidogrel Use

	No Angiography		Angiography Without Disease		Angiography With Disease	
	No Clopidogrel (n=4819)	Clopidogrel (n=2926)	No Clopidogrel (n=985)	Clopidogrel (n=509)	No Clopidogrel (n=2381)	Clopidogrel (n=2534)
Demographics						
Median age (IQR), y	84.0 (78.0, 89.0)	85.0 (79.0, 89.0)	76.0 (71.0, 81.0)	74.0 (70.0, 80.0)	77.0 (71.0, 82.0)	76.0 (71.0, 82.0)*
Female sex, %	57.8	57.5*	77.5	74.5*	44.0	44.4*
Median BMI (IQR), kg/m²	25.6 (22.1, 29.5)	25.6 (22.3, 29.6)*	26.5 (22.9, 31.1)	27.0 (23.4, 31.6)*	27.2 (24.1, 31.2)	27.2 (23.9, 31.0)*
Nonwhite race, %	13.5	12.7*	15.3	12.6*	11.3	11.1*
Medical history, %						
Hypertension	83.2	85.2	79.0	83.3	84.1	84.1*
Diabetes mellitus	36.3	39.1	25.3	23.4*	38.5	37.5*
Peripheral artery disease	15.5	18.6	6.7	6.9*	17.2	15.2*
Recent smoker	7.9	8.0*	11.3	9.8*	14.7	15.8*
Dyslipidemia	53.3	58.7	55.6	60.7*	67.8	71.6
Prior MI	28.1	32.5	12.1	16.3	34.7	31.8
Prior PCI	13.3	17.3	7.5	15.5	23.3	23.7*
Prior CABG	21.1	22.9*	4.3	9.4	36.0	34.4*
Prior CHF	35.6	31.5	12.7	12.4*	23.7	17.7
Prior stroke	17.0	16.4*	7.1	8.3*	11.7	11.1*
Comorbidity index >3	34.4	32.1	15.9	12.0	23.0	18.7
Features on admission						
Cardiogenic shock, %	0.8	0.9*	1.1	0.6*	0.9	0.8*
Heart failure, %	41.4	39.9*	18.5	14.0	27.8	20.7
Median heart rate (IQR), bpm	91 (76, 108)	88 (74, 105)	86 (72, 103)	80 (68, 96)	86 (72, 104)	81 (69, 97)
Median SBP (IQR), mm Hg	139 (117, 160)	142 (121, 162)	145 (124, 167)	147 (127, 170)*	145 (125, 165)	147 (127, 169)
Median baseline Hgb (IQR), g/dL	12.2 (10.8, 13.5)	12.3 (11.1, 13.6)	13.2 (12.2, 14.3)	13.3 (12.3, 14.3)*	13.1 (11.7, 14.3)	13.3 (12.0, 14.4)
Renal dysfunction (CrCl ≤30 mL/min or dialysis), %	35.0	34.5*	10.9	8.3*	13.0	11.6*
LVEF >50%, %	51.0	48.5	63.5	66.3*	49.7	55.8
Transfer in, %	13.8	15.7	27.7	32.8	31.7	34.6
In-hospital events, %						
Stroke	0.6	0.5*	0.5	0.4*	0.5	0.4*
Major bleeding	11.5	8.2	6.5	3.5	11.0	8.0
PRBC transfusion	13.5	7.7	4.4	1.6	10.0	6.0
Discharge medications, %						
Aspirin	91.1	97.0	91.1	98.8	95.8	97.9
β-Blocker	91.4	96.3	88.9	95.4	94.6	97.1
Statin	67.5	82.5	72.1	83.6	83.2	90.9
ACEI/ARB	61.0	69.2	66.6	73.0	70.8	74.7
Warfarin	20.9	5.7	21.1	6.0	24.0	6.7

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CHF, congestive heart failure; Hgb, hemoglobin.

*P-values were calculated for pairwise comparisons of no clopidogrel vs clopidogrel within no angiography, angiography without disease, and angiography with disease groups. All P-values <0.05 unless indicated by an asterisk.
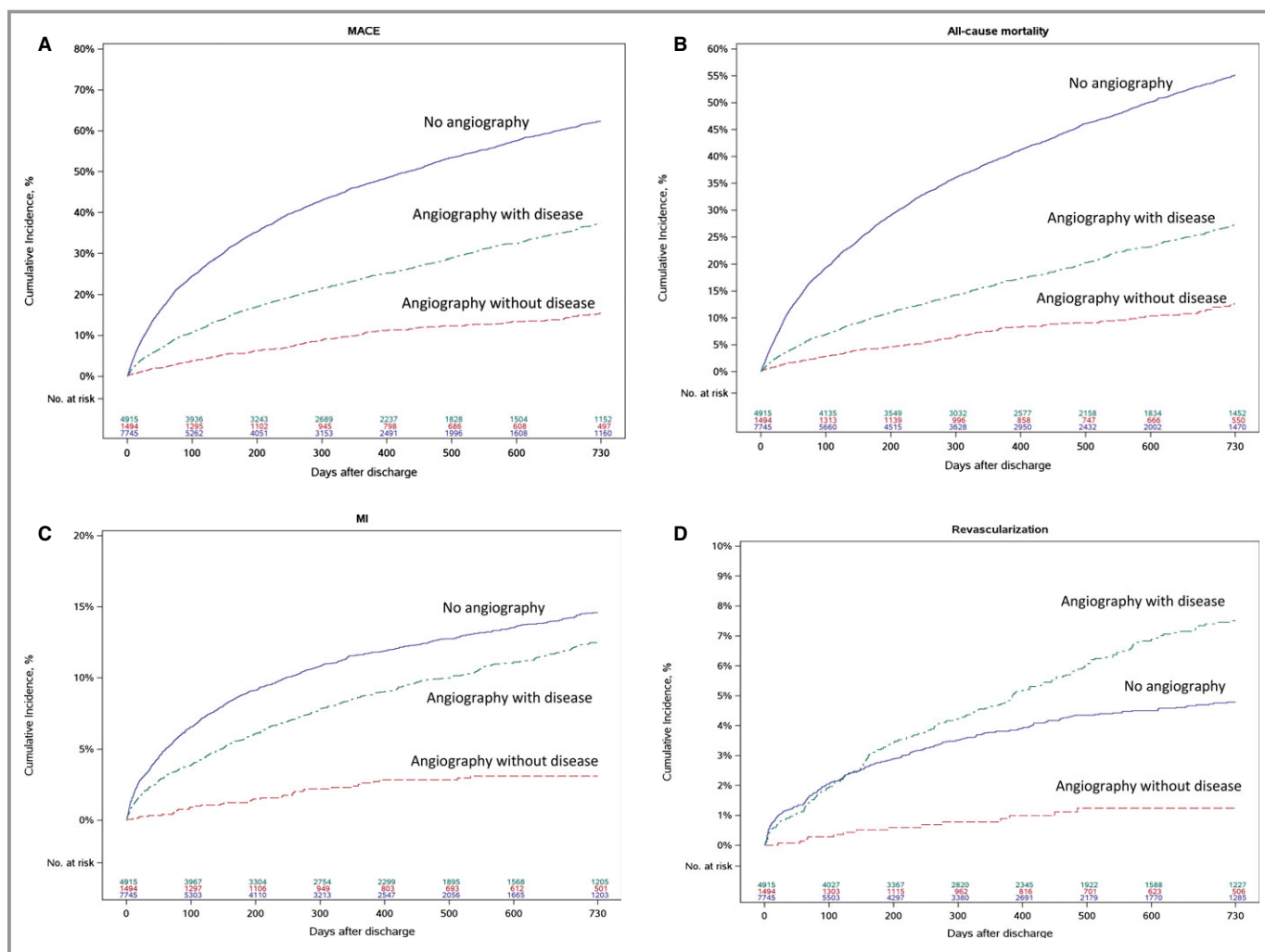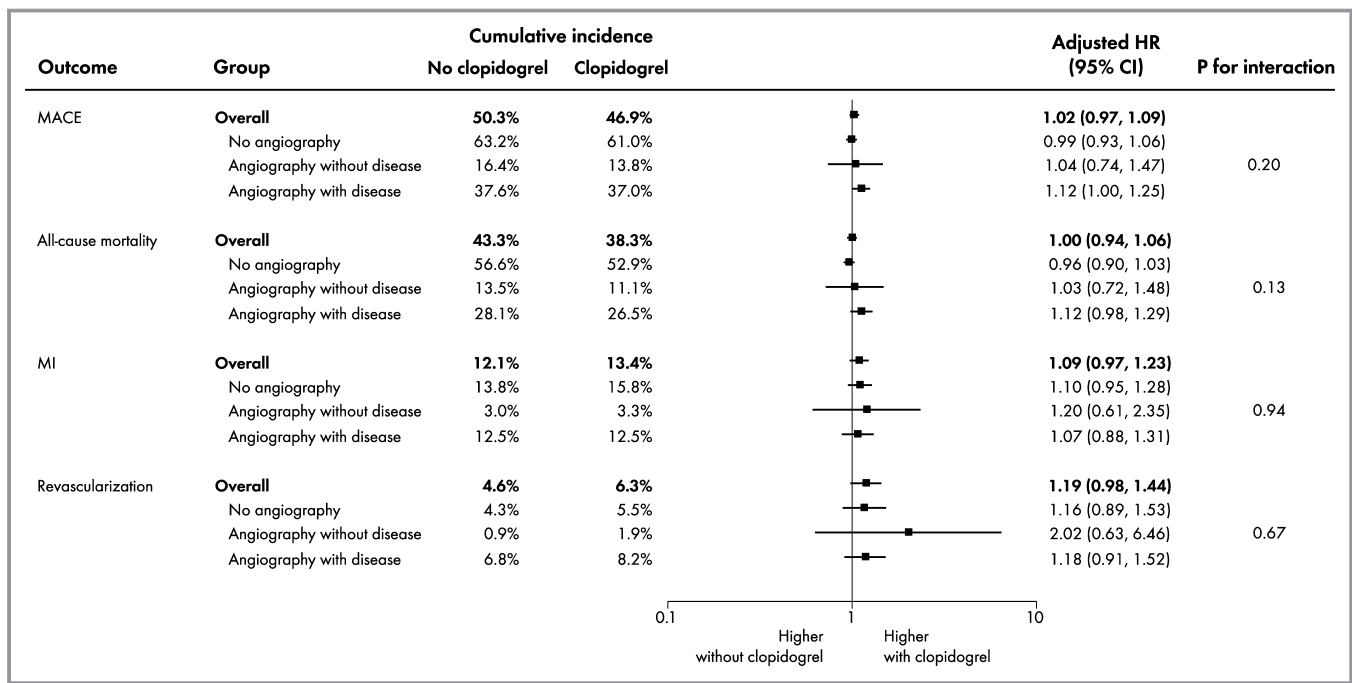
Figure 3. Outcomes according to angiography and disease. Shown are the 2-year cumulative incidence curves for (A) MACE; (B) all-cause mortality; (C) MI; and (D) revascularization among patients not undergoing angiography, patients undergoing angiography without disease, and patients undergoing angiography with disease. MACE indicates major adverse cardiac events; MI, myocardial infarction.

ACS),[3] and post-hoc analyses showed that the efficacy of clopidogrel was similar regardless of revascularization strategy, including a 20% relative risk reduction in the primary end point among patients who were medically managed. Although CURE was an older trial and was conducted in a setting where evidence-based medicines were less optimally used, more recent observational data appear to support the 12-month recommendation for clopidogrel. In a study of unrevascularized NSTE ACS patients from 2003 to 2008, postdischarge clopidogrel use was associated with lower mortality compared with no clopidogrel use,[12] especially among NSTEMI and older patients. In contrast, prospective data regarding the use of higher potency P2Y12 receptor inhibitors for unrevascularized NSTEMI patients are mixed. Ticagrelor was superior to clopidogrel for the reduction of ischemic events without increased bleeding in all-comer patients presenting with NSTE ACS, the majority of whom underwent in-hospital coronary

angiography.[13] This benefit and safety of ticagrelor over clopidogrel was maintained among patients intended for a planned noninvasive strategy, as well as those ultimately managed without coronary revascularization.[14] While prasugrel reduced ischemic events compared with clopidogrel among patients managed invasively,[15] no benefit for prasugrel compared with clopidogrel was found among unrevascularized NSTE ACS patients,[16] although there was a suggestion of benefit for prasugrel in patients undergoing angiography before randomization.[9,17–19] Based on these data, clinical practice guidelines recommend up to 12 months of dual antiplatelet treatment with clopidogrel or ticagrelor (but not prasugrel) in NSTEMI patients managed without coronary revascularization.[1]

Our analysis adds to existing knowledge in the field. First, patients enrolled in clinical trials are generally younger and healthier than the overall population,[20] and care may be

Outcome	Group	Cumulative incidence			Adjusted HR (95% CI)	P for interaction
		No clopidogrel	Clopidogrel			
MACE	Overall	50.3%	46.9%		1.02 (0.97, 1.09)	
	No angiography	63.2%	61.0%		0.99 (0.93, 1.06)	
	Angiography without disease	16.4%	13.8%		1.04 (0.74, 1.47)	0.20
	Angiography with disease	37.6%	37.0%		1.12 (1.00, 1.25)	
All-cause mortality	Overall	43.3%	38.3%		1.00 (0.94, 1.06)	
	No angiography	56.6%	52.9%		0.96 (0.90, 1.03)	
	Angiography without disease	13.5%	11.1%		1.03 (0.72, 1.48)	0.13
	Angiography with disease	28.1%	26.5%		1.12 (0.98, 1.29)	
MI	Overall	12.1%	13.4%		1.09 (0.97, 1.23)	
	No angiography	13.8%	15.8%		1.10 (0.95, 1.28)	
	Angiography without disease	3.0%	3.3%		1.20 (0.61, 2.35)	0.94
	Angiography with disease	12.5%	12.5%		1.07 (0.88, 1.31)	
Revascularization	Overall	4.6%	6.3%		1.19 (0.98, 1.44)	
	No angiography	4.3%	5.5%		1.16 (0.89, 1.53)	
	Angiography without disease	0.9%	1.9%		2.02 (0.63, 6.46)	0.67
	Angiography with disease	6.8%	8.2%		1.18 (0.91, 1.52)	

Figure 4. Outcomes according to discharge clopidogrel use. Unadjusted rates and adjusted HRs for MACE, all-cause mortality, MI, and revascularization comparing discharge clopidogrel vs no discharge clopidogrel are shown for the total cohort, as well as for subgroups of patients referred for angiography, patients undergoing angiography without disease, and patients undergoing angiography with disease. *P*-values correspond to the test for interaction between discharge clopidogrel use and subgroups of interest. *P*-values <0.05 indicate that the effect of discharge clopidogrel differs significantly between subgroup levels. HR indicates hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction.

directed by trial protocol recommendations. We focused on older NSTEMI patients using registry data representing routine clinical practice patterns. Second, prior studies specifically examining clopidogrel use in this area used older, regional data, and/or were limited to assessments of in-hospital outcomes.[3,12,21] Our more recent data may better reflect improved use of concomitant evidence-based therapies and secondary prevention for NSTEMI in contemporary practice across US hospitals. We also studied 2-year outcomes to investigate whether any long-term benefit is associated with clopidogrel use in this unique population. Third, mechanistically, one might expect more benefit from antiplatelet therapy among patients with obstructive CAD in whom recurrent cardiovascular events are more likely to be platelet mediated. Our study was novel in stratifying medically managed patients not only according to use of angiography, but also according to the presence or absence of obstructive CAD.

We found that ≈40% of older unrevascularized NSTEMI patients were discharged on clopidogrel. Treatment guidelines recommend up to 1 year of post-NSTEMI clopidogrel. Nevertheless, providers may be reluctant to prescribe clopidogrel for this length of time because of higher bleeding risk in this older patient population, particularly since these patients have been under-represented in randomized clinical trials. For

example, the primary analysis of the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) trial specifically excluded patients older than 75 years.[16] Furthermore, clinical trials of P2Y12 inhibitor therapies did not necessarily distinguish between type I and II MIs but intended to predominantly enroll patients with type I MIs. The lower rate of clopidogrel use observed in our study population may also reflect provider belief that antiplatelet therapy has limited benefits in patients with a type II MI due to demand ischemia rather than plaque rupture. In support of this latter hypothesis is the overall lower use of other evidence-based medicines for MI (eg, β-blocker, statin, angiotensin-converting enzyme inhibitor) among patients in all subgroups who were not discharged on clopidogrel.

An observational study conducted by the Kaiser Permanente network, as well as the secondary analysis of the TRILOGY-ACS trial, suggested benefit to antiplatelet therapy in medically managed NSTE ACS patients with angiographically confirmed CAD,[12,19] yet we found no association between clopidogrel and ischemic outcomes regardless of angiography use, even among patients with obstructive CAD diagnosed at angiography. Our observational study is limited by lack of randomization, but discrepant results may be due to several factors: (1) our study population was substantially

older compared with prior studies (median age 77 years compared with 68 in the Kaiser Permanente population and 63 in the randomized TRILOGY-ACS study); (2) we focused on NSTEMI patients, whereas prior studies also included patients with unstable angina; and (3) ACTION Registry-GWTG is a retrospective registry designed to include consecutive NSTEMI patients, so some of these patients (screened by discharge diagnosis or biomarker elevation) may have had type II rather than type I MIs. The results of our study question the clinical effectiveness of P2Y12 inhibition in a population of older medically managed NSTEMI patients typically encountered in routine practice. While current guidelines recommend P2Y12 inhibitor therapy regardless of MI type,[1] there is little clinical trial support of their use in patients with type II MIs. Based on our study findings, the risk–benefit ratio should be individually assessed when applying P2Y12 inhibitor therapy to medically managed NSTEMI patients older than 65 years, even among those with type I MIs, since these older-aged patients are under-represented in prior randomized studies and, consequently, have weaker evidence supporting benefit of P2Y12 inhibitor therapy use. Future prospective studies of P2Y12 receptor inhibitors should more broadly include older patients, and for those studying the medically managed population, should distinguish between type I and type II MI patients, to provide better understanding of how to apply these antiplatelet agents to clinical practice.

There are several important limitations of this analysis. First, this was an observational study, so despite multivariable adjustment, residual confounding exists. Second, there is selection bias regarding which patients are referred for angiography and which patients are treated with clopidogrel. ACTION Registry-GWTG mandates data collection for all patients presenting with acute MI, but the registry cannot distinguish type I from type II MI events. Patients who were not referred for angiography were markedly different from patients undergoing catheterization, yet we found no significant interactions when patients were stratified by use of angiography or presence of disease. We also tried to mitigate selection bias for clopidogrel use by examining use at discharge, rather than use in the first 24 hours of hospitalization when decisions may be more closely associated with invasive strategy decision-making. Despite these efforts, we could not account for all factors and events that might have influenced provider choices. Third, it is possible that angiography status and use of clopidogrel, a guideline recommendation, might be surrogates for other unmeasured patient and hospital characteristics that might impact outcomes of interest. Fourth, our analysis was based on registry and administrative claims data, and events were not adjudicated. Fifth, we did not have data regarding medication adherence or consistent use of postdischarge clopidogrel, and given the timeframe of our study relative to therapy uptake, we were unable to examine newer P2Y12 receptor inhibitors. Finally, we studied Medicare patients, and our results may not be generalizable to the younger NSTEMI population.

In conclusion, we examined more than 14 000 NSTEMI patients older than 65 years treated in routine practice and discharged without in-hospital revascularization at 463 US sites. We found more than 50% of these patients were treated upfront with a noninvasive strategy; overall, these patients had worse outcomes than those found to have significant CAD on angiography for whom a decision was made not to revascularize. We found no association between discharge clopidogrel use and long-term ischemic outcomes, regardless of referral to angiography and/or presence of CAD at angiography. These results need to be further explored with prospective studies, particularly focused on older MI patients who are at higher risk of both adverse cardiovascular events and bleeding.

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Disclosures

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