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Temporal trends and practice variations in clopidogrel loading doses in patients with non-ST-elevation myocardial infarction, from the NCDR

Creighton W. Don, MD, PhD^{*,‡}, Matthew T. Roe, MD, MHS[†], Shuang Li, MS[†], Elizabeth Fraulo, MS[†], Eugene Pomerantsev, MD, PhD[‡], Igor Palacios, MD[‡], and Stephen D. Wiviott, MD[§]

^{*}Division of Cardiology, University of Washington Medical Center, Seattle WA

[†]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC

[‡]Division of Cardiology, Massachusetts General Hospital, Boston MA

[§]Cardiovascular Division and Thrombolysis in Myocardial Infarction Study Group, Brigham and Women's Hospital, Boston MA

Abstract

Background—A higher loading dose of clopidogrel achieves a more rapid and consistent degree of platelet inhibition than standard dosing, although the clinical benefit of higher doses has not been clearly established. The use of the different doses in clinical practice is not known. We evaluated the patient, procedural and hospital characteristics associated clopidogrel loading doses given to patients with non-ST-segment elevation myocardial infarction (NSTEMI).

Methods—The NCDR ACTION-GWTG Registry was queried for patients with NSTEMI admitted from 2007–2008. Demographic, clinical, and procedural information was collected on standardized data forms. Patients were categorized according to the clopidogrel loading dose received. Temporal trends in the use of different doses were evaluated in quarterly time intervals.

Results—Between January 1, 2007 and December 31, 2008, the use of a 600 mg clopidogrel loading dose increased steadily from 36.4% to 45.5%, while the use of 300 mg decreased slightly from 40.1% to 37.1%. Patients loaded with clopidogrel prior to cardiac catheterization were more likely to receive 300 mg, while those receiving a loading dose at the time of catheterization more often received 600 mg. The temporal increase in the use of 600 mg clopidogrel loading doses was not explained by temporal changes in peri-procedural loading, use of early invasive management of NSTEMI patients, or use of antithrombotics or glycoprotein 2b/3a inhibitors.

Conclusions—Higher loading dose clopidogrel increased between 2007–2008. Higher dose clopidogrel was more frequently used in lower-risk patients undergoing an early invasive strategy and receiving peri-procedural loading.

INTRODUCTION

The benefit of clopidogrel in patients with non-ST-segment elevation myocardial infarction (NSTEMI) have been demonstrated in randomized clinical trials,^{1, 2} but its optimal dosing

CORRESPONDING AUTHOR: Creighton W. Don, MD, PhD, University of Washington, 1959 NE Pacific St., Box 356422, Seattle, WA 98195, 206-616-8039 (office), cwdon@u.washington.edu.

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has not been clearly established. Platelet aggregation studies have reported a wide variation in the rate and degree of platelet inhibition attained by a 300 mg loading dose,^{3, 4} that can in part be offset with earlier loading prior to percutaneous intervention⁵ or with higher loading doses that more quickly achieve a higher level of platelet inhibition.⁶⁻⁹

Despite recommendations that clopidogrel be loaded as early as possible in patients with NSTEMI,¹² some practitioners have expressed concerns about preloading prior to diagnostic catheterization, particularly if a patient eventually requires bypass surgery, leading to variability in dosing and timing of clopidogrel loading. We examined the trends in the use of clopidogrel loading doses and timing of the preload, in patients presenting with NSTEMI. Understanding patterns of adoption of the high-dose strategy in routine practice would be informative, particularly as more potent and rapidly loaded antiplatelet agents are introduced, which have the potential of reducing cardiovascular events, at the expense of increasing bleeding.

METHODS

This is a retrospective cohort study of data collected through NCDR ACTION Registry-Get With the Guidelines (GWTG), a quality improvement registry in which sites enroll all consecutive patients admitted with a diagnosis of myocardial infarction. Baseline patient characteristics, medications, procedures, and outcomes were collected from standardized definitions and data forms that have been collected from January 1, 2007 through December 31, 2008.¹³

Patient population

There were 63,232 patients with NSTEMI who were evaluated. Patients already taking clopidogrel at home, with contraindications to clopidogrel, whose loading dose of clopidogrel was missing or unknown, who received a loading dose in excess of 600 mg, or whose loading dose was incorrectly recorded (values not consistent with tablet doses) were also excluded. This resulted in a total analysis population of 45,504 (Figure 1).

Analyses of arrival-to-procedure times include only patients directly admitted and exclude transfer patients. Discharge medications excluded patients who died or were transferred out of a National Cardiovascular Data Registry (NCDR) site prior to discharge.

For analysis of acute loading, patients were categorized according to their clopidogrel loading dose within the first 24 hours after first medical contact. In the analysis of pre- versus peri-catheterization, and pre- versus peri-PCI dosing, the patients were categorized by the loading dose they received in relation to timing of the dose and the procedure, regardless of the time elapsed from admission.

Definitions

The definitions for data collected for the NCDR ACTION Registry – GTWG Version 2.1.1. are publically available.¹³ NSTEMI was defined by the universal classification for myocardial infarction.¹⁴ Coronary artery bypass grafting (CABG) was recorded if a patient underwent CABG at during the index admission.

Patients who received any clopidogrel within 24 hours after first medical contact were categorized as having acute clopidogrel loading, while those who did not were defined as having “no-acute clopidogrel.” Pre-catheterization and pre-PCI were defined as anytime from hospital presentation up to one hour before catheterization or PCI. Peri-catheterization and peri-PCI were defined as less than one hour before catheterization or PCI to anytime after the procedure.

Major bleeding was defined by an absolute hemoglobin drop of ≥ 4 g/dL, intracranial hemorrhage, observed retroperitoneal bleeding, or a red blood cell transfusion if baseline hemoglobin ≥ 9 g/dL or if baseline hemoglobin ≤ 9 g/dL with a witnessed bleeding event. Patient comorbidities were used to compute the risk of in hospital mortality using the Global Registry of Acute Coronary Events (GRACE) non-ST elevation acute coronary syndrome in hospital mortality score.¹⁵

Comparisons

The loading dose of clopidogrel within 24 hours (none, 75–300 mg, 300 mg, and 600 mg) was considered the key outcome of interest. The group receiving a clopidogrel load >75 and <300 mg is hereafter labeled “ <300 mg.” Patients were compared by baseline clinical, treatment and procedural characteristics (including time to treatment and time to coronary catheterization and PCI among patients undergoing an invasive strategy), and by the characteristics of the hospital in which they were treated.

Temporal trends in the use of different doses were performed in eight quarterly time intervals from Q1-2007 through Q4-2008. The trends were stratified by timing of catheterization, timing of clopidogrel dosing, and use of thrombin inhibitors and glycoprotein (GP) 2b/3a inhibitors.

Statistical Methods

Patient demographics, characteristics, medical therapy used, in-hospital procedures and cardiac findings were summarized in patients without acute clopidogrel, with acute clopidogrel <300 mg, 300 mg, or 600 mg using frequencies and percentages for categorical variables, median (first quartile, third quartile) for continuous variables. Comparisons of categorical variables used Mantel-Haenszel chi-square tests. For comparisons of continuous variables, Kruskal-Wallis tests were used among patients without acute clopidogrel, with acute clopidogrel <300 mg, 300 mg, or 600 mg, and Wilcoxon rank sum test were used between patients without acute clopidogrel and patients with acute clopidogrel. The ACTION in-hospital major bleeding model was used to adjust major bleeding events for the following variables: presentation heart rate and systolic blood pressure, baseline hemoglobin, female, baseline creatinine, age, ST-segment changes, heart failure (CHF) on presentation, shock, diabetes, peripheral arterial disease, weight, and home warfarin.

P-values were reported without adjustment for multiple comparisons. The significance of variables was assessed at the 0.05 alpha level. Evaluation of hospital and regional differences were compared using STATA 9.2 (StataCorp, College Station, TX). All other analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

There were 63,232 patients with NSTEMI admitted from January 1, 2007 through December 31, 2008, of whom 45,504 patients met the inclusion and exclusion criteria (Figure 1). Of these, 21,106 patients (46.4%) did not receive clopidogrel within the first 24-hours after first medical contact, although 7,385 of these patients eventually received clopidogrel at discharge. Of the 24,398 patients (53.6%) who received clopidogrel loading within the first 24 hours, 5,037 (20.7%) received a loading dose less than 300 mg, 9,367 (38.4%) a 300 mg loading dose, and 9,994 (41.0%) a 600 mg loading dose.

Among the 17,728 excluded patients, 9,516 patients were excluded because they were already taking clopidogrel at time of admission, although 991 (10.4%) received a 300 mg reloading dose and 574 (6.0%) were reloaded with a 600 mg dose within the first 24 hours after first medical contact.

Baseline Characteristics

The baseline demographic and clinical characteristics of the different dosing groups are shown in Table I. The median age of patients in the no-acute clopidogrel group was 10 years higher than the 600 mg loading group, and the median ages of the other two dosing groups fell between these. For almost all cardiovascular risk factors the percentage of comorbidities decreased as clopidogrel dose increased, with the 600 mg group having the lowest rates of hypertension, diabetes, dialysis, chronic lung disease, prior myocardial infarction and revascularization, atrial fibrillation, stroke, or peripheral arterial disease ($p < 0.0001$ test of trend). Patients who did not receive clopidogrel acutely had two to three times the prevalence of atrial fibrillation and use of home warfarin compared to the other groups. There was an incrementally greater proportion of patients presenting with CHF symptoms as loading dose decreased ($p < 0.0001$), with patients receiving 600 mg having the least and patients without acute clopidogrel dosing having the highest percentage of patients with CHF. Tobacco use and obesity were the exception, as these characteristics were more prevalent among patients with higher loading doses, with those receiving a 600 mg dose having the highest percentages.

Increasing loading dose correlated with decreasing comorbidities, as evidenced by the GRACE in-hospital mortality risk score. The patients without clopidogrel had the highest GRACE score, with incrementally lower scores among patients receiving <300 mg, followed by those receiving 300 mg, and finally by those given 600 mg of clopidogrel, who had the lowest predicted risk ($p < 0.0001$).

Medical therapy

The home use of aspirin, warfarin, beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, aldosterone antagonists, and statins incrementally decreased as clopidogrel dose increased, with the patients receiving 600 mg clopidogrel least likely to have been taking these medications.

The use of unfractionated heparin, bivalirudin, and GP 2b/3a inhibitors during hospitalization and guideline based medical therapies at discharge was associated with higher dose clopidogrel. The patients in the 600 mg group were more likely to receive these medications compared to patients loaded with lower doses or given no acute clopidogrel (Table II). Fondaparinux, argatroban, and lepirudin were rarely used and did not differ among clopidogrel loading dose groups.

Patients who received a 600 mg loading dose were most likely to be given this peri-PCI, while those receiving a 300 mg dose and lower were more likely to be given a pre-loading dose prior to PCI (Figure 2). Excluding patients who died or were transferred out, 4.3% of the patients with no-acute clopidogrel had a contraindication to clopidogrel, compared to 3.7% among those who did receive a loading dose in the first 24 hours. As with admission, warfarin prescription at discharge was also inversely associated with initial clopidogrel loading dose.

Patients who received clopidogrel loading peri-PCI were more likely to receive concomitant GP 2b/3a inhibitors (76.9%) than those who were pre-loaded with clopidogrel (67.1%), $p < 0.0001$. In patients with peri-PCI loading, those receiving the 300 mg dose received more GP 2b/3a inhibitors (83.5%) than those receiving 600 mg (74.6%), $p < 0.0001$.

Procedural Characteristics and Outcomes

Comparisons of procedural characteristics across clopidogrel loading doses are shown in Table III. Diagnostic coronary catheterization was performed in 34,949 patients (88.3%).

The patients in the no-acute clopidogrel group were more likely to be medically managed and have a contraindication to coronary catheterization (19.9% v. 7.0%, $p < 0.0001$). The former had a higher frequency of diffuse coronary disease, and a higher rate of CABG during their hospital stay, three times higher than that of their counterparts. There was a significant trend for higher rates of PCI and lower rates of CABG as the clopidogrel loading dose increased (Figure 3). Diagnostic angiography, early catheterization within 24 and 48 hours, and PCI (both angioplasty and stenting) all increased incrementally as dose increased ($p < 0.0001$ for trend). Patients being given 600 mg of clopidogrel had the shortest times to first electrocardiogram, catheterization, and revascularization.

Patients undergoing an invasive strategy who received pre-catheterization clopidogrel were most likely to receive a 300 mg dose (51.2%) while only 23.7% received a 600 mg dose. Among patients who received peri-PCI clopidogrel, 69.6% received a 600 mg loading dose, while only 24.4% received 300 mg. For patients undergoing PCI the use of drug eluting stents was essentially equivalent among the <300 mg, 300 mg, and 600 mg dosing groups (61.4% v. 60.0% v. 62.0%, respectively, $p = 0.03$).

The patients in the 600 mg group were most likely to have single vessel disease, and least likely to have triple-vessel disease (24.3%) compared to patients given 300 mg and less of clopidogrel (29.8% for both), $p < 0.0001$. Overall, the rate of CABG was very low in the 600 mg loading dose group (3.2%) compared to 8.8% in the <300 mg group and 8.8% in the 300 mg loading dose group and 19.9% in the no-acute clopidogrel group ($p < 0.0001$), but this was highly dependent on the timing of clopidogrel loading. For patients who were loaded pre-catheterization, the rates of CABG were more similar, 9.7% in the 600 mg group, compared to 11.5% in the <300 mg group and 12.8% in the 300 mg group ($p < 0.0009$).

In-hospital major bleeding events and mortality were inversely related to clopidogrel dose, with the lowest bleeding and mortality rates observed in the 600 mg loading dose group. After adjustment for major comorbidities, there was no difference in the risk for major bleeding among the groups ($p = 0.2872$).

Temporal Trends

Between January 1, 2007 and December 31, 2008, among patients with acute clopidogrel in the first 24 hours, the use of a 600 mg clopidogrel loading dose increased steadily from 36.4% to 45.5% of doses, while the use of 300 mg and lower doses decreased slightly from 40.1% to 37.1% (Figure 4). Patients receiving clopidogrel pre-catheterization were more likely to receive 300 mg, while those receiving peri-catheterization loading most often dosed with 600 mg. Nevertheless, in both the pre and peri-catheterization groups, the use of the higher loading dose increased over time. The same trends were seen among patients undergoing PCI, for the pre-catheterization and peri-PCI clopidogrel loading groups (Figure 5).

The trends in clopidogrel dosing persisted despite stratification by bivalirudin and GP 2b/3a inhibitor use. Bivalirudin increased from 13.5% to 20.6% between the first quarter of 2007 and the last quarter of 2008. Although the 600 mg clopidogrel loading dose was more likely to be used with bivalirudin, the temporal increase in the use of 600 mg was seen in patients who did and did not receive bivalirudin. The use of GP 2b/3a inhibitors decreased from 65.3% to 56.4% in this same time period. Nevertheless, the use of the 600 mg loading dose increased over time irrespective of GP 2b/3a inhibitor use.

Regional and Hospital Differences

There was regional and hospital variability in clopidogrel loading doses. Hospitals in the Western and Midwestern states are more likely to use 600 mg than the Northeast and South

(West 48.1%, Midwest 46.1%, Northeast 31.4%, South 36.2%, $p < 0.0001$), while the hospitals in the Northeast and South used 300 mg more frequently (West 41.9%, Midwest 43.9%, Northeast 68.6%, South 63.8%, $p < 0.0001$). Academic centers used more acute clopidogrel overall (62.7% v. 50.7%, $p < 0.0001$) compared to non-academic centers. Among patients who were given a loading dose, academic centers used a 300 mg dose (44.8%) more frequently than a 600 mg dose (36.5%), while non-academic centers used a 300 mg loading dose (18.2%) less frequently than the 600 mg dose (21.3%).

DISCUSSION

We report the observation that the clinical use of the 600 mg clopidogrel loading dose has been increasing over the two-year period evaluated in the NCDR ACTION-GWTG Registry, and is now used more frequently than the standard, FDA approved, 300 mg dose. In 2007, midway through this observation period, the use of the higher loading dose was suggested as a reasonable option in the ACC/AHA guidelines on the management of patients with unstable angina/non-ST-elevation MI, although it was emphasized that “uncertainty exists about optimum dosing of clopidogrel.”¹⁴ The results of the CURRENT – OASIS 7 trial, the first adequately powered clinical trial to address the safety and efficacy of a higher clopidogrel dosing strategy, were not reported until after this observation period.

Prior to 2007, several small studies showed earlier and greater platelet inhibition in patients receiving 600 mg loading doses and reductions in cardiovascular endpoints compared to those given 300 mg.^{6, 8, 9} In light of this, many operators had started using 600 mg in patients undergoing PCI, especially those who have not had pretreatment with clopidogrel, or other platelet inhibitors.¹⁶

In the NCDR ACTION-GWTG registry, the 600 mg loading dose was the predominant dose overall, and was notably higher among patients who underwent early catheterization within 24 hours or who were loaded with clopidogrel at the time of PCI. Since the proportion of patients undergoing early catheterization remained stable and the proportion of patients receiving peri-PCI clopidogrel decreased significantly, this would not explain the increase in the use of the higher loading dose. The temporal increase in the higher loading dose was also observed within subsets stratified by antithrombin or antiplatelet therapy. Thus, changes in the frequency of an early invasive approach, peri-PCI clopidogrel loading, or the use of antithrombin and other antiplatelet agents do not explain the temporal increases in the use of the 600 mg dose.

The use of less aggressive therapy in patients with higher risk, the so called “risk treatment paradox,” has been previously reported in other observational studies of physician management of cardiovascular disease.^{17, 18} Our data points strongly toward an inverse association between dose and patient comorbidities. Patients who were older, had a history of atrial fibrillation, prior stroke, warfarin use, and multiple cardiac risk factors were given lower loading doses. Rather than representing a ‘paradox’ in which patients with greater risk are given less intensive therapy, it is likely that physicians selected lower loading doses for patients who have risk factors associated with increased bleeding.^{19–21} This conclusion is justified by the finding that the differences in major bleeding events between the groups are attenuated when adjusting for bleeding risk factors. The marked inverse association of mortality with clopidogrel dose most likely represents a similar selection bias.

The variability in patterns of dosing and timing of the clopidogrel loading dose for patients with NSTEMI have important implications in gauging how physicians might utilize more potent antiplatelet regimens such as higher dose clopidogrel, prasugrel, and ticagrelor in future practice. The increasing trends in the use of a 600 mg loading dose demonstrates an

increasing enthusiasm for using more potent antiplatelet regimens for NSTEMI patients, even preceding clinical data for efficacy and safety.

There was a strong inverse relationship between higher clopidogrel doses and multivessel disease and CABG associated with the timing of the clopidogrel dose. There appear to be two dosing patterns, one in which patients are pre-loaded with 300 mg of clopidogrel prior to catheterization, and another in which patients undergo catheterization first and are loaded with 600 mg only if PCI is performed. Practitioners who do not routinely preload clopidogrel prior to catheterization likely wait for coronary anatomy to be defined before deciding whether and how much clopidogrel to administer, since patients with surgical disease would not likely be given clopidogrel if they had not received it yet.^{22, 23} The greater use of GP 2b/3a inhibitors in patients with peri-PCI loading suggests that physicians who withheld clopidogrel, chose instead to use reversible platelet inhibitors while in the process of determining if CABG is needed.

The preferential use of higher clopidogrel doses in peri-PCI loading implies that practitioners are inclined to use more potent, rapidly acting agents to reduce peri-PCI events, but are less willing to accept the increased bleeding risk of a more potent agent by preloading patients who are unlikely to undergo an early invasive approach, are medically managed without revascularization, or require surgery. The practice of withholding clopidogrel for patients with surgical coronary artery disease likely explains our finding that higher risk patients, even those who would be expected to have higher platelet reactivity, were given lower loading doses. It is possible that some patients were not loaded with clopidogrel because their coronary anatomy was already known and CABG surgery was planned prior to admission, but we expect that this is a small minority of patients.

This data also points to the important finding that many practitioners do not administer clopidogrel to all ACS patients as soon as possible on admission or use loading doses of at least 300 mg or at discharge, despite recommendations to do so by several guideline writing committees.¹² While our data shows this is partially offset by the need for surgery, higher use of GP 2b/3a inhibitors, and bleeding risks, this deviation from guideline based therapy deserves further exploration.

Several limitations should be considered in interpreting these results. We evaluated a relatively short interval Q1 2007 through Q4 2008; nevertheless, this captures an important period during which the ACC/AHA guidelines were amended to reflect new data regarding dosing and the OASIS-7 CURRENT results were reported. Our data reflect only the dosing patterns for patients not taking clopidogrel at presentation. Several patients were already taking clopidogrel at admission (15.0%) who were not evaluated. There were also patients with missing or incorrectly recorded doses, although this was a small proportion (2.9%). Finally, limited conclusions can be drawn from the in-hospital mortality and major bleeding rates due to significant residual confounding associated with selection bias.

CONCLUSION

Between 2007 and 2008, the use of a higher clopidogrel loading dose has increased steadily, becoming dose used in the majority of patients. The 600 mg dose was used most frequently in lower-risk patients who were given the loading dose peri-PCI, and were the least likely to undergo CABG or be medically managed. The increased use of the higher dose indicates that as new more potent antiplatelet agents are introduced, many practitioners would be expected to adopt them, although timing and patient selection will vary widely. Centers that routinely preload patients with clopidogrel may continue to use lower doses.

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Figure 1.

Inclusion and exclusions and initial clopidogrel loading dose.

* All patients were included who *did not* have documented contraindications to clopidogrel, missing, unknown or incorrectly recorded loading doses of clopidogrel, doses in excess of 600 mg, pre-admission clopidogrel use, or repeat admission within the study period.

Figure 2.
Percentage of patients receiving clopidogrel loading pre-PCI versus peri-PCI associated with dose <300 mg, 300 mg, or 600 mg.
PCI = percutaneous coronary intervention.

Figure 3.

Percentage of patients undergoing PCI versus CABG associated with clopidogrel loading dose.

PCI: percutaneous coronary intervention; CABG: Coronary artery bypass grafting. ($p < 0.0001$ test of trend)

Figure 4.
Temporal changes in clopidogrel loading dose (Q1 2007 through Q4 2008)

A. Clopidogrel loading pre-coronary catheterization **B. Clopidogrel loading peri-percutaneous coronary intervention**

C. Temporal changes in the timing of clopidogrel loading, pre-catheterization versus peri-percutaneous coronary intervention (PCI)

Figure 5.

Temporal changes clopidogrel loading dose (Q1 2007 through Q4 2008) according to timing of first dose (A. Clopidogrel loading pre-catheterization, B. Clopidogrel loading peri-percutaneous coronary intervention, C. Temporal changes in the timing of clopidogrel loading, pre-catheterization versus peri-percutaneous coronary intervention (PCI))

Table 1

Baseline demographic and clinical characteristics according to loading clopidogrel dose within the first 24 hours for patients with non-ST-elevation myocardial infarction.

	No Acute	< 300 mg	300 mg	600 mg	p-value
Baseline characteristics					
Age-years, median (25th,75th)	N = 21,106 70 (58, 81)	N = 5,037 68 (56, 80)	N = 9,367 63 (53, 75)	N = 9,994 60 (51, 70)	
Gender, male (%)	57.0	59.4	64.5	69.6	<0.0001
Race (%)					
• White	82.9	82.9	84.5	85.9	<0.0001
• Black	9.6	9.7	8.7	6.7	
• Asian	1.6	1.2	0.9	1.3	
• Hispanic	3.6	3.8	3.6	3.6	
• Other	1.8	1.8	1.8	1.9	
Medical History (%)					
Current/recent smoker (<1 year)	25.9	29.6	34.7	38.5	<0.0001
Hypertension	73.8	73.9	68.5	64.7	<0.0001
Dyslipidemia	53.2	56.6	55.8	54.8	<0.0001
Currently on dialysis	3.0	2.6	1.3	1.0	<0.0001
Chronic lung disease	16.6	15.8	14.3	10.9	<0.0001
Diabetes mellitus	33.6	33.3	27.1	24.3	<0.0001
• Insulin dependent	35.9	35.0	29.5	26.1	<0.0001
Prior MI	23.1	27.2	19.8	17.	<0.0001
Prior CHF	17.4	15.3	8.7	5.4	<0.0001
Prior PCI	14.8	21.0	17.2	16.7	<0.0001
Prior CABG	15.8	18.8	14.7	11.3	<0.0001
Prior revascularization	25.9	32.9	26.6	23.8	<0.0001
Atrial fibrillation or flutter	11.3	7.4	5.6	3.6	<0.0001
Cerebrovascular disease	14.0	15.3	8.9	5.8	<0.0001
Prior stroke	9.5	9.6	5.8	4.3	<0.0001
Peripheral Arterial Disease	11.2	11.4	7.0	5.8	<0.0001
Patient Presentation (%)					

	No Acute	< 300 mg	300 mg	600 mg	p-value
Heart Failure	24.7	21.0	13.4	9.2	<0.0001
Cardiogenic shock	1.3	0.9	0.7	1.1	<0.0001
Tachycardia (HR > 100)	26.6	20.2	16.9	13.4	<0.0001
Hypotensive (systolic BP ≤ 90)	3.7	2.8	2.1	2.2	<0.0001
GRACE in-hospital mortality score, median (25th, 75th)	142 (112, 174)	136 (108, 168)	124 (99, 152)	118 (96, 142)	<0.0001
<u>In-hospital events (%)</u>					
Major bleeding	10.3	9.6	7.8	6.4	<0.0001
Death	5.2	2.9	2.0	1.3	<0.0001

MI: myocardial infarction; CHF: congestive heart failure; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; BP: blood pressure.

Admission medications and in-hospital medical therapy used according to loading clopidogrel dose for patients with non-ST-elevation myocardial infarction

Table II

	No Acute	< 300	300	600	p-value
	N=21,106	N=5,037	N=9,367	N=9,994	
Home Medications (%)					
Aspirin	44.1	42.8	41.3	38.5	<0.0001
Warfarin	9.1	5.4	4.3	3.1	<0.0001
Hospital treatment (%)					
<u>Antiplatelet agents</u>					
Aspirin	94.5	97.9	98.6	98.8	<0.0001
Clopidogrel pre-cath loading	n/a	68.7	60.7	23.3	<0.0001
Clopidogrel peri-PCI loading	n/a	30.8	42.6	78.5	<0.0001
GP IIb-IIIa	27.8	41.5	55.7	66.0	<0.0001
<u>Anticoagulants</u>					
Heparin: Unfractionated	50.1	51.1	63.3	68.4	<0.0001
Heparin: Low Molecular	44.9	48.7	42.0	31.2	<0.0001
<u>Antithrombins</u>					
Bivalirudin	6.7	10.6	13.4	22.8	<0.0001

Percentages are among patients without a contraindication to the medication. ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; PCI: percutaneous coronary intervention; Cath: coronary catheterization; GP IIb-IIIa: glycoprotein IIb-IIIa inhibitor. *Ideal patients were those with ejection fraction <40

In-hospital procedures and cardiac findings according to loading clopidogrel dose within the first 24 hours for patients with non-ST-elevation myocardial infarction

Table III

	No acute clopidogrel	<300 mg	300 mg	600 mg	p-value
<u>In-Hospital Procedures (%)</u>					
	N = 21,106	N = 5,037	N = 9,367	N = 9,994	
Diagnostic cath	80.4	87.0	93.5	98.0	<0.0001
Cath w/in 24h of arrival	35.5	52.3	68.7	86.9	<0.0001
<u>Interventional Procedures (%)</u>					
PCI	25.8	41.9	62.9	87.0	<0.0001
PCI w/in 24h of arrival	9.5	31.4	51.9	79.5	<0.0001
CABG	15.9	7.3	8.2	3.1	<0.0001
Revascularization	52.4	59.7	76.0	91.3	<0.0001
Medically managed-no cath	29.8	24.9	9.2	1.9	<0.0001
<u>Timing of procedure from presentation</u>					
Arrival to Cath-hrs, median (25th,75th)	30.9 (18.7, 55.2)	22.8 (11.2, 44.1)	17.2 (5.8, 27.8)	9.7 (2.9, 18.9)	<0.0001
Arrival to PCI-hrs, median (25th,75th)	41.7 (26.1, 64.9)	22.2 (8.9, 42.1)	16.1 (4.9, 25.5)	9.6 (3.4, 19.1)	<0.0001

Cath: coronary catheterization; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.