DOI: 10.1161/CIRCULATIONAHA.114.014992

The Association of Discharge Aspirin Dose With Outcomes After Acute Myocardial Infarction: Insights From the TRANSLATE-ACS Study

Running title: *Xian et al.; Aspirin Dose and Outcomes*

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Journal Subject Code: Ethics and policy:[100] Health policy and outcome research

DOI: 10.1161/CIRCULATIONAHA.114.014992

Abstract

***Background*—**Aspirin is the most widely used antiplatelet drug post-myocardial infarction (MI), yet its optimal maintenance dose after percutaneous coronary intervention (PCI) with stenting remains uncertain.

***Methods and Results*—**We compared outcomes of 10,213 MI patients who underwent PCI and were discharged on dual antiplatelet therapy at 228 United States hospitals in the TRANSLATE-ACS study from 2010–2012. Major adverse cardiovascular events (MACE) and bleeding within 6 months post-discharge were compared between high- (325 mg) and low-dose aspirin (81 mg) using regression models with inverse probability-weighted propensity adjustment. Overall, 6,387 patients (63%) received high-dose aspirin at discharge. MACE risk was not significantly different between groups (high vs. low: unadjusted 8.2% vs. 9.2%; adjusted hazard ratio 0.99, 95% confidence interval [CI] 0.85–1.17). High-dose aspirin use was associated with greater risk of any Bleeding Academic Research Consortium (BARC)-defined bleeding events (unadjusted 24.2% vs. 22.7%; adjusted odds ratio [OR] 1.19, 95% CI 1.06–1.33), driven mostly by minor BARC type 1 or 2 bleeding events not requiring hospitalization (unadjusted 21.4% vs. 19.5%; adjusted OR 1.19, 95% CI 1.05–1.34). Bleeding events requiring hospitalization were similar by aspirin dosing groups (unadjusted 2.8% vs. 3.2%, adjusted OR 1.22, 95% CI 0.87–1.70). Similar associations were observed in landmark analyses accounting for aspirin dosing change over time, and across subgroup analyses by age, sex, baseline aspirin use, and type of ADP receptor inhibitor (clopidogrel vs. prasugrel/ticagrelor).

***Conclusions*—**Among PCI-treated MI patients, high maintenance dose aspirin was associated with similar rates of MACE, but greater risk of minor bleeding compared with those discharged on low-dose aspirin.

Key words: aspirin, acute myocardial infarction, major adverse cardiac event, bleeding, outcome

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Aspirin, alone or in combination with adenosine diphosphate (ADP) receptor inhibitors, has been the standard of care for patients undergoing percutaneous coronary intervention (PCI) and those with acute myocardial infarction (AMI).[1-4] However, randomized direct comparison studies of high- versus low-dose aspirin are limited. The dose of aspirin used in clinical trials evaluating antithrombotic therapy following PCI or AMI was often dictated by study protocol or left to the discretion of local investigators. Observational studies and post-hoc analyses of clinical trial data suggested no benefit and potentially increased harm with high-dose aspirin use.[5-11] More recently, a factorial randomized trial of double- versus standard-dose clopidogrel and high- versus low-dose aspirin found similar outcomes in high- versus low-dose aspirin users, but patients were followed for only one month.[12] Based on these limited data, the American Heart Association/American College of Cardiology (AHA/ACC) NSTE ACS guidelines recently revised the recommendations to change the maintenance dose from high dose to low dose.[13-15] In the context of these recent data and recommendation changes, current prescribing patterns for aspirin in the United States (U.S.) remain unclear.

Using data from the Treatment with ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) observational study, the goals of our study were as follows: 1) describe current patterns of aspirin dosing among MI patients following PCI with stenting in contemporary U.S. clinical practice; 2) examine the association of aspirin dosing with major adverse cardiovascular events (MACE) and bleeding; and 3) determine whether the relationships between aspirin dose and these outcomes vary by clinically relevant subgroups of age, sex, home aspirin use, discharge ADP receptor inhibitor type (clopidogrel vs. higher potency ADP receptor inhibitors), or change in aspirin dose over time.

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Methods

Data Source

The primary data source was the TRANSLATE-ACS study, a multicenter, prospective, longitudinal, observational study of more than 12,000 MI patients managed with PCI. Details of the design and conduct of the TRANSLATE-ACS study have been previously described.[16] In brief, TRANSLATE-ACS included patients with either ST-segment elevation MI (STEMI) or non-STEMI (NSTEMI), who underwent PCI during the index hospitalization and were treated with ADP receptor inhibitors. Trained personnel at participating hospitals collected detailed clinical data during the index hospitalization, including baseline patient characteristics, bleeding history, presentation features, angiographic and procedural details, and in-hospital treatment and outcomes, using data element definitions aligned with the National Cardiovascular Data Registry® (NCDR) where possible. Post-discharge follow-up occurred at 6 weeks, and at 6, 12, and 15 months post-MI via a centralized telephone interview conducted by trained study personnel at the Duke Clinical Research Institute (DCRI). The follow-up interviews collected information on current medication (including aspirin dose), rehospitalizations, and changes in health status. Medical bills for all rehospitalizations were obtained. If a study endpoint was suspected based on billed diagnoses or treatments, medical records including hospital discharge summary, procedural reports, or angiographic films were obtained for endpoint validation by independent study physicians at the DCRI using protocol-defined criteria.[16]

Study Population

These analyses included all acute MI patients enrolled in the TRANSLATE-ACS study between April 2010 and October 2012, except for patients who died in-hospital (n=14), those who were not discharged on aspirin or were missing aspirin dosing information (n=228), or those who did

not have a stent implantation (n=473). To understand post-discharge aspirin dosing changes (elicited via interview), we further limited our study population to patients who completed both 6-week and 6-month interviews, or just 6-week interviews if patients had died (excluding 1,007 patients). Since the majority of patients in the U.S. were prescribed a daily aspirin dose of 81 mg or 325 mg, we excluded patients with a discharge aspirin dose other than 81 mg or 325 mg (n=431). After these exclusions, our final study population consisted of 10,213 patients discharged from 228 U.S. hospitals.

Data Definitions

The discharge aspirin dose was abstracted from the medical record of the index hospitalization. Patients were divided into two groups according to aspirin dose at discharge: high dose (325 mg per day) versus low dose (81 mg per day). Clinical outcomes were MACE (the composite of death, MI, stroke, or unplanned revascularization) and Bleeding Academic Research Consortium (BARC)-defined bleeding events from discharge to 6 months.[17] Briefly, BARC bleeding is classified into the following hierarchical categories characterizing the severity of the bleeding: type 0 (no bleeding); type 1 (bleeding that is not actionable); type 2 (overt, actionable bleeding that does not fit the criteria for type 3, 4, or 5, but does require nonsurgical, medical intervention by a healthcare professional, leading to hospitalization or increased level of care, or prompting evaluation); type 3 (clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses); type 4 (coronary artery bypass graft [CABG]-related bleeding); and type 5 (fatal bleeding). For the purpose of this study, we reported any BARC bleeding (type 1–5), minor BARC 1 or 2 bleeding that did not require rehospitalization, and any other BARC bleeding that required rehospitalization. MACE and hospitalized bleeding events were independently validated via medical record review.

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Statistical Analyses

Medians (with interquartile ranges) and percentages were used to describe the distribution of continuous and categorical variables, respectively. Baseline characteristics were compared between patients on high- versus low-dose aspirin by Pearson χ^2 test or Fisher Exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. Cox proportional hazard models were performed to investigate the relationship between aspirin dosing and MACE up to 6 months after discharge. Logistic regression models were derived to evaluate the association between aspirin dosing and bleeding.

We chose covariates based on their previous known association or clinical relevance to the outcomes. These included age, sex, race, medical history of prior MI, PCI, CABG surgery, stroke or transient ischemic attack (TIA), peripheral artery disease, atrial fibrillation/flutter, diabetes mellitus, hypertension, dyslipidemia, dialysis, current/recent smoker, chronic lung disease, gastrointestinal or genitourinary bleeding within last 6 months, EuroQoL-5 dimension (EQ-5D) index, cardiac arrest within 24 hours, cardiogenic shock within 24 hours, heart failure within 2 weeks, transfer from another acute care, body mass index, home aspirin use, home warfarin use, admission systolic blood pressure, pre-procedure hemoglobin, pre-procedure creatinine, and left ventricular ejection fraction ≤40 at discharge. We also included in-hospital treatment (unfractionated heparin, low molecular weight heparin, bivalirudin, glycoprotein IIb/IIIa inhibitor, radial vs. other access, arterial closure device), in-hospital bleeding events, and discharge medications (clopidogrel, prasugrel, ticlopidine, ticagrelor, anticoagulants, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and beta blockers). These covariates were used for inverse probability weighting (IPW) to adjust for potential confounding. A logistic regression model was constructed to estimate the propensity score for high- versus low-dose aspirin discharge.

For high-dose patients, weights were calculated by dividing the marginal probability of high-dose by the individual patient's propensity score. Weights for low-dose patients were calculated by dividing one minus the marginal probability of high-dose by one minus the individual patient's propensity score. Pre- and post-IPW balance of the covariates between aspirin dose groups were assessed using Cramer's Phi for categorical variables and R-squared for continuous variables.[18, 19] Values closer to zero indicate better balance. After IPW adjustment, all of the continuous variables were <0.0025 and all of the categorical variables were <0.05, indicating reasonable balance between high- and low-dose groups (**Supplemental Figure 1**).

The primary analyses were based on the intention-to-treat principle. To account for aspirin dose change over time, a landmark model was used to assess the risk of MACE using the 6-week interview date as time 0 and assessed events up to 6 months post-discharge.[20] Due to the possibility of confounding by selection bias, subgroup analyses for MACE and bleeding were performed according to age (<65 vs. ≥65 years), sex, home aspirin use, and discharge ADP receptor inhibitor (clopidogrel vs. higher potency ADP receptor inhibitor [prasugrel or ticagrelor]). We used robust standard errors to account for within hospital clustering in all models and robust sandwich covariance estimator for the Cox proportional hazards models.. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). All p-values are 2-sided, with $p<0.05$ considered statistically significant. Based on the event rates and sample size, our study has more than 90% power to detect a 11% relative reduction with high-dose aspirin. Each patient provided informed consent prior to the study enrollment. The institutional review board of the Duke University Health System approved the study.

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Results

Patient Characteristics

Of 10,213 patients eligible for our analysis, 6387 (62.6%) received high-dose aspirin (325 mg) and 3826 (37.4%) received low-dose aspirin (81 mg) at discharge. There were substantial variations in aspirin dosing across hospitals, with the proportion of high-dose aspirin ranging from 0–100% (**Supplemental Figure 2**). The median frequency of high-dose aspirin use was 70%, with an interquartile range between 50 and 80%.

Differences in baseline characteristics, in-hospital treatment strategies, discharge medications, and in-hospital events are illustrated in **Tables 1 and 2**. Due to the large sample size, some p-values were statistically significant, but measured differences were small and unlikely to be clinical relevant. Compared with patients on low-dose aspirin, patients prescribed high-dose aspirin at discharge were less likely to have a prior history of MI, PCI, CABG, atrial fibrillation/flutter, cerebrovascular disease, diabetes, or already be on aspirin or oral anticoagulant before the index admission (**Table 1**). Patients discharged on high-dose aspirin were more likely to receive drug-eluting stents, glycoprotein IIb/IIIa inhibitor, clopidogrel, and less likely to receive radial artery access and bivalirudin during cardiac catheterization or receive ticagrelor and oral anticoagulant at discharge (**Table 2**). The unadjusted incidences of in-hospital MACE (high vs. low: 2.1% vs. 2.7%, p=0.065) and in-hospital major bleeding events (3.0% vs. 3.4%, p=0.350) were not significantly different between groups.

Post-Discharge Clinical Outcomes

The incidence of MACE was 8.2% in the high-dose aspirin group compared with 9.2% in the low-dose group by 6 months post-discharge (**Table 3**). After multivariable adjustment using IPW, there was no significant difference in MACE between high- and low-dose aspirin groups

(adjusted hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.85–1.17). The unadjusted rates of any BARC-defined bleeding events (24.2% vs. 22.7%) and bleeding not requiring hospitalization (21.4% vs. 19.5%) were higher in the high-dose aspirin group (**Table 3**). After IPW adjustment, patients prescribed high-dose aspirin were more likely to report any BARC-defined bleeding events (adjusted odds ratio [OR] 1.19, 95% CI 1.06–1.33); this was mainly driven by an increased risk of minor BARC type 1 or 2 bleeding events not requiring hospitalization (21.4% vs. 19.5%; adjusted OR 1.19, 95% CI 1.05–1.34). The risk of higher BARC bleeding types requiring hospitalization was not statistically significant (2.8% vs. 3.2%; adjusted OR 1.22, 95% CI 0.87–1.70).

A total of 19.2% (1,224) and 34.9% (2,227) patients discharged on high-dose aspirin were switched to a lower dose by 6 weeks and 6 months post-discharge, respectively. In contrast, fewer patients who discharged on low-dose aspirin were switched to high-dose at 6 weeks (7.8% [300]) or at 6 months (7.9% [304]). In a landmark analysis stratified by aspirin dose at 6 weeks post-MI, there were no statistically significant differences in MACE between the two groups (**Figure 1**). Again, we observed higher risk of any bleeding or minor BARC type 1 or 2 bleeding events among patients prescribed high-dose aspirin, but no significant difference in the risk of more severe bleeding requiring rehospitalization, compared with patients prescribed low-dose aspirin (**Figure 2**).

In subgroup analyses, there were no significant differences in MACE between high- and low-dose aspirin groups when stratified by age, sex, baseline aspirin use and discharge ADP receptor inhibitor type (**Figure 1**). However, the higher risks of any BARC-defined and minor BARC bleeding events associated with high-dose aspirin were more prominent in younger patients, male, in patients receiving aspirin prior to admission, or those prescribed a higher potency ADP receptor inhibitor (prasugrel or ticagrelor) at discharge (**Figure 2**).

Discussion

In this large nationwide study of contemporary MI patients treated with PCI and dual antiplatelet therapy in the U.S., we found that high maintenance dose aspirin was prescribed at discharge in nearly two-thirds of patients. While commonly prescribed, high-dose aspirin was not associated with lower risk of MACE; however, high-dose aspirin was associated with an increased risk of minor bleeding events not requiring hospitalization. Similar trends were observed across subgroup analyses by age, sex, home aspirin use, and discharge ADP receptor inhibitor, as well as a landmark analysis accounting for aspirin dose change over time. Collectively, these findings provide empiric support for the current AHA/ACC guideline recommendations of aspirin 81 mg in preference to higher maintenance doses after PCI in the setting of an acute MI.[13-15]

Aspirin has been a mainstay therapy for patients with coronary artery disease for decades, yet the optimal maintenance dose after PCI has been a matter of significant debate. While thromboxane production can be completely inhibited by a daily dose of aspirin as low as 30 mg,[21, 22] high-dose aspirin (≥300 mg) is commonly used in long-term maintenance therapy of patients following PCI in the U.S.[6, 23] We continue to observe frequent use of high-dose aspirin in contemporary U.S. practice after the changes in guideline recommendations. While predisposing factors to bleeding and use of more potent ADP receptor inhibitor or anticoagulant might influence treatment selection, we found marked variation in aspirin dosing across U.S. hospitals, with some hospitals where treatment with high-dose aspirin was universal, and others where it was infrequent. This large variation in practice underscores the paucity of comparative data to guide appropriate dosing of aspirin after PCI.

A randomized clinical trial (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events Seventh Organization to Assess Strategies in Ischemic Symptoms,

[CURRENT-OASIS 7]) and post-hoc analyses of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trials evaluating dual antiplatelet therapy (clopidogrel and aspirin) suggest similar reductions in cardiovascular events with similar or increased risk of bleeding associated with high- versus low-dose aspirin.[5, 8, 10-12] Although these data generally favor low-dose aspirin, there are few comparative data evaluating aspirin dose and long-term outcomes among contemporary MI patients—especially those who are concurrently treated with more potent ADP receptor inhibitors such as prasugrel and ticagrelor. Exploratory analyses from the Platelet Inhibition and Patient Outcomes (PLATO) study suggested that higher doses of aspirin might have neutralized the benefit of more potent ticagrelor over clopidogrel.[23] The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) study demonstrated no effect modification of discharge aspirin dose on clinical outcomes observed with prasugrel versus clopidogrel, although a direct comparison between higher and lower dose aspirin was not made.[6]

In our study of more than 10,000 MI patients, we found no difference between high- and low-dose aspirin in the risk of MACE up to 6 months after discharge. However, high-dose aspirin was associated with higher risk of bleeding events, mainly driven by minor bleeding not requiring hospitalization. Similar trends were detected in subgroups based on age, sex, home aspirin use and discharge ADP receptor inhibitor. Importantly, increased bleeding risks seem more prominent among patients on higher-potency ADP receptor inhibitors even after adjustment for observed differences in patient risk profiles. Notably, there were very few ticagrelor patients in the study, especially among those on high-dose aspirin. As a result, a direct

comparison between high- and low-dose aspirin among patients on ticagrelor cannot be made. Nonetheless, our data suggest no added benefit and potential harm of bleeding events associated with high-dose aspirin, regardless of whether clopidogrel or a more potent ADP receptor inhibitor was used. In light of these results, low-dose aspirin appears to be a reasonable option for long-term maintenance therapy following PCI for all patients treated with clopidogrel, prasugrel, or ticagrelor.

Limitations

Our study had several limitations. First, our study is based on observational data and, therefore, includes all inherent limitations of such analyses. Importantly, aspirin doses were not randomly assigned. We were unable to determine the rationale for drug choice or treatment dosing. We included in the propensity model a comprehensive list of covariates, including baseline patient and clinical risk factors, bleeding history, and home medication use to minimize the impact of potential treatment selection on longitudinal clinical outcomes; nevertheless, treatment selection and unmeasured confounding may bias outcomes comparisons. Second, although MACE and hospitalized bleeding events were independently validated via medical chart review, patient-reported bleeding events not requiring hospitalization could not be validated. This being said, there is no reason to believe patients would differentially report bleeding events based on aspirin dose. Third, there were relatively high rates of switching during follow-up. While our study was able to account for aspirin dosing changes at the 6-week landmark date, we could not exclude the possibility of switching throughout the entire follow-up period and the impact of switching on outcomes. Finally, TRANSLATE-ACS is a U.S. study requiring written patient informed consent for longitudinal follow-up; therefore, the generalizability of our findings to non-participating centers/patients and to other regions of the world remains to be established.

In conclusion, we observed that high-dose aspirin (325 mg) was prescribed at discharge in the majority of PCI-treated MI patients in the U.S. We found no evidence supporting the benefit of high-dose aspirin compared with low-dose aspirin (81 mg) in terms of MACE, but high-dose aspirin was associated with greater risk of minor bleeding events. These trends were similar in patients treated with clopidogrel, as well as in those treated with more potent ADP receptor inhibitors. Collectively, our observational results support current guidelines for recommending low-dose aspirin as the preferred maintenance dose following MI.

Acknowledgments: We thank Erin Hanley, MS, Duke Clinical Research Institute, for editorial assistance and article preparation. Ms. Hanley did not receive compensation for her assistance, apart from her employment at the institution where the study was conducted.

Funding Sources: The TRANSLATE-ACS study (NCT01088503) is sponsored by Daiichi Sankyo, Inc. and Lilly USA. The Duke Clinical Research Institute is the coordinating center for this study, which represents a collaborative effort with the American College of Cardiology.

Conflict of Interest Disclosures: Dr. Xian reports research funding to Duke Clinical Research Institute from the American Heart Association, Daiichi Sankyo, Janssen Pharmaceuticals, and Genentech. Dr. Wang reports institutional research grant support from Eli Lilly, Daiichi Sankyo, Gilead Sciences, Glaxo Smith Kline, and the American College of Cardiology; honoraria from AstraZeneca and the American College of Cardiology. Ms. McCoy has no relevant disclosures to report. Dr. Effron reports being an employee and shareholder of Eli Lilly and Company. Dr. Henry reports consulting honorarium from Eli Lilly and Daiichi Sankyo. Dr. Bach reports institutional research grant support from Eli Lilly, Gilead Sciences, Glaxo Smith Kline, and Merck; consulting (Clinical Event Committee activities only) for Novo Nordisk (significant), Eli Lilly (modest), and Pfizer (modest). Dr. Zettler reports being an employee of Eli Lilly and Company. Dr. Baker reports being an employee of Daiichi Sankyo, Inc. Dr. Fonarow reports being a consultant to Novartis (significant) and Janssen (modest). Dr. Peterson reports research

funding to Duke Clinical Research Institute from the American College of Cardiology, American Heart Association, Eli Lilly & Company, and Janssen Pharmaceuticals; consulting (including CME) for Merck & Co., Boehringer Ingelheim, Genentech, Janssen Pharmaceuticals, and Sanofi-Aventis.

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DOI: 10.1161/CIRCULATIONAHA.114.014992

Table 1. Baseline Characteristics of Patients Receiving High-dose versus Low-dose Aspirin at Discharge.

Characteristics	Aspirin 325 mg n=6,387	Aspirin 81 mg n=3,826	p-value
Demographics			
Age, years	60 (52-67)	61 (53-69)	<0.001
Female	1,737 (27.2)	1,117 (29.2)	0.029
Race			
White	5,730 (89.7)	3,340 (87.3)	<0.001
Black	469 (7.4)	386 (10.1)	<0.001
Asian	91 (1.4)	34 (0.9)	0.019
Hispanic	218 (3.4)	108 (2.8)	0.099
Medical history			
Prior MI	1131 (17.7)	808 (21.1)	<0.001
Prior PCI	1248 (19.5)	864 (22.6)	<0.001
Prior CABG	547 (8.6)	403 (10.5)	0.001
Atrial fibrillation/flutter	246 (3.9)	238 (6.2)	<0.001
Prior stroke or TIA	309 (4.8)	251 (6.6)	<0.001
Peripheral artery disease	381 (6.0)	266 (7.0)	0.049
Diabetes mellitus	1,603 (25.1)	1,051 (27.5)	0.009
Hypertension	4,213 (66.0)	2,635 (68.9)	0.003
GI/GU bleeding within last 6 months	51 (0.8)	45 (1.2)	0.055
EQ-5D index	75 (60-85)	75 (60-85)	0.243
Medication prior to admission			
Aspirin	2,422 (37.9)	1,674 (43.8)	<0.001
ADP receptor inhibitor	772 (12.1)	478 (12.4)	0.358
Anticoagulant	107 (1.7)	196 (5.1)	<0.001
Admission features			
STEMI presentation	3365 (52.7)	1933 (50.5)	0.034
Transfer from another acute care facility	2,639 (41.3)	1,459 (38.1)	0.002
Cardiac arrest on presentation	212 (3.3)	117 (3.1)	0.440
Cardiogenic shock on presentation	135 (2.1)	75 (2.0)	0.569
HF within 2 weeks	389 (6.1)	263 (6.9)	0.135
BMI	28.3 (25.9-33.4)	29.1 (25.8-33.2)	0.123
Systolic blood pressure	140 (121-158)	139 (121-158)	0.870
Pre-procedure hemoglobin, g/dL	14.4 (13.2-15.5)	14.2 (12.9-15.3)	<0.001
Pre-procedure creatinine, mg/dL	1.0 (0.80-1.2)	1.0 (0.8-1.2)	0.111

ADP indicates adenosine diphosphate inhibitor; BMI, body mass index; CABG, coronary artery bypass grafting; EQ-5D, EuroQol-5 dimension; GI/GU, gastrointestinal/genitourinary; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack

Categorical variables presented as number (frequency), continuous variables expressed as median (25 to 75 percentiles).

DOI: 10.1161/CIRCULATIONAHA.114.014992

Table 2. In-hospital Treatment and Discharge Medications of Patients Receiving High-dose versus Low-dose Aspirin at Discharge.

Characteristics	Aspirin 325 mg n=6,387 (%)	Aspirin 81 mg n=3,826 (%)	p-value
In-hospital medications			
Aspirin	6,315 (98.9)	3,782 (98.9)	0.789
ADP receptor inhibitor			
Clopidogrel	4,963 (77.7)	2,730 (71.4)	<0.001
Prasugrel	1,908 (29.9)	1,199 (31.3)	0.022
Ticagrelor	30 (0.5)	285 (7.5)	<0.001
Unfractionated heparin	4,824 (75.5)	2,821 (73.7)	0.090
LMWH	1,177 (18.4)	798 (20.9)	0.008
Bivalirudin	2,993 (46.9)	1,963 (51.3)	<0.001
GP IIb/IIIa inhibitor	3,011 (47.1)	1,509 (39.4)	<0.001
Fibrinolytic therapy	271 (8.1)	126 (6.5)	0.097
Cardiac catheterization data			
Radial access	633 (9.9)	535 (14.0)	<0.001
Culprit lesion			0.529
Left main	55 (0.9)	32 (0.8)	
Left anterior descending	2,361 (37.0)	1,470 (38.4)	
Left circumflex	1,424 (22.3)	852 (22.3)	
Right coronary artery	2,528 (39.6)	1,469 (38.4)	
DES used	4,807 (75.3)	2,732 (71.4)	<0.001
In-hospital event			
In-hospital major adverse cardiac event	134 (2.1)	102 (2.7)	0.065
In-hospital major bleeding event*	194 (3.0)	129 (3.4)	0.350
Discharge medications			
Clopidogrel	4,505 (70.5)	2,451 (64.1)	<0.001
Prasugrel or ticagrelor	1,858 (29.1)	1,363 (35.6)	<0.001
Prasugrel	1,847 (28.9)	1,110 (29.0)	0.91
Ticagrelor	11 (0.2)	253 (6.6)	<0.001
Anticoagulant	169 (2.7)	356 (9.3)	<0.001

GP indicates glycoprotein; LMWH, low molecular weight heparin

*A major bleeding event observed and documented in the medical record that was associated with a hematocrit drop of ≥10% and/or a hemoglobin drop of ≥3g/dL; or that required transfusion or surgical intervention.

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Table 3. MACE and BARC Bleeding within 6 Months According to Discharge Aspirin Dose Group: Primary Analysis.

Endpoint	Aspirin 325 mg n=6,387 (%)	Aspirin 81 mg n=3,826 (%)	Unadjusted (95% CI)	Adjusted (95% CI)
MACE	522 (8.2)	352 (9.2)	0.89 (0.77-1.02)*	0.99 (0.85-1.17)*
Any BARC bleeding†	1,547 (24.2)	870 (22.7)	1.09 (0.98-1.20)‡	1.19 (1.06-1.33)‡
Higher BARC bleeding§	178 (2.8)	124 (3.2)	0.88 (0.70-1.10)‡	1.22 (0.87-1.70)‡
Lower BARC bleeding□	1,369 (21.4)	746 (19.5)	1.12 (1.01-1.25)‡	1.19 (1.05-1.34)‡

BARC indicates Bleeding Academic Research Consortium; CI, confidence interval; MACE, major adverse cardiac event (a composite endpoint of death, myocardial infarction, stroke, or unplanned revascularization)
*Hazard ratio (high vs. low)
†Any BARC bleeding (type 1-5).
‡Odds ratio (high vs. low)
§Higher BARC requiring hospitalization (type 3, 4, 5 and some type 2).
□Lower BARC type not requiring hospitalization (type 1 and some type 2).

Figure Legends:

Figure 1. Major adverse cardiac events within 6 months according to discharge aspirin dose (325 mg versus 81 mg).

Figure 2. Bleeding Academic Research Consortium (BARC) defined bleeding events within 6 months according to discharge aspirin dose (325 mg versus 81 mg).

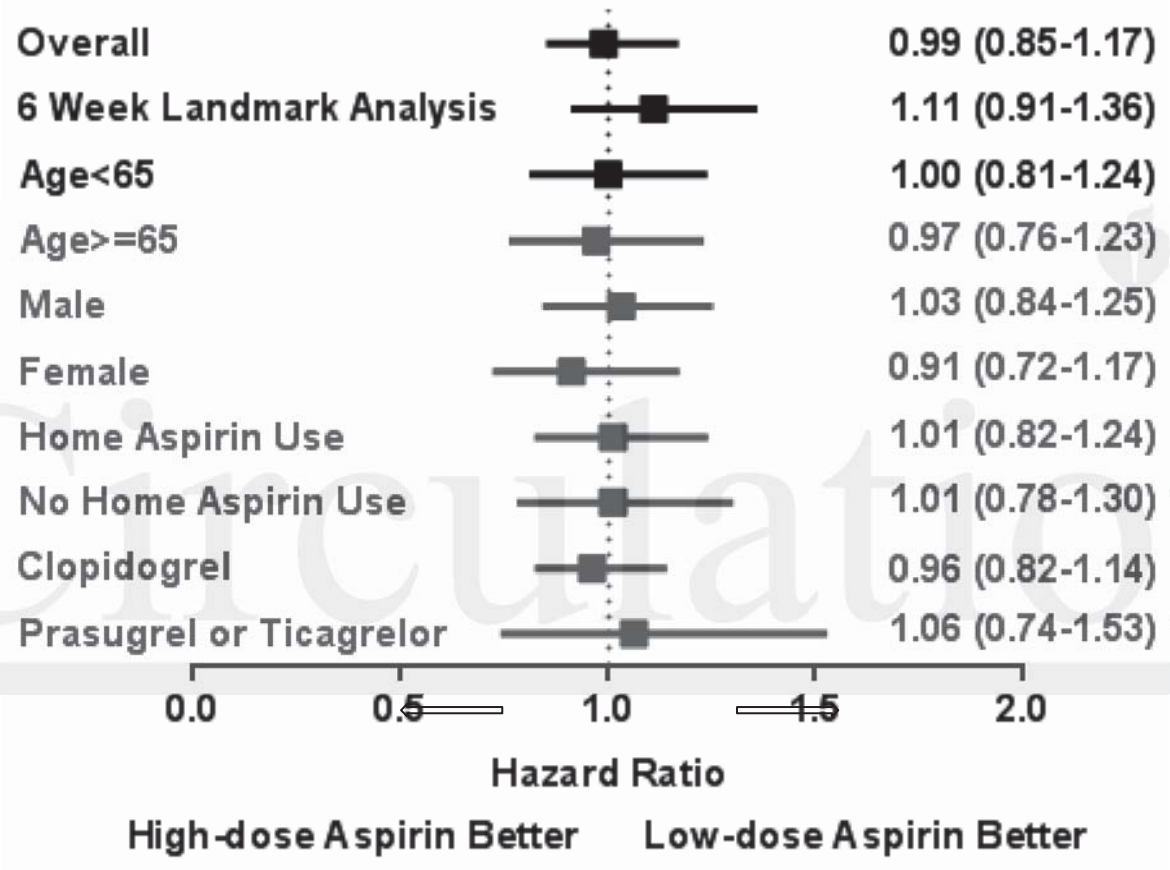


Figure 1

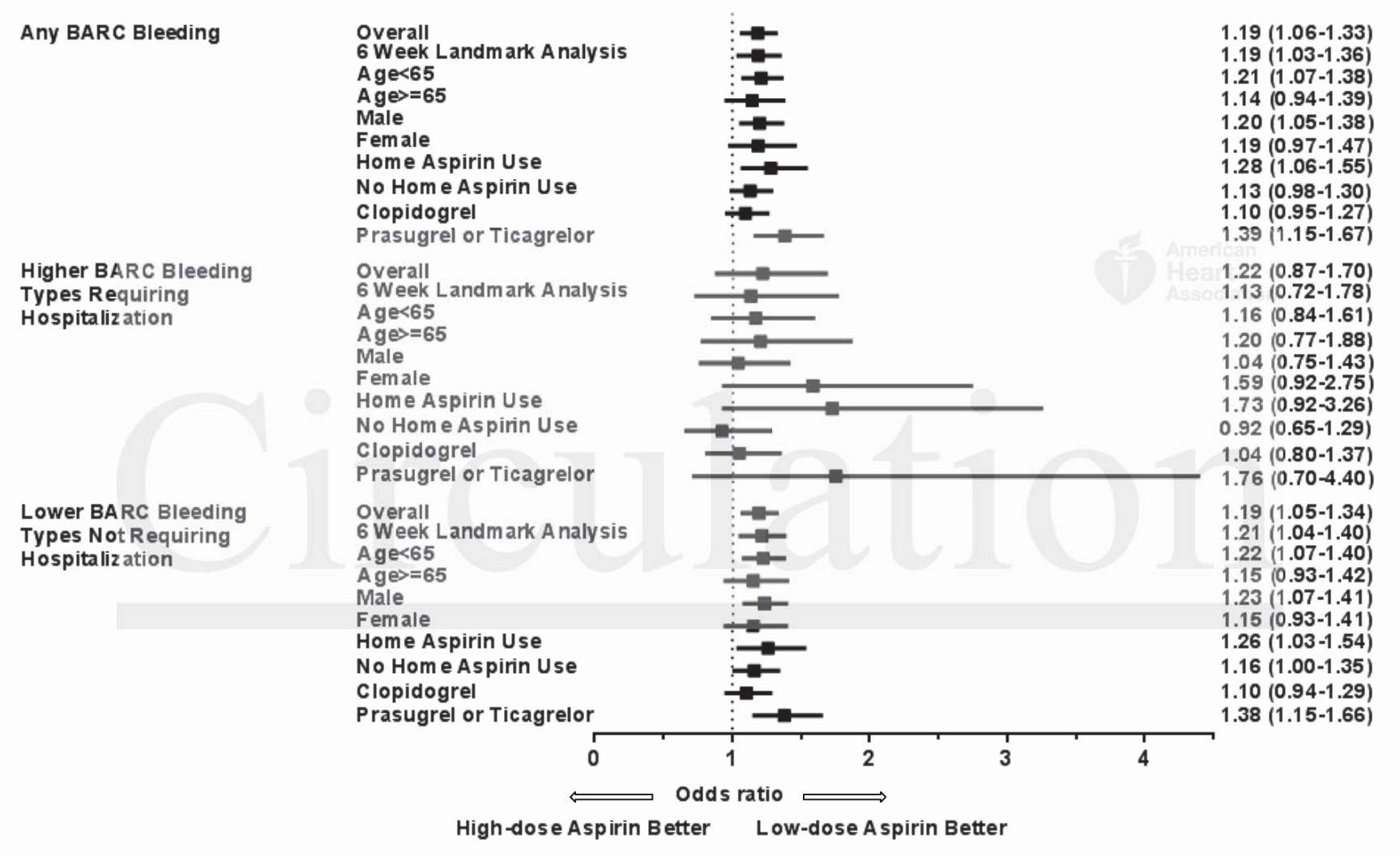


Figure 2

SUPPLEMENTAL MATERIAL

Supplemental Figure Legends.

Figure 1. Balance of Covariates

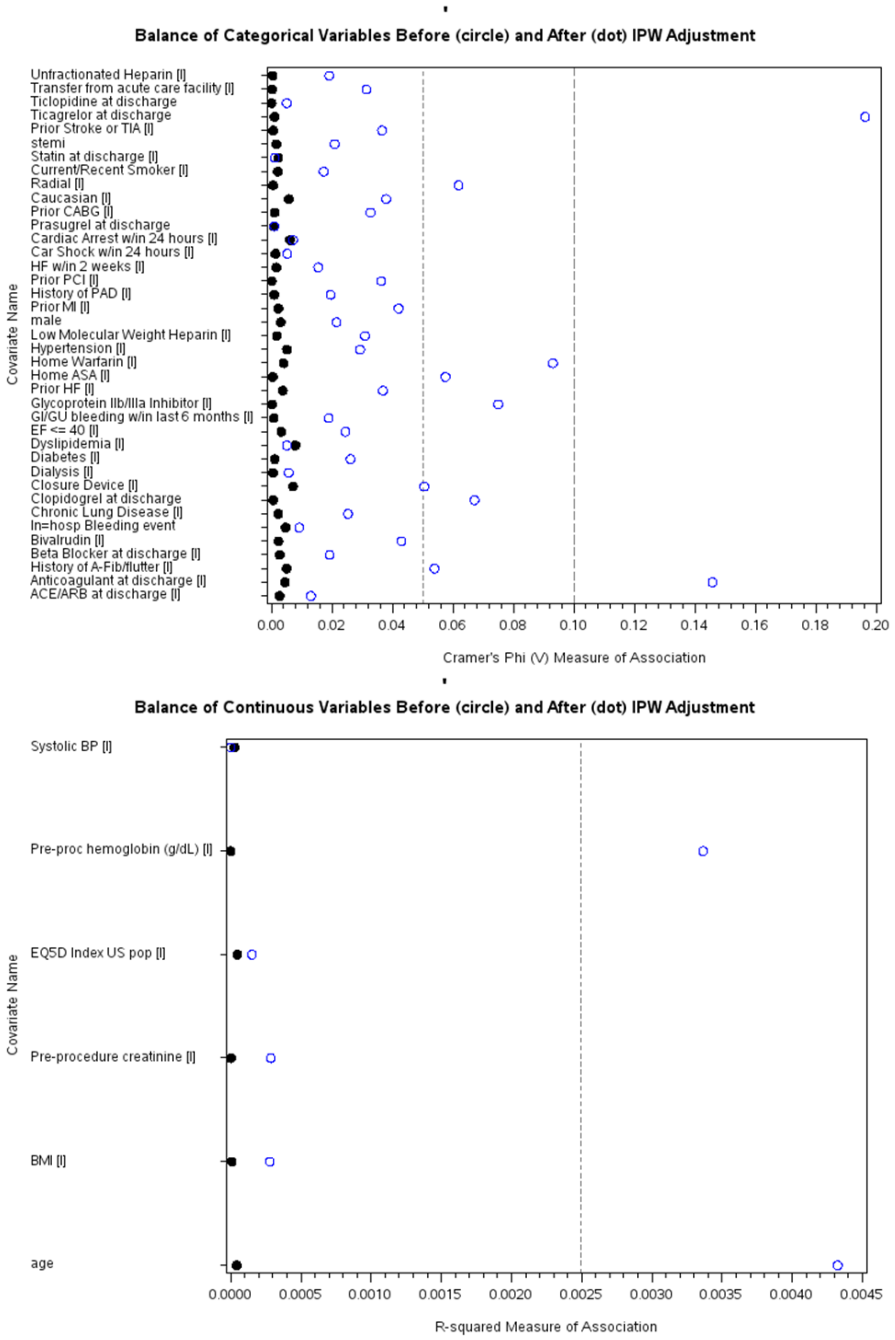
Balance of covariates before (circle) and after (dot) inverse probability-weighting adjustment.

Figure 2. Distribution of Aspirin Dose

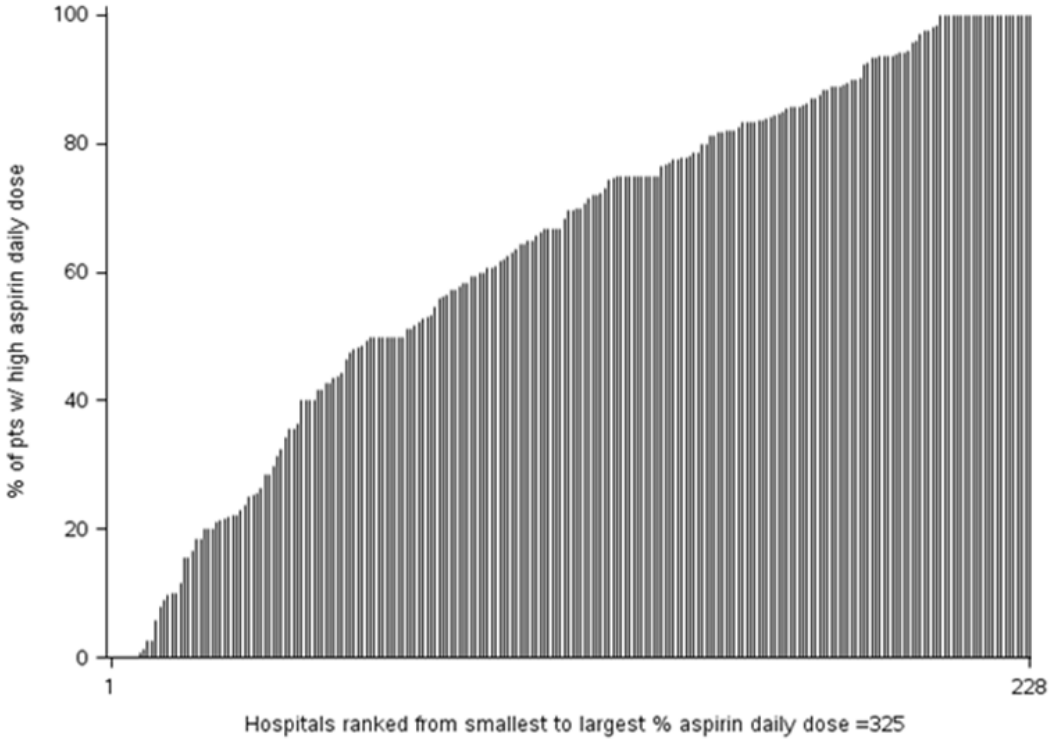
This figure displays the distribution of discharge aspirin dose in participating hospitals.

Pts indicates patients

Supplemental Figure 1



Supplemental Figure 2



The Association of Discharge Aspirin Dose With Outcomes After Acute Myocardial Infarction: Insights From the TRANSLATE-ACS Study

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Circulation. published online May 20, 2015;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539